

Health Technology Assessment Program  
Selected Technologies 2016

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STATE OF WASHINGTON  
**HEALTH CARE AUTHORITY**

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April 18, 2016

To whom it may concern:

**SUBJECT: Health Technology Assessment Topic Selection 2016**

As the Director of the Health Care Authority (HCA) and per the Health Technology Assessment (HTA) law (70.14 RCW) I select technologies for review by the program in consultation with other agencies and the Health Technology Clinical Committee. Technologies are selected when there are concerns about safety, efficacy or value (cost-effectiveness), when state expenditures are or could be high, and there is adequate evidence to conduct a review. Technologies are selected for re-review when new evidence is available that could change a previous determination. In addition, anyone may petition for a technology review.

For the current selection cycle, I have reviewed the proposed topics as well as the comments received from the interested individuals and groups who responded in the first comment period (February 26 – March 11, 2016). Based on the information provided by the Health Technology Assessment program, and the recommendations from HCA, Department of Labor and Industries and Department of Corrections, I have selected the following technologies for review:

Technology	Safety	Efficacy	Cost
<b>1 Extracorporeal Shock Wave Therapy for Musculoskeletal Conditions</b>	<b>High</b>	<b>High</b>	<b>Med/High</b>
<b>Policy Context/Reason for selection:</b> Extracorporeal shock wave therapy (ESWT) is a noninvasive treatment based on ultrasound technology. ESWT is used for a variety of conditions including treatment of kidney stones. ESWT for soft tissue injuries is applied with the goal of promoting healing. ESWT may have multiple effects thought to impact healing including breaking calcium deposits and causing an inflammatory response that may stimulate tissue healing.			
<b>2 Interventions for Treatment of Migraines/Headaches</b>	<b>Med/High</b>	<b>Med/High</b>	<b>Med/High</b>
<b>Policy Context/Reason for selection:</b> Interventions for the treatment of headaches include botulinum toxin injections, transcranial magnetic stimulation, nerve destruction, acupuncture and massage. The topic is proposed to determine the safety, efficacy and value of interventions for treatment for migraines and other headaches types.			
<b>3 Varicose Veins</b>	<b>Medium</b>	<b>High</b>	<b>Medium</b>
<b>Policy Context/Reason for selection:</b> A variety of treatments for varicose veins are available. Treatment goals include reducing pain or discomfort and for cosmetic reasons. The topic is identified based on uncertainties related to the safety, efficacy and value of the certain procedures including chemical ablation, stab phlebectomy and laser ablation.			

Technology	Safety	Efficacy	Cost
<b>4 Skin Substitutes</b>	<b>Low</b>	<b>Med/High</b>	<b>Med/High</b>

**Policy Context/Reason for selection:** A variety of skin substitute products are available for treatment of complex and/or non-healing wounds. The level of evidence available varies for different products and the safety, efficacy and value of the products is uncertain. The reason for proposing this topic is to identify and review the available evidence to determine coverage for products that are demonstrated to be safe and effective for treatment of wounds.

<b>5 Mammogram: Computer Aided Detection Mammogram</b>	<b>Low</b>	<b>High</b>	<b>Med/Low</b>
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**Policy Context/Reason for selection:** Computer aided detection (CAD) and diagnosis for mammography is used as an adjunct to traditional reading of images by radiologists. CAD technology has developed to try to improve early detection of disease to then reduce deaths caused by breast cancer. Evidence addressing the utility of CAD for mammography will be reviewed to determine coverage for CAD as an adjunct to mammography screening and diagnosis.

<sup>1</sup> [Link to Primary Criteria Ranking](#).

One topic, the Left Atrial Appendage Device was proposed and based on comments and new information, including a Centers for Medicare and Medicaid Services decision, is not selected for review at this time.

Additionally, I have selected *Artificial Disc Replacement* for re-review based on the newly available published evidence.

Upon publication of the selected list of technologies, a 30-day comment period will begin whereby any interested person or group may provide information relevant to review of these topics. HTA will begin work to review these technologies following this comment period.

Should you have any questions or concerns, please contact Josh Morse, HTA Program Director, by telephone at 360-725-0839 or via email at [Josh.morse@hca.wa.gov](mailto:Josh.morse@hca.wa.gov).

Sincerely,



Dorothy F. Teeter, MHA  
Director

## Technologies Selected

Technology	Safety	Efficacy	Cost
<b>1 Extracorporeal Shock Wave Therapy for Musculoskeletal Conditions</b> <b>Policy Context/Reason for Selection:</b> Extracorporeal shock wave therapy (ESWT) is a noninvasive treatment based on ultrasound technology. ESWT is used for a variety of conditions including treatment of kidney stones. ESWT for soft tissue injuries is applied with the goal of promoting healing. ESWT may have multiple effects thought to impact healing including breaking calcium deposits and causing an inflammatory response that may stimulate tissue healing.	High	High	Med/High
<b>2 Interventions for Treatment of Migraines/Headaches</b> <b>Policy Context/Reason for selection:</b> Non-pharmacologic treatments for headaches include Botox injections, transcranial magnetic stimulation, nerve destruction, acupuncture and massage. The topic is proposed to determine the safety, efficacy and value of non-drug treatments for migraines and other headaches types.	Med/High	Med/High	Med/High
<b>3 Varicose Veins</b> <b>Policy Context/Reason for selection:</b> A variety of treatments for varicose veins are available. Treatment goals include reducing pain or discomfort and for cosmetic reasons. The topic is identified based on uncertainties related to the safety, efficacy and value of the certain procedures including chemical ablation, stab phlebectomy and laser ablation.	Medium	High	Medium
<b>4 Skin Substitutes</b> <b>Policy Context/Reason for Selection:</b> A variety of skin substitute products are available for treatment of complex and/or non-healing wounds. The level of evidence available varies for different products and the safety, efficacy and value of the products is uncertain. The reason for proposing this topic is to identify and review the available evidence to determine coverage for products that are demonstrated to be safe and effective for treatment of wounds.	Low	Med/High	Med/High
<b>5 Mammogram: Computer-Aided Detection (CAD)</b> <b>Policy Context/Reason for selection:</b> Computer aided detection (CAD) and diagnosis for mammography is an adjunct to traditional reading of images by radiologists. CAD technology has developed to improve early detection of disease to then reduce deaths caused by breast cancer. Evidence addressing the utility of CAD for mammography will be reviewed to determine coverage for CAD as an adjunct to mammography screening and diagnosis.	Low	High	Med/Low

**Technologies Considered, Not Proposed**

<b>Technology</b>	
1	Peripheral Artery Stenting
2	Interventions for Overactive Bladder
3	Hysterectomy/Fibroid Tumor Removal
4	Carpal Tunnel Treatments
5	Non-pharmacologic Therapy for Pain in Primary Care
6	PET Beta Amyloid and Tau Scanning for Alzheimer's and Mild Cognitive Impairment

**Technologies Selected for Re-review:**

Technologies are considered for re-review at least once every eighteen months based on availability of new evidence that may change the decision. (*Detailed criteria are included below*). All technologies with determinations beyond 18 months since the final determination previously reviewed by the Health Technology Clinical Committee (HTCC) are listed below, along with information on whether they have been selected for re-review.

<b>Technology</b>	<b>Originally Reviewed</b>	<b>Recommended for Re-review</b>
1 <b>Artificial Disks (Cervical &amp; Lumbar)</b>	October 2008	Yes

New indications. New literature identified. Surveillance report attached.

For the current period, the program has not received or identified new evidence to support review of the following:

<b>HTA Decisions</b>	<b>Latest Review/ Scan</b>
1 Arthroscopic Knee Surgery	October, 2008
2 Computed Tomographic Angiography (CTA)	May, 2009
3 Calcium Scoring	May, 2010
4 Knee Joint Replacement or Knee Arthroplasty	December, 2010
5 Vertebroplasty, Kyphoplasty and Sacroplasty	March, 2011
6 Glucose Monitoring	June, 2011
7 Positron Emission Tomography (PET) Scans for Lymphoma	November, 2011
8 Microprocessor-controlled Lower Limb Prosthetics	March, 2012
9 Osteochondral Allograft / Autograft Transplantation	March, 2012
10 Sleep Apnea Diagnosis and Treatment	May, 2012
11 Bone Morphogenetic Protein	May, 2012
12 Upright / Positional MRI	June, 2012

	<b>HTA Decisions</b>	<b>Latest Review/ Scan</b>
13	Hip Resurfacing	August, 2012
14	Robotic Assisted Surgery	September, 2012
15	Upper Endoscopy for GERD and GERD-like symptoms	September, 2012
16	Virtual Colonoscopy or Computed Tomographic Colonography (CTC)	December, 2012
17	Vitamin D Screening and Testing	March, 2013
18	Hyperbaric Oxygen for Wound Healing	May, 2013
19	Cervical Spinal Fusion for DDD	May, 2013
20	Ablation Procedures for Supraventricular Tachycardia	September, 2013
21	Cochlear Implants	September, 2013
22	Discography	November, 2013
23	Implantable Infusion Pumps	November, 2013
24	Electrical Neural Stimulation (ENS)	November, 2013
25	Hyaluronic Acid / Viscosupplementation	November, 2013
26	Routine Ultrasound for Pregnancy	November, 2013
27	Intensity Modulated Radiation Therapy	November, 2013
28	Carotid Artery Stenting	November, 2013
29	Cardiac Nuclear Imaging	November, 2013
30	Spinal Cord Stimulators	January, 2014

# Artificial Disc Replacements (ADR): Assessing Signals for Update

Provided by:



**Spectrum Research, Inc.**

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Prepared by:

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Krystle Pagarigan, BS  
January 22, 2016

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## 1. Introduction

A Health Technology Assessment titled: **Artificial Disc Replacement**, was published on September 19, 2008 by the Health Care Authority. Findings and Coverage Decision was released on October 17, 2008 and adopted on March 20, 2009. The Committee's Coverage Decision is summarized below.

### HTCC Coverage Determination

Cervical and Lumbar Artificial Disc Replacement is a covered benefit only under criteria identified in the reimbursement determination

### HTCC Reimbursement Determination

Limitations of Coverage:

Lumbar Artificial Disc Replacement (L-ADR)

- 1) Patients must first complete a structured, intensive, multi-disciplinary program for management of pain, if covered by the agency;
- 2) Patients must be 60 years or under;
- 3) Patients must meet FDA approved indications for use and not have any contra-indications. FDA approval is device specific but includes:
  - Failure of at least six months of conservative treatment
  - Skeletally mature patient
  - Replacement of a single disc for degenerative disc disease at one level confirmed by patient history and imaging

Artificial Disc Replacement FDA general contra-indications:

Active systemic infection or infection localized to site of implantation

Allergy or sensitivity to implant materials

Certain bone and spine diseases (e.g. osteoporosis, spondylosis)

Cervical Artificial Disc Replacement (C-ADR)

- 1) Patients must meet FDA approved indications for use and not have any contra-indications. FDA approval is device specific but includes:
  - Skeletally mature patient
  - Reconstruction of a disc following single level discectomy for intractable symptomatic cervical disc disease (radiculopathy or myelopathy) confirmed by patient findings and imaging.

Artificial Disc Replacement FDA general contra-indications:

- Active systemic infection or infection localized to site of implantation
- Allergy or sensitivity to implant materials
- Certain bone and spine diseases (e.g. severe spondylosis or marked cervical instability)

Non-Covered Indications

Non-FDA approved uses

### Committee Conclusions

Having made findings as to the most significant and relevant evidence regarding health outcomes, key factors and identified evidence related to those factors, primarily based on the evidence based technology assessment report, the committee concludes:

### **1. Evidence availability and technology features**

The committee concludes that the best available evidence on artificial disc replacement has been collected and summarized.

- 1.1. There is moderate evidence from 5 randomized controlled trials and about 40 uncontrolled studies about several important health outcomes for artificial disc replacement. The randomized trials have shared limitations: some methodological flaws, fusion as only comparator, non-inferiority design, lack of long term data, and measure/definition of success.
- 1.2. The controlled studies compare surgical options only. Fusion surgery as a treatment for spine pain is still not established a clearly superior option, so the lack of inclusion of optimized medical management severely limits the results.
- 1.3. As compared to fusion, a currently approved alternative, the overall evidence is moderate and demonstrates at least equivalence of ADR in short term safety and efficacy.
- 1.4. Longer follow up data, especially around safety events and reoperation rates is needed (often this evidence comes from non RCT data such as registries). Also, the post approval FDA studies requiring up to seven year follow up should be monitored.

### **2. Is it safe?**

The committee concludes that the comprehensive evidence reviewed shows that the technology has been proven at least equally safe as a currently offered alternative, fusion. Key factors to the committee's conclusion include:

- 2.1. Moderate evidence demonstrated that L-ADR has a similar safety profile as lumbar anterior or circumferential fusion two years following surgery. Longer term safety on L-ADR is not known.
- 2.2. Moderate evidence demonstrated that C-ADR tends to be safer than fusion as measured by the risk of device failure and surgical complications up to two years following surgery. Longer term safety on C-ADR is not known.

### **3. Is it effective?**

The committee concludes that the comprehensive evidence reviewed shows that the technology has been proven equally or more effective as a currently offered alternative, fusion. Key factors to the committee's conclusion include:

- 3.1. While there is no evidence comparing ADR with non-operative care, there are five moderate quality, controlled studies comparing ADR with a currently performed alternative, fusion. Based on the limited comparator and other evidence limitations, the evidence of efficacy should not be generalized beyond carefully selected patients that match trial and FDA indications.
- 3.2. Moderate evidence demonstrated that the efficacy/effectiveness of L-ADR is comparable with fusion up to two years following surgery based on a composite measure for FDA approval of overall clinical success, pain improvement, an ODI and SF-36 improvement..
- 3.3. Moderate evidence demonstrated that the efficacy/effectiveness of C-ADR is equal to fusion for pain and function and potentially superior to fusion for neurological and overall success up to two years following surgery.
- 3.4. There is insufficient evidence to draw conclusions regarding the safety and efficacy of ADR in special populations or populations outside those studied for FDA approval. Thus, coverage should be limited to studied indications.

### **4. Is it cost-effective?**

The Committee concludes that the comprehensive evidence review does not show that the technology is more cost effective. Although cost-effectiveness was not a major decision factor, the committee concluded cost-effectiveness is unproven because of insufficient evidence.

4.1. The cost analyses were limited by short time horizons, comparators chosen, and differences with US health system, and provided mixed answers. For L-ADR, one assessment showed an increase in cost based on the device cost and another showed similar or possibly reduced cost based primarily on shorter hospital stays for L-ADR. For C-ADR, one cost analysis showed similar surgical costs, but higher total cost with C-ADR due to device cost.

### **5. Medicare Decision and Expert Treatment Guidelines**

The committee deliberations included a discussion of National Medicare Decisions and expert treatment guidelines, and an understanding that the committee must find substantial evidence to support a decision that is contrary. RCW 70.14.110. The independent evidence report identified a national Medicare coverage decision on lumbar fusion and no expert treatment guidelines. The committee's conditional coverage is consistent with the national Medicare decision to not cover L-ADR for patients older than 60 years of age.

## **2. Purpose of Report**

The purpose of this literature update is to determine whether or not there is sufficient evidence published after the original report to conduct a re-review of this technology based on the presence of preset signal criteria. The key questions included the following:

### **Key question 1**

What is the evidence of efficacy and effectiveness of ADR compared with comparative therapies (including non-operative therapy; spinal fusion; other surgery)?

### **Key Question 2**

What is the evidence related to the ADR safety profile? (including device failure, reoperation)

### **Key Question 3**

What is the evidence of differential efficacy or safety issues amongst special populations (including but not limited to the elderly and workers compensation populations)?

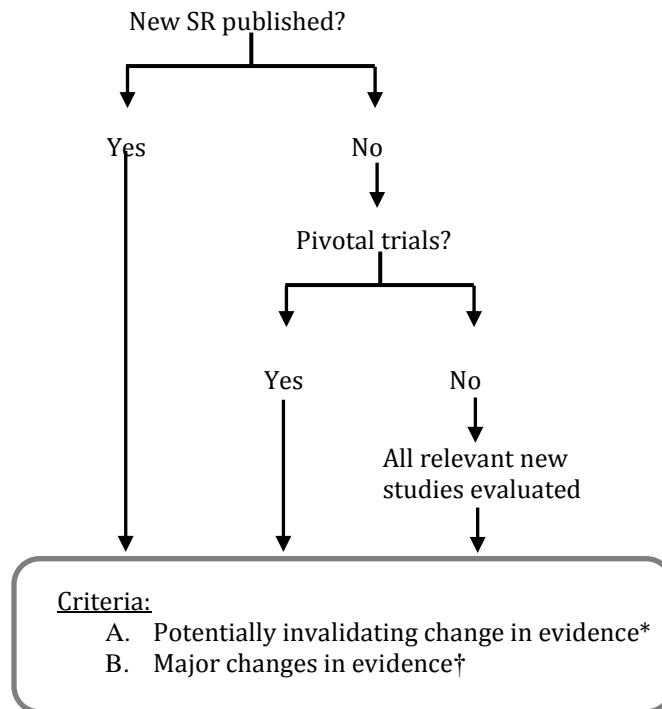
### **Key Question 4**

What are the cost implications and cost effectiveness for ADR?

## **3. Methods**

To determine the need for systematic review update, the following algorithm was followed:

**Figure 1. Algorithm of the modified Ottawa Method of Identifying Signals for SR Updates**



- \*A-1. Opposing findings: Pivotal trial or SR including at least one new trial that characterized the treatment in terms opposite to those used earlier
- A-2. Substantial harm: Pivotal trial or SR whose results called into question the use of the treatment based on evidence of harm or that did not proscribe use entirely but did potentially affect clinical decision making
- A-3. Superior new treatment: Pivotal trial or SR whose results identified another treatment as significantly superior to the one evaluated in the original review, based on efficacy or harm.
- †B-1. Important changes in effectiveness short of “opposing findings”
- B-2. Clinically important expansion of treatment
- B-3. Clinically important caveat
- B-4. Opposing findings from discordant meta-analysis or nonpivotal trial

**3.1 Literature Searches**

We conducted a limited electronic literature of Medline for systematic reviews with meta-analysis during the period January 1, 2008 through January 8, 2016 using search terms used for the original report. Appendix A includes the search methodology for this topic. In addition, we searched the FDA website to determine if there was approval of new indications for ADR. Finally, we searched for individual cost-effectiveness studies for KQ 4.

**3.2 Study selection**

We sought systematic reviews of randomized controlled trials (RCTs) of efficacy and safety with meta-analysis that included articles that met inclusion and exclusion criteria similar to the original report. In addition we sought systematic reviews reflecting updates or new advances for the technology. Secondary to the large number of citations returned, we focused on screening only systematic reviews and meta-analyses of RCTS published between 2012 and 2015. Although quality of systematic reviews

was not formally evaluated for this report, we chose two systematic reviews, one for the lumbar and one for the cervical spine that were the most comprehensive and of high quality based on the following: report of search strategies (two or more data bases and description of dates searched), number of included relevant RCTs, pre-stated inclusion and exclusion criteria, information on methodologies used for synthesis of data, inclusion of patient reported or safety outcomes and evaluation of the strength of the body of literature using GRADE or another analogous system. A summary of the two SRs is found in Appendix B.

## 4. Results

### 4.1 Search

We identified 11 lumbar and 24 cervical systematic reviews from the electronic search that addressed in part or in full key questions 1 and 2, Figure 2. We reviewed the full text of four lumbar and 16 cervical studies. We chose one systematic review for each anatomical region (lumbar and cervical) that we felt most closely met the inclusion criteria (see excluded studies and the reasons for exclusion in Appendix C). There were no systematic reviews on differential efficacy or safety (key questions 3). We found three cervical cost-effectiveness studies (Key Question 4) where there were none in the previous report.

The FDA approved one device (Mobi-C) for two- level cervical disc reconstruction since our initial report.

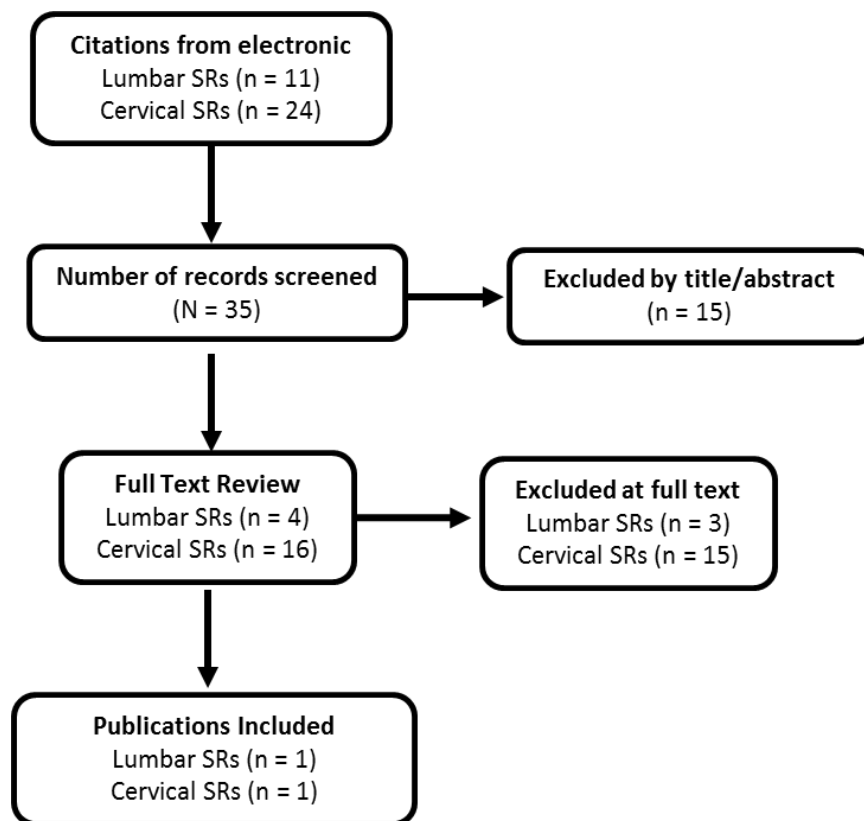


Figure 2. Electronic search results for systematic reviews

**4.2 Identifying signals for re-review**

Table 1 shows the original key questions, the conclusions of the original report, the new sources of evidence, the new findings, and the recommendations of Spectrum Research, Inc. (SRI) regarding the need for update.

**Table 1. ADR Summary Table for Key Question 1.**

<b>Key Question 1. What is the evidence of efficacy and effectiveness of ADR compared with comparative therapies (including nonoperative therapy, spinal fusion, other surgery)?</b>			
<b>Conclusions from CER Executive Summary</b>	<b>New Sources of Evidence</b>	<b>New Findings</b>	<b>Conclusion from SRI</b>
<p><b><u>L-ADR vs. nonoperative care</u></b> No evidence available</p>	<p>Systematic Review  Jacobs et al<sup>1</sup></p>	<ul style="list-style-type: none"> <li>• A systematic review identified one study that compared disc replacement against rehabilitation and found a statistically significant advantage in ODI in favor of surgery, which, however, did not reach the predefined threshold for clinical relevance.</li> </ul>	<p>This section of the report is NOT valid. A new comparison group is added and the report needs updating</p>
<p><b><u>L-ADR vs. lumbar fusion</u></b></p> <ul style="list-style-type: none"> <li>• There is moderate evidence that the efficacy of L-ADR as measured by the composite measure of overall clinical success, Oswestry Disability Index (ODI) improvement, pain improvement, neurological success, SF-36 improvement, and patient satisfaction is comparable with anterior lumbar interbody fusion or circumferential fusion up to two years following surgery.</li> <li>• This evidence is based on two moderate quality randomized controlled trials conducted as FDA Investigational Device Exemption non-inferiority trials.</li> <li>• Overall clinical success (a composite measure considering most or all of the following: ODI improvement, device failure, complications, neurological change, SF-36 change and radiographic success) was achieved in 56% of patients receiving L-ADR and 48% receiving lumbar fusion.</li> <li>• Though the results suggest that 24 month outcomes</li> </ul>	<p>Systematic Review  Jacobs et al<sup>1</sup></p>	<ul style="list-style-type: none"> <li>• A systematic review (Jacobs) included 39 publications, describing six unique RCT's. The follow-up of the studies was 24 months, with only one extended to five years. Five studies had a low risk of bias, although there is a risk of bias in the included studies due to sponsoring and absence of any kind of blinding.</li> <li>• The six studies found that the mean improvement in VAS back pain was 5.2 mm (of 100 mm) higher (two studies, 676 patients; 95% confidence interval (CI) 0.18 to 10.26) with a low quality of evidence, while from the same studies leg pain showed no difference.</li> <li>• The improvement of Oswestry score at 24 months in the disc replacement group was 4.27 points more than in the fusion group (five studies; 1207 patients; 95% CI 1.85 to 6.68) with a low quality of evidence.</li> <li>• Both upper bounds of the confidence intervals for VAS back pain and Oswestry score were below the predefined clinically relevant difference. Choice of</li> </ul>	<p>This section of the report is still valid and does not need updating.</p>

<b>Key Question 1. What is the evidence of efficacy and effectiveness of ADR compared with comparative therapies (including nonoperative therapy, spinal fusion, other surgery)?</b>			
<b>Conclusions from CER Executive Summary</b>	<b>New Sources of Evidence</b>	<b>New Findings</b>	<b>Conclusion from SRI</b>
<p>for L-ADR are similar to lumbar fusion, it should be noted that a non-inferiority trial requires that the reference treatment have an established efficacy or that it is in widespread use. For the lumbar spine, the efficacy of the comparator treatment, lumbar fusion, for degenerative disc disease remains uncertain, especially when it is compared with nonoperative care. Given what is known about lumbar fusion as a comparator and having evidence that only compares L-ADR with lumbar fusion limits the ability to fully answer the efficacy/effectiveness question.</p> <ul style="list-style-type: none"> <li>• There are no (medium-) or long-term follow-up data assessing efficacy/effectiveness from the two index RCTs at this time</li> </ul>		<p>control group (circumferential or anterior fusion) did not appear to result in different outcomes.</p>	
<p><b><u>C-ADR vs. nonoperative care</u></b> No evidence available</p>	No new evidence	No new evidence	This section of the report is still valid and does not need updating.
<p><b><u>C-ADR vs. cervical fusion</u></b></p> <ul style="list-style-type: none"> <li>• There is moderate evidence for the cervical spine that C-ADR is superior to ACDF with respect to overall clinical success (77% versus 68%) and neurological success (92% versus 86%), and is comparable with ACDF with respect to Neck Disability Index (NDI), and pain up to two years following surgery.</li> <li>• The evidence is based on two moderate quality randomized controlled FDA Investigational Device Exemption non-inferiority trials. An interim analysis of approximately 65% of a third RCT was reported in an FDA Panel Executive Summary. If the results following completion of the trial are</li> </ul>	<p>Systematic Review  Zhang et al<sup>2</sup></p>	<p>19 RCTs (n = 4516) <b><u>Short-term follow-up (2-3 years)</u></b></p> <ul style="list-style-type: none"> <li>• The C-ADR group had statistically lower NDI scores (SMD, -0.34; 95% CI: -0.68 to 0.00, P = 0.05) than the ACDF group. However, there existed a substantial heterogeneity. In sensitivity analysis, the result also showed that C-ADR group had better NDI scores (SMD, -0.13; 95% CI: -0.25 to -0.02, P = 0.02) compared with ACDF group.</li> <li>• The C-ADR group had a statistically higher NDI success rate than the ACDF group (OR, 0.72; 95% CI: 0.54 to 0.95, P = 0.02).</li> <li>• A higher neurological success rate was seen in the C-ADR group than in the ACDF group (OR, 0.62; 95% CI:</li> </ul>	This section of the report is NOT valid. There are new data for medium-term follow-up of 4-5 years.

<b>Key Question 1. What is the evidence of efficacy and effectiveness of ADR compared with comparative therapies (including nonoperative therapy, spinal fusion, other surgery)?</b>			
<b>Conclusions from CER Executive Summary</b>	<b>New Sources of Evidence</b>	<b>New Findings</b>	<b>Conclusion from SRI</b>
<p>similar to the interim results of that same trial, the confidence in the evidence that C-ADR is superior to ACDF will increase.</p> <ul style="list-style-type: none"> <li>There is evidence that segmental motion is maintained or improved up to three years in the L-ADR patients and up to four years in C-ADR patients compared with preoperative motion. It is unclear the true extent to which preserving segmental motion by using ADR instead of fusion influences rates of adjacent segment disease (ASD). Whether ASD is a continuation of a disease process necessitating fusion or a result of fusion continues to be disputed. Furthermore, there continues to be debate on whether the presence of ASD is clinically important given that patients with marked radiographic ASD often have no symptoms.</li> </ul>		<p>0.45 to 0.85, P = 0.003).</p> <ul style="list-style-type: none"> <li>C-ADR group had significantly lower neck pain scores in three studies using numerical rating scales (SMD, -0.14; 95% CI: -0.27 to -0.01) and lower neck (SMD -1.28; 95% CI: -2.16 to 0.40) and arm pain scores (SMD -0.19; 95% CI: -0.35 to -0.03) vs. ACDF in three studies using VAS.</li> <li>The C-ADR group presented a significantly higher overall composite success rate (OR, 0.59; 95% CI: 0.48 to 0.74, P &lt; 0.00001)</li> </ul> <p><b><u>Medium-term (4-5 years)</u></b></p> <ul style="list-style-type: none"> <li>NDI scores in the C-ADR group were lower than those of the ACDF group in two studies (SMD, -0.31; 95% CI: -0.47 to -0.15, P = 0.0002).</li> <li>Neurological success from two studies occurred more frequently in the C-ADR group than in the ACDF group (OR, 0.55; 95% CI: 0.30 to 1.01, P = 0.05).</li> <li>Neck (SMD, -0.28; 95% CI: -0.44 to -0.12, P = 0.0008) and arm pain scores (SMD, -0.19; 95% CI: -0.35 to -0.03, P = 0.02) were lower in two studies using NRS scores.</li> </ul>	



Table 2. ADR Summary Table for Key Question 2.

<b>Key Question 2: What is the evidence related to the ADR safety profile (including complications, adverse events, device failure, reoperation)?</b>			
<b>Conclusions from CER Executive Summary</b>	<b>New Sources of Evidence</b>	<b>New Findings</b>	<b>Conclusion from SRI</b>
<p><b><u>L-ADR vs. nonoperative care</u></b> No evidence available</p>	<p>Systematic Review  Jacobs et al<sup>1</sup></p>	<ul style="list-style-type: none"> <li>A systematic review (Jacobs) identified one study that compared disc replacement against rehabilitation. Among those receiving L-ADR, six patients (8%) had complications resulting in impairment at two year follow-up, and the reoperation rate was 6.5% (n=5).</li> </ul>	<p>This section of the report is NOT valid. A new comparison group is added and the report needs updating</p>
<p><b><u>L-ADR vs. lumbar fusion</u></b></p> <ul style="list-style-type: none"> <li>There is moderate evidence that L-ADR results in a similar proportion of device-related complications (7 to 18%) compared with lumbar fusion (4 to 20%)</li> <li>There is moderate evidence that L-ADR results in a similar proportion of major complications (0 to 1%) compared with lumbar fusion (0 to 1%)</li> <li>There are no (medium-) or long-term follow-up data assessing safety from the two index RCTs at this time</li> </ul>	<p>Systematic Review  Jacobs et al<sup>1</sup></p>	<ul style="list-style-type: none"> <li>There were 63 of 810 (7.8%) re-operations in the total disc replacement group and 35 of 384 (9.1%) in the fusion group. There is very low quality evidence from five studies that the difference in re-operations up to 24 months was not statistically significant.</li> <li>Only one secondary publication of a low risk of bias study reported neurological complications and found no difference between the two groups.</li> <li>There is very low quality evidence from one low risk of bias study that the difference in adjacent segment degeneration at 24 months was not statistically different. This one study only marginally reported adjacent segment degeneration mentioning six of 72 cases of fusion and only one of 80 cases of total disc replacement with adjacent segment problems.</li> <li>There is very low quality of evidence from one low risk of bias study that the occurrence of facet joint degeneration is not statistically significantly different.</li> </ul>	<p>This section of the report is still valid and does not need updating.</p>
<p><b><u>C-ADR vs. nonoperative care</u></b> No evidence available</p>	<p>No new evidence</p>	<p>No new evidence</p>	<p>This section of the report is still valid and does not need updating.</p>
<p><b><u>C-ADR vs. cervical fusion</u></b></p> <ul style="list-style-type: none"> <li>Complication rates varied among the studies but generally device related or device/surgical procedure related complications or adverse events occurred less frequently among the C-</li> </ul>	<p>Systematic Review  Zhang et al<sup>2</sup></p>	<p><b><u>Short-term follow-up (2-3 years)</u></b></p> <ul style="list-style-type: none"> <li>Adverse events occurred more frequently in the ACDF group than in the C-ADR group (OR, 0.58; 95% CI: 0.43 to 0.80, P = 0.0007) in eight studies.</li> <li>Secondary surgical procedures were defined as any</li> </ul>	<p>This section of the report is NOT valid. There are new data for medium-term follow-up of 4-5</p>

<b>Key Question 2: What is the evidence related to the ADR safety profile (including complications, adverse events, device failure, reoperation)?</b>			
<b>Conclusions from CER Executive Summary</b>	<b>New Sources of Evidence</b>	<b>New Findings</b>	<b>Conclusion from SRI</b>
<p>ADR patients (5%) than anterior fusion patients (10%).</p> <ul style="list-style-type: none"> <li>There are no (medium-) or (medium-) or long-term follow-up data assessing safety from the five index RCTs at this time</li> </ul>		<p>hardware removal, revisions, supplemental fixations, and reoperations. They were typically used to resolve persistent neck or shoulder pain, dysphagia, prosthesis flexibility or adjacent level degeneration. Secondary surgical procedures were recorded at the index level and the adjacent level. C-ADR group had significantly fewer secondary surgical procedures at the index (OR, 0.32; 95% CI: 0.19 to 0.53, P &lt; 0.00001) and the adjacent level (OR, 0.28; 95% CI: 0.11 to 0.72, P = 0.008).</p> <p><b><u>Medium-term (4-5 years)</u></b></p> <ul style="list-style-type: none"> <li>Only one study with 74 patients had valid adverse-event data for midterm follow-up, no data given for this study.</li> <li>The rate of secondary surgical procedures at the adjacent level (OR, 0.76; 95% CI: 0.47 to 1.22, P = 0.25) was not significantly different between the groups in five studies. There were significantly fewer secondary surgical procedures related to the index level in the C-ADR group in five studies (OR, 0.45; 95% CI: 0.29 to 0.68, P = 0.0002).</li> </ul>	<p>years.</p>

**Table 3. ADR Summary Table for Key Questions 3 and 4.**

<b>Key Question 3: What is the evidence of differential efficacy or safety issues amongst special populations (including but not limited to the elderly and workers compensation populations)?</b>			
<b>Conclusions from CER Executive Summary</b>	<b>New Sources of Evidence</b>	<b>New Findings</b>	<b>Conclusion from SRI</b>
There is insufficient evidence to draw conclusions regarding the safety and efficacy of LADR in the few special populations studied (elderly, smokers, athletes). No studies or sub-analyses were found on the use of C-ADR in special or subpopulations.	No new evidence	No new evidence	This section of the report is still valid and does not need updating.
<b>Key Question 4: What are the cost implications and cost effectiveness for ADR?</b>			
<b>Conclusions from CER Executive Summary</b>	<b>New Sources of Evidence</b>	<b>New Findings</b>	<b>Conclusion from SRI</b>
There are inadequate data from partial economic studies reflecting short time horizons for L-ADR and no economic studies for C-ADR to truly assess the potential cost effectiveness of ADR technology. One report and one previously done HTA suggest that the type of fusion may influence complication rates and therefore costs.	1 lumbar <sup>3</sup> ; 2 cervical (1 single- <sup>4</sup> and 1 two-level replacement <sup>5</sup> )	<p><b>Lumbar:</b> L-ADR was cost-effective compared with multi-disciplinary rehab after 2 years when using EQ-5D for assessing QALYs gained and a willingness to pay. L-ADR was not cost-effective when SF-6D was used. Longer follow-up is needed to accurately assess cost-effectiveness of L-TDR.</p> <p><b>Cervical:</b> Single level – One study suggests that a non-significant added benefit versus ACDF comes at a reasonable cost, whether actual hospital costs or Medicare reimbursement values are used. Two-level – One study concludes that the incremental cost-effectiveness ratio of C-ADR compared with traditional ACDF is lower than the commonly accepted threshold of \$50,000 per QALY.</p>	This section of the report is NOT valid. Studies of cost-effectiveness are now available for 1-level L-ADR versus conservative care, 1-level C-ADR versus 1-level cervical fusion, and 2-level C-ADR versus 2-level cervical fusion. Therefore, this section of the report needs updating.

## 5. Conclusions

### L-ADR

- There are several systematic reviews that include new RCTs since the publication of the original ADR report. From a review of these systematic reviews, there is one new RCT that evaluates L-ADR versus conservative (non-operative) care. This is the first study making this comparison and warrants an update of the section comparing efficacy and safety of ADR versus a treatment other than ACDF, (criteria B-3, Figure 1).
- New studies comparing the efficacy and safety of L-ADR versus ACDF are consistent with the original ADR HTA. This section does not need an update.
- One study on cost effectiveness of L-ADR intervention has been published since the original HTA comparing L-ADR versus conservative (non-operative) care. Therefore, this section of the report needs updating.

### C-ADR

- There are no new data for C-ADR versus new comparisons other than cervical fusion.
- One C-ADR, the Mobi-C, has been approved by the FDA for 2-level fusion. This is a new indication since the original report. There is at least 1 RCT (the FDA trial) that reports 2 year results on 2-level C-ADR. This warrants an update of the section of the report on efficacy and safety of C-ADR, (criteria B-2, Figure 1).
- The results of integrating new RCTs (total number: 19 RCTs, 4,516 patients) are similar to the original report with respect to pain and function for the short-term (24 months). However, there are new efficacy and safety data for medium-term (4-5 years) that were not present in the original report. Therefore, this section needs updating for both efficacy and safety.
- There were no new studies on differential efficacy or safety. This section of the report does not need updating.
- Two studies on cost effectiveness of C-ADR intervention have been published since the original HTA; 1-level C-ADR versus 1-level cervical fusion, and 2-level C-ADR versus 2-level cervical fusion. Therefore, this section of the report needs updating.

**REFERENCES**

1. Jacobs W, Van der Gaag NA, Tuschel A, et al. Total disc replacement for chronic back pain in the presence of disc degeneration. *Cochrane Database Syst Rev* 2012; **9**: CD008326.
2. Zhang Y, Liang C, Tao Y, et al. Cervical total disc replacement is superior to anterior cervical decompression and fusion: a meta-analysis of prospective randomized controlled trials. *PLoS One* 2015; **10**(3): e0117826.
3. Johnsen LG, Hellum C, Storheim K, et al. Cost-effectiveness of total disc replacement versus multidisciplinary rehabilitation in patients with chronic low back pain: a Norwegian multicenter RCT. *Spine (Phila Pa 1976)* 2014; **39**(1): 23-32.
4. Warren D, Andres T, Hoelscher C, Ricart-Hoffiz P, Bendo J, Goldstein J. Cost-utility analysis modeling at 2-year follow-up for cervical disc arthroplasty versus anterior cervical discectomy and fusion: A single-center contribution to the randomized controlled trial. *Int J Spine Surg* 2013; **7**: e58-66.
5. Ament JD, Yang Z, Nunley P, Stone MB, Kim KD. Cost-effectiveness of cervical total disc replacement vs fusion for the treatment of 2-level symptomatic degenerative disc disease. *JAMA Surg* 2014; **149**(12): 1231-9.

## **APPENDIX A. SEARCH STRATEGIES**

Below is the search strategy for PubMed.

**(artificial[TI] OR TOTAL[TI] OR ARTHROPLASTY[TI] OR PROSTHETIC\*[TI] OR PROSTHES\*[TI]) AND (DISC[TI] OR DISK[TI]) AND (LOW BACK[TIAB] OR LUMBAR[TIAB]) AND META-ANALYS\***

**(artificial[TI] OR TOTAL[TI] OR ARTHROPLASTY[TI] OR PROSTHETIC\*[TI] OR PROSTHES\*[TI]) AND (DISC[TI] OR DISK[TI]) AND (NECK[TIAB] OR CERVICAL[TIAB]) AND META-ANALYS\***

**(artificial[TI] OR TOTAL[TI] OR ARTHROPLASTY[TI] OR PROSTHETIC\*[TI] OR PROSTHES\*[TI]) AND (DISC[TI] OR DISK[TI]) AND (LOW BACK[TIAB] OR LUMBAR[TIAB]) AND COST\*[TI]**

**(artificial[TI] OR TOTAL[TI] OR ARTHROPLASTY[TI] OR PROSTHETIC\*[TI] OR PROSTHES\*[TI]) AND (DISC[TI] OR DISK[TI]) AND (NECK[TIAB] OR CERVICAL[TIAB]) AND COST\*[TI]**

**APPENDIX B. SUMMARY OF INCLUDED SYSTEMATIC REVIEWS.**

Assessment (year) Search dates	Purpose	Condition	Treatments v s. controls	Primary Outcomes	Evidence-base Used	Primary Conclusions
Jacobs (2012) Database inception to 12/2011	To assess the effect of total disc replacement for chronic low-back pain in the presence of lumbar disc degeneration	Chronic low-back pain	Lumbar total disc replacement vs. lumbar fusion	Pain, overall improvement, patient satisfaction, back-specific function status, quality of life	5 RCTs (1,301 patients)	Total disc replacement has slightly better outcomes in terms of back pain and function than those who had fusion surgery, but these differences were not clinically significant.
Zhang (2015) Database inception to 12/2014	To determine if cervical total disc replacement is superior to cervical fusion.	Symptomatic cervical disc disease	Cervical total disc replacement vs. anterior cervical decompression and fusion	Pain, function, quality of life, adverse events, overall success	19 RCTs (4,516 patients)	At short- and mid-term follow-up, cervical total disc replacement is superior to anterior cervical decompression and fusion with regards to efficacy and safety. However, longer-term multicenter studies are needed to better evaluate the long-term efficacy and safety.

**APPENDIX C. SYSTEMATIC REVIEWS EXCLUDED AT FULL TEST REVIEW**

**Excluded systematic reviews, lumbar spine.**

Citation	Reason for exclusion
Nie H, Chen G, Wang X, Zeng J. Comparison of Total Disc Replacement with lumbar fusion: a meta-analysis of randomized controlled trials. <i>J Coll Physicians Surg Pak.</i> 2015;25(1):60-67.	Not comprehensive; lacks inclusion/exclusion criteria; no GRADE
Wei J, Song Y, Sun L, Lv C. Comparison of artificial total disc replacement versus fusion for lumbar degenerative disc disease: a meta-analysis of randomized controlled trials. <i>Int Orthop.</i> 2013;37(7):1315-1325.	Lacks inclusion/exclusion criteria; no GRADE
Rao MJ, Cao SS. Artificial total disc replacement versus fusion for lumbar degenerative disc disease: a meta-analysis of randomized controlled trials. <i>Arch Orthop Trauma Surg.</i> 2014;134(2):149-158.	Combined studies with short and medium f/u; no GRADE

**Excluded systematic reviews, cervical spine.**

Citation	Reason for exclusion
Zhu Y, Tian Z, Zhu B, Zhang W, Li Y, Zhu Q. Bryan Cervical Disc Arthroplasty Versus Anterior Cervical Discectomy and Fusion for Treatment of Cervical Disc Diseases: A Meta-Analysis of Prospective Randomized Controlled Trials. <i>Spine (Phila Pa 1976).</i> 2015.	Not comprehensive; metaanalyses of one manufacturer’s disc results
Jee YM, Bak JS, Weinlander E, Anderson PA. Comparing Nonrandomized Observational Studies With Randomized Controlled Trials in Cervical Disc Arthroplasty: A Meta-analysis. <i>Spine (Phila Pa 1976).</i> 2015.	Not comparison of interest; RCT vs observational studies
Wu AM, Xu H, Mullinix KP, et al. Minimum 4-year outcomes of cervical total disc arthroplasty versus fusion: a meta-analysis based on prospective randomized controlled trials. <i>Medicine (Baltimore).</i> 2015;94(15):e665.	No comprehensive; only looked at 4+ year f/u
Rao MJ, Nie SP, Xiao BW, Zhang GH, Gan XR, Cao SS. Cervical disc arthroplasty versus anterior cervical discectomy and fusion for treatment of symptomatic cervical disc disease: a meta-analysis of randomized controlled trials. <i>Arch Orthop Trauma Surg.</i> 2015;135(1):19-28.	Combined studies with short and medium f/u; no GRADE
Yao Q, Liang F, Xia Y, Jia C. A meta-analysis comparing total disc arthroplasty with anterior cervical discectomy and fusion for the treatment of cervical degenerative diseases. <i>Arch Orthop Trauma Surg.</i> 2015.	No GRADE
Luo J, Huang S, Gong M, et al. Comparison of artificial cervical arthroplasty versus anterior cervical discectomy and fusion for one-level cervical degenerative disc disease: a meta-analysis of randomized controlled trials. <i>Eur J Orthop Surg Traumatol.</i> 2015;25 Suppl 1:S115-125	No GRADE
Zhao H, Cheng L, Hou Y, et al. Multi-level cervical disc arthroplasty (CDA) versus single-level CDA for the treatment of cervical disc diseases: a meta-analysis. <i>Eur Spine J.</i> 2015;24(1):101-112.	Not comparison of interest; single vs. multilevel
Ren C, Song Y, Xue Y, Yang X. Mid- to long-term outcomes after cervical disc arthroplasty compared with anterior discectomy and fusion: a systematic review and meta-analysis of randomized controlled trials. <i>Eur Spine J.</i> 2014;23(5):1115-1123.	Not comprehensive; 4 year only
Verma K, Gandhi SD, Maltenfort M, et al. Rate of adjacent segment disease in cervical disc arthroplasty versus single-level fusion: meta-analysis of prospective studies. <i>Spine (Phila Pa 1976).</i> 2013;38(26):2253-2257.	Not comprehensive; adjacent segment disease as primary outcome
Gao F, Mao T, Sun W, et al. An Updated Meta-Analysis Comparing Artificial Cervical Disc Arthroplasty (CDA) Versus Anterior Cervical Discectomy and Fusion (ACDF) for the Treatment of Cervical Degenerative Disc Disease (CDDD). <i>Spine (Phila Pa 1976).</i> 2015;40(23):1816-1823	Not comprehensive; limited studies; no GRADE



Citation	Reason for exclusion
Boselie TF, Willems PC, van Mameren H, de Bie R, Benzel EC, van Santbrink H. Arthroplasty versus fusion in single-level cervical degenerative disc disease. <i>Cochrane Database Syst Rev.</i> 2012;9:CD009173.	Not comprehensive; limited studies
Nunley PD, Jawahar A, Cavanaugh DA, Gordon CR, Kerr EJ, 3rd, Utter PA. Symptomatic adjacent segment disease after cervical total disc replacement: re-examining the clinical and radiological evidence with established criteria. <i>Spine J.</i> 2013;13(1):5-12.	Not comprehensive; adjacent segment disease as primary outcome
Luo J, Gong M, Huang S, Yu T, Zou X. Incidence of adjacent segment degeneration in cervical disc arthroplasty versus anterior cervical decompression and fusion meta-analysis of prospective studies. <i>Arch Orthop Trauma Surg.</i> 2015;135(2):155-160.	Not comprehensive; adjacent segment disease as primary outcome
Yang B, Li H, Zhang T, He X, Xu S. The incidence of adjacent segment degeneration after cervical disc arthroplasty (CDA): a meta analysis of randomized controlled trials. <i>PLoS One.</i> 2012;7(4):e35032	Not comprehensive; adjacent segment disease as primary outcome
Chen J, Wang X, Bai W, Shen X, Yuan W. Prevalence of heterotopic ossification after cervical total disc arthroplasty: a meta-analysis. <i>Eur Spine J.</i> 2012;21(4):674-680.	Not comprehensive; heterotopic ossification as primary outcome



## 2016 HTA Topics (New and Re-review)

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### Response to Public Comments

*April 14, 2015*

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## Health Technology Assessment Program Selected Technologies 2016

This document responds to all comments received on the 2016 proposed technology topics. Public comments were accepted on the topics from February 26, to March 11, 2016. Comments were received from the following individuals and groups:

- Jim C. Blankenship, MD, MHCM, FSCAI, President Society for Cardiovascular Angiography & Interventions Foundation
- Karen L. Campbell, PharmD, Sr. Medical Scientific Manager, Alergen
- Wendy Chan, Senior Manager, Health Economics & Reimbursement, Boston Scientific
- Gracie Farias, MBA, Senior Manager of Reimbursement, Medtronic
- Donald Fetterolf, MD, MBA, FACP, Chief Medical Officer, MiMedx Group, Inc
- Jeff Hughes, Director of Reimbursement, Integra
- Andrew McIntyre, President, WA East Asian Medicine Association
- Pamela McKeown, Dir of Health Policy, MiMedx Group, Inc
- Chad Redinbo, New Leaf Hyperbarics
- Paul Radensky, MD, JD, Principal, Smith & Nephew, PLC
- Dirk Sutherland, Regional Director Health Policy, Alliqua Biomedical
- Diana L. Thompson, LMP, 2nd VP, AMTA-WA, American Massage Therapy Association – WA
- Pooja Voria, MD, MBA, Vice President, WA State Radiological Society

Topic	Comments	Response
<b>Artificial Disc Replacement (ADR)</b>		
<p><b>Gracie Farias, MBA,</b> Senior Manager of Reimbursement, Medtronic</p>	<p>Complete comments with information attached below.</p>	<p>Thank you for your comments. The intent of selecting ADR for update is to include consideration of new indications for 2 level cervical disc arthroplasty. All references provided will be considered in review.</p>
<p style="text-align: right;">No change to proposed technologies.</p>		
<b>CAD Mammography</b>		
<p><b>Pooja Voria, MD MBA,</b> Vice President, WA State Radiological Society</p>	<p>Complete comments with information attached below.</p>	<p>Thank you for your comments. Though the legislation may apply to Medicare coverage it does not apply to state purchased health care programs and it is not clear that the law prevents an evidence-based review and policy for CAD Mammography.</p>
<p style="text-align: right;">No change to proposed technologies.</p>		
<b>Left Atrial Appendage Closure Device (LAAC)</b>		
<p><b>Wendy Chan,</b> Senior Manager, Health Economics &amp; Reimbursement, Boston Scientific</p>	<p>Complete comments with information attached below.</p>	<p>Thank you for the information and comments on this topic and the CMS policy including coverage with evidence development and national coverage determination.</p>
<p style="text-align: right;">Based upon a review of the new CMS policy this topic is not selected for review at this time.</p>		
<p><b>Jim C. Blankenship, MD, MHCM, FSCAI,</b> President, Society for Cardiovascular Angiography &amp; Interventions Foundation</p>	<p>Complete comments with information attached below.</p>	<p>Thank you for the information and comments on this topic and the CMS policy including coverage with evidence development and national coverage determination.</p>
<p style="text-align: right;">Based upon a review of the new CMS policy this topic is not selected for review at this time.</p>		
<b>Interventions for treatment for migraines/headaches</b>		
<p><b>Karen L. Campbell, PharmD,</b> Senior Medical Scientific Manager, Allergan</p>	<p>Complete comments with information attached below.</p>	<p>Thank you for the comments. We have modified the topic title to remove the term “non-pharmacologic”. The focus of the review will include interventions or procedures to address headaches.</p>

Topic	Comments	Response
		We have reviewed the supporting documents and feel a review of the evidence for all headache types including chronic migraine will be helpful to establish an appropriate evidence-based coverage determination for interventions that may include botulinum toxin.
<b>Chad Redinbo,</b> New Leaf Hyperbarics	Complete comments with information attached below.	Thank you for your comments. In 2012 WA Health Technology Assessment Program reviewed Hyperbaric Oxygen Therapy for a number of conditions including headache.  No change to proposed technologies.
<b>Diana L. Thompson, LMP,</b> 2nd Vice President, American Massage Therapy Association - WA	Complete comments with information attached below.	Thank you for the comments and citations. Information provided will be considered for inclusion in the review.  No change to proposed technologies.
<b>Andrew McIntyre,</b> President, Washington East Asian Medicine Association	Complete comments with information attached below.	Thank you for the comments. Cited references will be considered for inclusion in the review.  No change to proposed technologies.
<b>Skin Substitutes</b>		
<b>Donald Fetterolf, MD, MBA, FACP,</b> Chief Medical Officer Pamela McKeown, Dir of Health Policy, MiMedx Group, Inc	Complete comments with information attached below.	Thank you for the comments. No change to proposed technologies
<b>Paul Radensky, MD, JD,</b> Principal, McDermott + Consulting on behalf of Smith and Nephew	Complete comments with information attached below.	Thank you for your comments and submission of supporting documentation. All references and other evidence will be considered for inclusion in the review of the topic.
<b>Dirk Sutherland,</b> Regional Director Health Policy, Alliqua Biomedical	Complete comments with information attached below.	Thank you for your comments and submission of supporting documentation. All references and other information will be considered for inclusion in the review of this topic.  No change to proposed technologies
<b>Jeff Hughes,</b> Director of Reimbursement, Payer Access, Integra LifeSciences Corporation	Complete comments with information attached below.	Thank you for your comments and supporting references. All references provided will be considered in the review of this topic.

Topic	Comments	Response
No change to proposed technologies		
<b>Petition for Review</b>		
<b>Dirk Sutherland,</b> Regional Director of Health Policy Alliqua Biomedical	Re: Petition for review of the MIST	We have reviewed the information submitted for this petition. A separate contact for further information has been initiated.

**From:** Farias, Gracie <gracie.farias@medtronic.com>  
**Sent:** Friday, March 11, 2016 8:04 AM  
**To:** HCA ST Health Tech Assessment Prog  
**Subject:** 2016 HTA Comments for the Re-Review Technology of Artificial Disk (Cervical & Lumbar)  
**Attachments:** Kang et al\_EurSpineJ\_2015\_Sep.pdf; Muheremu et al\_EurJOrthopSurgTraumatol\_2015\_Jul.pdf; Radcliff et al\_Spine(PhyilaPa1976)\_2015\_Apr.pdf; Hellum et al\_BMJ\_2011 May 19\_342\_d2786.pdf  
**Follow Up Flag:** Follow up  
**Flag Status:** Completed

The following are comments and/or recommendation regarding the Re-Review Technologies for “Artificial Disk (Cervical & Lumbar).”

Page 1 – Introduction, Cervical Artificial Disc Replacement (C-ADR) : Assuming you will also consider FDA approvals for 2-level, as such PI/IFU indication(s) would be device dependent.

Page 6 – Table 1. ADR Summary Table for Key Question 1. L-ARD vs. non-operative care indicates no evidence available.

There is a prospective randomized multicenter study done in Norway on conservative treatment vs L-ADR.

Bibliography:

Hellum C, Johnsen LG, Storheim K, Nygaard OP, Brox JI, Rossvoll I, Rø M, Sandvik L, Grundnes O; Norwegian Spine Study Group. Surgery with disc prosthesis versus rehabilitation in patients with low back pain and degenerative disc: two year follow-up of randomised study. *BMJ*. 2011 May 19;342:d2786. doi: 10.1136/bmj.d2786. PubMed PMID: 21596740; PubMed Central PMCID: PMC3100911.

Page 9 – Table 2. ADR Summary Table for Key Question 2. L-ARD vs. non-operative care again indicates no evidence available.

There is a prospective randomized multicenter study done in Norway on conservative treatment vs L-ADR

Bibliography:

Hellum C, Johnsen LG, Storheim K, Nygaard OP, Brox JI, Rossvoll I, Rø M, Sandvik L, Grundnes O; Norwegian Spine Study Group. Surgery with disc prosthesis versus rehabilitation in patients with low back pain and degenerative disc: two year follow-up of randomised study. *BMJ*. 2011 May 19;342:d2786. doi: 10.1136/bmj.d2786. PubMed PMID: 21596740; PubMed Central PMCID: PMC3100911.

Page 11 – Table 3. ADR Summary Table for Key Questions 3 and 4. Key Question 3: What is the evidence of differential efficacy or safety issues amongst special populations (including but not limited to the elderly and workers compensation populations)?

I believe this publication might be relevant to this topic:

Kang J, Shi C, Gu Y, Yang C, Gao R. Factors that may affect outcome in cervical artificial disc replacement: a systematic review. *Eur Spine J*. 2015 Sep;24(9):2023-32. doi: 10.1007/s00586-015-4096-6. Epub 2015 Jul 9. PubMed PMID: 26155894.

Page 11 – Table 3. ADR Summary Table for Key Questions 3 and 4. Key Questions 4: What are the cost implications and cost effectiveness for ADR?

I believe this publication to be highly relevant to cost effectiveness for C-ADR:



Radcliff K, Zigler J, Zigler J. Costs of cervical disc replacement versus anterior cervical discectomy and fusion for treatment of single-level cervical disc disease: an analysis of the Blue Health Intelligence database for acute and long-term costs and complications. *Spine (Phila Pa 1976)*. 2015 Apr 15;40(8):521-9. doi: 10.1097/BRS.0000000000000822. PubMed PMID: 25868092.

I did not see this article mentioned or a citation. The purpose of this study was to determine the reoperation rates, adverse event rate, as well as the direct and follow-on costs of cervical disc arthroplasty (CDA) compared with anterior cervical discectomy and fusion (ACDF) in a "real-world" population of patients with single-level symptomatic cervical disc disease. It was retrospective, but it utilized the insurance companies' own data.

The authors concluded that patients who underwent CDA for single-level degenerative disease had lower readmission rates, lower reoperation rates, and reduced index and total costs than those treated with ACDF. CDA was effective in reducing the monthly cost of care compared with ACDF.

Thanks in advance for your consideration.

**Gracie Farias | MBA**

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# Factors that may affect outcome in cervical artificial disc replacement: a systematic review

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## Abstract

**Purpose** To identify the factors that may affect outcome in C-ADR and provide the pooled results of postoperative success rate of implanted segment range of motion (ROM), incidence of heterotopic ossification (HO), incidence of radiographic adjacent segment degeneration (r-ASD)/adjacent segment disease (ASD), and surgery rate for ASD. **Methods** We systematically searched in PubMed, Embase, Cochrane library and Web of knowledge from 2001 to May 2015. Two independent reviewers screened the primary records. Eleven questions regarding the effect of patient selection issues and radiographic parameters issues on outcome were posed previously. Studies addressing the framed questions were included for analysis. **Results** Twenty-two studies were included for the final analysis. Results showed that number of surgical level (single versus double-level) had no effect on primary clinical outcome and radiographic outcome, surgical level had no effect on clinical and radiographic outcome, and

smoking habits had negative effect on clinical outcome. No evidence for the effect of patient's age and pathology category (radiculopathy or myelopathy) on outcome was found. The overall success rate of ROM was 79.4 %. ROM of the implanted segment and cervical sagittal alignment had no effects on clinical outcome. The pooled incidences of grade 1–4 HO and grade 3–4 HO were 27.7 and 7.8 %, respectively. The pooled incidence of r-ASD and surgery rate for ASD were 42.4 and 3.8 %, respectively.

**Conclusions** The available evidence showed that most of the pre-selected factors had no effect on outcome after C-ADR, and the ROM success rate, incidence of HO and r-ASD/ASD, and surgery rate for ASD are acceptable. There is a lack of evidence from RCTs for some factors.

**Keywords** Artificial disc replacement · Systematic review · Factors · Outcome · Pooled results

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## Introduction

Cervical artificial disc replacement (C-ADR) has been proposed as an alternative to anterior cervical discectomy and fusion (ACDF) for patients with symptomatic cervical degenerative disc disease (DDD) during the last decade. It has been demonstrated that C-ADR can maintain physiological cervical mobility, thereby reducing the risk of development of radiographic adjacent segment degeneration (r-ASD) and adjacent segment disease (ASD) secondary to altered mechanics at adjacent segments of the fusion site [1]. This is also the primary rationale for the development and use of artificial disc devices.

Although C-ADR is becoming more widely used, there is also some conflicting evidence regarding the incidence of ASD after C-ADR, and the correlation between outcome and a variety of factors are still unclear [2]. However, from arthrodesis to arthroplasty is a trend of the surgical evolution, and it is expected that the future growth of ADR will come either from indications for surgery not present today, or from elimination of current contraindications [3]. For the evidence-based medicine approach can integrate the best clinical research evidence, such a review that assesses the factors that may affect outcome in C-ADR is apparently essential and beneficial to the surgeons and patients who need to undergo C-ADR. Therefore, we performed a systematic review of all the relevant literature relating to randomized controlled trials (RCTs) on C-ADR to identify the factors that may affect outcome and provide the pooled results of success rate of implanted segment range of motion (ROM), incidence of heterotopic ossification (HO), incidence of r-ASD/ASD, and surgery rate for ASD.

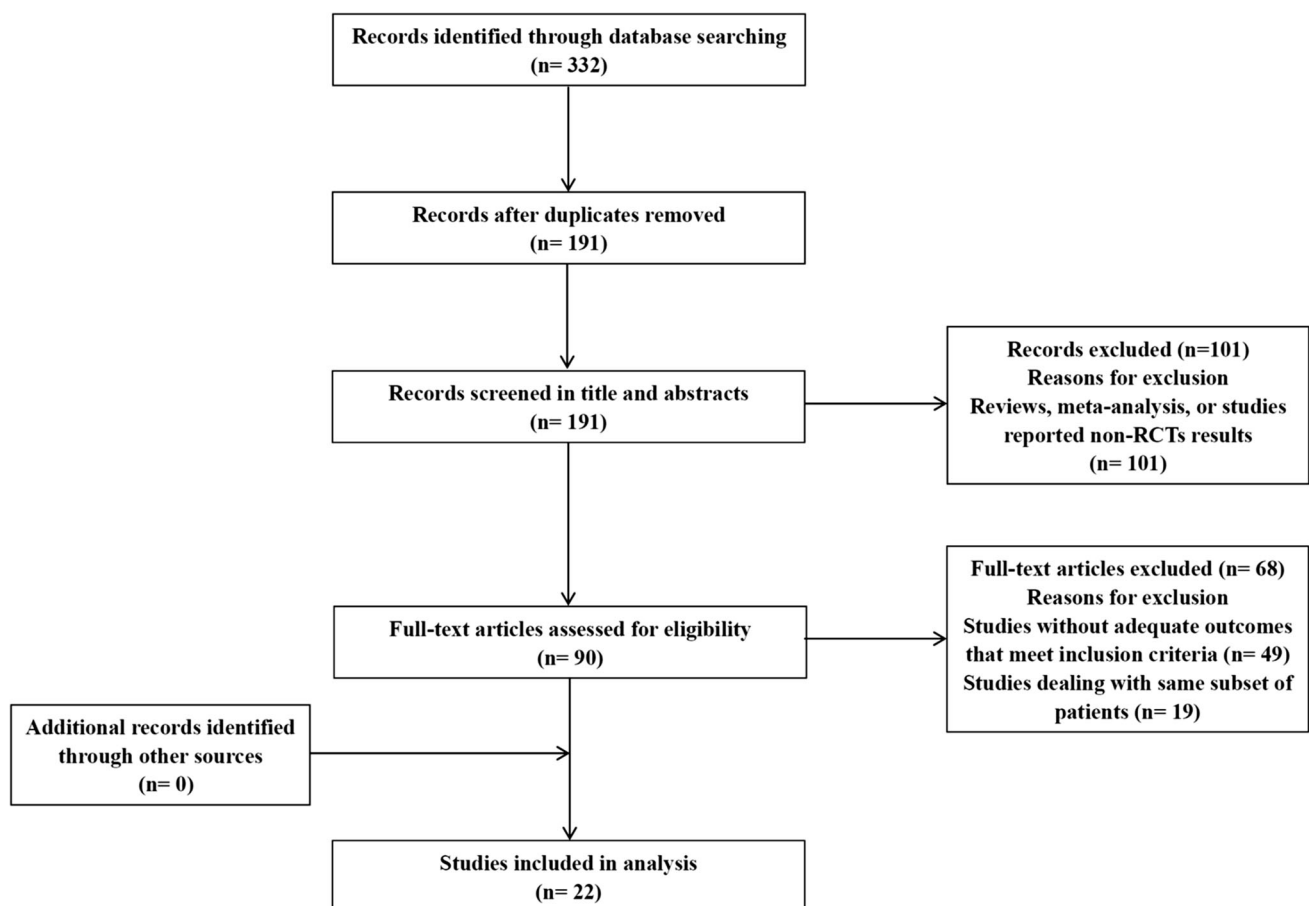
## Materials and methods

### Literature search strategy

The literature search was conducted in the PubMed, Embase, Cochrane library and Web of knowledge on May 14, 2015, and all English-language publications on C-ADR since 2001 were retrieved. The search terms that we selected were “(artificial disc OR total disc OR disc arthroplasty OR arthroplasty OR non fusion OR disc replacement) AND (cervical spine) AND (randomized OR randomization)” which were mainly based on the official thesaurus (MeSH). Duplicate studies were removed. We screened the references of the related articles as supplementary search. Figure 1 shows the search strategy and its corresponding flow chart.

### Study selection

Specific questions about factors that might affect the clinical and radiographic outcomes after C-ADR were posed in



**Fig. 1** Flow diagram of study selection

advance by referring to the previous lumbar-ADR review [3]. These posed 11 questions were grouped into 2 categories: (a) Questions about patient selection issues: (i) effect of single-level versus double-level implantation, (ii) effect of the level of implantation, (iii) effect of patient's age, (iv) effect of radiculopathy versus myelopathy, (v) effect of smoking habits. (b) Questions about radiographic parameters issues: (i) success rate of the implanted segment ROM ( $ROM \geq 4^\circ$ ), (ii) effect of ROM on outcome, (iii) effect of postoperative cervical sagittal alignment on outcome, (iv) incidence of HO, (v) incidence of r-ASD/ASD, (vi) surgery rate for ASD.

All initial search results were reviewed by the title and abstract. Then, the potential RCTs or studies reporting the results of C-ADR outcome from RCTs were all identified; full texts were obtained and reviewed for further data retrieving. Studies addressing the above framed questions were identified and included for the final analysis. In the case of multiple publications of the same study or data set, we selected only the most recent version for analysis. Previous systematic reviews on C-ADR were also not included.

Data extraction was performed by two of the authors independently, whereas another author checked the results. If a disagreement existed, the relevant procedures were repeated until a consensus was achieved between the reviewers. Importantly, results from non-RCTs were not included for analysis.

### Statistical analysis

Meta-analysis for the pooled results of success rate of implanted segment ROM, incidence of HO, incidence of r-ASD, and surgery rate for ASD were performed. Statistical heterogeneity was measured using Cochran's Q test; a *P* value less than 0.05 was considered significant for heterogeneity. The random-effects model was used when there was significant heterogeneity, and the 95 % confidence interval was also calculated. Analyses were performed with StatDirect Statistical software, version 2.7.0.2 (<http://www.statsdirect.com>) [4].

## Results

A total of 332 studies were identified in the selected database. After applying the inclusion/exclusion criteria to these studies and those identified from a manual search of the reference lists, 22 studies were deemed relevant to the formulated questions and were therefore subjected to the final review process, including 19 published studies and 3 conference abstracts (Fig. 1).

### Patient selection issues

*Is the outcome after single-level implantation similar to double-level implantation?*

Two studies were found (Table 1). Both of them provided direct comparison results [5, 6]. One study reported no difference in neck disability index (NDI) and visual analog scale (VAS) (primary clinical outcome) between 1-level and 2-level replacement, however, the difference was significant in European quality of life 5-Dimensions questionnaire (EQ-5D) [5]. Another study found there were no differences in NDI, VAS, the 12-item short form health survey (SF-12), ROM, HO incidence of the surgical level, and even the incidence of r-ASD [6].

*Does spinal level of C-ADR affect outcome?*

Two studies were found. In a multicenter trial consisting of 164 ProDisc patients, 44 underwent an ADR at C6/C7, 96 at C5/C6, 18 at C4/C5, and 6 at C3/C4. Results showed there were no significant differences at a mean of 24 months in sagittal segmental ROM between C3/C4 (3.9), C4/C5 (6.1°), C5/C6 (5.8°), and C6/C7 (5.3°). And there was also no significant difference in the delta lateral ROM (difference between pre- and postoperative) between the segments C3/C4, C4/C5, C5/C6, and C6/C7 [7]. In another single-center trial consisting of 22 Bryan patients, the effect of treatment level on clinical outcome was observed, and the result showed there was no difference in

**Table 1** Effect of single-level versus double-level implantation on clinical and radiographic outcome

References	Prosthesis	Design	FU (months)	No. pts	Evaluation scale	Effect on outcome
Skeppholm et al. [5]	Discover	Multicenter	24	1 level: 58 2 level: 23	NDI, VAS, EQ-5D	No difference in NDI, VAS; greater mean value of EQ-5D in the double-level
Bae et al. [6]	Mobi	Multicenter	48	1 level: 164 2 level: 225	NDI, VAS, SF-12, ROM, HO, r-ASD	No difference

*FU* follow-up, *No.Pts* number of patients, *NDI* neck disability index, *VAS* visual analog scale, *EQ-5D* European quality of life 5-Dimensions questionnaire, *SF* short form health survey, *ROM* range of motion, *HO* heterotopic ossification, *r-ASD* radiographic adjacent segment degeneration

NDI improvement between C5/6 treatment and C6/7 treatment [8].

*Does patient’s age affect outcome?*

No evidence from RCTs was identified.

*Is the outcome of patients with radiculopathy similar to those with myelopathy?*

No evidence from RCTs was identified.

*Does smoking affect outcome?*

Only one study was found. In this multicenter trial using Discover prosthesis, 31 % of the patients were smokers. Comparison between smokers and nonsmokers showed

unfavorable outcome for the smokers in NDI value at the 2-year follow-up [5].

**Radiographic parameters issues**

*What is the success rate of implanted segment ROM?*

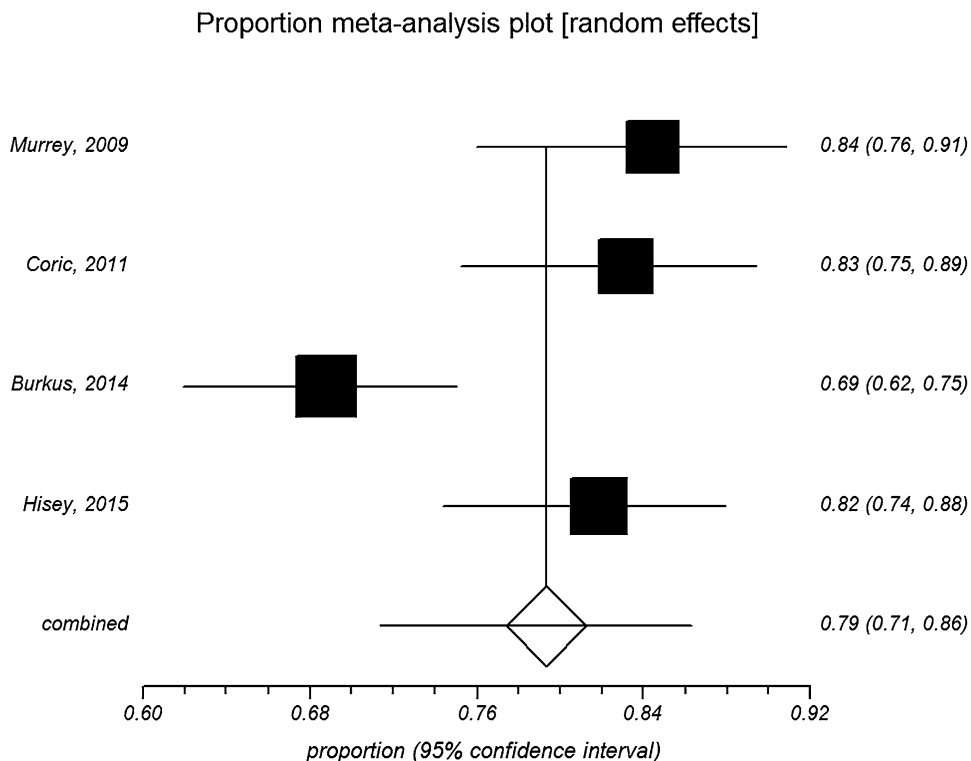
Four studies were found (Table 2). To answer this question, we first defined ROM success as at least 4° of motion in flexion/extension X-ray at the implanted segment according to the literature [9–12]. One large multicenter trial consisting of 205 Prestige patients found that ROM success was seen in 70.5 % of patients at 60 months and 68.8 % at 84 months [11]. The success rate of implanted segment ROM in the four studies ranged from 68.8 to 84.5 %. Overall, the pooled success rate of implanted segment ROM was 79.4 % ( $P = 0.002$ ; 95 % CI 71.4–86.3 %) (Fig. 2).

**Table 2** Success rate of range of motion at the implanted segment

References	Prosthesis	Design	FU (months)	No. pts	Success rate (%)
Murrey et al. [9]	ProDisc	Multicenter	24	103	84.5
Coric et al. [10]	Kineflex	Multicenter	24	119	83.2
Burkus et al. [11]	Prestige	Multicenter	84	205	68.8
Hisey et al. [12]	Mobi	Multicenter	48	138	81.9
Pooled rate					79.4

*FU* follow-up, *No.Pts* number of patients

**Fig. 2** Pooled success rate of range of motion at the implanted segment



*Does ROM of the implanted segment affect outcome?*

Only one study was found. A total of 191 target levels with Bryan prosthesis were included for analysis at the 24-month follow-up, results showed the mean ROM was 7.95°, and only 7 % of patients had 2° or less motion. No correlation between ROM of the implanted segment and NDI or VAS was found. Furthermore, there was also no correlation between ROM at adjacent levels and NDI or VAS scores, and a low postoperative ROM was significantly associated with a low preoperative ROM [13].

*Does postoperative cervical sagittal alignment affect outcome?*

Three studies were found (Table 3). In these trials, segmental sagittal alignment was evaluated by functional spinal unit (FSU) angle, and overall sagittal alignment was evaluated by the angle between the inferior endplates of C2 and C7. Results showed both segmental sagittal alignment and overall sagittal alignment had no effect on clinical outcome when evaluated by NDI, VAS, or SF-12/SF-36 [8, 14, 15].

*What is the incidence of HO at the implanted segment?*

Four studies were found (Table 4). In this analysis, only studies in which HO was evaluated by McAfee classification were included [16]. The incidence of grade 1–4 HO and

grade 3–4 HO in these studies ranged from 12.5 to 32.7 % and 1.8 to 24.8 %, respectively [6, 17–19]. In the largest RCT that includes 314 Mobi patients with at least 48 months follow-up, results showed 24.8 % of the patients had grade 3–4 HO [6]. Overall, the pooled incidences of grade 1–4 HO and grade 3–4 HO were 27.7 % ( $P < 0.0001$ ; 95 % CI 13.8–44.2 %) and 7.8 % ( $P < 0.0001$ ; 95 % CI 0.7–21.4 %), respectively (Figs. 3, 4).

*What is the incidence of r-ASD and ASD after C-ADR?*

Four studies were found, three in r-ASD and one in ASD (Table 5). The incidence of r-ASD in these three large multicenter trials ranged from 39.1 to 47.5 % evaluated by Kellgren–Lawrence scale or Walraevens scale [20, 21], with an overall incidence of 42.4 % ( $P = 0.46$ ; 95 % CI 38.3–46.6 %) (Fig. 5) [6, 18, 22]. In the study of Bae et al., the author also compared the incidence of r-ASD between single-level and double-level patients, results showed the incidence was not statistically different [22]. The incidence of ASD was only found in one study. ASD was evaluated by Hilibrand criteria, and the patients should be demonstrated a clinical–radiological correlation between their symptoms and radiographic studies [23]. Results showed the incidence of ASD was 15.2 %, with an annual incidence of 3.14 %, and the mean period for freedom from ASD was 70.4 months. The author also found osteopenia and lumbar degenerative disc disease were independent risk factors for ASD [24].

**Table 3** Effect of postoperative cervical sagittal alignment on clinical outcome

References	Prosthesis	Design	FU (months)	No. pts	Sagittal parameters (°)	Evaluation scale	Effect on clinical outcome
Xu et al. [14]	Bryan	Single center	6	Investigational: 19 (FSU) Control: 20 (FSU)	Investigational: -1 (FSU) Control: 4 (FSU)	NDI, SF-36	No effect
Sasso et al. [8]	Bryan	Single center	24	22	4.4 (overall) -3.9 (FSU)	NDI	No effect
Hisey et al. [15]	Mobi	Multicenter	24	141	9.6 (overall)	NDI, VAS, SF-12	No effect

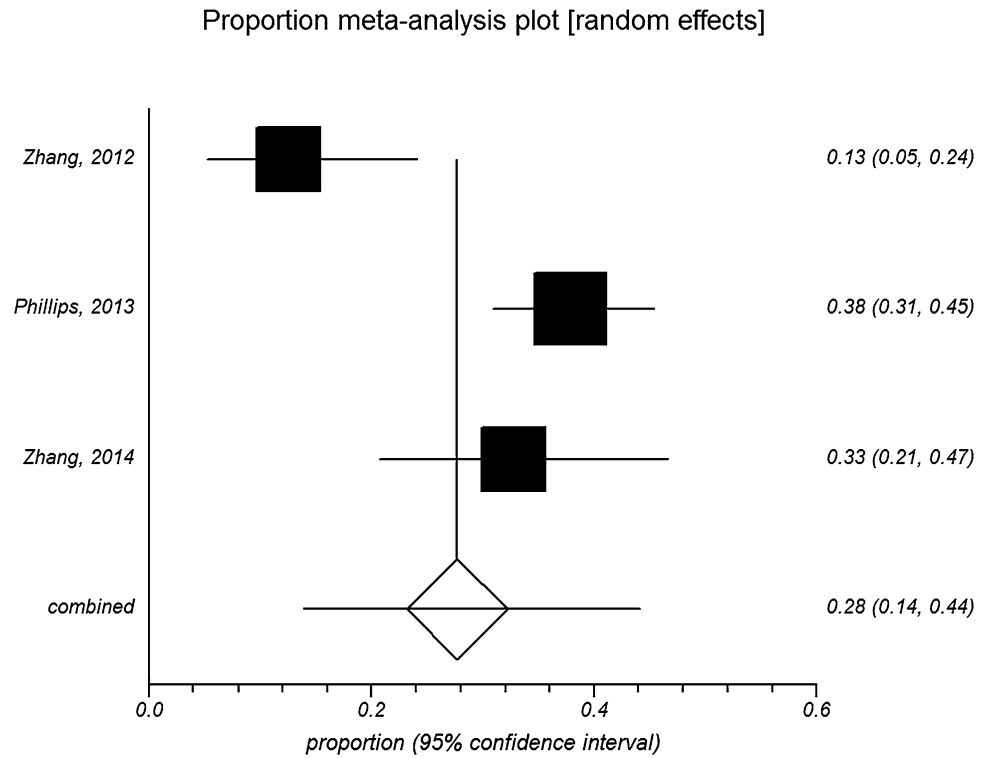
*FU* follow-up, *No.Pts* number of patients, *FSU* functional spinal unit angle, *NDI* neck disability index, *SF* short form health survey, *overall* sagittal alignment from C2 to C7, *VAS* visual analog scale

**Table 4** Incidence of postoperative heterotopic ossification

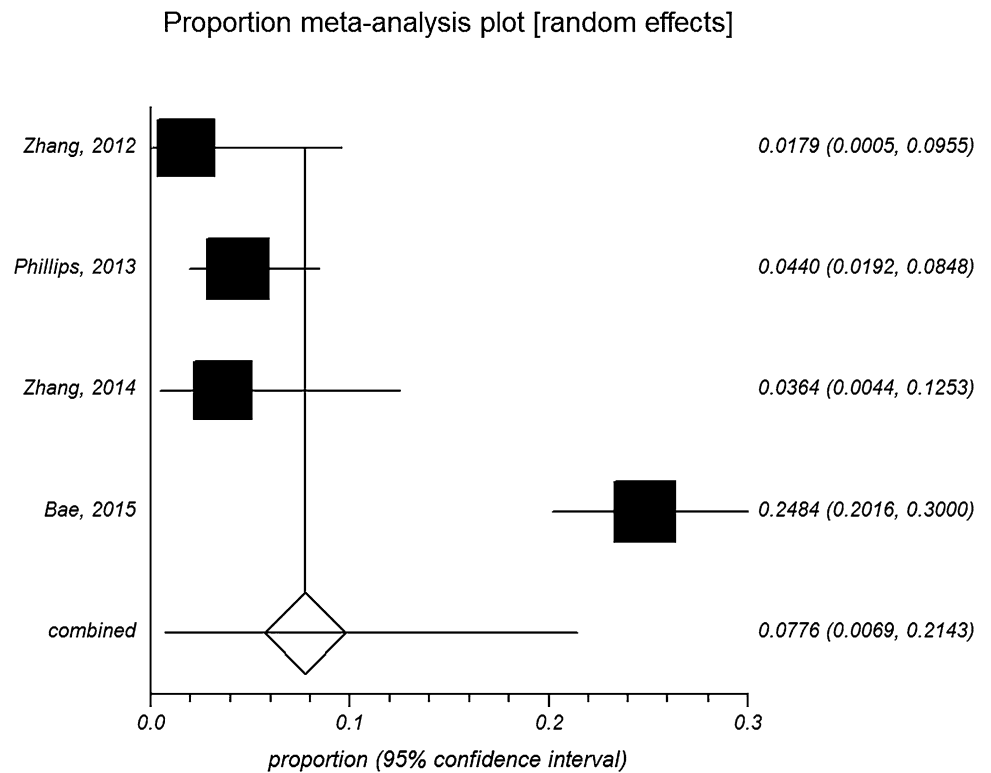
References	Prosthesis	Design	FU (months)	No. pts	Grade 1–4 HO (%)	Grades 3–4 HO (%)
Zhang et al. [17]	Bryan	Multicenter	24	56	12.5	1.8
Phillips et al. [18]	PCM	Multicenter	24	182	37.9	4.4
Zhang, 2014 [19]	Mobi	Multicenter	48	55	32.7	3.6
Bae, 2015 [6]	Mobi	Multicenter	48	314	–	24.8
Pooled incidence					27.7	7.8

*FU* follow-up, *No.Pts* number of patients, *HO* heterotopic ossification

**Fig. 3** Pooled incidence of grade 1–4 heterotopic ossification



**Fig. 4** Pooled incidence of grade 3–4 heterotopic ossification

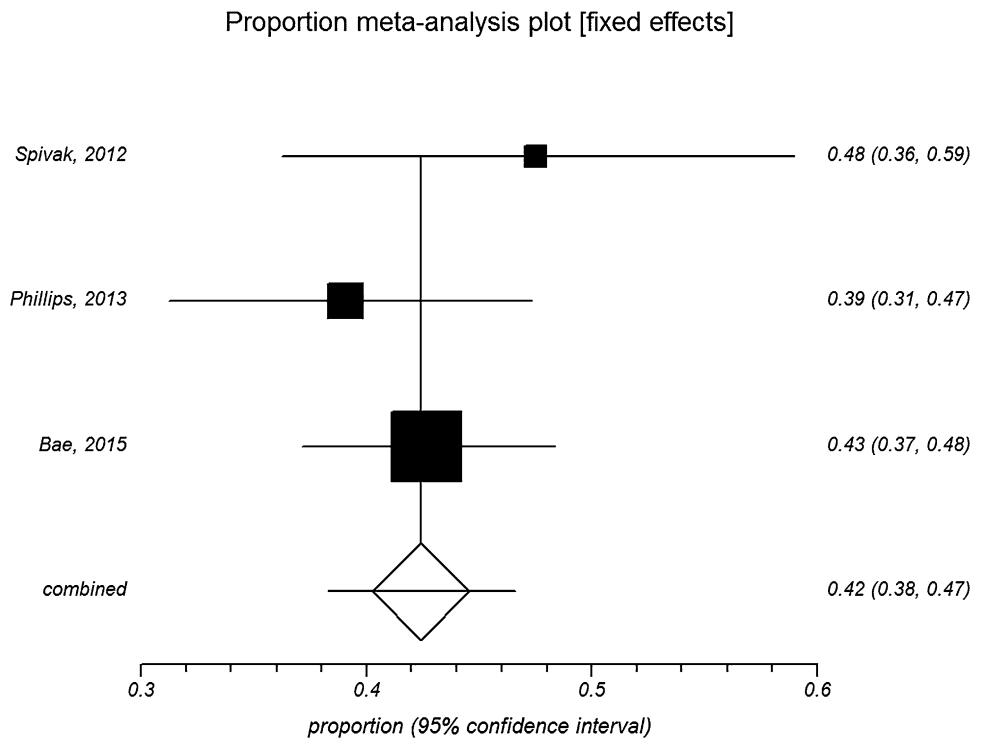


**Table 5** Incidence of postoperative radiographic adjacent segment degeneration and adjacent segment disease

Author	Prosthesis	Design	FU (months)	No. Pts	Evaluation scale	Incidence (%)
Radiographic adjacent segment degeneration						
Spivak et al. [22]	ProDisc	Multicenter	60–84	80	Kellgren–Lawrence scale [20]	47.5
Phillips et al. [18]	PCM	Multicenter	24	151	Walraevens scale [21]	39.1
Bae et al. [6]	Mobi	Multicenter	48	314	Kellgren–Lawrence scale [20]	42.7
Pooled incidence						42.4
Adjacent segment disease						
Nunley et al. [24]	Bryan; ProDisc; Kineflex; Mobi;	Multicenter	51	171	Hilibrand criteria [23]	15.2

FU follow-up, No.Pts number of patients

**Fig. 5** Pooled incidence of radiographic adjacent segment degeneration



What is the surgery rate for adjacent segment disease after C-ADR?

Thirteen studies were found (Table 6). The surgery rates in these studies ranged from 0.9 to 7.6 % [5, 10–12, 17, 19, 24–30]. In the study with the longest follow-up (84 months), the surgery rate was 4.6 % in 239 patients [11]. Overall, the pooled surgery rate for ASD was 3.8 % ( $P = 0.09$ ; 95 % CI 2.8–5.1 %) (Fig. 6).

**Discussion**

This systematic review identified the current available level I evidence (RCTs) to document the factors that may affect outcome in C-ADR. It is reported that evidence-based

medicine can apply the best available evidence gained from the scientific method to medical decision making. It seeks to assess the strength of evidence of the risks and benefits of treatments and diagnostic tests [31]. The included studies in this review covered all high-quality clinical researches in C-ADR. In addition, the previously framed questions covered most of the related factors that may affect the clinical and radiographic outcome.

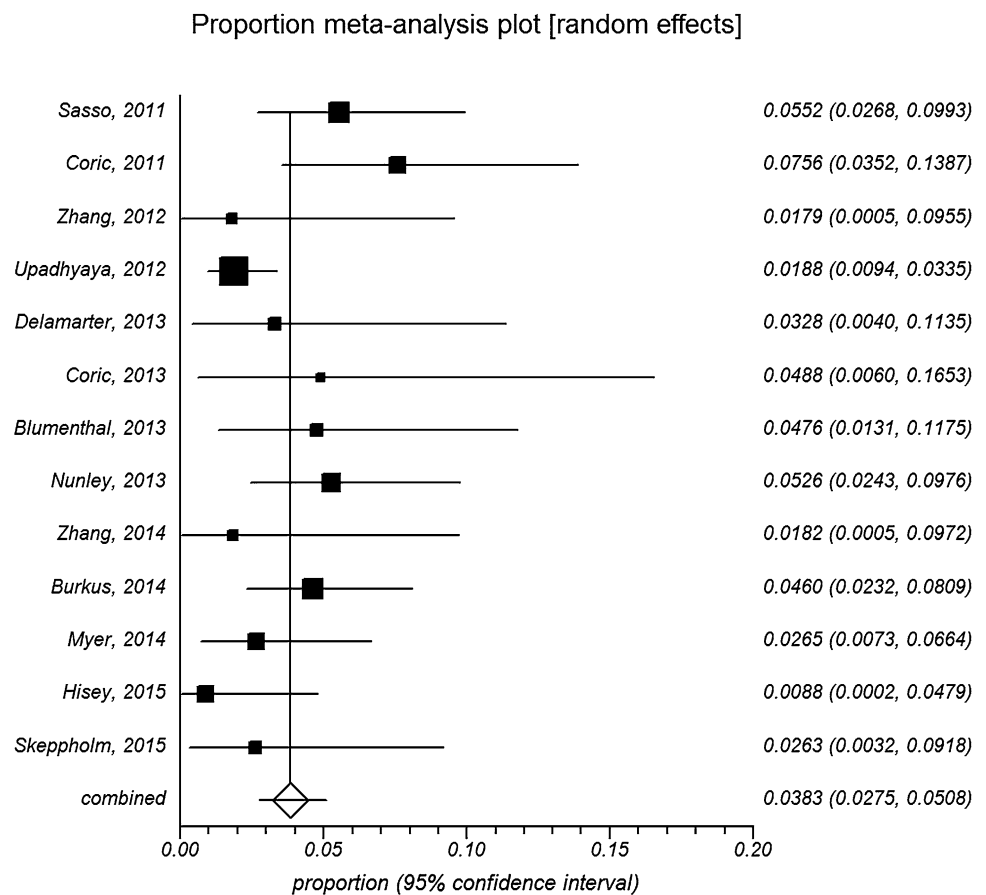
C-ADR as a successful alternative to ACDF gradually emerges in the last 10 years in light of mobility preservation and leads to preventing or reducing ASD [1]. There have been several meta-analysis and systematic reviews that assess the safety and efficacy of C-ADR versus ACDF. Results in these reviews showed that C-ADR is the same or slightly superior to ACDF in morbidity or neurological success [31–34]. However, these analyses were all limited



**Table 6** Surgery rate for adjacent segment disease after C-ADR

Author	Prosthesis	Design	FU (months)	No. Pts	Surgery rate
Sasso et al. [25]	Bryan	Multicenter	48	181	5.5
Coric et al. [10]	Kineflex	Multicenter	24	119	7.6
Zhang et al. [17]	Bryan	Multicenter	24	56	1.8
Upadhyaya et al. [26]	Bryan; Prestige; ProDisc	Multicenter	24	584	1.9
Delamarter et al. [27]	ProDisc	Multicenter	60	61	3.3
Coric et al. [28]	Bryan; Kineflex	Single center	48	41	4.9
Blumenthal et al. [29]	ProDisc; Kineflex; Mobi; Discover; Neodisc; Advent	Single center	55	84	4.8
Nunley et al. [24]	Bryan; ProDisc; Kineflex; Mobi	Multicenter	51	171	5.3
Zhang et al. [19]	Mobi	Multicenter	48	55	1.8
Burkus et al. [11]	Prestige	Multicenter	84	239	4.6
Myer et al. [30]	Secure	Multicenter	72	151	2.6
Hisey et al. [12]	Mobi	Multicenter	48	114	0.9
Skeppholm et al. [5]	Discover	Multicenter	24	76	2.6
Pooled rate					3.8

FU follow-up, No.Pts number of patients

**Fig. 6** Pooled surgery rate for adjacent segment disease

in the comparison between the two surgical procedures. Which factors can affect outcomes in C-ADR is still unclear.

In the patient selection issues, results showed there was no difference in primary clinical outcome evaluated by NDI and VAS between single-level and double-level

patients, although it is slightly conflicting on quality of life when evaluated by SF-12 and EQ-5D [5]. The surgical level had no effect on clinical and radiographic outcome, and smoking habits had negative effect on clinical outcome. There was no evidence for the questions on patient's age and pathology category (radiculopathy or myelopathy) from RCTs. It is probably because there was no older or younger patients in RCTs due to the strict inclusion criteria, and most of the patients could present with radiculopathy and myelopathy simultaneously which made them hardly to be divided into two groups in a prospective study. Further studies about these factors are necessary.

When considering the role of ROM at the implanted segment and cervical sagittal alignment, evidence showed that there were no effects on clinical outcome [8, 13–15]. When defining  $ROM \geq 4^\circ$  as ROM success, the overall success rate was 79.4 %. Furthermore, the factors that affect ROM and cervical sagittal alignment were also evaluated in these studies. Results showed preoperative ROM had a significant correlation with postoperative ROM, and preoperative focal kyphosis had a significant correlation with postoperative focal kyphosis [8, 13].

HO is frequently seen after arthroplasty, but the incidence of HO following C-ADR is still unclear. In this part, to avoid heterogeneity of the data, only studies using the McAfee classification of HO were included. In the McAfee's classification of HO, grade 0–2 HO has nearly no effect on the motion, while grade 3–4 HO partly or totally blocks the motion [16]. The pooled incidences of grade 1–4 HO and grade 3–4 HO were 27.7 and 7.8 %, respectively, in this analysis. It should be noted that, HO could be a normal body response after C-ADR, unless HO invaded the spinal canal requiring another operation, lower grades of HO (even grade 4) had no influence on clinical outcome. In a recent Meta-analysis of prospective cohort and retrospective studies, VAS and NDI between the patients with and without HO showed no significant difference after C-ADR [34].

Prevention of the accelerated degeneration at the adjacent segments is one of the main theoretical advantages of ADR. In this issue, we identified the incidence of r-ASD and ASD, and surgery rate for ASD. Also, to avoid heterogeneity, only studies with the Kellgren–Lawrence scale or Walraevens scale for r-ASD, and Hilibrand diagnosis criteria for ASD were included [22–24]. The pooled incidence of r-ASD and surgery rate for ASD were 42.4 and 3.8 %, respectively. In the study evaluating incidence of ASD, the author also found the annual incidence of ASD after C-ADR was 3.14 %, and the independent risk factors for ASD were osteopenia and lumbar degenerative disc disease [24].

A limitation of the present study is that the previously framed questions did not cover all factors that might affect

outcome in C-ADR. Factors in this study were selected mainly by referring to the previous lumbar-ADR review [3]. Undoubtedly, there are various factors that might affect clinical and radiographic outcome in C-ADR, such as compression type (osteophyte or soft disc herniation) and coexistent lumbar DDD. Furthermore, no evidence for the factors of patient's age and pathology category (radiculopathy or myelopathy) on outcome was found in this analysis, suggesting there is a lack of clinical studies that attempt to determine the possible demographic factors that could affect the outcome. Further clinical studies that explain the discrepancy in outcome of patients undergoing C-ADR within RCTs are needed, such as Nunley's research in determining the factors that affect reoperations after C-ADR [24].

## Conclusion

From the available evidence, factors such as number of surgical level (single- versus double-level) had no effect on primary clinical outcome and radiographic outcome, surgical level had no effect on clinical and radiographic outcome, and smoking habits had negative effect on clinical outcome. The overall success rate of ROM was 79.4 %. ROM and cervical sagittal alignment had no effects on clinical outcome. The pooled incidences of grade 1–4 HO and grade 3–4 HO were 27.7 and 7.8 %, respectively. The pooled incidence of r-ASD and pooled surgery rate for ASD were 42.4 and 3.8 %, respectively. Because of no evidence for some questions (patient's age and pathology category), further clinical studies that systematically identify the possible demographic factors that could affect outcome are still needed.

**Conflict of interest** None.

## References

1. Acosta FL Jr, Ames CP (2005) Cervical disc arthroplasty: general introduction. *Neurosurg Clin N Am* 16:603–607
2. Jawahar A, Cavanaugh DA, Kerr EJ 3rd, Birdsong EM, Nunley PD (2010) Total disc arthroplasty does not affect the incidence of adjacent segment degeneration in cervical spine: results of 93 patients in three prospective randomized clinical trials. *Spine J* 10:1043–1048
3. Zindrick MR, Tzermiadianos MN, Voronov LI, Lorenz M, Hadjipavlou A (2008) An evidence-based medicine approach in determining factors that may affect outcome in lumbar total disc replacement. *Spine* 33:1262–1269
4. Liao Z, Gao R, Xu C, Li ZS (2010) Indications and detection, completion, and retention rates of small-bowel capsule endoscopy: a systematic review. *Gastrointest Endosc* 71:280–286
5. Skeppholm M, Lindgren L, Henriques T, Vavruch L, Löfgren H, Olerud C (2015) The Discover artificial disc replacement versus

- fusion in cervical radiculopathy—a randomized controlled outcome trial with 2-year follow-up. *Spine J* [Epub ahead of print]
6. Bae HW, Kim KD, Nunley PD, et al (2015) Comparison of clinical outcomes of one and two-level total disc replacement: 4-year results from a prospective, randomized, controlled, multicenter ide clinical trial. *Spine* [Epub ahead of print]
  7. Park JJ, Quirno M, Cunningham MR, Schwarzkopf R et al (2010) Analysis of segmental cervical spine vertebral motion after prodisc-C cervical disc replacement. *Spine* 35:E285–E289
  8. Sasso RC, Metcalf NH, Hipp JA, Wharton ND, Anderson PA (2011) Sagittal alignment after Bryan cervical arthroplasty. *Spine* 36:991–996
  9. Murrey D, Janssen M, Delamarter R et al (2009) Results of the prospective, randomized, controlled multicenter Food and Drug Administration investigational device exemption study of the ProDisc-C total disc replacement versus anterior discectomy and fusion for the treatment of 1-level symptomatic cervical disc disease. *Spine J* 9:275–286
  10. Coric D, Nunley PD, Guyer RD et al (2011) Prospective, randomized, multicenter study of cervical arthroplasty: 269 patients from the Kineflex/C artificial disc investigational device exemption study with a minimum 2-year follow-up: clinical article. *J Neurosurg Spine* 15:348–358
  11. Burkus JK, Traynelis VC, Haid RW Jr (2014) Mummaneni PV (2014) Clinical and radiographic analysis of an artificial cervical disc: 7-year follow-up from the Prestige prospective randomized controlled clinical trial: clinical article. *J Neurosurg Spine* 21:516–528
  12. Hisey MS, Bae HW, Davis RJ et al (2015) Prospective, randomized comparison of cervical total disk replacement versus anterior cervical fusion: results at 48 months follow-up. *J Spinal Disord Tech* 28:E237–E243
  13. Sasso RC, Best NM, Metcalf NH, Anderson PA (2008) Motion analysis of bryan cervical disc arthroplasty versus anterior discectomy and fusion: results from a prospective, randomized, multicenter, clinical trial. *J Spinal Disord Tech* 21:393–399
  14. Xu JX, Zhang YZ, Shen Y, Ding WY (2009) Effect of modified techniques in Bryan cervical disc arthroplasty. *Spine* 34:1012–1017
  15. Hisey MS, Davis RJ, Hoffman GA et al (2014) Sagittal alignment of one-level tdr and acdf patients: an analysis of patient outcomes from a randomized, prospective, clinical trial. *Spine J* 14:S124–S125
  16. McAfee PC, Cunningham BW, Devine J, Williams E, Yu-Yahiro J (2003) Classification of heterotopic ossification (HO) in artificial disk replacement. *J Spinal Disord Tech* 16:384–389
  17. Zhang X, Zhang X, Chen C et al (2012) Randomized, controlled, multicenter, clinical trial comparing BRYAN cervical disc arthroplasty with anterior cervical decompression and fusion in China. *Spine* 37:433–438
  18. Phillips FM, Lee JY, Geisler FH et al (2013) A prospective, randomized, controlled clinical investigation comparing PCM cervical disc arthroplasty with anterior cervical discectomy and fusion. 2-year results from the US FDA IDE clinical trial. *Spine* 38:E907–E918
  19. Zhang HX, Shao YD, Chen Y et al (2014) A prospective, randomized, controlled multicentre study comparing cervical disc replacement with anterior cervical decompression and fusion. *Int Orthop* 38:2533–2541
  20. Kellgren JH (1957) Lawrence JS (1957) Radiological assessment of osteo-arthritis. *Ann Rheum Dis* 16:494–502
  21. Walraevens J, Liu B, Meerschaert J et al (2009) Qualitative and quantitative assessment of degeneration of cervical intervertebral discs and facet joints. *Eur Spine J* 18:358–369
  22. Spivak JM, Delamarter RB, Murrey DB, Zigler JE, Janssen ME, Goldstein JA (2012) Adjacent level radiographic degenerative changes following single-level artificial disc replacement or ACDF at five- to seven- year follow-up. *Spine J* 12:S62
  23. Hilibrand AS, Carlson GD, Palumbo MA, Jones PK, Bohlman HH (1999) Radiculopathy and myelopathy at segments adjacent to the site of a previous anterior cervical arthrodesis. *J Bone Joint Surg Am* 81:519–528
  24. Nunley PD, Jawahar A, Cavanaugh DA, Gordon CR, Kerr EJ 3rd, Utter PA (2013) Symptomatic adjacent segment disease after cervical total disc replacement: re-examining the clinical and radiological evidence with established criteria. *Spine J* 13:5–12
  25. Sasso RC, Anderson PA, Riew KD, Heller JG (2011) Results of cervical arthroplasty compared with anterior discectomy and fusion: four-year clinical outcomes in a prospective, randomized controlled trial. *J Bone Joint Surg Am* 93(18):1684–1692
  26. Upadhyaya CD, Wu JC, Trost G et al (2012) Analysis of the three United States Food and Drug Administration investigational device exemption cervical arthroplasty trials. *J Neurosurg Spine* 16(3):216–228
  27. Delamarter RB, Zigler J (2013) Five-year reoperation rates, cervical total disc replacement versus fusion, results of a prospective randomized clinical trial. *Spine* 38(9):711–717
  28. Coric D, Kim PK, Clemente JD, Boltes MO, Nussbaum M, James S (2013) Prospective randomized study of cervical arthroplasty and anterior cervical discectomy and fusion with long-term follow-up: results in 74 patients from a single site. *J Neurosurg Spine* 18:36–42
  29. Blumenthal SL, Ohnmeiss DD, Guyer RD, Zigler JE (2013) Reoperations in cervical total disc replacement compared with anterior cervical fusion: results compiled from multiple prospective food and drug administration investigational device exemption trials conducted at a single site. *Spine* 38:1177–1182
  30. Myer J, Beutler W, McConnell JR, Lindley JG (2014) The incidence of symptomatic adjacent segment disease requiring treatment: cervical arthroplasty versus ACDF. *Spine J* 14:S160
  31. Cepoiu-Martin M, Faris P, Lorenzetti D, Prefontaine E, Noseworthy T, Sutherland L (2011) Artificial cervical disc arthroplasty: a systematic review. *Spine* 36:E1623–E1633
  32. Chen J, Wang X, Bai W, Shen X, Yuan W (2012) Prevalence of heterotopic ossification after cervical total disc arthroplasty: a meta-analysis. *Eur Spine J* 21:674–680
  33. Gao Y, Liu M, Li T, Huang F, Tang T, Xiang Z (2013) A meta-analysis comparing the results of cervical disc arthroplasty with anterior cervical discectomy and fusion (ACDF) for the treatment of symptomatic cervical disc disease. *J Bone Joint Surg Am* 95:555–561
  34. Zhou HH, Qu Y, Dong RP, Kang MY, Zhao JW (2015) Does heterotopic ossification affect the outcomes of cervical total disc replacement? A meta-analysis. *Spine* 40:E332–E340

# Costs of Cervical Disc Replacement *Versus* Anterior Cervical Discectomy and Fusion for Treatment of Single-Level Cervical Disc Disease

*An Analysis of the Blue Health Intelligence Database for Acute and Long-term Costs and Complications*

Kris Radcliff, MD\* Jeff Zigler, JD† and Jack Zigler, MD‡

**Study Design.** Retrospective review of prospectively collective administrative data.

**Objective.** The purpose of this study was to determine the reoperation rates, adverse event rate, as well as the direct and follow-up costs of cervical disc arthroplasty (CDA) compared with anterior cervical discectomy and fusion (ACDF) in a “real-world” population of patients with single-level symptomatic cervical disc disease.

**Summary of Background Data.** Until very recently, there was a paucity of human clinical data to demonstrate that CDA lowers the rate of adjacent segment disease over ACDF.

**Methods.** This was a retrospective, matched cohort analysis of a prospectively collected database of costs and outcomes for patients aged 18 to 60 years, who were continuously enrolled in a Blue Cross Plan contributing data to a claims database. Inclusion criteria were as follows: all patients who were treated surgically with either CDA or ACDF between January 2008 and December 2009, with single-level cervical pathology and claims reflecting at least 6 weeks of nonsurgical preoperative care without claims history of prior surgery.

**Results.** There were 6635 ACDF patients and 327 CDA patients. There were no significant differences in the incidence of comorbidities or mean follow-up time (ACDF 25.7 mo vs. CDA 26.1 mo) between groups. By 36 months postoperatively, the reoperation rate was significantly increased in the ACDF group (10.5%) *versus*

the CDA group (5.7%) (hazard ratio,  $P = 0.0214$ ). The index surgery and 90-day global window costs were significantly lower in the CDA groups. At final follow-up, there was a statistically significant reduction in total costs paid by insurer in CDA patients (CDA \$34,979 vs. ACDF \$39,820).

**Conclusion.** Patients who underwent CDA for single-level degenerative disease had lower readmission rates, lower reoperation rates, and reduced index and total costs than those treated with ACDF. CDA was effective in reducing the monthly cost of care compared with ACDF.

**Key words:** cervical disc replacement, cervical arthroplasty, anterior cervical discectomy and fusion, cervical arthroplasty *versus* fusion costs, comparative effectiveness of cervical disc replacement, cervical disc replacement costs, cervical fusion costs.

**Level of Evidence:** 2

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Symptomatic cervical radiculopathy and/or myelopathy are common indications for surgical intervention. Both anterior cervical decompression and fusion (ACDF) and cervical disc arthroplasty (CDA) have been demonstrated by many level I studies to achieve clinical success, relieve symptoms of neural compression, and improve health-related quality of life.<sup>1-7</sup> Biomechanical models have shown that CDA maintains normal cervical range of motion and kinematics at adjacent levels as compared with ACDF.<sup>8-16</sup>

Recent investigational device exemption (IDE) studies have demonstrated lower rates of reoperation in patients who undergo CDA than in patients who undergo ACDF.<sup>2,4,17-19</sup> However, the effect of CDA on reoperation rates has not been observed in all studies,<sup>20-25</sup> nor confirmed in all meta-analyses.<sup>26-31</sup> Also, due to the rare incidence of reoperation,<sup>32</sup> many prospective, randomized trials may be underpowered to detect differences in reoperation.<sup>4,26</sup> This results in limited data on the cost-effectiveness of CDA compared with ACDF.<sup>1,33</sup>

Payers and other assessors of health technology routinely consider “real-world” evidence that corroborates data

obtained during controlled clinical studies.<sup>34</sup> The purpose of this study was to compare the total short- and long-term costs of surgery routine postoperative care, complications, and reoperation rates between similar groups of patients who underwent ACDF and CDA for single-level cervical degenerative disease in a large, geographically diverse population under “real-world” conditions, outside of an IDE study.

## MATERIALS AND METHODS

This was a retrospective, matched cohort analysis of a prospectively collected database of patients enrolled in the Blue Health Intelligence (BHI) national claims database. The BHI database is a national, prospectively collected database of 110 million patients enrolled in 18 of the BlueCross BlueShield Association plans across the United States, and it includes all inpatient, outpatient, and office-setting care reported by procedure and diagnosis codes.

### Eligible Population

The study population in this retrospective claims analysis was patients with single-level degenerative cervical disease similar to the US Food and Drug Administration IDE clinical studies of cervical disk replacements (ProDisc, Prestige, and Bryan).<sup>2,35,36</sup>

### Inclusion/Exclusion Criteria

We queried the database for all consecutive patients aged 18 to 60 years who were continuously enrolled and treated surgically with either CDA or ACDF between January 2008 and December 2009 for single-level degenerative disc disease, with at least 6 weeks of conservative care and without history of cervical surgery.

### Index Surgery and Health Care Utilization Tracking

Patients identified in the eligible population were assessed presurgery, at the index surgery event, and then followed longitudinally to determine postoperative health care costs related to the surgery, as well as the timing of any future surgical interventions. The analysis of reoperation rate was calculated to include only the first reoperation event because this would be a reflection of the index procedure (ACDF vs. CDA), and subsequent reoperation may be attributable to either the index procedure or the reoperation. However, the cost analyses included all future reoperations. Prior to surgery, the extent of nonsurgical treatment was assessed by calculating the costs and count of physical therapy claims, identified by CPT procedure codes, pain management procedures by cervical epidural injection codes, and durable medical equipment (bracing/collars) by cervical equipment codes.

### Adverse Event Analysis

Adverse events (AEs) were determined by reviewing study population patients' claims for subsequent care, which contained the presence of specific *International Classification of Diseases, Ninth Revision (ICD-9)* diagnosis or procedure coding.

## Statistics

AEs were calculated using the Cox Proportional Hazards model to compare the rate of events between treatment groups. The Anderson-Gill (A-G) model was used because it was deemed most appropriate when modeling multiple failure time data where patients can experience more than 1 AE of the same type over time. Cumulative event probability curves were presented by treatment group for each AE type where, for each time segment, the probability of not experiencing an AE for the Andersen-Gill model was calculated as the time since the beginning of the trial to the first event and the time between events. Estimated hazard ratios were presented along with the *P* value for testing the null hypothesis that this ratio is 1 (*i.e.*, event hazard rates are the same).

For the cost analyses, payer allowed amounts inclusive of the index procedure event, as well as allowed amounts for all care provided within the specified windows, were calculated to estimate and compare acute care costs by treatment group. To normalize the costs by the length of follow-up, the total allowable amounts were then calculated as dollar amount allowed per person, per month of follow-up, to derive the true cost of care at varying follow-up periods. Because the amount of allowable reimbursement for the index procedures may have been subject to market factors, or provider-specific contracting for remuneration of the index procedure, we also calculated the cost of ongoing care per person, per month of CDA and ACDF patients, excluding the cost of the index procedure.

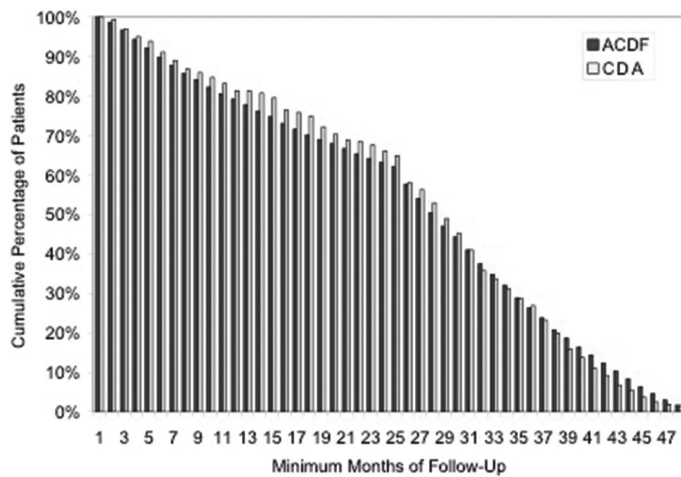
## RESULTS

### Study Population

There were 25,518 eligible ACDF patients and 533 eligible CDA patients between January 1, 2008, and December 31, 2009. Of these, there were 6962 patients who comprised the study population, including 6635 ACDF patients and 327 CDA patients. Between groups, there were no significant differences in mean follow-up (CDA 26.01 mo vs. ACDF 25.67 mo, *P* = 0.7140) (Figure 1). Approximately 65%, 26%, and 2% of patients have at least 24, 36, and 48 months of follow-up, respectively. The CDA group was slightly younger (CDA 43.97 yr vs. ACDF 46.57 yr, *P* = 0.0001). There were no significant differences in the incidence of comorbidities between groups (ACDF 25.05% vs. CDA 21.41%, *P* = 0.0884) (see Supplemental Digital Content Table 1, available at <http://links.lww.com/BRS/A956>).

### Acute Postoperative Course

There was a shorter length of stay after cervical arthroplasty (CDA 1.17 vs. ACDF 1.32 d, *P* = 0.0036). There were no significant differences (*P* > 0.05) in readmission rates between groups. Patients with comorbidities had significantly increased rates of readmission compared with patients without comorbidity. There were no significant differences (*P* > 0.05) in readmission rates between groups with comorbidities and without comorbidities. The characteristics of the patients who underwent readmission are displayed in Table 2.



**Figure 1.** Percentage of patients' follow-up by month. ACDF indicates anterior cervical discectomy and fusion; CDA, cervical disc arthroplasty.

**Postoperative Complications**

The most common, relevant AEs were grouped into pain management, dysphagia, mechanical (device-related), and miscellaneous reoperation categories. There were no significant differences in the incidence of pain AEs (including referral for specialized procedures, imaging, or treatment due to pain) during the study period (3.47% *vs.* 3.84%, hazard ratio: 1.38 [95% confidence interval (CI): 0.87–2.19, *P* = 0.1654]) (Table 3). There were no mechanical (device-related) complications such as fracture or implant migration in the CDA group. By contrast, there was an increased incidence of mechanical complications in the ACDF group *versus* the CDA group (Table 4). The incidence of dysphagia complications was not significantly different between groups at 6 weeks (CDA 0% *vs.* ACDF 0.03%, *P* = 1) or 3 months (CDA 0% *vs.* ACDF 0.016%, *P* = 1). By 24 months, the incidence of dysphagia in both groups was 0%. (see Supplemental Digital Content Table 5, available at <http://links.lww.com/BRS/A957>). The incidence of medical AEs was compared between groups (see Supplemental Digital Content Table 6, available at <http://links.lww.com/BRS/A958>). There was an increased incidence of medical complications in the ACDF patients at each time point.

The incidence of reoperation complications was examined (see Supplemental Digital Content Table 7, available at <http://links.lww.com/BRS/A959>). The cumulative 36-month incidence of reoperation in the ACDF patients (10.5%, 95% CI: 9.4%–11.6%) was almost twice that of the CDA patients (5.7%, 95% CI: 2.6%–8.6%, *P* = 0.0214, hazard ratio: 1.91, *P* = 0.0214) (Figure 2). There was a significant decrease in long-term (up to 4 yr) survival in the ACDF group (95.51%) *versus* CDA group (91.42%) (Table 8). Of the patients who underwent reoperation, there was an increase in the percentage of medical comorbidities in the ACDF patients (25.65%) *versus* the CDA patients (10%, *P* = 0.43) (Table 9).

**TABLE 2.** Characteristics of Patients Who Were Readmitted Within 90 Days After Index Procedure

	All Readmission Patients	ACDF	CDA
N	371	358	13
% Male	45.28	44.97	53.85
Postindex Data Availability (mo)	25.91	25.87	26.84
Average age (yr)	46.86	46.91	45.46
Average length of stay	1.71	1.74	1
% With existing comorbidity	27.22	27.37	23.08
% Using BMP	2.70	2.79	0.00
7-d readmission	65.77%	66.20%	53.85%
30-d Readmission	73.85%	74.30%	61.54%
90-d readmission	100.00%	100.00%	100.00%
Distribution of complications in readmission patients			
Myocardial infarction	1.89%	1.68%	7.69%
Congestive heart failure	1.89%	1.96%	0.00%
Peripheral vascular disease	0.27%	0.28%	0.00%
Cerebrovascular disease	3.50%	3.63%	0.00%
Dementia	0.00%	0.00%	0.00%
Pulmonary disease	12.13%	12.29%	7.69%
Rheumatic	2.16%	2.23%	0.00%
Peptic ulcer	0.81%	0.84%	0.00%
Mild liver	2.16%	1.96%	7.69%
Without complications	3.77%	3.91%	0.00%
Diabetes (with complications)	0.00%	0.00%	0.00%
Neurological	1.35%	1.40%	0.00%
Renal	0.81%	0.84%	0.00%
Malignancy	2.70%	2.79%	0.00%
Moderate-severe liver disease	0.00%	0.00%	0.00%
Metastatic cancer	0.27%	0.28%	0.00%
AIDS	0.27%	0.28%	0.00%
Atherosclerosis	5.66%	5.59%	7.69%
Cancer	2.70%	2.79%	0.00%
Diabetes (sum)	3.77%	3.91%	0.00%
Percentage with comorbidity present	27.22%	27.37%	23.08%

ACDF indicates anterior cervical discectomy and fusion; CDA, cervical disc arthroplasty; BMP, bone morphogenetic protein; AIDS, acquired immunodeficiency syndrome.

**TABLE 3. Pain Complications (Percentage of Patients With at Least 1 Event)**

Time Period	ACDF, %	CDA, %
0–6 wk	0.17	0.00
6 wk to 3 mo	0.20	0.00
3 mo to 6 mo	0.45	0.32
6 mo to 12 mo	0.70	1.03
12 mo to 18 mo	0.68	0.75
18 mo to 24 mo	0.59	1.27
24 mo to 36 mo	0.68	0.47

*ACDF indicates anterior cervical discectomy and fusion; CDA, cervical disc arthroplasty.*

**TABLE 4. Mechanical Complications (Percentage of Patients With at Least 1 Event)**

Time Period	ACDF, %	CDA, %
0–6 wk	0.06	0.00
6 wk to 3 mo	0.06	0.00
3 mo to 6 mo	0.10	0.00
6 mo to 12 mo	0.15	0.00
12 mo to 18 mo	0.21	0.00
18 mo to 24 mo	0.17	0.00
24 mo to 36 mo	0.10	0.00

*ACDF indicates anterior cervical discectomy and fusion; CDA, cervical disc arthroplasty.*

**Costs**

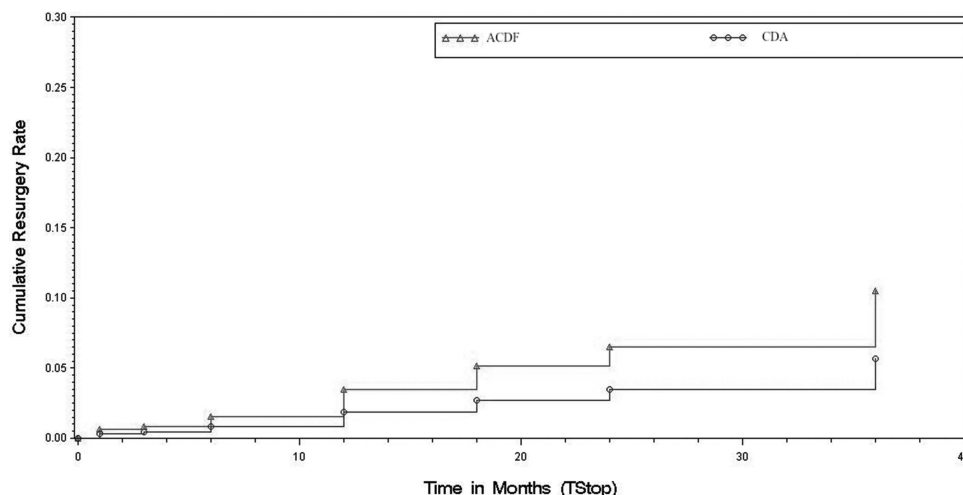
Costs were considered at the index surgery, 90-day global period, and in total at 2, 3, and 4 years until patients’ final month of continuous enrollment was exhausted (Table 10) (Figure 3). There were no significant differences in mean baseline cost for the 6 months of preoperative treatment (CDA \$5744 *vs.* ACDF \$6339, *P* = 0.72). The mean index surgery cost was lower in the CDA *versus* ACDF groups (CDA \$20,722 *vs.* ACDF \$22,379, *P* = 0.016). The index surgery and global 90-day window costs (including payment to all relevant health care providers and facilities, except drug costs) were significantly lower in the CDA *versus* ACDF groups (CDA \$22,761 *vs.* ACDF \$25,029, *P* = 0.0086). For the index allowed amount, the median values are \$20,022.75 and \$18,890.81 for ACDF and CDA, respectively. For the Index + 90 Days allowed amount, the medians are \$21,812.27 and \$20,310.36 for the ACDF and CDA groups, respectively (Figure 4).

Consequently, by 2 years postindex procedure (Table 10), there was a significant reduction in all costs in cervical arthroplasty patients *versus* ACDF patients (CDA \$34,979 *vs.* ACDF \$39,820). Because of the variable follow-up period, based on exhaustion of health plan enrollment, costs were

also calculated as mean cost per person, per month of follow-up. There was a significant decrease in total overall cost per person, per month of follow-up in CDA *versus* ACDF groups at all time points. There was also a lower cost per patient per month in CDA patients excluding those patients with medical comorbidities (Table 11). We also calculated the cost of ongoing care per person, per month between CDA and ACDF patients, excluding the cost of the index procedure (Table 12) and found no difference between groups.

**DISCUSSION**

In a “real-world” population of patients with cervical pathology outside of IDE study conditions, we found that patients who underwent CDA for single-level cervical degenerative disc disease have lower readmission rates, fewer mechanical complications, and, most importantly, lower reoperation rates than ACDF patients. Furthermore, we have determined that the cost of care is reduced in CDA patients at the time of the index procedure and throughout the postoperative course. Not surprisingly, patients with medical comorbidities in both groups had increased rates of readmission and increased costs compared with patients without comorbidities.



**Figure 2.** Cumulative reoperation rate in ACDF (arrow) and CDA (circle) patients. ACDF indicates anterior cervical discectomy and fusion; CDA, cervical disc arthroplasty.

**TABLE 8. Reoperation-Free Survival of ACDF and CDA Groups**

Approximate Survival	All, %	ACDF, %	CDA, %
Up to 6 wk	99.35	99.32	100.00
6 wk to 3 mo	99.21	99.17	100.00
3 mo to 6 mo	98.55	98.50	99.68
6 mo to 12 mo	96.81	96.72	98.68
12 mo to 18 mo	95.29	95.16	97.93
18 mo to 24 mo	94.25	94.11	97.11
24 mo to 36 mo	92.71	92.51	96.65
36 mo to 48 mo	91.62	91.42	95.51

*ACDF indicates anterior cervical discectomy and fusion; CDA, cervical disc arthroplasty.*

A major strength of the current observational study is that patients were treated outside of strict IDE study conditions. Investigational study conditions may not imitate actual clinical practice and, therefore, the conclusions may not be readily extrapolated to “real-world” conditions. To control for selection bias in a study, there may be disparities between IDE study conditions and “real-world” practice in prevalence of contraindications<sup>37,38</sup> and consequently reoperation rates<sup>39</sup> between CDA and ACDF patients. Our study evaluated patients operated upon outside the IDE milieu and had available to study a number of Food and Drug Administration–approved cervical CDA devices. Therefore, we think that the methodology in the current study of observational data on a large population captures patients who otherwise might not enroll in a prospective, randomized IDE study. Other advantages of this study include the large number of patients and the high rate of long-term follow-up. These factors enable comparison of relatively rare events, such as reoperation, that smaller studies may be underpowered to detect. In addition, the decision sensitivity for further treatment (such as pain injections) or reoperation can be influenced by IDE study conditions in some cases.<sup>39</sup> We, therefore, think that our data more accurately reflect the “real-world” rate of pain-related complications, mechanical complications, reoperation, and other health care utilization, more so than IDE study data. Finally, patients in our study are less likely to be subject to affirmation bias due to the “winning” effect of receiving the investigational intervention as in a prospective, randomized study.<sup>3</sup>

Overall, CDA was found to have a lower rate of mechanical, device-related complications than ACDF. This finding is expected because failure of ACDF fusion devices has been described in the setting of pseudarthrosis.<sup>40</sup> The differential in mechanical complications may reflect the relative expertise of a smaller group of surgeons who have undergone specialized training to perform CDA whereas ACDF is likely practiced by a larger percentage of orthopedic spine and neurosurgeons. There were no significant differences in pain complications

**TABLE 9. Comparison of Patients Who Underwent Reoperation in ACDF Versus CDA Populations**

Patients With Reoperation	ACDF	CDA
N	421	10
Average index cost	\$21,352.02	\$26,317.05
Index cost SD	\$13,067.04	\$14,136.58
Average enrollment (mo)	30.6	29.4
Enrollment SD (mo)	11.4	10.4
Myocardial infarction	0.48%	0.00%
Congestive heart failure	0.95%	0.00%
Peripheral vascular disease	0.24%	0.00%
Cerebrovascular disease	3.56%	0.00%
Dementia	0.00%	0.00%
Chronic pulmonary disease	13.06%	10.00%
Rheumatic disease	2.14%	0.00%
Peptic ulcer disease	1.19%	0.00%
Mild liver disease	1.43%	0.00%
Diabetes without chronic complication	3.09%	0.00%
Diabetes with chronic complication	0.48%	0.00%
Neurological	0.71%	0.00%
Renal disease	0.48%	0.00%
Any malignancy, except neoplasm of skin	1.66%	0.00%
Moderate or severe liver disease	0.00%	0.00%
Metastatic solid tumor	0.24%	0.00%
AIDS/HIV	0.00%	0.00%
Myocardial infarction and/or congestive heart failure and/or peripheral vascular disease and/or cerebrovascular disease	4.28%	0.00%
Metastatic solid tumor and/or any malignancy, except neoplasm of skin	1.66%	0.00%
Diabetes without chronic complication and/or diabetes with chronic complication	3.09%	0.00%
% With existing comorbidity	25.65	10.00

*ACDF indicates anterior cervical discectomy and fusion; CDA, cervical disc arthroplasty.*

between the ACDF and CDA patient cohorts. This finding suggests that patients in both groups underwent successful decompression of radiculopathy and stabilization. We would not expect significant differences in early pain after either



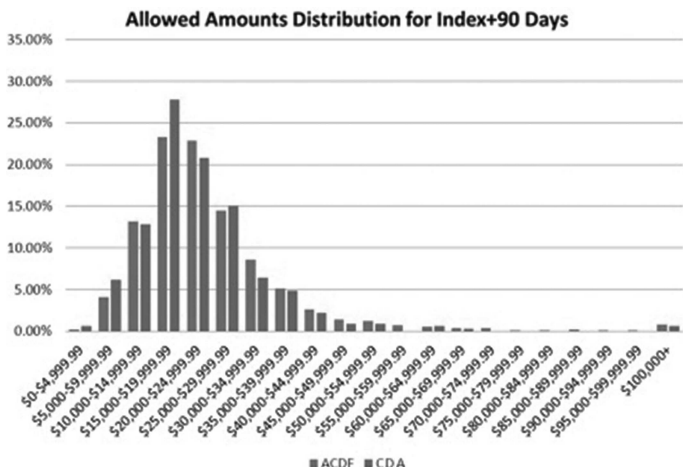
**TABLE 10. Mean Payer Index and Available Follow-up Costs Per Patient (CDA vs. ACDF)**

	CDA Surgery	N	ACDF Surgery	N
Index event	\$20,722	327	\$22,379	6635
Index Event + 90 Day global post-operative period	\$22,761	317	\$25,029	6416
Continuously Enrolled Patients Available at Follow-up				
	CDA F/U	N	ACDF F/U	N
Discharge to 6 wk	\$791	327	\$1236	6635
6 wk to 3 mo	\$1216	317	\$1497	6416
3–6 mo	\$2147	317	\$2631	6260
6–12 mo	\$4127	291	\$4566	5825
12–18 mo	\$3106	266	\$3914	5163
18–24 mo	\$2862	236	\$3596	4576
24–36 mo	\$3753	212	\$4806	4124
36–48 mo	\$1040	76*	\$1526	1576*
Total	\$34,979		\$39,820	

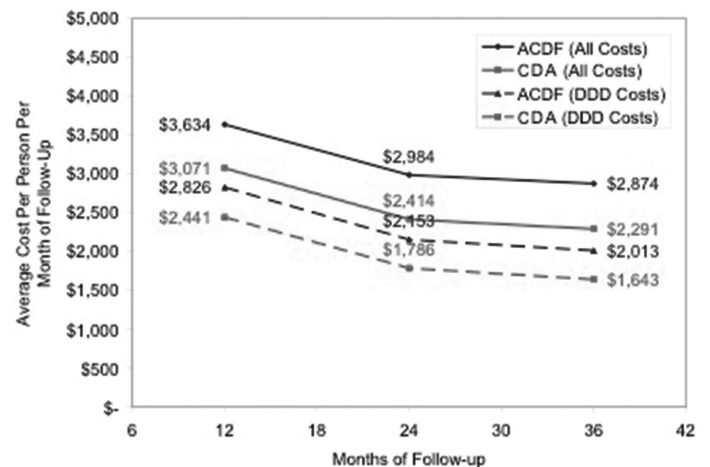
\*CDA: 76.8% attrition at 37-month time point. ACDF: 76.2% attrition at 37-month time point.  
 ACDF indicates anterior cervical discectomy and fusion; CDA, cervical disc arthroplasty.

procedure, if performed successfully. Most importantly, the reoperation rate is reduced after CDA *versus* ACDF at 1, 2, and 3 years postoperatively. These findings are similar to other studies in the literature that demonstrate a lower long-term reoperation rate after CDA *versus* ACDF.<sup>4</sup> The 36-month cumulative reoperation rate in the ACDF population current study (10.5%, 95% CI: 9.4%–11.8%)<sup>4</sup> was similar to that of IDE studies.<sup>4,24,41</sup> Given the equivalent pain complication rates in both groups, we think that the main drivers of reoperation are mechanical complications and development of adjacent-level pathology.

We found that CDA resulted in less total cost than ACDF at the time of the index procedure (\$1657) during the 90-day postoperative period (\$2268) and by 2 years postoperatively (\$4841). Per month costs during this follow-up period were also lower (\$583 at 3 yr) for CDA over ACDF patients. Excluding the cost of the index procedure, there was a trend for lower (\$221) per patient per month maintenance costs (excluding the direct index surgical procedure cost) at up to 3 years' follow-up. Not surprisingly, patients with comorbidities had significantly increased readmissions, complications, and higher health care costs than patients without



**Figure 3.** Distribution of cost for the surgery and 90-day global period for ACDF and CDA patients. ACDF indicates anterior cervical discectomy and fusion; CDA, cervical disc arthroplasty.



**Figure 4.** Average cost/patient/month excluding the index procedure cost for ACDF and CDA patients. ACDF indicates anterior cervical discectomy and fusion; CDA, cervical disc arthroplasty.

**TABLE 11. Specific Comorbidity Rates Between ACDF and CDA Groups in Patients With Greater Than 70,000 Cost**

	All	ACDF	CDA
N	64	62	2
% Male	51.56	53.23	100.00
Postindex data availability (mo)	27.8	27.92	24
Average age (yr)	46.78	46.98	40.5
Average length of stay	5.63	5.77	1
% With existing comorbidity	37.50	38.71	0.00
% Using BMP	0.09	0.10	0.00
7-d readmission	10.94%	11.29%	0.00%
30-d readmission	9.38%	9.68%	0.00%
90-d readmission	17.19%	16.13%	50.00%
Incidence of comorbidities			
Myocardial infarction	3.13%	3.23%	0.00%
Congestive heart failure	1.56%	1.61%	0.00%
Peripheral vascular disease	3.13%	3.23%	0.00%
Cerebrovascular disease	0.00%	0.00%	0.00%
Dementia	1.56%	1.61%	0.00%
Pulmonary disease	18.75%	19.35%	0.00%
Rheumatic	3.13%	3.23%	0.00%
Peptic ulcer	1.56%	1.61%	0.00%
Mild liver	1.56%	1.61%	0.00%
Diabetes (without complications)	4.69%	4.84%	0.00%
Diabetes (with complications)	0.00%	0.00%	0.00%
Neurological	3.13%	3.23%	0.00%
Renal	1.56%	1.61%	0.00%
Malignancy	4.69%	4.84%	0.00%
Moderate-severe liver disease	0.00%	0.00%	0.00%
Metastatic cancer	0.00%	0.00%	0.00%
AIDS	0.00%	0.00%	0.00%
Atherosclerosis	6.25%	6.45%	0.00%
Cancer	4.69%	4.84%	0.00%
Diabetes (sum)	4.69%	4.84%	0.00%
Percentage with comorbidity present	37.50%	38.71%	0.00%

ACDF indicates anterior cervical discectomy and fusion; CDA, cervical disc arthroplasty; BMP, bone morphogenetic protein.

comorbidities. Our procedure costs were slightly higher than those reported in the literature by Carreon *et al*<sup>42</sup> (current study \$22, 1579 *vs.* \$15,714), although the Carreon results are normalized to the 2012 Medicare Fee Schedule, whereas our costs are indicative of commercially contracted private insurance rates across varying regions of the United States.

One limitation of this study is that the distribution of product brands (ProDisc, Bryan, Prestige) is unknown. Based on the years of the study distribution, we speculate that the majority of patients underwent ProDisc-C, Prestige, or Bryan disc arthroplasty. However, different brands of cervical arthroplasty have been combined in other meta-analyses for

this purpose<sup>16,26-31,42</sup> because, to the authors' knowledge, no specific brand of CDA has been shown to reduce reoperation over other CDA brands. Although our study was industry-funded by a grant from Synthes, the database analysis and writing was subsequently performed "blinded" to the specific product brand being used. In addition, although the study was funded by a grant from industry, one could argue that the medical device industry would benefit from the study regardless of the outcome of the study. We think that use of a third-party health insurer database (BHI) may reduce the possibility of systemic biases in data collection and reporting, inherent in some other industry-funded studies.<sup>43</sup> Another limitation

**TABLE 12. Per Person Per Month Costs of ACDF Versus CDA Excluding the Index Procedure Cost**

	ACDF	CDA	P (Wilcoxon Rank Sum Test)
Total costs less index costs (per person per month of follow-up up to 1 yr)	932.38	754.7	P = 0.0082
Total costs less index costs (per person per month of follow-up up to 2 yr)	953.34	751.63	P = 0.0080
Total costs less index costs (per person per month of follow-up up to 3 yr)	982.35	761.75	P = 0.0057

ACDF indicates anterior cervical discectomy and fusion; CDA, cervical disc arthroplasty.

of our study is that pain medication usage was not included. Therefore, the cost estimates also do not include pain medication. We excluded pain medication on the basis of the significant variability in drug coverage, drug costs, and co-pays for individuals within a single health insurance plan. Similarly, the procedure cost data in our study also reflects direct costs of care for patients with ACDF or CDA. It is not adjusted to account for variability in patient benefit plans, geographic factors, or physician-hospital reimbursement contracts. We are also unable to identify surgeon- (specialty, experience, volume) or patient- (pain distribution, degree of neural element compression, duration of symptoms, facet arthrosis, pseudarthrosis, or sagittal balance) specific factors after either type of surgical intervention. The lower number of patients receiving CDA as opposed to ACDF likely reflects a combination of surgeon's experience and insurance reimbursement issues. Certainly, other surgery-specific factors such as bone graft choice, use of biologic products, plate usage, or post-operative orthosis usage can influence our analyses of cost, readmission, reoperation, and complications. We think that our data accurately reflect the actual length of stay, complications, and costs of treatment of this condition, despite the clinical heterogeneity of practice patterns and the lack of a standard of care. These limitations are inherent to any administrative database study.<sup>44</sup> Finally, the long-term follow-up is another limitation of the study. However, the poor follow-up rate in our opinion in this study merely reflects the fact that patients do not stay with a particular insurance company for more than 2 years. The follow-up numbers are low in this study because the majority of these patients had switched to another carrier, not because Blue Health Intelligence (or the study investigators) failed to track them.

## CONCLUSION

After cervical arthroplasty, patients have lower readmission rates, fewer mechanical complications, and lower reoperation rates than those in patients receiving ACDF, resulting in a

lower cost of care from a payer perspective. The costs savings of CDA are realized at the index procedure and maintained throughout the follow-up period of this study. Patients with comorbidities in both groups had increased rates of readmission and increased costs compared with patients without medical comorbidities, underscoring the need for careful patient selection prior to utilization of either surgical procedure. Based on these findings, and within the limitations noted previously, one could conclude that CDA is a safe and less costly operation than ACDF and is more likely to reduce the rate of reoperation in patients with single-level disease. Aside from clinical decision-making, purchasing, and health care utilization, decision-makers are now provided a cost-conscious alternative in CDA for appropriately selected patients.

## ➤ Key Points

- ❑ After cervical arthroplasty, patients have lower readmission rates, fewer mechanical complications, and lower reoperation rates than those in patients receiving ACDF.
- ❑ The costs savings of CDA are realized at the index procedure and maintained throughout the follow-up period of this study.
- ❑ Patients with comorbidities in both groups had increased rates of readmission and increased costs compared with patients without medical comorbidities.

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## References

1. Kepler CK, Wilkinson SM, Radcliff KE, et al. Cost-utility analysis in spine care: a systematic review. *Spine J* 2012;12:676–90.
2. Murrey D, Janssen M, Delamarter R, et al. Results of the prospective, randomized, controlled multicenter Food and Drug Administration investigational device exemption study of the ProDisc-C total disc replacement versus anterior discectomy and fusion for the treatment of 1-level symptomatic cervical disc disease. *Spine J* 2009;9:275–86.
3. Zigler JE, Delamarter R, Murrey D, et al. ProDisc-C and ACDF as surgical treatment for single level cervical symptomatic degenerative disc disease: five-year results of an FDA study. *Spine* 2013;38:203–9.
4. Delamarter RB, Zigler J. Five-year reoperation rates, cervical total disc replacement versus fusion, results of a prospective randomized clinical trial. *Spine* 2013;38:711–7.
5. Nesterenko SO, Riley LH III, Skolasky RL. Anterior cervical discectomy and fusion versus cervical disc arthroplasty: current state and trends in treatment for cervical disc pathology. *Spine* 2012;37:1470–4.
6. Park JY, Kim KH, Kuh SU, et al. What are the associative factors of adjacent segment degeneration after anterior cervical spine surgery? Comparative study between anterior cervical fusion and arthroplasty with 5-year follow-up MRI and CT. *Eur Spine J* 2013;22:1078–89.
7. Sasso RC, Anderson PA, Riew KD, et al. Results of cervical arthroplasty compared with anterior discectomy and fusion: four-year

- clinical outcomes in a prospective, randomized controlled trial. *J Bone Joint Surg Am* 2011;93:1684–92.
8. Cunningham BW, Hu N, Zorn CM, et al. Biomechanical comparison of single- and two-level cervical arthroplasty versus arthrodesis: effect on adjacent-level spinal kinematics. *Spine J* 2010;10:341–9.
  9. Dmitriev AE, Kuklo TR, Lehman RA Jr, et al. Stabilizing potential of anterior, posterior, and circumferential fixation for multilevel cervical arthrodesis: an in vitro human cadaveric study of the operative and adjacent segment kinematics. *Spine* 2007;32:E188–96.
  10. Park JJ, Quirno M, Cunningham MR, et al. Analysis of segmental cervical spine vertebral motion after prodisc-C cervical disc replacement. *Spine* 2010;35:E285–9.
  11. Finn MA, Brodke DS, Daubs M, et al. Local and global subaxial cervical spine biomechanics after single-level fusion or cervical arthroplasty. *Eur Spine J* 2009;18:1520–7.
  12. Auerbach JD, Anakwenze OA, Milby AH, et al. Segmental contribution toward total cervical range of motion: a comparison of cervical disc arthroplasty and fusion. *Spine* 2011;36:E1593–9.
  13. Wigfield C, Gill S, Nelson R, et al. Influence of an artificial cervical joint compared with fusion on adjacent-level motion in the treatment of degenerative cervical disc disease. *J Neurosurg* 2002;96(suppl):17–21.
  14. Chang UK, Kim DH, Lee MC, et al. Changes in adjacent-level disc pressure and facet joint force after cervical arthroplasty compared with cervical discectomy and fusion. *J Neurosurg Spine* 2007;7:33–9.
  15. Terai T, Faizan A, Sairyo K, et al. Operated and adjacent segment motions for fusion versus cervical arthroplasty: a pilot study. *Clin Orthop Relat Res* 2011;469:682–7.
  16. DiAngelo DJ, Foley KT. An improved biomechanical testing protocol for evaluating spinal arthroplasty and motion preservation devices in a multilevel human cadaveric cervical model. *Neurosurg Focus* 2004;17:E4.
  17. Robertson JT, Papadopoulos SM, Traynelis VC. Assessment of adjacent-segment disease in patients treated with cervical fusion or arthroplasty: a prospective 2-year study. *J Neurosurg Spine* 2005;3:417–23.
  18. Mummaneni PV, Amin BY, Wu JC, et al. Cervical artificial disc replacement versus fusion in the cervical spine: a systematic review comparing long-term follow-up results from two FDA trials. *Evidence-based Spine Care J* 2012;3:59–66.
  19. Mummaneni PV, Burkus JK, Haid RW, et al. Clinical and radiographic analysis of cervical disc arthroplasty compared with allograft fusion: a randomized controlled clinical trial. *J Neurosurg Spine* 2007;6:198–209.
  20. Sasso RC, Anderson PA, Riew KD, et al. Results of cervical arthroplasty compared with anterior discectomy and fusion: four-year clinical outcomes in a prospective, randomized controlled trial. *Orthopedics* 2011;34:889.
  21. Nabhan A, Ishak B, Stuedel WI, et al. Assessment of adjacent-segment mobility after cervical disc replacement versus fusion: RCT with 1 year's results. *Eur Spine J* 2011;20:934–41.
  22. Pimenta L, McAfee PC, Cappuccino A, et al. Superiority of multilevel cervical arthroplasty outcomes versus single-level outcomes: 229 consecutive PCM prostheses. *Spine* 2007;32:1337–44.
  23. Heller JG, Sasso RC, Papadopoulos SM, et al. Comparison of BRYAN cervical disc arthroplasty with anterior cervical decompression and fusion: clinical and radiographic results of a randomized, controlled, clinical trial. *Spine* 2009;34:101–7.
  24. Coric D, Nunley PD, Guyer RD, et al. Prospective, randomized, multicenter study of cervical arthroplasty: 269 patients from the Kineflex/C artificial disc investigational device exemption study with a minimum 2-year follow-up: clinical article. *J Neurosurg Spine* 2011;15:348–58.
  25. Bartels RH, Donk RD, Pavlov P, et al. Comparison of biomechanical properties of cervical artificial disc prosthesis: a review. *Clin Neurol Neurosurg* 2008;110:963–7.
  26. Botelho RV, Moraes OJ, Fernandes GA, et al. A systematic review of randomized trials on the effect of cervical disc arthroplasty on reducing adjacent-level degeneration. *Neurosurg Focus* 2010;28:E5.
  27. Jawahar A, Cavanaugh DA, Kerr EJ III, et al. Total disc arthroplasty does not affect the incidence of adjacent segment degeneration in cervical spine: results of 93 patients in three prospective randomized clinical trials. *Spine J* 2010;10:1043–8.
  28. Yang B, Li H, Zhang T, et al. The incidence of adjacent segment degeneration after cervical disc arthroplasty (CDA): a meta analysis of randomized controlled trials. *PLoS One* 2012;7:e35032.
  29. Fallah A, Akl EA, Ebrahim S, et al. Anterior cervical discectomy with arthroplasty versus arthrodesis for single-level cervical spondylosis: a systematic review and meta-analysis. *PLoS One* 2012;7:e43407.
  30. Boselie TE, Willems PC, van Mameren H, et al. Arthroplasty versus fusion in single-level cervical degenerative disc disease. *Cochrane Database Syst Rev* 2012;9:CD009173.
  31. Bartels RH, Donk R, Verbeek AL. No justification for cervical disk prostheses in clinical practice: a meta-analysis of randomized controlled trials. *Neurosurgery* 2010;66:1153–60; discussion 1160.
  32. Hilibrand AS, Carlson GD, Palumbo MA, et al. Radiculopathy and myelopathy at segments adjacent to the site of a previous anterior cervical arthrodesis. *J Bone Joint Surg Am* 1999;81:519–28.
  33. Steinmetz MP, Patel R, Traynelis V, et al. Cervical disc arthroplasty compared with fusion in a workers' compensation population. *Neurosurgery* 2008;63:741–7; discussion 747.
  34. Scott C. BlueCross/BlueShield. *J Tennessee Dental Assoc* 2009;89:6.
  35. Sasso RC, Smucker JD, Hacker RJ, et al. Clinical outcomes of BRYAN cervical disc arthroplasty: a prospective, randomized, controlled, multicenter trial with 24-month follow-up. *J Spinal Disord Tech* 2007;20:481–91.
  36. Mummaneni PV, Robinson JC, Haid RW Jr. Cervical arthroplasty with the PRESTIGE LP cervical disc. *Neurosurgery* 2007;60(suppl 2):310–4; discussion 314–5.
  37. Auerbach JD, Jones KJ, Fras CI, et al. The prevalence of indications and contraindications to cervical total disc replacement. *Spine J* 2008;8:711–6.
  38. Quirno M, Goldstein JA, Bendo JA, et al. The incidence of potential candidates for total disc replacement among lumbar and cervical fusion patient populations. *Asian Spine J* 2011;5:213–9.
  39. Singh K, Phillips FM, Park DK, et al. Factors affecting reoperations after anterior cervical discectomy and fusion within and outside of a Federal Drug Administration investigational device exemption cervical disc replacement trial. *Spine J* 2012;12:372–8.
  40. Ning X, Wen Y, Xiao-Jian Y, et al. Anterior cervical locking plate-related complications; prevention and treatment recommendations. *Int Orthop* 2008;32:649–55.
  41. Burkus JK, Haid RW, Traynelis VC, et al. Long-term clinical and radiographic outcomes of cervical disc replacement with the Prestige disc: results from a prospective randomized controlled clinical trial. *J Neurosurg Spine* 2010;13:308–18.
  42. Carreon LY, Anderson PA, Traynelis VC, et al. Cost effectiveness of single-level anterior cervical discectomy and fusion five years after surgery. *Spine* 2013;38:471–5.
  43. Bhandari M, Busse JW, Jackowski D, et al. Association between industry funding and statistically significant pro-industry findings in medical and surgical randomized trials. *CMAJ* 2004;170:477–80.
  44. Campbell PG, Malone J, Yadla S, et al. Comparison of ICD-9-based, retrospective, and prospective assessments of perioperative complications: assessment of accuracy in reporting. *J Neurosurg Spine* 2011;14:16–22.

# Comparison of the short- and long-term treatment effect of cervical disk replacement and anterior cervical disk fusion: a meta-analysis

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## Abstract

**Background** Anterior cervical discectomy and fusion (ACDF) has been used as a gold standard for the treatment of cervical spondylosis, but it may cause complications such as pseudarthrosis and junctional degeneration. Cervical disk arthroplasty (CDA) may help overcome such problems, but there are inconsistencies among the published literature on its effectiveness comparing with ACDF.

**Methodology** We searched “PubMed” (2000.1–2013.10), “Medline” (2000.1–2013.10), “Elsevier” (2000.1–2013.10), Cochrane library (2008.1–2013.10) databases with the key words of “cervical disk arthroplasty”, “CDA”, “anterior cervical disk fusion”, “ACDF”, “cervical”, “randomized controlled study”, “RCT” and searched for randomized controlled trials comparing the efficacy of ACDF and CDA for the treatment of cervical spondylosis.

Neck disability index (NDI), VAS arm pain score, VAS neck pain score, ROM of the adjacent level, SF36-PCS score, SF36-MCS score and patient satisfaction were calculated by Revman5.2 software.

**Results** From 1,400 papers found, we chose 18 randomized controlled trials and cohorts evaluating the efficacy of CDA and ACDF on symptomatic cerebral spondylosis. The total number of patients is 3,056, in which 1,576 were in the CDA group and 1,480 were in the ACDF group. The CDA group demonstrated better results than the ACDF group concerning VAS arm pain score 1, 2, 4 years after the surgery, VAS neck pain score 1, 2, 4 years after the surgery, ROM of the adjacent level 1 and 2 years after the surgery, patient satisfaction 1, 2, 4 years after the surgery, NDI scores 1, 2, 4 years after the surgery, SF36-PCS score 1 and 2 years after the surgery and SF36-MCS score at 1 and 4 years after the surgery. There are no significant differences between the groups concerning SF36-PCS score 4 years after the surgery and SF36-MCS score at 2 years after the surgery.

**Conclusions** CDA can be an effective alternative method to ACDF for the treatment of cervical spondylosis.

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**Keywords** Anterior cervical discectomy and fusion · Cervical disk arthroplasty · Meta-analysis

## Introduction

Cervical spondylosis is a common condition that may result in chronic and progressive neck pain, radiculopathy and myelopathy. Cervical disk degenerates through age and may eventually prolapse or form osteophytes, which can pressure the spinal cord, causing myelopathy or radiculopathy. For the treatment of symptomatic degenerative

cervical diseases, anterior cervical discectomy and fusion (ACDF), originally described by Cloward [1] and Smith and Robinson [2], has been used as a gold standard.

Although ACDF can effectively alleviate the symptoms, it may cause several complications such as pseudarthrosis and junctional degeneration.

Intervertebral disk replacement can effectively preserve motion of adjacent levels, which is a positive element for preventing adjacent level degeneration after the surgery. As a result, cervical disk arthroplasty (CDA) has been applied by more surgeons as an alternative to ACDF for the treatment of symptomatic cervical spondylosis [3, 4].

Several RCTs have been published comparing the ACDF and CDA and provided valuable first-hand material for further application of these techniques; however, most of these studies have relatively small patient number, and the clinical outcome is not all the same. Moreover, as most of these studies were designed as non-inferiority trials, there might be certain study design bias comparing the outcomes of two procedures. This makes it necessary to find a combined effect of current reports and provide a conclusion based on larger number of patient basis.

Meta-analysis is a statistical method that can combine treatment effects of several comparable studies and merged effect of these studies. In the current paper, we have analyzed all the RCTs published between 2000 and 2013 by meta-analysis to compare the effectiveness of emerging CDA and the current gold standard ACDF.

## Materials and methods

### Inclusion of studies

Assuming that there might be not enough papers about CDA and ACDF for the treatment of cervical spondylosis, we applied a broad search strategy using the following mesh terms: “cervical disk arthroplasty”, “CDA”, “anterior cervical disk fusion”, “ACDF”, “cervical”, “randomized controlled study”, “RCT” in databases PubMed, OVID, Embase, Cochrane library. Two independent evaluators reviewed all English and Chinese language articles published between January 2000 and June 2013.

Two authors independently reviewed titles, abstracts and some of the full text articles that may be potentially eligible for the inclusion criteria. In the case of disputes over the eligibility of a study for the inclusion, a third author made the final decision.

Included studies reported the effects of CDA and ACDF on cervical spondylosis. Where there were insufficient data presented for inclusion, authors were contacted for further details. All randomized controlled trials investigating the efficacy of CDA and ACDF for cervical spondylosis were

**Table 1** Inclusion and exclusion criteria for article selection

	Inclusion criteria	Exclusion criteria
Type of study	Randomized control trials	Prospective trials, retrospective trials expert opinion, biomechanical and individual case studies
Patients	18 years old or older	Patients less than 18 years old
Type of condition	Symptomatic cervical disc disease required single-level CDA	Acute spinal fracture, infection, tumor, osteoporosis, rheumatoid arthritis, severe spondylosis or symptomatic cervical disc disease required multi-level CDA
Treatment	Single-level CDA versus ACDF	Studies not included CDA versus ACDF
Publication date	Published between 2000 and 2013	Published before 2000
Language	All English and Chinese papers	Non-English or non-Chinese papers

included. All the included studies were carried out independently, but used similar inclusion criteria with little difference (Table 1).

### Study quality assessment

Two authors independently assessed the quality of the included studies by the 12 criteria recommended by the Cochrane Back Review Group [5]. Each study was scored by “+” (positive), “-” (negative) and “?” (unclear). In the case of disputes, a third author made the final decisions. Studies scores less than 6 “+” were recognized as with low methodological quality and high risk of bias. The methodological quality of the included trials was outlined in Table 2.

### Data extraction

Data in the included trials were extracted by two independent reviewers: authors of each study, study design, patients’ size, patients’ age, origin, time of follow-up as well as intervention methods. Trials results, such as neck and arm pain scores, NDI, ROM of the adjacent level, SF36-PCS score, SF36-MCS score and patient satisfaction, were extracted and recorded in specific tables. In the cases that the same patients were analyzed in more than one study, they were extracted and analyzed as one patient population.

Data were analyzed and processed in Review Manager 5.2 as supplied by the Cochrane Collaboration (Oxford, UK). Two authors checked the data input to make sure

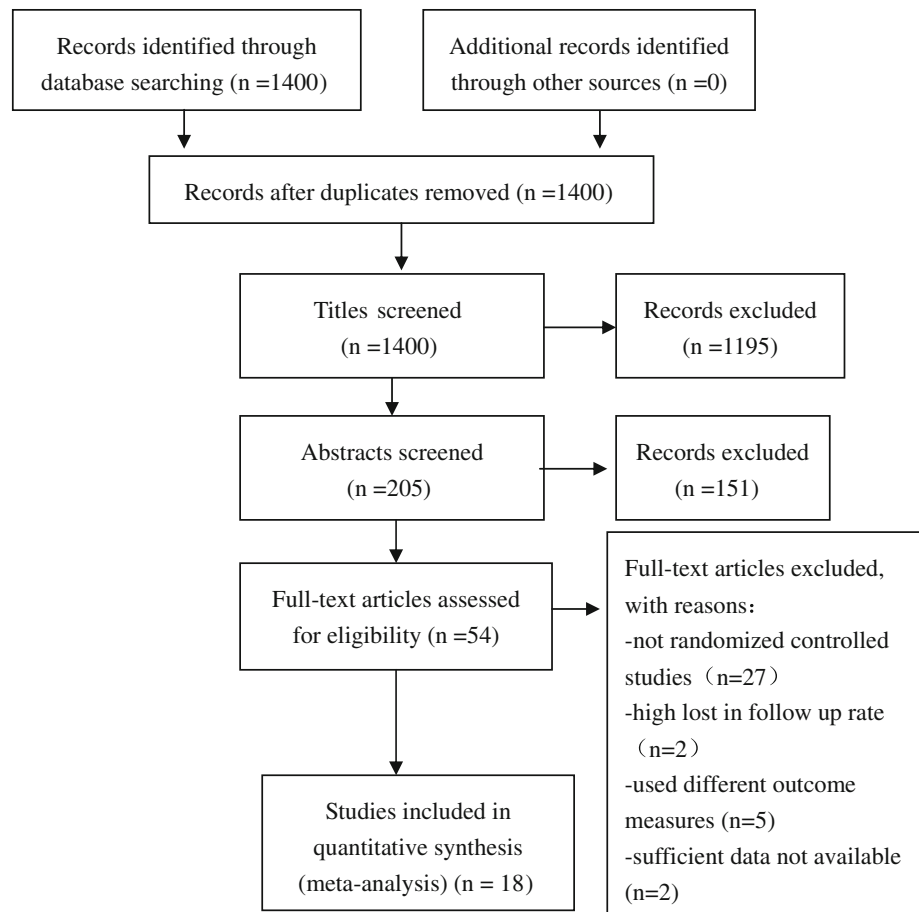
**Table 2** Demographics of studies involved

Study	Groups	Subject no	Age	Source of participants	Design	Randomization method	country	Time of research	Follow-up (month)		Intervention
									Years	%	
Nabhan [6]	Experimental	19	44±	Patients in admission	RCT	Drawing cards and sealed envelopes	Germany	April 2004–May 2005	1	100 %	ProDisc-C Prosthesis for TDA and Solis cage ACDF
	Control	21	44±								
Kelley [7]	Experimental	100	42.1 ± 8.4	Patients in admission	RCT	Random number table	USA	August 2003–October 2004	2	95.2 %	ProDisc-C for TDA
	Control	99	43.5 ± 7.1								
Nabhan [19]	Experimental	10	43	Patients in admission	RCT	Drawing cards and sealed envelopes	Germany	January 2006–August 2007	1	100 %	ProDisc-C Prosthesis for TDA and Solis cage ACDF
	Control	10	43								
Sun [9]	Experimental	12	42	Patients in admission	RCT	Not described	China	Not mentioned	1	100 %	Not given
	Control	12	42								
Nabhan [6]	Experimental	19	43	Patients in admission	RCT	Drawing cards and sealed envelopes	Germany	April 2004–May 2005	3	100 %	Synthesis Spine for TDA, PEEK and anterior titanium alloy plate for ACDF
	Control	20	43								
Coric [10]	Experimental	17	43	Patients in admission	RCT	Not described	USA	August 2003–August 2004	2	100 %	Bryan Cervical Disc System for TDA
	Control	13	43								
Hacker [11]	Experimental	22	Not given	Patients in admission	RCT	Not described	USA	2002–2004	1	100 %	Bryan Cervical Disc System for TDA
	Control	24	Not given								
Garrido [12]	Experimental	21	40.0	Patients	RCT	Not described	USA	Not given	5	93.6 % at 2 Y, 81 % at 5 Y	Bryan Cervical Disc System for TDA
	Control	26	43.3								
Wang [13]	Experimental	28	42	Patients in admission	RCT	Not described	China	December 2003–May 2005	2	74.6 %	Bryan Cervical Disc System for TDA
	Control	31	41								
Ding [22]	Experimental	44	46.2	Patients in admission	RCT	Not described	China	January 2008–March 2010	2	89.7 %	Prestige LP (Medtronic Sofamor Danek) for TDA
	Control	43	45.3								
Murry [14]	Experimental	44	44.6 ± 6.8	Patients in admission	RCT	By a blocked randomization schedule	USA	August 2003–October 2004	2	Not given	ProDisc-C (Synthes, West Chester, Pennsylvania) is used for TDA
	Control	43	43 ± 9.4								

Table 2 continued

Study	Groups	Subject no	Age	Source of participants	Design	Randomization method	country	Time of research	Follow-up (month)		Intervention
									Years	%	
Jawahar [15]	Experimental	59	Not given	Patients in admission	RCT	Compute regenerated randomization method	USA	December 2005–Feb 2010	4	Not given	Kineflex-C (SpinalMotion Inc., USA), Mobi-C (LDR spine, USA), Advent Cervical Disc (Blackstone Inc, USA).
	Control	34	Not given								
Coric [16]	Experimental	57	46.6	Patients in admission	RCT	Not given	USA	Not given	5	91.8 %	Bryan cervical disc, Kineflex/C disc, Discover cervical disc
	Control	41	46.3								
Sasso [17]	Experimental	56	42.5 ± 7.8	Patients in admission	RCT	Not given	USA	Not given	2	86.1 %	Bryan artificial disc
	Control	59	46.1 ± 7.8								
Auerbach [18]	Experimental	93	41.9 ± 7.5	Patients in admission	RCT	Block randomization schedule	USA	Not given	2	96.5 %	ProDisc-C (Synthes Spine, West Chester, PA)
	Control	94	42.0 ± 7.9								
Murry [8]	Experimental	103	43.5 ± 7.1	Patients in admission	RCT	By a blocked randomization schedule	USA	August 2003 and October 2004	4	96.5 %	ProDisc-C
	Control	106	42.1 ± 8.4								
Coric [20]	Experimental	136	43.7 ± 7.8	Patients in admission	RCT	Not given	USA	Not given	2	87.0 %	Kineflex/C (SpinalMotion, Inc.) cervical artificial disc
	Control	133	43.9 ± 7.4								
Phillips [21]	Experimental	218	45.9 ± 9.0	Patients in admission	RCT	Not given	USA	January 2005 and December 2007	2	85.9 %	Porous Coated Motion (PCM) Cervical Disc (NuVasive Inc., San Diego, CA)
	Control	185	43.7 ± 8.3								
Heller [4]	Experimental	242	44.4	Patients in admission	RCT	Centrally generated randomization schedule	USA	May 2002 – October 2004	2	91.6	Bryan Cervical Disc
	Control	221	44.7								
Mummaneni [23]	Experimental	276	43.3	Patients in admission	RCT	By Plan Procedure in Statistical Analysis System	USA	October 2002 and August 2004.	2	1 year: 91.1 %, 2 years: 77.8 %.	PRESTIGE ST Cervical Disc System
	Control	265	43.9								



**Fig. 1** Schematic chart for inclusion of studies

that no errors were made. Considering that there can be publication bias between the papers, the analyses were performed using random-effects models.  $I^2$  test was used to test the heterogeneity. Studies were considered to have significant heterogeneity if  $I^2 > 50\%$ . Subgroup or sensitivity analysis was used at the incidence of significant heterogeneity due to methodological quality of included trials. The differences in each study were defined by standard mean difference with 95% confidence intervals (95% CI) for continuous value and the odds ratio (OR) with 95% confidence intervals (95% CI) of the categorical outcome frequencies in the study groups and the control groups, respectively. Standard mean difference and OR of each individual trial were showed in a forest plot.

## Results

### Studies included

In total, 1,400 English and Chinese language articles were identified through the bibliographic literature search. Two authors independently reviewed the titles and abstracts to

identify studies meeting the inclusion/exclusion criteria. Based on the title and abstract, 1,346 studies were excluded. The full text of the remaining 54 were subsequently reviewed (Fig. 1).

Based on the inclusion and exclusion criteria above, 18 articles [6, 23] were included in the meta-analysis. No significant differences were found about demographic characteristics of patients in the two groups (CDA and ACDF). The total number of patients included is 3,056, in which 1,576 in the CDA group and 1,480 were in the ACDF group (Table 2).

### Quality of the included studies

Most of the included studies scored more than 6, indicating high liability of the outcomes that were extracted from these studies to perform meta-analysis (Table 3).

### Combined results of studies

#### VAS arm pain score

Thirteen studies including 2014 patients (1,054 patients from the CDA group and 960 patients from the ACDF

**Table 3** The Dephli list assessing the risk of bias in all included papers

Studies	Adequate random sequence generation?	Adequate allocation concealment?	Adequate blinding of patterns?	Adequate blinding of care providers?	Adequate blinding of outcome assessment?	Incomplete outcome data addressed? (loss to follow-up)	Intention-to-treat analysis?	Groups similar at baseline?	Influence of cointerventions unlikely?	Adequate compliance with primary Intervention?	Timing of outcome assessments similar?	Absence of other bias?	Total score
Hacker [11]	?	?	-	-	?	+	+	+	+	?	-	?	4
Coric [10]	?	?	-	-	+	+	+	+	+	+	-	?	5
Nabhan [6]	+	+	-	-	?	+	+	+	+	+	-	-	7
Mummaneni [23]	+	+	?	-	+	-	?	+	+	+	?	+	7
Sasso [17]	?	+	?	-	+	+	-	+	+	+	?	?	6
Murry [14]	+	+	-	-	?	+	?	+	+	+	-	+	7
Sun [9]	?	-	?	-	?	+	?	+	+	+	+	?	5
Wang [13]	?	?	-	-	?	-	-	+	+	+	-	?	3
Heller [4]	+	+	+	-	+	+	-	+	+	+	?	+	9
Murry [8]	+	+	+	-	+	+	-	+	+	+	-	?	8
Jawahar [15]	+	+	+	-	+	+	?	+	+	+	-	-	8
Coric [16]	?	+	+	-	?	+	?	+	+	+	?	?	6
Garrido [12]	?	?	-	-	?	?	-	+	+	+	?	-	3
Coric [20]	?	+	?	-	+	+	-	+	+	+	?	?	6
Auerbach [18]	+	+	-	-	+	+	-	+	+	+	-	?	7
Nabhan [19]	+	+	?	-	+	-	-	+	?	+	+	?	6
Ding [22]	-	?	-	-	-	-	-	+	+	+	-	?	3
Phillips [21]	?	+	+	-	+	+	-	+	+	+	-	+	8

group) have reported Visual analog scale (VAS) arm pain scores at different time points after the surgical treatment. The mean difference between the groups is 1.46 (0.91–2.01) a year after the surgery, 0.73 (0.28, 1.18) 2 years after the surgery, 1.03 (0.31, 1.74) 4 years after the surgery. The CDA group gained better arm pain scores than the ACDF group 1, 2, 4 years after the surgery ( $P < 0.01$ ) (Figs. 2, 3, 4).

VAS neck pain score

Fifteen studies including 2,265 patients (1,203 patients from the CDA group and 1,062 patients from the ACDF group) have reported Visual analog scale (VAS) neck pain scores at different time points after the surgical treatment. The mean difference between groups is 0.96 (0.44–1.47) a year after the surgery, 0.96 (0.38, 1.55) 2 years after the surgery, 1.47 (0.78,

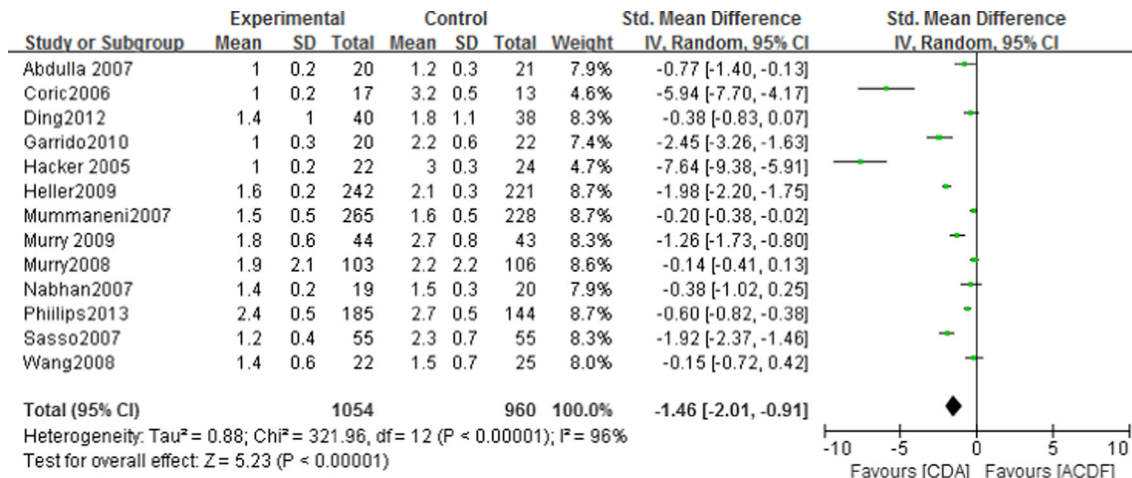


Fig. 2 VAS arm pain score at 1 year postoperatively

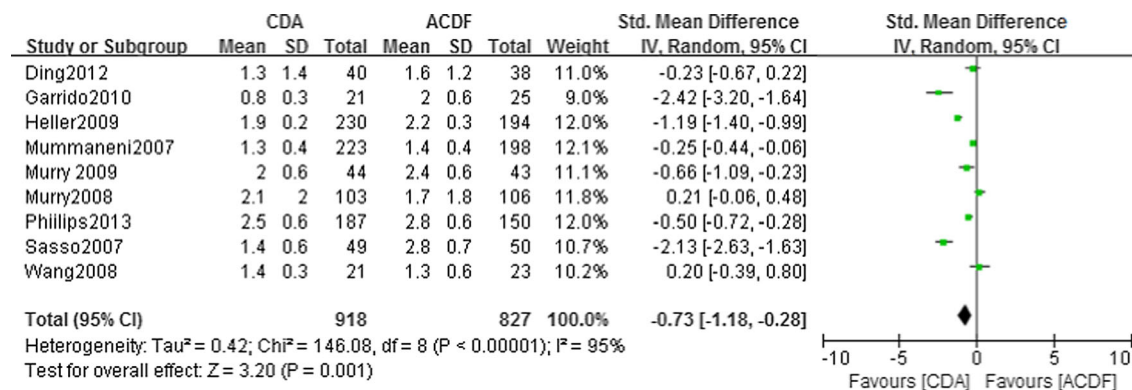


Fig. 3 VAS arm pain score at 2 years postoperatively

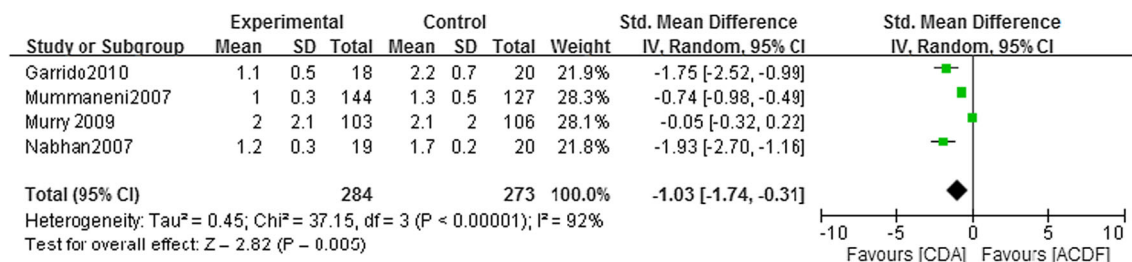
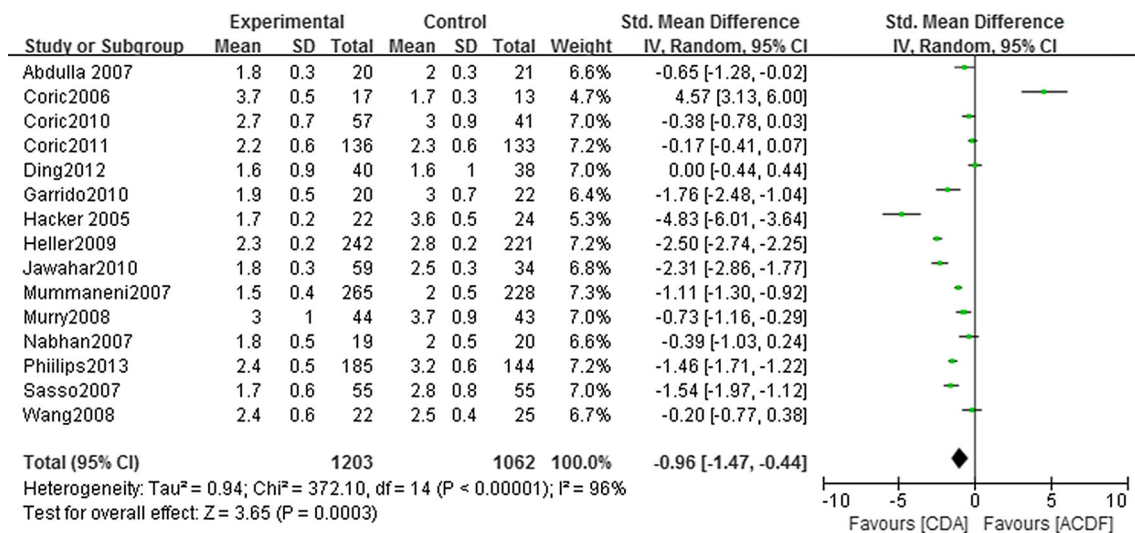
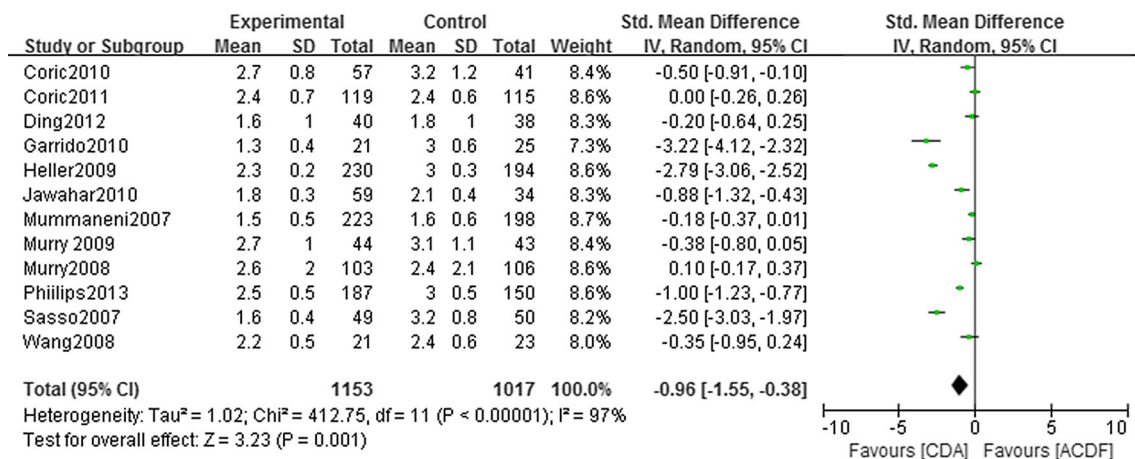


Fig. 4 VAS arm pain score at 4 years postoperatively



**Fig. 5** VAS neck pain score at 1 year postoperatively



**Fig. 6** VAS neck pain score at 2 years postoperatively

2.15) 4 years after the surgery. The CDA group gained better neck pain scores than the ACDF group 1, 2, 4 years after the surgery ( $P < 0.01$ ) (Figs. 5, 6, 7).

#### ROM of the adjacent level

Seven studies including 1,404 patients (740 patients from the CDA group and 664 patients from the ACDF group) have reported ROM of the adjacent level at different time points after the surgical treatment. The mean difference between the groups is 2.55 (0.77–4.32) a year after the surgery and 3.08 (1.35, 4.82) 2 years after the surgery. The CDA group gained better ROM of the adjacent level than the ACDF group 1 and 2 years after the surgery ( $P < 0.01$ ) (Figs. 8, 9).

#### NDI score

Eleven studies including 1,810 patients (964 patients from the CDA group and 846 patients from the ACDF group) have reported NDI score at different time points after the surgical treatment. The mean difference between the groups is 0.8 (0.26–1.34) a year after the surgery, 2.97 (0.85, 5.09) 2 years after the surgery and 1.11 (0.35, 1.87) 4 years after the surgery. The CDA group gained better NDI score than the ACDF group 1, 2, 4 years after the surgery ( $P < 0.01$ ) (Figs. 10, 11, 12).

#### SF36-PCS score

Nine studies including 1,679 patients (890 patients in the CDA group and 786 patients in the ACDF group) have

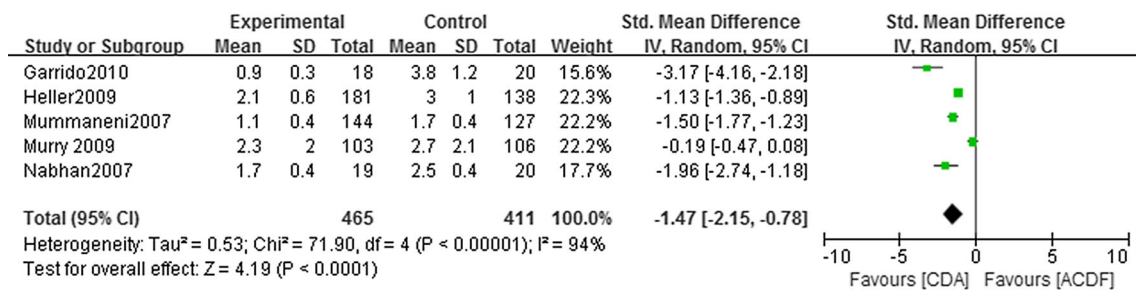


Fig. 7 VAS neck pain score at 4 years postoperatively

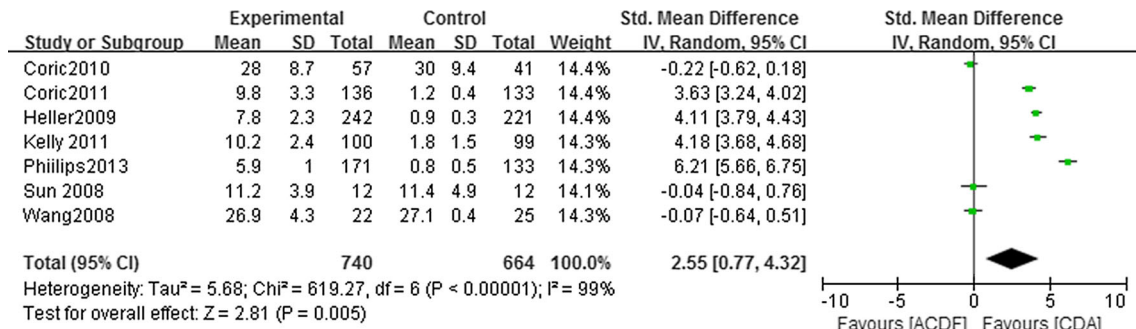


Fig. 8 ROM of the adjacent level at 1 year postoperatively

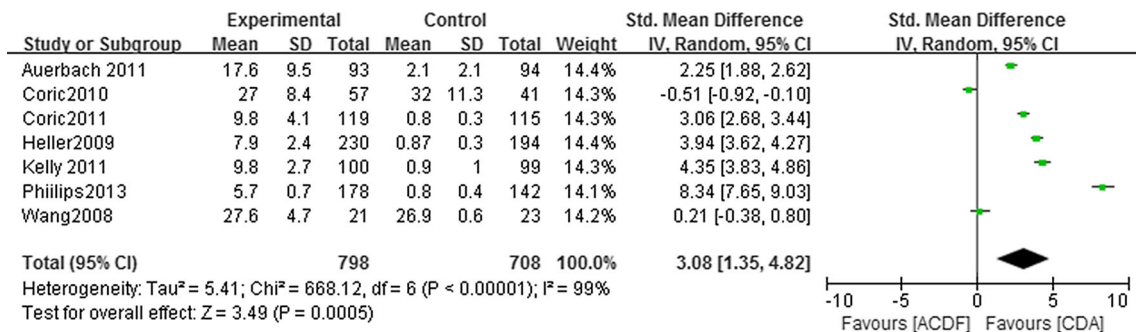


Fig. 9 ROM of the adjacent level at 2 years postoperatively

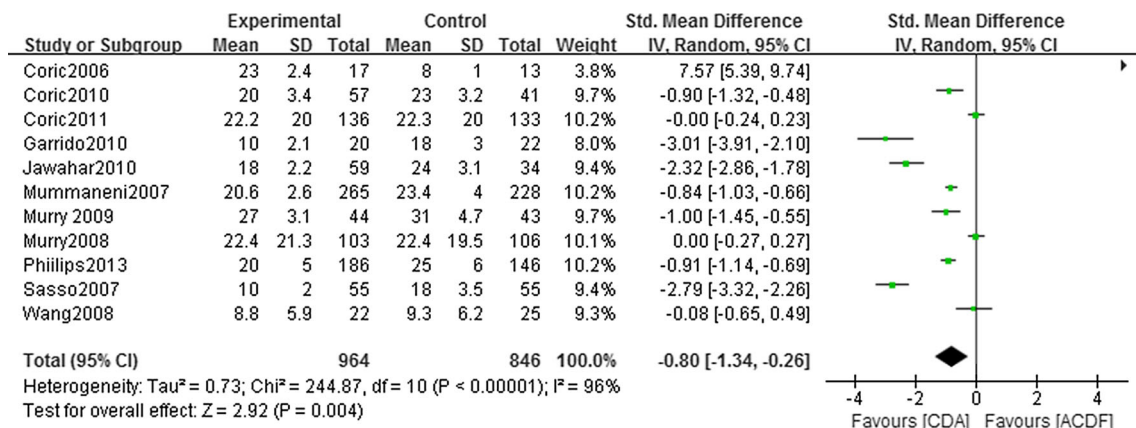


Fig. 10 NDI score at 1 year postoperatively

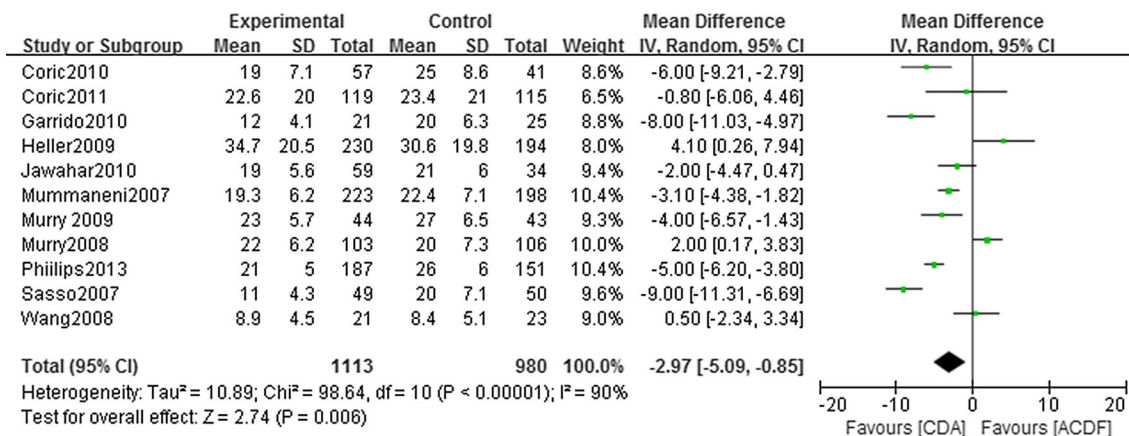


Fig. 11 NDI score at 2 years postoperatively

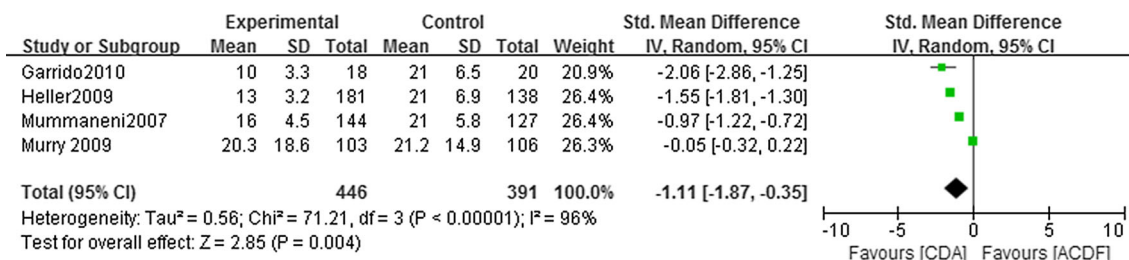


Fig. 12 NDI score at 4 years postoperatively

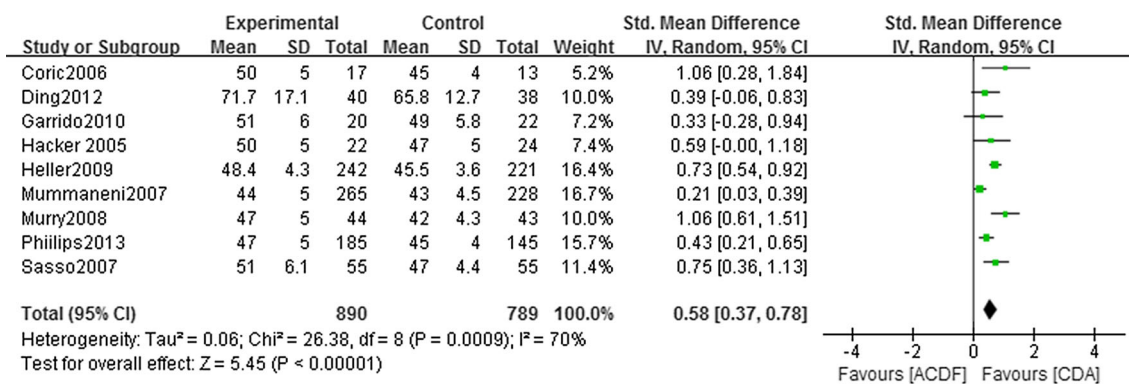


Fig. 13 SF36-PCS score at 1 year postoperatively

reported SF36-PCS score at different time points after the surgical treatment. The mean difference between the groups is 0.58 (0.37–0.78) a year after the surgery, 0.32 (0.19, 0.46) 2 years after the surgery and 0.13 (–0.36, 0.61) 4 years after the surgery. The CDA group gained better SF36-PCS score than the ACDF group 1 and 2 years after the surgery (P < 0.01), but has no significant difference 4 years after the surgery (Figs. 13, 14, 15).

SF36-MCS score

Nine studies including 1,679 patients (890 patients in the CDA group and 786 patients in the ACDF group) have reported SF36-MCS score at different time points after the surgical treatment. The mean difference between the groups is 0.52 (0.32–0.72) a year after the surgery, 0.05 (–0.09, 0.20) 2 years after the surgery and 0.67

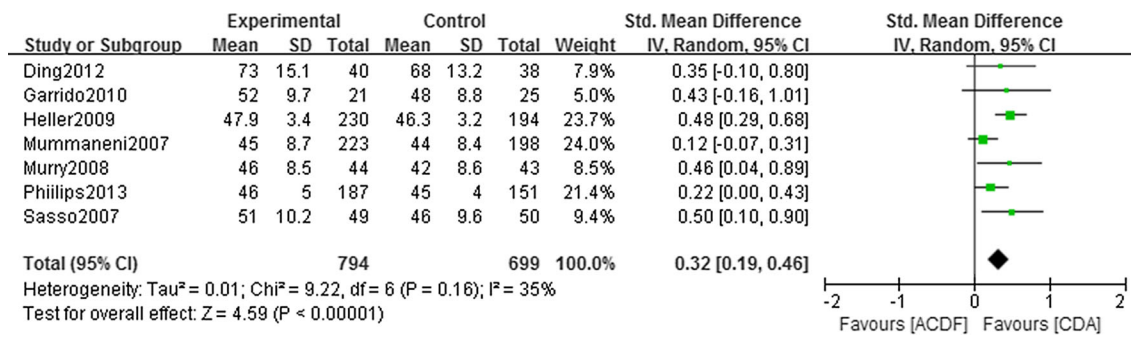


Fig. 14 SF36-PCS score at 2 years postoperatively

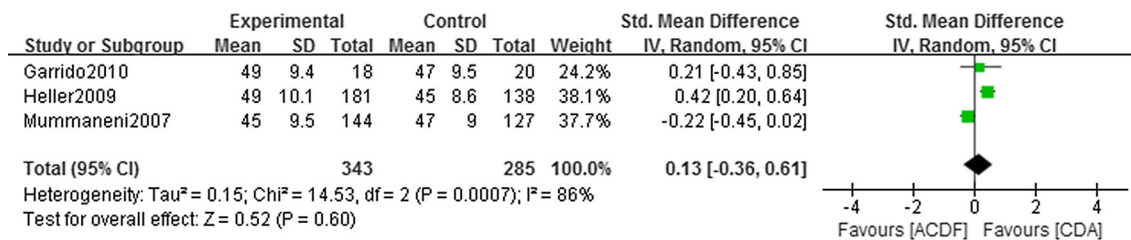


Fig. 15 SF36-PCS score at 4 years postoperatively

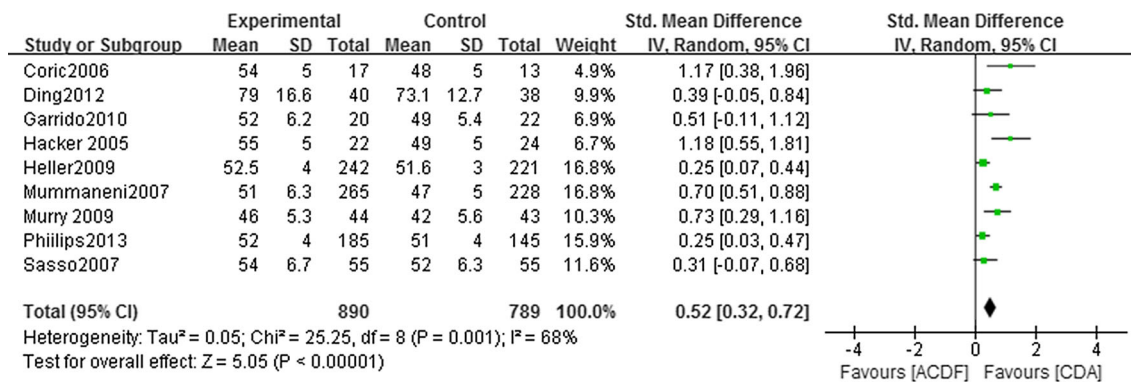


Fig. 16 SF36-MCS score at 1 year postoperatively

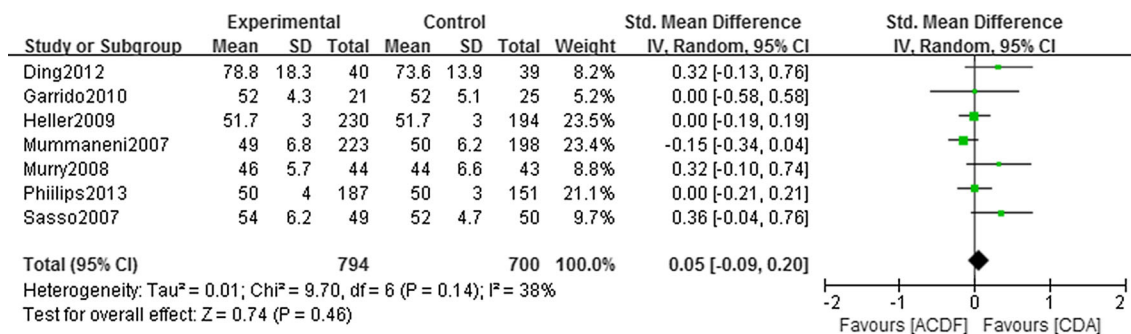


Fig. 17 SF36-MCS score at 2 years postoperatively

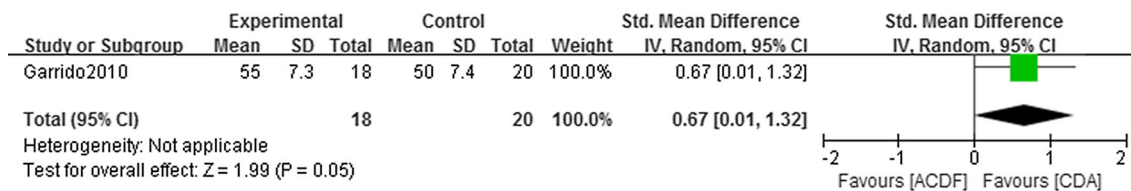


Fig. 18 SF36-MCS score at 4 years postoperatively

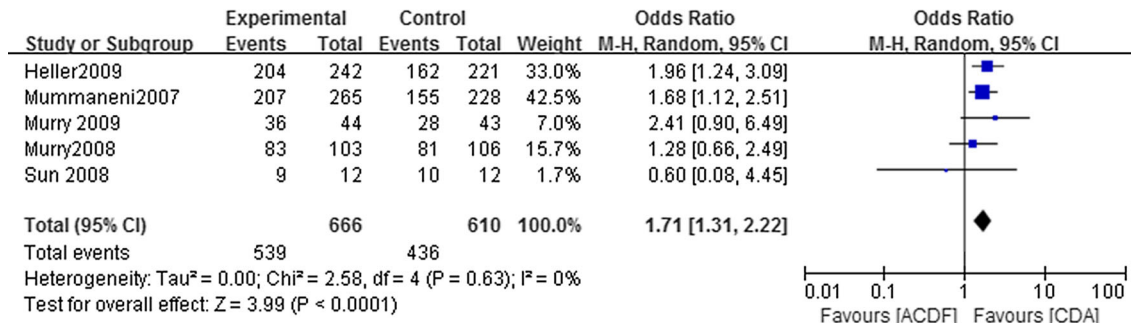


Fig. 19 Patient satisfaction at 1 year postoperatively

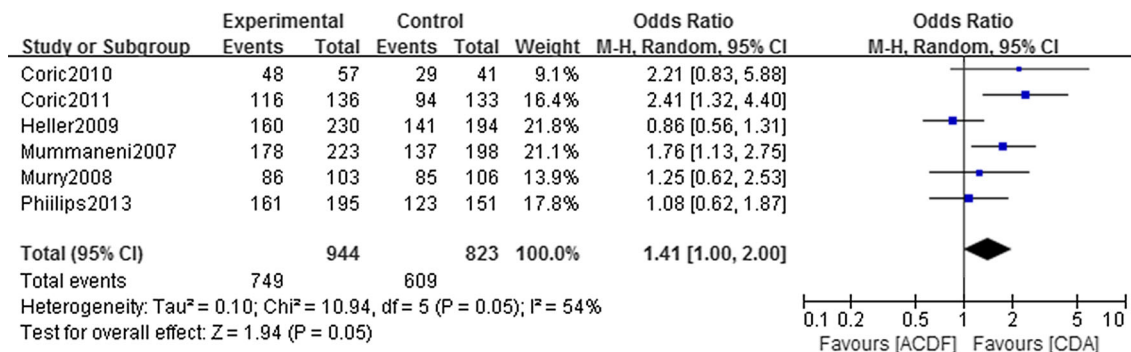


Fig. 20 Patient satisfaction at 2 years postoperatively

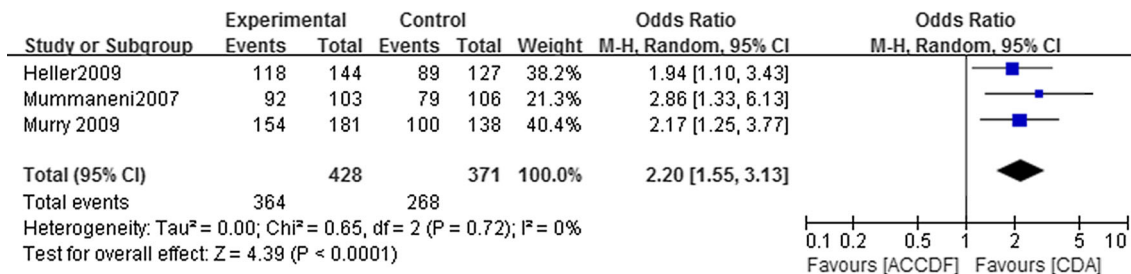


Fig. 21 Patient satisfaction at 4 years postoperatively

(0.01–1.32) 4 years after the surgery. The CDA group gained better SF36-MCS score than the ACDF group 1 (P < 0.01) and 4 years (P = 0.05) after the surgery, but has no significant difference 2 years after the surgery (Figs. 16, 17, 18).

*Patient satisfaction*

Six studies including 1,667 patients (944 patients in the CDA group and 823 patients in the ACDF group) have reported patient satisfaction rates at different time points after the



surgical treatment. The Odds ratio is 1.71 (1.31–2.22) a year after the surgery, 1.41 (1.00, 2.00) 2 years after the surgery and 2.20 (1.55–3.13) 4 years after the surgery. The CDA group gained better patient satisfaction rates than the ACDF group 1 ( $P < 0.01$ ), 4 ( $P = 0.05$ ) and 4 ( $P < 0.01$ ) years after the surgery (Figs. 19, 20, 21).

## Discussion

The first part of surgical procedure for both ACDF and CDA is rather similar: the discectomy. In fusion, autograft material is placed in the disk space after the interposition of a cage which followed by the plate and screw fixation. In arthroplasty, only the movable disk prosthesis is implanted intervertebrally. Although the procedure of CDA may take a little longer and more traumatic than that of ACDF, there are similar surgical risks such as esophageal, vertebral arterial and neural injuries [24].

The current meta-analysis included more studies, has larger number of patients, and applied subgroups, sensitivity analysis to avoid bias caused by heterogeneity, which makes its results more reliable.

In our meta-analysis, we have applied the random-effects model as it can account for both within- and among-trial variability. A possible advantage of applying the random-effects model is that it tends to equalize the weights of trials in different sizes and has wider CIs as the estimated trial heterogeneity can be another origin of uncertainty. Therefore, random-effects model has more conservative results than those in the fixed-effects model [25].

The conclusions of our study are limited by the fact that a complete meta-analysis was not possible. Although we performed a meta-analysis on some variables, the inconsistencies of reported data made pooling of our data impossible at times. Moreover, the lack of patient homogeneity and the presence of confounding factors limited our ability to perform meta-analyses on the entire group. The inability to differentiate treatment options based on the fracture pattern also limited our study.

Bias in the assignment of quality scores is another possible limitation of this study. We attempted to minimize potential bias with the use of predetermined inclusion and exclusion criteria, standard evaluation forms, two reviewers and a blinded statistician.

This meta-analysis indicates that CDA can be an effective alternative to ACDF for the treatment of symptomatic cervical spondylosis. Future studies should include the use of more large multicenter randomized trials to overcome the limitations of small patient populations and low-quality study data currently present in the literature.

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**Conflict of interest** None.

## References

1. Cloward RB (1958) The anterior approach for removal of ruptured cervical disks. *J Neurosurg* 15:602–617
2. Smith GW, Robinson RA (1958) The treatment of certain cervical-spine disorders by anterior removal of the intervertebral disc and interbody fusion. *J Bone Joint Surg Am* 40-A:607–624
3. Murrey D, Janssen M, Delamarter R et al (2009) Results of the prospective, randomized, controlled multicenter Food and Drug Administration investigational device exemption study of the ProDisc-C total disc replacement versus anterior discectomy and fusion for the treatment of 1-level symptomatic cervical disc disease. *Spine J* 9:275–286
4. Heller JG, Sasso RC, Papadopoulos SM et al (2009) Comparison of BRYAN cervical disc arthroplasty with anterior cervical decompression and fusion. *Spine* 34:101–107
5. Furlan AD, Pennick V, Bombardier C, van Tulder M (2009) updated method guidelines for systematic reviews in the Cochrane Back Review Group. *Spine (Phila Pa 1976)* 34(18):1929–1941
6. Nabhan A, Ahlhelm F, Shariat K, Pitzen T, Steimer O, Steudel W-I, Pape D (2007) The ProDisc-C Prosthesis: clinical and radiological experience 1 year after surgery. *Spine* 32:1935–1941
7. Kelly MP, Mok JM, Frisch RF, Tay BK (2011) Adjacent segment motion after anterior cervical discectomy and fusion versus ProDisc-C cervical total disk arthroplasty. *Spine* 36:1171–1179
8. Murrey D, Janssen M, Delamarter R, Goldstein J, Zigler J, Tay B, Darden B (2009) Results of the prospective, randomized, controlled multicenter Food and Drug Administration investigational device exemption study of the ProDisc-C total disc replacement versus anterior discectomy and fusion for the treatment of 1-level symptomatic cervical disc disease. *Spine J* 9:275–286
9. Sun P-F, Jia Y-H (2008) Cervical disc prosthesis replacement and interbody fusion- a comparative study. *Int Orthop SICOT* 32:103–106
10. Coric D, Finger F, Bolles P (2006) Prospective randomized controlled study of the Bryan Cervical Disc: early clinical results from a single investigational site. *J Neurosurg Spine* 4:31–35
11. Hacker RJ (2005) Cervical disc arthroplasty: a controlled randomized prospective study with intermediate follow-up results. *J Neurosurg Spine* 3:424–428
12. Garrido BJ, Taha TA, Sasso RC (2010) Clinical outcomes of Bryan cervical disc arthroplasty a prospective, randomized, controlled, single site trial with 48-month follow-up. *J Spinal Disord Tech* 23:367–371
13. Wang Y, Cai B, Zhang X, Xiao S, Wang Z, Lu N (2008) Clinical outcomes of single level Bryan cervical disc arthroplasty: a prospective controlled study. *Chin J Surg* 46:328–332
14. Murrey DB, Janssen ME, Odum SM, Gottlieb JR, Spector LR, Darden BV (2008) Two-year results of a randomized controlled clinical trial comparing ProDisc-C and anterior cervical discectomy and fusion. *SAS J* 2:76–85
15. Jawahar A, Cavanaugh DA, Kerr EJ III, Birdsong EM, Nunley PD (2010) Total disc arthroplasty does not affect the incidence of adjacent segment degeneration in cervical spine: results of 93 patients in three prospective randomized clinical trials. *Spine J* 10:1043–1048
16. Coric D, Cassis J, Carew JD, Boltes MO (2010) Prospective study of cervical arthroplasty in 98 patients involved in 1 of 3 separate

- investigational device exemption studies from a single investigational site with a minimum 2-year follow-up. *J Neurosurg Pediatr* 13:715–721
17. Sasso RC, Smucker JD, Hacker RJ, Heller JG (2007) Artificial disc versus fusion a prospective, randomized study With 2-year follow-up on 99 patients. *Spine* 32:2933–2940
  18. Auerbach JD, Anakwenze OA, Milby AH, Lonner BS, Balderston RA (2011) Segmental contribution toward total cervical range of motion a comparison of cervical disc arthroplasty and fusion. *Spine* 36:1593–1599
  19. Nabhan A, Ishak B, Steudel W, Ramadhan S, Steimer O (2011) Assessment of adjacent-segment mobility after cervical disc replacement versus fusion: RCT with 1 year's results. *Eur Spine J* 20:934–941
  20. Coric D, Nunley PD, Guyer RD, Musante D, Carmody CN (2011) Prospective, randomized, multicenter study of cervical arthroplasty: 269 patients from the Kineflex|C artificial disc investigational device exemption study with a minimum 2-year follow-up. *J Neurosurg Spine* 15:348–358
  21. Phillips FM, Lee JYB, Geisler FH, Cappuccino A, Chaput CD (2013) A prospective, randomized, controlled clinical investigation comparing PCM cervical disc arthroplasty with anterior cervical discectomy and fusion. *Spine* 38:907–918
  22. Ding C, Liu H, Hu T, Shi R, Li T, Geng Q, Hong Y (2012) Clinical outcomes of Prestige LP cervical disc replacement a prospective controlled single site trail with 24-month follow up. *Chin J Orthop* 32:32–38
  23. Mummaneni PV, Burkus JK, Haid RW, Traynelis VC, Zdeblick TA (2007) Clinical and radiographic analysis of cervical disc arthroplasty compared with allograft fusion: a randomized controlled clinical trial. *J Neurosurg Spine* 6:198–209
  24. Bertagnoli R, Yue JJ, Pfeiffer F, Fenk-Mayer A, Lawrence JP, Kershaw T, Nanieva R (2005) Early results after ProDisc-C cervical disc replacement. *J Neurosurg Spine* 2:403–410
  25. Ponnuraja C (2010) An empirical investigation of meta-analysis using randomized controlled clinical trials in a particular centre. *Appl Quant Methods Med* 5:166–175



# Surgery with disc prosthesis versus rehabilitation in patients with low back pain and degenerative disc: two year follow-up of randomised study

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## ABSTRACT

**Objective** To compare the efficacy of surgery with disc prosthesis versus non-surgical treatment for patients with chronic low back pain.

**Design** A prospective randomised multicentre study.

**Setting** Five university hospitals in Norway.

**Participants** 173 patients with a history of low back pain for at least one year, Oswestry disability index of at least 30 points, and degenerative changes in one or two lower lumbar spine levels (86 patients randomised to surgery). Patients were treated from April 2004 to September 2007.

**Interventions** Surgery with disc prosthesis or outpatient multidisciplinary rehabilitation for 12-15 days.

**Main outcome measures** The primary outcome measure was the score on the Oswestry disability index after two years. Secondary outcome measures were low back pain, satisfaction with life (SF-36 and EuroQol EQ-5D), Hopkins symptom check list (HSCL-25), fear avoidance beliefs (FABQ), self efficacy beliefs for pain, work status, and patients' satisfaction and drug use. A blinded independent observer evaluated scores on the back performance scale and Prolo scale at two year follow-up.

**Results** The study was powered to detect a difference of 10 points on the Oswestry disability index between the groups at two years. At two years there was a mean difference of -8.4 points (95% confidence interval -13.2 to -3.6) in favour of surgery. In the analysis of prespecified secondary outcomes, there were significant differences in favour of surgery for low back pain (mean difference -12.2, -21.3 to -3.1), patients' satisfaction (63% (n=46) v 39% (n=26)), SF-36 physical component score (mean difference 5.8, 2.5 to 9.1), self efficacy for pain (mean difference 1.0, 0.2 to 1.9), and the Prolo scale (mean difference 0.9, 0.1 to 1.6). There were no significant differences in return to work, SF-36 mental component score, EQ-5D, fear avoidance beliefs, Hopkins symptom check list, drug use, and the back performance scale. One serious complication of leg amputation occurred during surgical revision of a polyethylene dislodgement. The drop-out rate was 20% (34) and the crossover rate was 6% (5).

**Conclusions** Surgical intervention with disc prosthesis for chronic low back pain resulted in a significantly greater improvement in the Oswestry score compared with rehabilitation, but this improvement did not clearly exceed the prespecified minimally important clinical difference between groups of 10 points, and the data are consistent with a wide range of differences between the groups, including values well below 10 points. The potential risks of surgery and the substantial amount of improvement experienced by a sizeable proportion of the rehabilitation group also have to be incorporated into overall decision making.

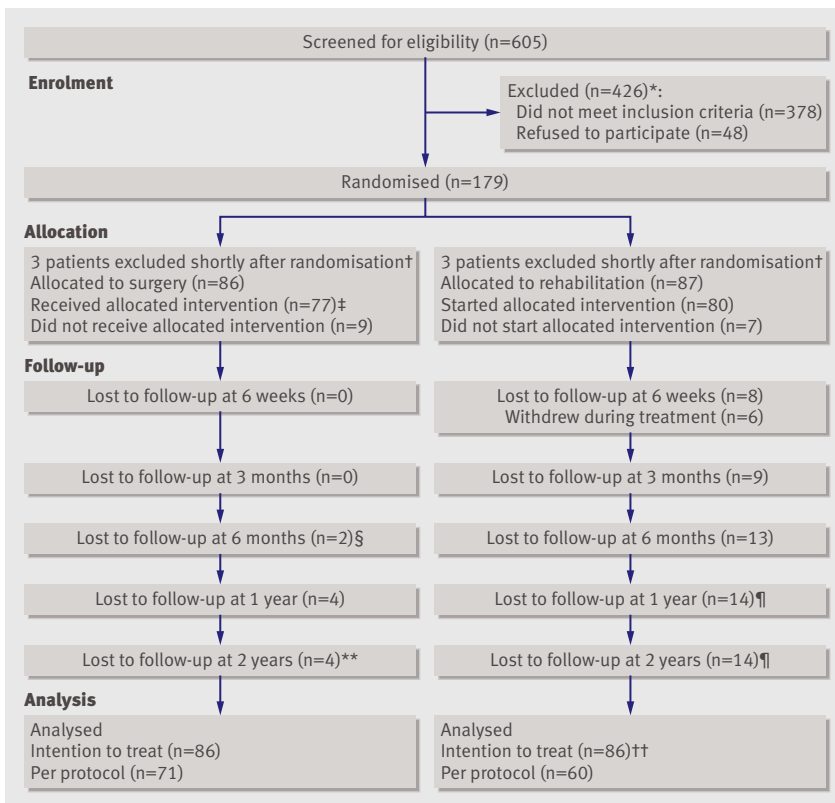
**Trial registration** www.clinicaltrial.gov NCT 00394732.

## INTRODUCTION

Low back pain is common with a lifetime prevalence of about 59-84%.<sup>1</sup> Although relatively few patients develop chronic low back pain with disability, it represents extensive individual, societal, and financial problems. In patients who have had longstanding or serious disabling low back pain in the previous 12 months, a third will improve and have less serious problems during the following year.<sup>2</sup> Most patients who develop chronic low back pain, however, stay in this condition for years.

Fusion of assumed symptomatic segments in patients with chronic low back pain has been used widely, but randomised studies comparing fusion with non-surgical treatment indicate that a rehabilitation programme can be as effective as surgery. Four randomised studies have compared lumbar fusion with non-operative treatment.<sup>3-7</sup> Fritzell et al found that fusion significantly reduced pain and disability compared with usual care.<sup>3</sup> Brox et al and Fairbank et al compared fusion with a multidisciplinary rehabilitation programme focusing on cognitive intervention and supervised exercise.<sup>4-7</sup> They found similar improvement in pain and disability in the two intervention groups.

During the past 25 years, insertion of a disc prosthesis has become an option. In the four published



**Fig 1** | Enrolment, randomisation, and follow-up of study patients, showing cumulative values at two years. \*Not enough degenerative change to satisfy inclusion criteria (n=29), degenerative changes in more than two lower lumbar discs (n=80), Oswestry disability index score too low (n=88), did not want to undergo surgery (n=28), did not want to participate in rehabilitation (n=20), too much general pain (n=20), had previously been through similar training programme (n=26), and other reasons (n=135; deformity, psoriasis arthritis, language problems, coccygodynia, age, fracture, previous operation, tumour, spondylodiscitis, hip arthrosis). †Coronary heart disease and heart attack some days after randomisation (n=1); obvious exclusion criterion discovered some days after randomisation (n=50; earlier large abdominal operation (n=1), not enough degenerative change to satisfy inclusion criteria (n=2), degenerative changes in more than two lower lumbar discs (n=2). ‡One patient received one of two disc prostheses because of bleeding. §One patient with serious vascular complication underwent secondary leg amputation and was lost to follow-up. ¶One patient crossed over between 6 months and 1 year and five patients between 1 year and 2 years. Five patients underwent surgery with disc prosthesis and one patient with fusion. \*\*Two patients underwent surgery with instrumented fusion before two year follow-up. ††One patient excluded because of missing baseline values and follow-up values

randomised studies comparing disc prosthesis with fusion, the clinical outcome of disc prosthesis was at least equivalent to that of fusion.<sup>8-11</sup> As surgical procedures should be evaluated against non-surgical methods,<sup>12,13</sup> we compared the efficacy of disc prosthesis and a multidisciplinary rehabilitation programme.

## METHODS

### Study design

A multicentre study conducted at five university hospitals in Norway included patients with low back pain and degenerative discs. Patients were included in the period between April 2004 and May 2007 and were treated within three months after randomisation. They were randomised in blocks with a website hosted by the medical faculty. Allocation was concealed for all people involved in the trial. A coordinating secretary

not involved in the treatment could access randomisation details on the internet. The patient and the treating unit were informed about the allocation shortly after randomisation. Randomisation was stratified by centre (the five university hospitals) and whether the patient had had previous surgery (microsurgical decompression) or not. Independent observers collected and entered data. Storage of data was allowed by the Norwegian data inspectorate.

### Participants

Patients were referred from all health regions in Norway. They were recruited from local hospitals or primary care to their nearest university hospital as usual without any supplemental recruitment attempt. An orthopaedic surgeon and a specialist in physical medicine and rehabilitation examined the patients before enrolment. All patients were informed about the procedures and told that neither of the treatment methods was documented as superior to the other. Eligible patients were aged 25-55 and had low back pain as the main symptom for at least a year, structured physiotherapy or chiropractic treatment for at least six months without sufficient effect, a score of at least 30 on the Oswestry disability index, and degenerative intervertebral disc changes in L4/L5 or L5/S1, or both. Degeneration had to be restricted to the two lower levels. We evaluated the following degenerative changes: at least 40% reduction of disc height,<sup>14</sup> Modic changes type I or II, or both,<sup>15</sup> high intensity zone in the disc,<sup>16</sup> and morphological changes classified as changes in signal intensity in the disc of grade 3 or 4.<sup>17</sup> The disc was classified as degenerative if the first criterion alone or at least two changes were found on magnetic resonance imaging. The discs were independently classified by two observers (orthopaedic surgeon/radiologist). When there was disagreement, a third observer classified the images and the outcome was decided by simple majority.

Degeneration of the facet joints was not an exclusion criterion, but symptoms of nerve root involvement were. Details of further inclusion and exclusion criteria, compliance with randomisation, and drop-outs are listed in the appendix 1 on [bmj.com](http://bmj.com).

### Study interventions

**Rehabilitation**—The rehabilitation was based on the treatment model described by Brox et al<sup>4</sup> and consisted of a cognitive approach and supervised physical exercise. A team of physiotherapists and specialists in physical medicine and rehabilitation directed the multidisciplinary treatment. Other specialists, such as psychologists, nurses, social workers, etc, could complete the team. The intervention was standardised through three seminars and videos and lecture sessions for the treatment providers before the study. The intervention was organised as an outpatient treatment in groups at the involved university hospitals and lasted for about 60 hours over three to five weeks. The treatment consisted of lectures and individual discussions focusing on relevant topics (such as anatomy and the

**Table 1** | Baseline characteristics in patients with low back pain and degenerative disc randomised to disc prosthesis surgery or rehabilitation. Figures are numbers (percentage) unless stated otherwise

	Surgery (n=86)	Rehabilitation (n=86)
Mean (SD) age (years)	41.1 (7.1)	40.8 (7.1)
Women	40 (47)	51 (59)
Mean (SD) duration of back pain (months)	76 (72)	85 (74)
Education:		
Primary school (9 years)	19 (22)	17 (20)
High school (12 years)	44 (51)	58 (67)
College	14 (16)	8 (9)
University	9 (11)	3 (4)
Mean (SD) body mass index (BMI)	25.6 (3.1)	25.5 (3.5)
Current smokers	42 (49)	37 (43)
Work status (working v not working):		
Working (includes part time sick leave)	24 (28)	22 (26)
On sick leave	25 (29)	34 (41)
Rehabilitation	29 (34)	25 (29)
Disability pension	3 (4)	0
Homemaker	0	2 (2)
Unemployed	1 (1)	0
Student	3 (4)	0
Unknown	1 (1)	3 (4)
Comorbidity	20 (23)	21 (24)
Daily consumption of narcotics	23 (27)	17 (20)
Previous surgery	23 (27)	25 (29)
Mean (SD) ODI score	41.8 (9.1)	42.8 (9.3)
Low back pain score*	64.9 (15.3)	73.6 (13.9)
Mean (SD) SF-36 score:		
Physical function	52.7 (17.6)	50.6 (17.7)
Role physical	25.3 (24.2)	23.9 (18.7)
Bodily pain	24.9 (16.5)	24.4 (12.1)
General health	57.9 (19.7)	55.9 (19.9)
Vitality	37.8 (20.2)	33.1 (19.9)
Social function	53.0 (30.6)	57.6 (26.7)
Role emotion	72.5 (33.3)	67.6 (32.7)
Mental health	71.7 (18.0)	65.8 (18.9)
Physical component summary score	30.5 (7.1)	30.8 (6.5)
Mental component summary score	47.7 (13.0)	45.2 (13.2)
Mean (SD) HSCL-25	1.8 (0.5)	1.9 (0.5)
Mean (SD) FABQ work	25.9 (11.3)	27.4 (9.9)
Mean (SD) FABQ physical	14.1 (5.8)	12 (5.5)

ODI=Oswestry disability index (0 to 100, lower scores indicate less severe symptoms); SF-36=short form-36 (0 to 100, higher scores indicate better health status); HSCL-25=Hopkins symptom check list (for emotional distress, scores range from 1 to 4, lower scores indicate less severe symptoms); FABQ=fear avoidance belief questionnaire (scale ranges from 0 to 24 (physical) and from 0 to 42 (work), lower scores indicate less severe symptoms).

\*Calculated with horizontal scale ranging from 0 (no pain) to 100 (worst pain imaginable), with word anchors at the beginning and end.

physiological aspects of the back, diagnostics, imaging, pain medicine, normal reactions, coping strategies, family and social life, and working conditions), daily workouts for increased physical capacity (endurance, strength, coordination, and specific training of the abdominal muscles and the lumbar multifidus muscles), and challenging patients' thoughts about, and participation in, physical activities previously labelled as not recommended (such as lifting, jumping, vacuum

cleaning, dancing, and ball games). Follow-up consultations were conducted at six weeks, three months, six months, and one year after the intervention. See appendix 2 on [bmj.com](http://bmj.com) for detailed description of the rehabilitation intervention.

**Surgery**—The surgical intervention consisted of replacement of the degenerative intervertebral lumbar disc with an artificial lumbar disc (ProDisc II, Synthes Spine). The ProDisc consists of three pieces: two metal endplates of cobalt chromium molybdenum alloy and a core (made from ultrahigh molecular weight polyethylene) fixed to the inferior endplate after insertion. Surgeons used a Pfannenstiel or a para-median incision with a retroperitoneal approach. A nearly complete discectomy was performed with removal of the cartilaginous endplates and a sufficient release of the posterior longitudinal ligament to ensure disc space mobilisation. A fluoroscope was used to ensure that the prosthesis was placed in the midline and sufficiently towards the posterior edge of the vertebrae. All hospitals participating in the study used the same artificial lumbar disc device. One surgeon at each centre had main responsibility for the operation (five centres and five surgeons). Surgeons were required to have inserted at least six disc prostheses before performing surgery in the study. There were no major postoperative restrictions. Patients were not referred for postoperative physiotherapy, but at six weeks' follow-up they could be referred for physiotherapy if required, emphasising general mobilisation and non-specific exercises.

### Outcome measures

The primary outcome measure was pain and disability measured with version 2.0 of the Oswestry disability index,<sup>18</sup> translated into Norwegian and tested for psychometric properties by Grotle et al.<sup>19</sup> (Scores range from 0 to 100, with lower score indicating less severe pain and disability.) Secondary outcomes included low back pain (measured with a visual analogue scale, ranging from 0 (no pain) to 100 (worst pain imaginable)) and general health status assessed with SF-36 (scores range from 0 to 100, higher scores correspond to better health status)<sup>20,21</sup> and EQ-5D (scores range from -0.59 to 1 (1 equals perfect health)).<sup>22</sup> For psychological variables we included emotional distress (Hopkins symptom check list (HSCL-25), scores range from 1 to 4, with lower scores indicating less severe symptoms) and the fear avoidance belief questionnaire (FABQ) for work and physical activity (scores range from 0 to 42 (work) and from 0 to 24 (physical), with lower scores indicating less severe symptoms).<sup>23,24</sup> Self efficacy beliefs for pain were registered by a subscale of the arthritis self efficacy scale (scores range from 1 to 10 and are summarised and divided by 5; lower scores indicate uncertainty in managing the pain).<sup>25</sup> Work status was evaluated as suggested by Fritzell et al.<sup>3</sup> (See table A in appendix 3 on [bmj.com](http://bmj.com).) We calculated a net back to work rate, subtracting patients who went back to work from patients who stopped working, satisfaction with the result of the treatment on a seven point

**Table 2** | Treatment and complications in 77 patients with low back pain and degenerative disc randomised to disc prosthesis surgery

Variable	Surgery group
No (%) by level of operation:	
L4/L5	17 (22)
L5/S1	35 (46)
L4/L5 and L5/S1	25 (33)
Median (range) operative time (min)	165 (72-570)
Median (range) blood loss (ml)	310 (50-6000)
Mean (SD) length of hospital stay (days)	7.2 (3.6)
No with complications:	
Intimal lesion in left common iliac artery*	1
Arterial thrombosis of dorsalis pedis artery†	1
Dural tear	0
Blood loss >1500 ml	4
Retrograde ejaculation (at one year)	1‡
Abdominal hernia	1
Superficial haematoma	1
Ileus	1
Temporary warm left foot	2
Temporary nausea at one year follow-up	1
Neurological deterioration:	
Motor deficit at two year follow-up	0
Temporary motor deficit	0
Sensory loss at two year follow-up	2
Temporary sensory loss	4
Radicular pain at two year follow-up	2
Temporary radicular pain	4
Infection:	
Superficial wound infection	0
Deep wound infection	0
Urinary tract infection	0
Total No (%) complications during two year follow-up	26 (34)
Additional spinal surgery within 2 years:	
Fusion	2§
Other	2¶

\*Repeat surgery with insertion of new polyethylene inlay.  
 †Associated with temporary slightly colder foot at follow-up.  
 ‡One patient reported retrograde ejaculation at baseline but not at one year follow-up, one at baseline and at follow-up, and one at follow-up but without baseline information.  
 §Fusion at level with disc prosthesis and level above.  
 ¶Resection of spinous process because of possible painful contact between adjacent levels.

Likert scale, and satisfaction with care on a five point Likert scale.<sup>26</sup> Further daily consumption of drugs was registered. Patients attended for follow-up visits at six weeks, three and six months, and one and two years (the main end point of follow-up was at two years). At two years we sent a questionnaire including the most important outcome measures to 29 of the 34 patients who were lost to follow-up (see table B in appendix 3 on bmj.com).

At the two year follow-up, two independent observers blinded to treatment evaluated patients using the back performance scale (consists of five tests with a score ranging from 0 to 15, worst possible)<sup>27</sup> and the Prolo scale (consists of functional and economic parts, which are summed to a worst score of 2 and a best score

of 10).<sup>28</sup> Patients were informed before this session not to reveal the treatment received, and had tape placed on their abdominal wall to hide the scarring from the operation. We also carried out a full health economic analysis, which will be reported elsewhere.

**Statistical considerations**

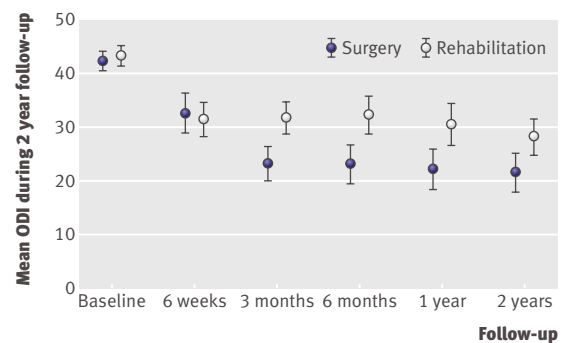
The trial was designed to have 80% power to detect a significant difference of at least 10 points in change in the mean Oswestry disability index score between the intervention groups at two year follow-up.<sup>5</sup> Baseline standard deviation was estimated at 18.<sup>18</sup> Considering these assumptions and adding 25% for a multicentre study design and 30% for possible drop-outs, we estimated we required 180 patients.

**Planned analyses**

The main statistical analysis was in the intention to treat population at one and two year follow-up. According to our protocol the analysis was performed with the assumption that patients who dropped out had no improvement after drop-out (last value carried forward). We also determined if different centres had different outcomes. We used  $\chi^2$  test or Fisher’s exact test to analyse categorical variables and independent two sided *t* test or analysis of variance to analyse continuous variables. A significance level of 5% was used throughout. All statistical analyses were performed with SPSS version 16.0. We did not adjust for significantly different baseline scores.

**Unplanned analyses (analyses not recorded in the original protocol)**

We conducted a per protocol analysis for the primary outcome variable (score on Oswestry disability index). Consistent with criteria from the Food and Drug Administration,<sup>8</sup> we considered an individual change in score of at least 15 points from baseline to two year follow-up as a minimal important change. A deterioration of 6 points in the score was considered a “change for the worse.”<sup>29</sup> We calculated the number needed to treat with confidence intervals.<sup>30</sup> A mixed model analysis was used to evaluate the effect of each efficacy



**Fig 2** | Primary outcome variable within intention to treat mixed model analysis. Mean difference in Oswestry disability index (ODI) was 6.9 points at two year follow-up, P<0.001 (adjusted for baseline index)

**Table 3** | Planned analysis of primary outcome in patients with low back pain and degenerative disc randomised to disc prosthesis surgery or rehabilitation. Mean (SD) outcome values on Oswestry disability index (ODI) at 12 and 24 months and treatment effect

	Mean outcome		Treatment effect* (95% CI)	P value†
	Surgery	Rehabilitation		
Baseline	41.8 (9.1)	42.8 (9.3)	—	—
1 year	22.3 (17.0)	33.0 (16.6)	-10.0 (-15.0 to -5.0)	<0.001
2 years	21.2 (17.1)	30.0 (16.0)	-8.4 (-13.2 to -3.6)	0.001

ODI=see footnote for table 1 for scale details.

\*Difference between groups in mean change from baseline.

†Two sided *t* test.

variable over time and between groups. In the mixed model patients were not excluded from the analysis of an efficacy variable if the variable was missing at some, but not all, time points after baseline. In the additional analysis (categorical or ordinal data at two year follow-up), missing data were not replaced. Significantly different baseline scores were not adjusted for in the longitudinal model. Each outcome variable was adjusted for the baseline values of the variable.

## RESULTS

Of the 605 patients screened for eligibility, 173 were included in the study and treated between April 2004 and September 2007 (86 with surgery and 87 with rehabilitation) (fig 1). The drop-out rate from inclusion to two year follow-up was 20% (n=34) (15% (n=13) in the surgical arm and 24% (n=21) in the rehabilitation arm). Five patients (6%) crossed over from rehabilitation to surgery, but none crossed from surgery to rehabilitation. Of the 34 patients lost to follow-up, 26 answered a questionnaire two and a half to five years after treatment (see table B in appendix 3 on bmj.com).

### Patients' characteristics

Most baseline characteristics were similar in the two treatment groups (table 1). Low back pain score and SF-36 mental health subscores, however, were significantly worse in the rehabilitation group than in the surgery group.

### Surgical treatment and complications

Of the patients randomised to surgery, 25 (33%) underwent two level surgery. Median surgical time was

165 minutes (range 72-570 minutes) and median blood loss was 310 ml (range 50-6000 ml) (table 2). Four patients had bleeding of more than 1500 ml.

Six patients (8%) had complications resulting in impairment at two year follow-up, and the reoperation rate was 6.5% (n=5) (table 2). One patient had a serious complication: at the three month follow-up, the polyethylene inlay was found to be dislodged. During revision surgery, injury to the left common iliac artery led to compartment syndrome resulting in a lower leg amputation. One patient reported retrograde ejaculation at one year follow-up. At two year follow-up, two patients reported sensory loss in the thigh and two patients reported new radicular pain. In addition, one patient had an arterial thrombosis of the dorsalis pedis artery, which temporarily resulted in a slightly colder foot. Table 2 presents further complications. Two patients had an additional fusion and two patients had partial resection of the spinous processes because of persistent back pain.

### Primary outcome

#### Planned analyses according to protocol

The mean change Oswestry disability index score from baseline to two year follow-up was 20.8 (95% confidence interval 16.4 to 25.2) in the surgery group and 12.4 (8.5 to 16.3) in the rehabilitation group (table 3). The mean treatment effect (difference between groups) at two year follow-up was -8.4 (-13.2 to -3.6) in the intention to treat analysis (last value carried forward). Subgroup analysis showed no differences in the main outcome variable between centres and level(s) operated on.

#### Unplanned analyses

In the mixed model analysis, the Oswestry score improved significantly more in the surgical group than in the rehabilitation group at all time points, in both the intention to treat (fig 2) and per protocol analyses (table 4). The mean change from baseline to two year follow-up was 22.5 (intention to treat) (95% confidence interval 18.5 to 26.4) in the surgery group and 15.6 (intention to treat) (11.7 to 19.5) in the rehabilitation group. The mean treatment effect (difference between groups) at two year follow-up was 6.9 (2.1 to 11.7) in the intention to treat analysis. In an analysis in

**Table 4** | Unplanned analysis of primary outcome in patients with low back pain and degenerative disc randomised to disc prosthesis surgery or rehabilitation. Mean (SD) outcome values on Oswestry disability index (ODI) at follow-up and treatment effect (difference (95% confidence interval)), minus values indicating larger improvement in outcome with surgery

	Intention to treat analysis			Per protocol analysis		
	Surgery	Rehabilitation	Treatment effect	Surgery	Rehabilitation	Treatment effect*
Baseline	41.8 (9.1)	42.8 (9.3)	—	42.2 (9.2)	42.1 (8.3)	—
6 weeks	31.5 (17.2)	30.2 (13.6)	1.3 (-3.5 to 6.1)	31.1 (17.3)	29.6 (13.5)	1.7 (-3.1 to 6.6)
3 months	21.5 (14.1)	30.6 (13.1)	-9.1 (-13.9 to -4.3)	20.7 (13.5)	30.3 (12.7)	-9.5 (-14.4 to -4.6)
6 months	21.4 (16.3)	31.1 (14.9)	-9.7 (-14.6 to -4.8)	20.7 (15.9)	29.9 (14.6)	-9.2 (-14.2 to -4.2)
1 year	20.3 (17.2)	29.2 (16.1)	-8.9 (-13.8 to -4.0)	19.7 (16.4)	27.0 (15.0)	-7.3 (-12.3 to -2.3)
2 years	19.8 (16.7)	26.7 (14.5)	-6.9 (-11.7 to -2.1)	18.8 (15.8)	26.9 (13.9)	-8.1 (-12.9 to -3.2)

ODI=see footnote for table 1 for scale details.

\*All  $P < 0.001$  for trend in treatment effect over time. Two sided *t* test.



**Table 5** | Planned analysis of secondary outcomes in patients with low back pain and degenerative disc randomised to disc prosthesis surgery or rehabilitation. Mean (SD) values at 12 and 24 months (unless stated otherwise) and treatment effect

Variable	Mean outcome		Treatment effect (95% CI)*	P value†
	Surgery	Rehabilitation		
<b>Back pain score‡:</b>				
Baseline	64.9 (15.3)	73.6 (13.9)		
1 year	35.6 (28.6)	53.2 (28.4)	-14.0 (-23.0 to -5.0)	0.003
2 years	35.4 (29.1)	49.7 (28.4)	-12.2 (-21.3 to -3.1)	0.009
<b>SF-36 physical component summary:</b>				
Baseline	30.5 (7.1)	30.8 (6.5)		
1 year	42.8 (12.2)	37.3 (11.0)	5.5 (1.9 to 9.1)	0.003
2 years	43.3 (11.7)	37.7 (10.1)	5.8 (2.5 to 9.1)	0.001
<b>SF-36 mental component summary‡:</b>				
Baseline	47.7 (13.0)	45.2 (13.2)		
1 year	50.2 (12.0)	49.2 (13.2)	0.2 (-3.5 to 3.8)	0.90
2 years	50.7 (11.6)	48.6 (12.8)	1.0 (-2.4 to 4.4)	0.50
<b>EQ-5D:</b>				
Baseline	0.30 (0.27)	0.27 (0.31)		
1 year	0.68 (0.34)	0.55 (0.32)	0.13 (0.01 to 0.25)	0.04
2 years	0.69 (0.33)	0.63 (0.28)	0.06 (-0.05 to 0.18)	0.26
<b>HSCL-25</b>				
Baseline	1.81 (0.50)	1.88 (0.51)		
1 year	1.51 (0.49)	1.67 (0.52)	-0.12 (-0.26 to 0.02)	0.10
2 years	1.50 (0.44)	1.63 (0.52)	-0.10 (-0.23 to 0.04)	0.20
<b>FABQ work:</b>				
Baseline	25.8 (11.2)	27.4 (27.4)		
1 year	19.2 (14.2)	23.1 (13.0)	-2.7 (-6.5 to 1.1)	0.20
2 years	18.1 (13.9)	21.2 (12.8)	-2.1 (-6.0 to 1.7)	0.30
<b>FABQ physical:</b>				
Baseline	14.0 (5.8)	12.5 (5.6)		
1 year	8.8 (6.7)	9.7 (5.8)	-1.3 (-3.2 to 0.6)	0.20
2 years	9.0 (6.8)	9.9 (6.0)	-1.5 (-3.4 to 0.5)	0.10
<b>Self efficacy:</b>				
Baseline	3.4 (1.5)	3.6 (1.6)		
1 year	6.3 (3.3)	5.2 (2.4)	1.2 (0.3 to 2.1)	0.01
2 years	6.1 (2.9)	5.3 (2.5)	1.0 (0.2 to 1.9)	0.02
No (%) returned to work at 2 years§:	21 (31)	15 (23)	—	0.31
No (%) satisfied with outcome at 2 years¶	46 (63)	26 (39)	—	0.005
No (%) satisfied with care at 1 year**	66 (90)	48 (73)	—	0.011
No (%) with drug consumption at 2 years††	16 (22)	14 (18)	—	0.30
Back performance scale at 2 years‡‡	3.2 (3.0)	4.0 (3.0)	-0.8 (-1.8 to 0.2)	0.10
Prolo scale at 2 years§§	7.0 (2.3)	6.1 (1.9)	0.9 (0.1 to 1.6)	0.019

ED-5Q score ranges from -0.59 to 1 (1 equals perfect health); self efficacy beliefs for pain scores ranges from 1 to 10 and are summarised and divided by 5. Lower scores indicate that he/she is very uncertain if he/she is able to manage pain. For other scores see footnote to table 1.

\*Treatment effect is difference between groups in mean change from baseline. Positive value in SF-36, EQ-5D, self efficacy for pain, and Prolo scale and negative values in remaining variables indicate larger improvement in outcome with surgery.

†Two sided t test for continuous variables and Pearson's  $\chi^2$  test for categorical variables.

‡Values not adjusted for significantly different baseline scores.

§Net back to work rate calculated by subtracting patients who went back to work from patients who stopped working.

¶7 point Likert scale (1=completely recovered, 2=much recovered to 7=vastly worsened); slightly improved not included as satisfied with outcome.

\*\*4 point global rating scale, not including slightly satisfied as satisfied with care.

††Use of drugs daily or not.

‡‡Scale comprises five tests with score ranging from 0 to 15 (worst possible).

§§Scale comprises functional and economic parts, summed to give worst score of 2 and best score of 10.

which the patient with lower leg amputation was given worst score in the group, the difference between the groups remained significant ( $P<0.001$ ). Some 70% ( $n=51$ ) of the patients in the surgery group and 47% ( $n=31$ ) of the patients in the rehabilitation group had an improvement in Oswestry score of at least 15 points ( $P<0.006$ ) (intention to treat). The number needed to treat was 4.4 (2.6 to 14.5). Worsening of low back pain was experienced by 11% ( $n=8$ ) of the surgical group and 9% ( $n=6$ ) of the rehabilitation group. Subgroup analysis showed no differences in the main outcome variable between centres and level(s) operated on.

**Secondary outcomes**

*Planned analyses according to protocol*

Low back pain, SF-36 physical summary, and patients' satisfaction improved significantly more in the surgical group than the rehabilitation group at two year follow-up (table 5). The mean difference between the groups in change from baseline to two year follow-up was -12.2 (95% confidence interval -21.3 to -3.1) for low back pain and 5.8 (2.5 to 9.1) for SF-36 physical summary. On the seven point global rating scale at two years, 63% (46) of patients in the surgery group and 39% (26) in the rehabilitation group ( $P=0.005$  for difference between treatment groups) considered themselves completely recovered or much improved. Self efficacy for pain favoured the surgical group. SF-36 mental summary, EQ-5D, FABQ work and physical, HSCL-25, return to work, and drug consumption did not differ at two year follow-up. At the start of the study, 28% (46) of patients were at work full or part time; at two year follow-up, this had increased to 56% ( $n=74$ ). There was a "net back to work" rate of 31% ( $n=21$ ) in the surgical group and 23% ( $n=15$ ) in the rehabilitation group ( $P=0.31$ ) (table 5). Scores on the back performance scale did not differ significantly between the groups (-0.8, -1.8 to 0.2;  $P=0.10$ ). The Prolo sum score favoured the surgical group, with a mean difference of 0.9 (0.1 to 1.6;  $P=0.019$ ).

*Unplanned analyses*

In the mixed model analysis, low back pain (table 6), SF-36 physical summary (table 8), and EQ-5D, HSCL-25, and self efficacy for pain (table 9) improved significantly more in the surgical group than the rehabilitation group at all time points. The mean difference between the groups in change from baseline to two year follow-up for low back pain was -12.7 (95% confidence interval -21.1 to -4.2, table 6) and SF-36 physical summary 4.3 (0.8 to 7.9, table 8). Further analyses are shown in tables 7, 8, and 9.

**DISCUSSION**

This randomised trial comparing disc prosthesis with multidisciplinary rehabilitation showed a significant difference in the primary outcome variable (Oswestry disability index after two years) in favour of surgery. The difference between groups of 8.4 points on the index (with intention to treat analysis) at two year follow-up, however, was smaller than the difference of 10

**Table 6** | Unplanned analysis in secondary outcome in patients with low back pain and degenerative disc randomised to disc prosthesis surgery or rehabilitation. Mean (SD) outcome values for back pain\* at follow-up and treatment effect (difference (95% confidence interval))

	Intention to treat analysis		
	Surgery	Rehabilitation	Treatment effect†
Baseline	64.9 (15.3)	73.6 (13.9)	—
6 weeks	34.7 (27.5)	51.1 (24.6)	-16.5 (-24.8 to -8.2)
3 months	29.3 (25.0)	55.4 (23.4)	-26.2 (-34.5 to -17.8)
6 months	36.1 (28.5)	50.0 (24.5)	-13.8 (-22.3 to -5.3)
1 year	33.0 (29.4)	48.7 (28.9)	-15.7 (-24.3 to -7.0)
2 years	32.7 (28.8)	45.3 (28.6)	-12.7 (-21.1 to -4.2)

\*See table 1 for score details.

†Negative values indicate larger improvement in outcome with surgery. All  $P < 0.001$  for trend in treatment effect over time. Two sided *t* test.

points that the study was designed to detect. As evident in the confidence intervals, the data are consistent with a wide range of differences between the groups, including values well below 10 points. There is, as far as we know, no agreement on the size of the clinically important difference between two treatment groups. As an alternative we can assess the proportion of patients achieving a clinically meaningful improvement.<sup>31</sup> By using a clinically meaningful improvement for an individual patient of 15 points on the Oswestry disability index,<sup>8</sup> 70% ( $n=51$ ) of patients in the surgical group and 47% ( $n=31$ ) of those in the rehabilitation group achieved at least this improvement (intention to treat). We will publish data on the estimated minimal clinically important change elsewhere, but the changes are in agreement with recommendations from FDA studies. As there is no consensus based agreement of how large a difference between groups must be to be of clinical importance it is impossible to conclude whether the effect found in our study is of clinical importance. As such a decision must be made before a new treatment can be recommended in clinical practice; our study underlines the need for such a consensus agreement.

The change in the Oswestry disability index score in our study is comparable with those seen in previous

studies. In our study, the mean score was reduced by 29% (12.4 points) in the rehabilitation group (intention to treat analysis). Brox et al<sup>4</sup> found a similar reduction of 29% (12.0 points) at one year follow-up, while Fairbank et al<sup>6</sup> and Fritzell et al<sup>3</sup> observed a smaller reduction at two year follow-up (8.7 and 5.5 points, respectively). In our study, there was a mean reduction in score of 50% (20.8 points) in the surgical arm (intention to treat analysis). Similar reductions have been reported in other studies,<sup>8,9,11</sup> though Zigler et al used the “chiropractor version” of the Oswestry index.<sup>32</sup> This questionnaire has not been sufficiently validated and consequently it is difficult to compare the outcome.<sup>18</sup>

It could be argued that patients who withdrew after randomisation or dropped out during or after treatment had a superior or inferior outcome. We therefore sent a questionnaire to such patients. The nine patients who withdrew after surgery experienced a reduction in Oswestry score of 30.2 (SD 4.5) points. The six who withdrew after rehabilitation had a reduction of 11.8 (SD 3.0), and the 11 patients who withdrew without treatment had no change (1.0 (SD 4.5) points) (see table B in appendix 3 on bmj.com). This might support the assumption of no improvement in outcome after drop-out, justifying use of the last value carried forward analysis.

Most changes in secondary variables measuring disability and pain favoured surgical treatment, though there were no significant differences between groups in FABQ work, FABQ physical, SF-36 mental health, EQ-5D, HSCL-25, drug consumption, return to work, and the back performance scale in the main analysis. In the surgical group we found a similar “net back to work” rate as reported by Fritzell et al.<sup>3</sup> Nevertheless, it has been argued that sick leave, to a large extent, is influenced by factors outside the domain of medical and therapeutic interventions.<sup>33</sup> The somewhat smaller difference between groups in the back performance scale than in the Oswestry disability index might be explained by differences in psychometric properties between the outcome measurements or by patients overstating the effect in a subjective questionnaire.

**Table 7** | Unplanned analysis in secondary outcomes in patients with low back pain and degenerative disc randomised to disc prosthesis surgery or rehabilitation. Mean (SD) outcome values for SF-36\*

Variable	Baseline		3 months		6 months		1 year		2 years		P value†
	Surgery	Rehabilitation	Surgery	Rehabilitation	Surgery	Rehabilitation	Surgery	Rehabilitation	Surgery	Rehabilitation	
Physical function	52.7 (17.6)	50.6 (17.8)	76.2 (18.3)	64.0 (22.4)	76.0 (21.4)	63.7 (21.0)	79.5 (20.6)	66.7 (22.9)	78.9 (20.2)	69.6 (22.2)	<0.001
Role physical	25.3 (24.2)	23.9 (18.7)	50.0 (31.5)	45.6 (31.9)	57.2 (35.1)	47.8 (31.2)	58.9 (37.3)	55.9 (33.9)	66.4 (33.5)	55.1 (35.0)	0.135
Bodily pain	24.9 (16.5)	24.4 (12.1)	48.2 (22.4)	34.9 (16.1)	50.8 (29.1)	39.1 (20.8)	52.5 (30.8)	43.5 (24.6)	55.5 (29.1)	44.4 (23.0)	<0.001
General health	57.9 (19.7)	55.9 (19.9)	67.6 (22.8)	60.7 (24.7)	65.5 (24.3)	60.1 (24.4)	68.1 (26.8)	61.7 (22.1)	65.7 (26.0)	61.1 (24.8)	0.125
Vitality	37.8 (20.2)	33.1 (20.0)	50.3 (21.6)	44.4 (22.1)	55.6 (23.7)	45.7 (22.9)	57.5 (27.5)	48.2 (24.9)	55.0 (27.1)	46.8 (23.5)	0.003
Social function	53.0 (30.6)	57.6 (26.7)	72.8 (25.0)	68.8 (25.6)	75.0 (28.6)	71.1 (26.7)	76.7 (25.7)	74.3 (26.8)	78.3 (26.8)	77.9 (27.4)	0.725
Role emotion	72.5 (33.3)	67.6 (32.7)	85.1 (23.3)	69.0 (34.7)	83.3 (26.3)	74.5 (29.8)	80.4 (31.0)	79.2 (26.3)	83.9 (25.6)	79.2 (29.0)	0.010
Mental health‡	71.7 (18.0)	65.8 (18.7)	78.6 (15.6)	72.4 (17.9)	79.5 (16.8)	74.1 (16.4)	80.4 (17.5)	73.8 (20.9)	78.3 (18.2)	75.8 (17.5)	0.007

\*See table 1 for score details.

†For trend in treatment effect over time.

‡Values are not adjusted for significantly different baseline scores.

**Table 8** | Unplanned analysis in secondary outcome in patients with low back pain and degenerative disc randomised to disc prosthesis surgery or rehabilitation. Mean (SD) outcome values for physical and mental component summary scores on SF-36\* at follow-up and treatment effect (difference (95% confidence interval))

	Surgery	Rehabilitation	Treatment effect†
<b>SF-36 physical component summary</b>			
Baseline	30.5 (7.1)	30.8 (6.5)	—
3 months	40.3 (10.9)	37.3 (8.9)	3.0 (−0.6 to 6.6)
6 months	41.4 (12.3)	37.2 (9.2)	4.2 (0.6 to 7.8)
1 year	43.5 (12.7)	39.4 (11.5)	4.2 (0.6 to 7.7)
2 years	43.9 (11.9)	39.6 (10.4)	4.3 (0.8 to 7.9)
<b>SF-36 mental component summary</b>			
Baseline	47.7 (13.0)	45.2 (13.2)	—
3 months	50.9 (10.4)	47.0 (12.9)	3.9 (−0.2 to 8.0)
6 months	52.0 (9.7)	49.5 (10.5)	2.5 (−1.6 to 6.6)
1 year	51.7 (11.6)	49.7 (12.0)	2.0 (−2.0 to 6.1)
2 years	51.0 (11.0)	50.5 (11.0)	0.5 (−3.4 to 4.5)

\*See table 1 for score details.

†Positive treatment effect indicates larger improvement in outcome for surgery. P=0.002 for physical and 0.166 for mental for trend in treatment effect over time.

### Strengths and limitations

Our study has several strengths. It was randomised and had few patients who crossed over to the other treatment regimen. In addition, an independent research assistant collected the data, the observers at the two year evaluation were blinded, the interventions were standardised, and the financing of the study was public. Choosing magnetic resonance imaging criteria for inclusion could be a strength or limitation. To our knowledge, there are no specific criteria to determine which degenerative changes should be operated on. When designing the study we wanted the inclusion of patients across centres to be as unanimous as possible, treating the same population, although this possibly would lead to less external validity of the study. It could also possibly lead to inclusion of more severe degenerated discs in our study compared with other studies.<sup>8,9</sup>

One limitation of our study is the lack of a placebo or sham group. The regression to the mean and the natural resolution of chronic low back pain must also be considered in both groups. When balancing a non-operative regimen with an operative treatment, there is probably a difference in placebo effect that is difficult to untangle from the treatment effect.<sup>34-37</sup> The placebo effect might be higher in the surgical group, although the possible placebo effect of rehabilitation over several weeks with personal contact with a therapist should not be underestimated. Furthermore, it could be argued that the patients included in the study wanted surgery, but the number of patients not wanting the rehabilitation programme was similar to the number of patients not wanting surgery (see figure and appendix 1 on bmj.com). Brox et al found no difference in treatment effect between patients who did and did not “believe” in surgery,<sup>4,5</sup> and a recent study found no significant relation between baseline

**Table 9** | Secondary outcomes in patients with low back pain and degenerative disc randomised to disc prosthesis surgery or rehabilitation. Mean (SD) outcome values on EQ-5D, HSCL-25, FABQ, and self efficacy at follow-up and treatment effect (difference (95% confidence interval))

Variable*	Surgery	Rehabilitation	Treatment effect†
<b>EQ-5D‡</b>			
Baseline	0.30 (0.30)	0.27 (0.31)	—
6 weeks	0.59 (0.30)	0.55 (0.29)	0.04 (−0.06 to 0.15)
3 months	0.70 (0.23)	0.48 (0.31)	0.22 (0.12 to 0.33)
6 months	0.68 (0.28)	0.51 (0.33)	0.17 (0.06 to 0.27)
1 year	0.67 (0.35)	0.54 (0.32)	0.13 (0.02 to 0.23)
2 years	0.68 (0.34)	0.60 (0.30)	0.08 (−0.03 to 0.18)
<b>HSCL-25§</b>			
Baseline	1.81 (0.50)	1.88 (0.51)	—
3 months	1.38 (0.34)	1.66 (0.51)	−0.27 (−0.44 to −0.11)
6 months	1.44 (0.45)	1.66 (0.49)	−0.22 (−0.38 to −0.05)
1 year	1.45 (0.50)	1.59 (0.49)	−0.14 (−0.30 to 0.03)
2 years	1.47 (0.49)	1.55 (0.50)	−0.09 (−0.25 to 0.08)
<b>FABQ work§</b>			
Baseline	25.8 (11.2)	27.4 (9.9)	—
3 months	20.0 (12.9)	24.3 (11.9)	−4.3 (−8.6 to 0.1)
6 months	18.7 (12.9)	23.0 (12.7)	−4.3 (−8.7 to 0.1)
1 year	18.2 (13.9)	21.3 (13.2)	−3.1 (−7.4 to 1.2)
2 years	16.7 (13.5)	18.5 (12.5)	−1.8 (−6.1 to 2.5)
<b>FABQ physical§</b>			
Baseline	14.0 (5.8)	12.5 (5.6)	—
3 months	8.8 (5.3)	9.1 (6.3)	−0.3 (−2.4 to 1.7)
6 months	8.6 (6.3)	9.3 (6.7)	−0.7 (−2.8 to 1.3)
1 year	8.0 (6.3)	8.9 (5.8)	−0.8 (−2.9 to 1.2)
2 years	8.0 (6.0)	8.3 (5.7)	−0.3 (−2.3 to 1.7)
<b>Self efficacy‡</b>			
Baseline	3.4 (1.5)	3.6 (1.6)	—
3 months	6.1 (2.3)	5.0 (2.2)	1.0 (0.2 to 1.9)
6 months	6.0 (2.6)	5.6 (2.4)	0.5 (−0.3 to 1.3)
1 year	6.4 (3.3)	5.5 (2.5)	0.9 (0.0 to 1.7)
2 years	6.2 (2.7)	5.6 (2.7)	0.5 (−1.4 to 2.8)

\*See tables 1 and 5 for score details.

‡EQ-5D P<0.001, HSCL P<0.001, FABQ work P=0.057, FABQ physical P=0.548, self efficacy P=0.019 for trend in treatment effect over time.

§Positive scores indicate larger improvement in outcome with surgery. ¶Negative scores indicate larger improvement in outcome with surgery.

expectations and follow-up scores.<sup>38</sup> On the other hand, “expectation being fulfilled” might be a predictor of global outcome.<sup>38</sup> During the inclusion process, we emphasised the advantages and disadvantages of the two treatment options and that none of the treatments are documented as superior to another. It is still possible, however, that patients in the rehabilitation group found themselves faced with “more of the same.” The lack of routine rehabilitation in the surgical arm could be another limitation in the study. We wanted to avoid the postoperative treatment containing elements from the rehabilitation programme. Hence, patients received only general advice when they were discharged from the hospital and received no rehabilitation in the first weeks after surgery. At six weeks, however, patients could be referred if required to a physiotherapist at their home for functional mobilisation and general muscle training.

**WHAT IS ALREADY KNOWN ON THIS TOPIC**

In patients with chronic low back pain, compared with fusion, the clinical outcome with disc prosthesis has been at least equivalent

Compared with multidisciplinary rehabilitation, improvement in disability and pain are similar

**WHAT THIS STUDY ADDS**

Surgery with disc prosthesis resulted in a significantly greater improvement in scores on the Oswestry disability index and variables measuring disability and pain, although the difference in Oswestry score between groups was lower than the study was designed to detect

There were no differences in return to work and several outcomes measuring mental health

Furthermore, some surgical patients underwent a second operation but repeat rehabilitation was not considered. Patients did not request a second chance for rehabilitation, though they were advised during follow-up consultations. Another weakness in our study is the difference in compliance between groups and the high drop-out rate. This difference in adherence to the protocol probably leads to an underestimate of the true effect of surgery, especially in the intention to treat analysis. In similar studies comparing surgery with rehabilitation, the drop-out rates were similar to ours.<sup>6,39-41</sup> The patients we included in our study were highly selected, with one or two level degenerative changes and good general health. Thus, our results are valid only in similar patients. Furthermore, we examined several secondary outcome variables that could lead to the detection of differences by chance. Although we conducted several unplanned analyses (not recorded in the original protocol), in common with similar studies, we consider it as an important asset to our data. Lately, similar studies have applied repeated measurements by using mixed models.<sup>40</sup> Using unplanned analysis could be considered a weakness, but our findings in these analyses support our main analyses and strengthen our conclusion. Nevertheless, caution should be used in interpreting the results of non-prespecified analyses.

**Potential harms of disc prosthesis surgery**

Surgery carries a risk of serious complications, as seen in one of our patients. In a review by Inamasu et al, the perioperative vascular injury rate for anterior lumbar interbody fusion was 0-18% (mean 3%).<sup>42</sup> This is an important drawback of surgery. No major differences in complication rates between insertion of a disc prosthesis and fusion have been found in a randomised setting.<sup>8,9,11</sup> The short term reoperation rate in our study was 6.5% (n=5) and the vascular injury rate was 6.5% (n=5) (table 2). Although vascular complications are reported, serious consequences like amputation and mortality are rare.<sup>43</sup> Recently Kurtz et al looked at the rates of short term revision and mortality total disc replacement.<sup>43</sup> They found similar reoperation rates as with anterior fusion surgery and hip arthroplasty. Four retrospective studies have reported long term reoperation rates of up to 13%.<sup>44-47</sup> Data on the

anterior revision rate of the prosthesis is difficult to extract from these studies but seems considerably lower. The potential long term revision rate with a higher complication rate on revisions needs to be considered.<sup>48</sup>

Earlier addressed but unresolved questions are the incidence of adjacent level degeneration after total disc replacement and distinct characteristics of patients associated with good outcome. Some studies have examined these issues but more information is needed.<sup>49-51</sup> In a univariate analysis we found indications that patients with Modic I or II changes have a superior result in the surgical arm and that patients with high Oswestry scores seem to be more suitable for rehabilitation. A full multivariate analysis of good outcomes will be published soon to answer these questions. Another important issue is the incidence of degeneration in the facet joints of the operated level. An analysis of adjacent level degeneration and degeneration of the operated level in addition to a full health economic analysis will be published later.

The total blood loss and operation time were higher in our study than in similar studies. The learning curve might be quite flat, and perhaps the participating surgeons should have carried out disc prosthesis surgery in more patients before the start of the study. Using a surgeon to expose the disc (access surgeon), might also have reduced the blood loss and operation time. Blumenthal et al and Zigler et al performed one level surgery, while a third of our patients underwent two level surgery.<sup>8,9</sup> This could explain some of the increased blood loss and operation time in our study. Because of the complexity of the surgery and the risk of serious complications, we think this kind of surgery should be confined to a few specialist centres with experienced spine surgeons and available vascular surgeons. A high quality rehabilitation programme should be available.

Our study was not designed to evaluate specific mechanisms of reduction of pain and disability. Possible explanations for the pain reduction are removal of the disc in the surgical group and better coping in the rehabilitation group, but the patients were heterogeneous and probably had a mixed aetiology difficult to separate. Even though we did not have a control group, the mixed causes of chronic low back pain, the association of surgery with potentially serious complications, and the considerable improvement in the rehabilitation group suggest that it is reasonable to consider a rehabilitation programme before surgery.

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**Stavanger University Hospital, Stavanger** (27 patients): Endre Refsdal (department of orthopaedic surgery).

**Oslo University Hospital, Oslo** (53 patients): Vegard Slettemoen, Kenneth Nilsen, Kjersti Sunde, Helen E Skaara (department of orthopaedics), Anne Keller, Berit Johannessen, Anna Maria Eriksdotter (department of physical medicine and rehabilitation).

**Contributors:** All authors had full access to the data, were responsible for study concept and design, and critically revised the manuscript for important intellectual content. Acquisition of data: CH, LGJ, KS, OPN, MR, OG acquired the data, which were analysed and interpreted by HC, LGJ, KS, OPN, JIB, LS, IR, and OG. CH drafted the manuscript. CH and LS did the statistical analysis. CH, LJ, KS, OPN, JIB, MR, and OG provided administrative, technical, or material support. CH, KS, OPN, JIB, IR, LS, and OG supervised the study. CH is guarantor.

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**Competing interests:** All authors have completed the Unified Competing Interest form at [www.icmje.org/doi\\_disclosure.pdf](http://www.icmje.org/doi_disclosure.pdf) (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

**Ethical approval:** The study was evaluated and approved by the regional committees for medical research ethics in east Norway and all participants gave written informed consent. We did not obtain participants' informed consent for data but the presented data are anonymised and risk of identification is low.

**Data sharing:** Dataset available from the corresponding author at [christian.hellum@medisin.uio.no](mailto:christian.hellum@medisin.uio.no).

- 1 Waddell G. *The back pain revolution*. 2nd ed. Churchill Livingstone, 2004.
- 2 Thomas E, Silman AJ, Croft PR, Papageorgiou AC, Jayson MI, Macfarlane GJ. Predicting who develops chronic low back pain in primary care: a prospective study. *BMJ* 1999;318:1662-7.
- 3 Fritzell P, Hagg O, Wessberg P, Nordwall A, for the Swedish Lumbar Spine Study Group. 2001 Volvo Award Winner in Clinical Studies: lumbar fusion versus nonsurgical treatment for chronic low back pain: a multicenter randomized controlled trial from the Swedish Lumbar Spine Study Group. *Spine* 2001;26:2521-32.
- 4 Brox JI, Sorensen R, Friis A, Nygaard O, Indahl A, Keller A, et al. Randomized clinical trial of lumbar instrumented fusion and cognitive intervention and exercises in patients with chronic low back pain and disc degeneration. *Spine* 2003;28:1913-21.
- 5 Brox JI, Reikeras O, Nygaard O, Sorensen R, Indahl A, Holm I, et al. Lumbar instrumented fusion compared with cognitive intervention and exercises in patients with chronic back pain after previous surgery for disc herniation: a prospective randomized controlled study. *Pain* 2006;122:145-55.
- 6 Fairbank J, Frost H, Wilson-MacDonald J, Yu LM, Barker K, Collins R. Randomised controlled trial to compare surgical stabilisation of the lumbar spine with an intensive rehabilitation programme for patients with chronic low back pain: the MRC spine stabilisation trial. *BMJ* 2005;330:1233.
- 7 Brox JI, Nygaard O, Holm I, Keller A, Ingebrigtsen T, Reikeras O. Four-year follow-up of surgical versus non-surgical therapy for chronic low back pain. *Ann Rheum Dis* 2009;69:1643-8.
- 8 Blumenthal S, McAfee PC, Guyer RD, Hochschuler SH, Geisler FH, Holt RT, et al. A prospective, randomized, multicenter Food and Drug Administration investigational device exemptions study of lumbar total disc replacement with the CHARITE artificial disc versus lumbar fusion: part I: evaluation of clinical outcomes *Spine* 2005;30:1565-75.
- 9 Zigler J, Delamarter R, Spivak JM, Linovitz RJ, Danielson GO III, Haider TT, et al. Results of the prospective, randomized, multicenter Food and Drug Administration investigational device exemption study of the ProDisc-L total disc replacement versus circumferential fusion for the treatment of 1-level degenerative disc disease. *Spine* 2007;32:1155-62.
- 10 Guyer RD, McAfee PC, Banco RJ, Bitan FD, Cappuccino A, Geisler FH, et al. Prospective, randomized, multicenter Food and Drug Administration investigational device exemption study of lumbar total disc replacement with the CHARITE artificial disc versus lumbar fusion: five-year follow-up. *Spine J* 2009;9:374-86.
- 11 Berg S, Tullberg T, Branth B, Olerud C, Tropp H. Total disc replacement compared to lumbar fusion: a randomised controlled trial with 2-year follow-up. *Eur Spine J* 2009;18:1512-9.
- 12 Gibson JN, Waddell G. Surgery for degenerative lumbar spondylosis. *Cochrane Database Syst Rev* 2005;4:CD001352.
- 13 Van den Eerenbeemt KD, Ostelo RW, van Royen BJ, Peul WC, van Tulder MW. Total disc replacement surgery for symptomatic degenerative lumbar disc disease: a systematic review of the literature. *Eur Spine J* 2010;19:1262-80.
- 14 Masharawi Y, Kjaer P, Bendix T, Manniche C, Wedderkopp N, Sorensen JS, et al. The reproducibility of quantitative measurements in lumbar magnetic resonance imaging of children from the general population. *Spine* 2008;33:2094-100.
- 15 Modic MT, Steinberg PM, Ross JS, Masaryk TJ, Carter JR. Degenerative disk disease: assessment of changes in vertebral body marrow with MR imaging. *Radiology* 1988;166:193-9.
- 16 Aprill C, Bogduk N. High-intensity zone: a diagnostic sign of painful lumbar disc on magnetic resonance imaging. *Br J Radiol* 1992;65:361-9.
- 17 Luoma K, Riihimaki H, Luukkonen R, Raininko R, Viikari-Juntura E, Lamminen A. Low back pain in relation to lumbar disc degeneration. *Spine* 2000;25:487-92.
- 18 Fairbank JCTM, Pynsent PBP. The Oswestry disability index. *Spine* 2000;25:2940-53.
- 19 Grotle M, Brox JI, Vollestad NK. Cross-cultural adaptation of the Norwegian versions of the Roland-Morris disability questionnaire and the Oswestry disability index. *J Rehabil Med* 2003;35:241-7.
- 20 Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30:473-83.
- 21 Ware JE Jr. SF-36 health survey update. *Spine* 2000;25:3130-9.
- 22 Euroqol Group. EuroQol—a new facility for the measurement of health-related quality of life. *Health Policy* 1990;16:199-208.
- 23 Derogatis LR, Lipman RS, Rickels K, Uhlenhuth EH, Covi L. The Hopkins symptom checklist (HSCL): a self-report symptom inventory. *Behav Sci* 1974;19:1-15.
- 24 Waddell G, Newton M, Henderson I, Somerville D, Main CJ. A fear-avoidance beliefs questionnaire (FABQ) and the role of fear-avoidance beliefs in chronic low back pain and disability. *Pain* 1993;52:157-68.
- 25 Lorig K, Chastain RL, Ung E, Shoor S, Holman HR. Development and evaluation of a scale to measure perceived self-efficacy in people with arthritis. *Arthritis Rheum* 1989;32:37-44.
- 26 Ostelo RW. Clinically important outcomes in low back pain. *Best Pract Res Clin Rheumatol* 2005;19:593-607.
- 27 Strand LI, Moe-Nilssen R, Ljunggren AE. Back performance scale for the assessment of mobility-related activities in people with back pain. *Phys Ther* 2002;82:1213-23.
- 28 Prolo DJ, Oklund SA, Butcher M. Toward uniformity in evaluating results of lumbar spine operations. A paradigm applied to posterior lumbar interbody fusions. *Spine* 1986;11:601-6.
- 29 Hagg O, Fritzell P, Nordwall A. The clinical importance of changes in outcome scores after treatment for chronic low back pain. *Eur Spine J* 2003;12:12-20.
- 30 Altman DG. Confidence intervals for the number needed to treat. *BMJ* 1998;317:1309-12.
- 31 Guyatt GH, Juniper EF, Walter SD, Griffith LE, Goldstein RS. Interpreting treatment effects in randomised trials. *BMJ* 1998;316:690-3.
- 32 Fairbank JC. Use and abuse of Oswestry disability index. *Spine* 2007;32:2787-9.
- 33 NACHEMSON A. Chronic pain—the end of the welfare state? *Qual Life Res* 1994;3(suppl 1):S11-7.
- 34 Pauza KJ, Howell S, Dreyfuss P, Pelozo JH, Dawson K, Bogduk N. A randomized, placebo-controlled trial of intradiscal electrothermal therapy for the treatment of discogenic low back pain. *Spine J* 2004;4:27-35.
- 35 Freeman BJ, Fraser RD, Cain CM, Hall DJ, Chapple DC. A randomized, double-blind, controlled trial: intradiscal electrothermal therapy versus placebo for the treatment of chronic discogenic low back pain. *Spine* 30:2369-77.
- 36 Buchbinder R, Osborne RH, Ebeling PR, Wark JD, Mitchell P, Wriedt C, et al. A randomized trial of vertebroplasty for painful osteoporotic vertebral fractures. *N Engl J Med* 2009;361:557-68.
- 37 Rousing R, Hansen KL, Andersen MO, Jespersen SM, Thomsen K, Lauritsen JM. Twelve-months follow-up in forty-nine patients with acute/semi-acute osteoporotic vertebral fractures treated

- conservatively or with percutaneous vertebroplasty: a clinical randomized study. *Spine* 2010;35:478-82.
- 38 Mannion AF, Junge A, Elfering A, Dvorak J, Porchet F, Grob D. Great expectations: really the novel predictor of outcome after spinal surgery? *Spine* 2009;34:1590-9.
- 39 Weinstein JN, Lurie JD, Tosteson TD, Skinner JS, Hanscom B, Tosteson AN, et al. Surgical vs nonoperative treatment for lumbar disk herniation: the Spine Patient Outcomes Research Trial (SPORT) observational cohort. *JAMA* 2006;296:2451-9.
- 40 Weinstein JN, Lurie JD, Tosteson TD, Hanscom B, Tosteson AN, Blood EA, et al. Surgical versus nonsurgical treatment for lumbar degenerative spondylolisthesis. *N Engl J Med* 2007;356:2257-70.
- 41 Peul WC, van Houwelingen HC, van den Hout WB, Brand R, Eekhof JA, Tans JT, et al. Surgery versus prolonged conservative treatment for sciatica. *N Engl J Med* 2007;356:2245-56.
- 42 Inamasu J, Guiot BH. Vascular injury and complication in neurosurgical spine surgery. *Acta Neurochir (Wien)* 2006;148:375-87.
- 43 Kurtz SM, Lau E, Iannuzzi A, Schmier J, Todd L, Isaza J, et al. National revision burden for lumbar total disc replacement in the United States: epidemiologic and economic perspectives. *Spine (Phila Pa 1976)* 2010; published online 26 Feb.
- 44 Putzier M, Funk JF, Schneider SV, Gross C, Tohtz SW, Khodadadyan-Klostermann C, et al. Charite total disc replacement—clinical and radiographical results after an average follow-up of 17 years. *Eur Spine J* 2006;15:183-95.
- 45 Lemaire JP, Carrier H, Sariali E, Skalli W, Lavaste F. Clinical and radiological outcomes with the Charite artificial disc: a 10-year minimum follow-up. *J Spinal Disord Tech* 2005;18:353-9.
- 46 Tropiano P, Huang RC, Girardi FP, Cammisa FP Jr, Marnay T. Lumbar total disc replacement. Seven to eleven-year follow-up. *J Bone Joint Surg Am* 2005;87:490-6.
- 47 David T. Long-term results of one-level lumbar arthroplasty: minimum 10-year follow-up of the CHARITE artificial disc in 106 patients. *Spine* 2007;32:661-6.
- 48 McAfee PC, Geisler FH, Saiedy SS, Moore SV, Regan JJ, Guyer RD, et al. Revisability of the CHARITE artificial disc replacement: analysis of 688 patients enrolled in the US IDE study of the CHARITE artificial disc. *Spine* 2006;31:1217-26.
- 49 Siepe CJ, Zelenkov P, Sauri-Barraza JC, Szeimies U, Grubinger T, Tepass A, et al. The fate of facet joint and adjacent level disc degeneration following total lumbar disc replacement: a prospective clinical, x-ray, and magnetic resonance imaging investigation. *Spine (Phila Pa 1976)* 2010;35:1991-2003.
- 50 Siepe CJ, Mayer HM, Wiechert K, Korge A. Clinical results of total lumbar disc replacement with ProDisc II: three-year results for different indications. *Spine* 2006;31:1923-32.
- 51 Guyer RD, Siddiqui S, Zigler JE, Ohnmeiss DD, Blumenthal SL, Sachs BL, et al. Lumbar spinal arthroplasty: analysis of one center's twenty best and twenty worst clinical outcomes. *Spine* 2008;33:2566-9.

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**From:** Pooja Voria - WSRS Vice President <wsrsvicepresident@gmail.com>  
**Sent:** Friday, March 11, 2016 1:09 PM  
**To:** HCA ST Health Tech Assessment Prog  
**Subject:** HTA review of CAD

**Follow Up Flag:** Follow up  
**Flag Status:** Completed

Dear members of the review committee –

As a practicing breast radiologist in Washington State I am personally committed to utilizing the best technologies to diagnose or rule out cancer for my patients. CAD is fundamental technology at this time and is helpful to many radiologists.

As the Vice President of the Washington State Chapter of the ACR, I am would like to share legislation that was passed with the Consolidated Appropriations Act signed into law December 18<sup>th</sup>, 2015. The law explicitly spells out in Section 229, all Medicare-recognized screening mammography modalities (including digital mammography, screening breast tomosynthesis, and computer-aided detection/CAD) must be covered without cost-sharing by all non-grandfathered health plans, for women 40 and older on an annual basis. My hope is that, rather than potentially creating addition confusion for patients, the HTA can support and implement this law so that women in Washington are provided access to these important breast screening services.

You may view the complete bill by following the link below:

<https://www.congress.gov/bill/114th-congress/house-bill/2029/text>

Thank you for your consideration on this issue,

Pooja Voria, MD, MBA  
Vice President – WA State Radiological Society





Boston Scientific Corporation  
300 Boston Scientific Way  
Marlborough, MA 01752  
(508) 683-4000  
www.bostonscientific.com

March 11, 2016

Health Technology Assessment Program  
628 8<sup>th</sup> Avenue SE  
Olympia, WA 98501

Attn: Christine Masters, Program Specialist

Via electronic submission at [shtap@hca.wa.gov](mailto:shtap@hca.wa.gov)

**RE: 2016 Prospective HTA Technology Topics: Left Atrial Appendage Closure (LAAC) Device**

Dear Ms. Masters,

Boston Scientific appreciates the opportunity to provide comment as it relates to the 2016 prospective HTA technology topic on Left Atrial Appendage Closure (LAAC) Device. We understand that Washington HTA is soliciting public feedback as to whether they should open up an HTA review on LAAC. We would like to provide our perspective that might be helpful in evaluating your decision. For the reasons discussed below, we recommend that Washington HTA not pursue a review of LAAC at this time.

**FDA Approval**

The WATCHMAN Device has been extensively studied in five clinical trials (e.g., PILOT (feasibility study), PROTECT AF (RCT-IDE), CAP (Registry), PREVAIL (RCT-IDE), and CAP2 (Registry) over the past 10 years. In the clinical trials, WATCHMAN demonstrated as good or better results than the current standard of care (warfarin). These clinical trials ultimately led to FDA approval of the WATCHMAN Device on March 13, 2015 as a non-pharmaceutical treatment for reducing the risk of stroke from thromboembolism originating in the LAA in patients with non-valvular atrial fibrillation (NVAF).<sup>1</sup> The FDA has provided appropriate guidance on which patients are at greatest risk, hence, to be a candidate to receive WATCHMAN therapy. To provide additional perspective, these NVAF patients who are at high risk of stroke are not absolutely contraindicated to oral anticoagulants (OACs), but the benefit of long-term OAC therapy is outweighed by the risks associated with lifelong exposure to OACs, particularly with respect to the risk of bleeding complications over time. Because of these risks, these patients may not take any OAC on a long-term basis and therefore would be left unprotected from stroke. (Importantly, these patients can use warfarin for short periods.) Such patients are in need of an alternative, non-pharmacologic, lifelong stroke risk reduction therapy. These patients are the target group for

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<sup>1</sup> The WATCHMAN is indicated to reduce the risk of thromboembolism from the left atrial appendage (LAA) in patients with non-valvular atrial fibrillation who:

- Are at increased risk for stroke and systemic embolism based on CHADS<sub>2</sub> or CHA<sub>2</sub>DS<sub>2</sub>-VASc scores and are recommended for anticoagulation therapy;
- Are deemed by their physicians to be suitable for warfarin; and
- Have an appropriate rationale to seek a non-pharmacologic alternative to warfarin, taking into account the safety and effectiveness of the device compared to warfarin.

LAAC as long as they can tolerate a defined period of short-term warfarin therapy following LAAC implantation (e.g., at least 45 days, as required per the current WATCHMAN FDA labeling). This specific guidance limits the therapy from being used inappropriately on candidates that are being well-managed on OACs for their stroke risk.

#### **CMS final decision memo on percutaneous LAAC therapy**

On February 8, 2016, CMS completed the national coverage analysis of percutaneous LAAC therapy with the publication of the [final decision memo](#) to support the national coverage determination (NCD). Boston Scientific has provided information and data to CMS over the past 18 months to support their extensive review of the clinical evidence, effectiveness, and safety of LAAC in their evaluation of health outcomes on Medicare beneficiaries. (Refer to **Appendix A** for key WATCHMAN publications) CMS is covering LAAC through coverage with evidence development (CED) with specific patient eligibility criteria, shared decision making discussion, operator and infrastructure requirements, and a national registry for continued data collection on LAAC procedures.

SCAI, ACC, and HRS (physician societies) jointly published their “Institutional and Operator Requirements for Left Atrial Appendage Occlusion” in December 2015.<sup>2</sup> This document establishes the best practices for operator training and infrastructure requirements to support safe and effective outcomes for LAAC. CMS reviewed these considerations and incorporated them in the NCD as part of the operator and institutional requirements.

As with most recent structural heart technologies such as TAVR (transcatheter aortic valve replacement) and TMVR (transcatheter mitral valve replacement), CMS is covering LAAC under CED as subset of their beneficiaries would benefit from the therapy but would like to better understand the long-term outcomes over time. Based on Boston Scientific’s clinical trial experience, the overwhelming majority of patients receiving this therapy are age  $\geq 65$  and represent a Medicare demographic. We anticipate that non-Medicare patients receiving this therapy in Washington will follow a similar process established by CMS in qualifying appropriate eligibility for LAAC. In addition to CMS’s finalization of the NCD, some major Blue Cross Blue Shield and private payer plans are now covering WATCHMAN LAAC when appropriate criteria are met. (Refer to **Appendix B**)

#### **Our recommendation**

Based on the above considerations, our recommendation is to not pursue opening a review for LAAC. WATCHMAN LAAC has been extensively reviewed to date by CMS and their recommendation for coverage under CED is pertinent as it allows for the technology to be continually assessed for efficacy and safety. Boston Scientific would appreciate the opportunity to discuss this topic in an in-person meeting with the HTA committee before they pursue the decision to initiate a review on LAAC.

If you have questions, please feel free to contact me at [wendy.chan@bsci.com](mailto:wendy.chan@bsci.com) or 661-949-4149.

Sincerely,



Wendy Chan, Sr. Manager, Health Economics and Reimbursement

---

<sup>2</sup> Kavinsky et al. SCAI/ACC/HRS Institutional and Operator Requirements for Left Atrial Appendage Occlusion. *JAAC* (2016), doi: 10.1016/j.jacc.2015.12.001.

## Appendix A: WATCHMAN Key Clinical and Cost Effectiveness Publications

1. Block P. Watching the WATCHMAN. *Journal of American College of Cardiology*. Vol 49. No. 13, 2007.
2. Sick P, Schuler G, Hauptmann K, et al. Initial worldwide experience with the WATCHMAN left atrial appendage system for stroke prevention in atrial fibrillation. *Journal of American College of Cardiology*. Vol 49. 2007. 1490-1495.
3. Stöllberger C, Schneider B, Finsterer J. Serious complications from dislocation of a WATCHMAN left atrial appendage occluder. *Journal of Cardiovascular Electrophysiology*. Vol 18, 2007. Aug 18(8): 880-881.
4. Budge L, Shaffer K, Moorman J, et al. Analysis of in vivo left atrial appendage morphology in patients with atrial fibrillation: A direct comparison of transesophageal echocardiography, planar cardiac CT, and segmented three-dimensional cardiac CT. *Journal of Interventional Cardiology Electrophysiology*. Vol 23, 2008.
5. Hara H, Matthews R, Virmani R, et al. Percutaneous left atrial appendage obliteration. *Journal of American College of Cardiology: Cardiovascular Imaging*. Vol 1, No 1, 2008.
6. Khumri T, Thibodeau J, Main M. Transesophageal echocardiographic diagnosis of left atrial appendage occluder device infection. *European Journal of Echocardiography*. Vol 9, 2008.
7. Möbius-Winkler S, Schuler G, Sick P. Interventional treatments for stroke prevention in atrial fibrillation with emphasis upon the WATCHMAN device. *Current Opinion in Neurology*. Vol 21, 2008.
8. Ahmed H, Reddy V. Technical advances in the ablation of atrial fibrillation. *Heart Rhythm Society*. 2009.05.005.
9. Di Biase L, Horton R, Wang Y, et al. Follow-up imaging of a left atrial appendage Device. *Heart Rhythm Society*. 2009.04.036.
10. De Meester P, Thijs V, Willems R, et al. Percutaneous closure of the left atrial appendage in atrial fibrillation: An alternative if standard treatment fails? *Interventional Cardiology*. 2009.1(1), 119-131.
11. Holmes D, Reddy V, Turi Z, et al. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: A randomized non-inferiority trial. *Lancet*. 2009. 374: 534-42.
12. Holmes D, Schwartz R. Left atrial appendage occlusion eliminates the need for warfarin. *Circulation*. Vol 120, 2009. 120:1919-1926.
13. Whitlock R, Healey J, Connolly S. Left atrial appendage occlusion does not eliminate the need for warfarin. *Circulation*. Vol 120, 2009. 120, 1927-1932.
14. Wrigley B, Lip G. Can the WATCHMAN device truly PROTECT from stroke in atrial fibrillation? *Lancet Neurology*. 2009.

15. Schwartz R, Holmes D, Van Tassel R, et al. Left atrial appendage obliteration; Mechanisms of healing and intracardiac integration. *Journal of American College of Cardiology*. Vol 3, No 8, 2010.
16. Reddy V, Holmes D, Doshi S, et al. Safety of percutaneous left atrial appendage closure: Results from the WATCHMAN left atrial appendage system for embolic protection in patients With AF (PROTECT AF) clinical trial and the Continued Access Registry. *Circulation*. Vol 123, 2011.
17. Singh S, Douglas P, Reddy V. The incidence and long-term clinical outcome of iatrogenic atrial septal defects secondary to transseptal catheterization with a 12F transseptal sheath. *Circulation: Arrhythmia and Electrophysiology*. 2011.
18. Bai R, Horton R, Di Biase L, et al. Intraprocedural and long-term incomplete occlusion of the left atrial appendage following placement of the WATCHMAN device: A single center experience. *Journal of Cardiovascular Electrophysiology*. Vol 23, 2012.
19. Gangireddy S, Halperin J, Fuster V, et al. Percutaneous left atrial appendage closure for stroke prevention in patients with atrial fibrillation: An assessment of net clinical benefit. *European Heart Journal*. Vol 33, 2012.
20. Viles-Gonzalez J, Kar S, Douglas P, Dukkipati S, Feldman T, Horton R, Holmes D, Reddy V. The clinical impact of incomplete left atrial appendage closure with the WATCHMAN device in patients with atrial fibrillation. *Journal of American College of Cardiology*. Vol 59, No. 10.2012.
21. Landmesser U, Holmes D. Left atrial appendage closure: A percutaneous transcatheter approach for stroke prevention in atrial fibrillation. *European Heart Journal*. Vol 33, 2012.
22. Perk G, Biner S, Kronzon I, et al. Catheter-based atrial appendage occlusion procedure: Role of echocardiography. *European Heart Journal-Cardiovascular Imaging*. Vol 13, 2012.
23. Walker D, Humphries J, Philips K. Combined catheter ablation for atrial fibrillation and WATCHMAN left atrial appendage occlusion procedures: A single centre experience. *Journal of Atrial Fibrillation*. Vol 5, 2012.
24. Reddy V, Doshi S, Sievert H, et al. Percutaneous left atrial appendage closure for stroke prophylaxis in patients with atrial fibrillation: 2.3-year follow up of the PROTECT AF (Watchman Left Atrial Appendage System for embolic protection in patients with atrial fibrillation) trial. *Circulation*. 2013;127:720-729;
25. Reddy VY, Möbius-Winkler S, Miller MA, Neuzil P, Schuler G, Wiebe J, Sick P, Sievert H, Left Atrial Appendage Closure with the Watchman Device in Patients with a Contraindication for Oral Anticoagulation: ASA Plavix Feasibility Study with Watchman Left Atrial Appendage Closure Technology (ASAP Study). *Journal of American College of Cardiology* (2013), doi: 10.1016/j.jacc.2013.03.035.
26. Alli O, Doshi S, Kar S, et al. Quality of Life Assessment in the Randomized PROTECT AF Trial of Patients at Risk for Stroke With Non-Valvular Atrial Fibrillation. *Journal of American College of Cardiology*. Vol 61, No 17, 2013; 1790-8.
27. Holmes DR, Kar S, Price M, Whisenant B, Sievert H, Doshi S, Huber K, Reddy V. Prospective randomized evaluation of the Watchman left atrial appendage Device in patients with atrial fibrillation versus long-

term warfarin therapy; the PREVAIL trial. *Journal of the American College of Cardiology.*, Vol. 4, No. 1, 2014, 1-11.

28. Reddy VY, Sievert H, Halperin J, et al. Percutaneous Left Atrial Appendage Closure vs Warfarin for Atrial Fibrillation: A randomized clinical trial. *JAMA*. 2014;312(19): 1988-1998.
29. Holmes DR et al. Left atrial appendage closure as an alternative to warfarin for stroke prevention in atrial fibrillation: a patient meta-analysis. *JACC*. 2015;65(24):2614-2623.
30. Reddy VY, Akehurst RL, Armstrong SO, Amorosi SL, Beard SM, Holmes DR, Jr. Time to Cost-Effectiveness Following Stroke Reduction Strategies in AF: Warfarin versus NOACs Versus LAA Closure. *J Am Coll Cardiol*. 2015;66(24):2728-2739. doi:10.1016/j.jacc.2015.09.084.
31. Price et al. Bleeding outcomes after left atrial appendage closure compared with long-term warfarin: a pooled, patient-level analysis of the WATCHMAN randomized trial experience. *JACC: Cardiovascular Interventions*. Vol 8(15), Dec 2015. 1925-1932.

**Appendix B: Current Private Payers Covering WATCHMAN LAAC Therapy**

<b>Insurer</b>	<b>Policy link</b>
BCBS Kansas City	<a href="http://medicalpolicy.bluekc.com/MedPolicyLibrary/Medicine/Cardiology/12-15_2_Percutaneous_Left_Atrial_Appendage_Closure_Devices.pdf">http://medicalpolicy.bluekc.com/MedPolicyLibrary/Medicine/Cardiology/12-15_2_Percutaneous_Left_Atrial_Appendage_Closure_Devices.pdf</a>
BCBS MS	<a href="http://www.bcbsms.com/index.php?q=provider-medical-policy-search.html&amp;action=viewPolicy&amp;path=%2Fpolicy%2Femed%2FLeft-Atrial+Appendage+Closure+Devices.html">http://www.bcbsms.com/index.php?q=provider-medical-policy-search.html&amp;action=viewPolicy&amp;path=%2Fpolicy%2Femed%2FLeft-Atrial+Appendage+Closure+Devices.html</a>
BCBS NE NY	<a href="https://securews.bsneny.com/content/dam/COMMON/Provider/Protocols/P/prov_prot_20226.pdf">https://securews.bsneny.com/content/dam/COMMON/Provider/Protocols/P/prov_prot_20226.pdf</a>
BCBS of AZ	<a href="https://www.azblue.com/~/_media/azblue/files/healthcare/resources/medical-coverage-guidelines/medicine/o616.pdf">https://www.azblue.com/~/_media/azblue/files/healthcare/resources/medical-coverage-guidelines/medicine/o616.pdf</a>
BCBS of MS	<a href="http://www.bcbsms.com/index.php?q=provider-medical-policy-search.html&amp;action=viewPolicy&amp;path=%2Fpolicy%2Femed%2FLeft-Atrial+Appendage+Closure+Devices.html">http://www.bcbsms.com/index.php?q=provider-medical-policy-search.html&amp;action=viewPolicy&amp;path=%2Fpolicy%2Femed%2FLeft-Atrial+Appendage+Closure+Devices.html</a>
BCBS of RI	<a href="https://www.bcbsri.com/sites/default/files/policies/Percutaneous%20L%20Atrial%20appendage%20Closure%20Devices%20for%20Stroke%20Prevention_Final%20V1.1_4.pdf">https://www.bcbsri.com/sites/default/files/policies/Percutaneous%20L%20Atrial%20appendage%20Closure%20Devices%20for%20Stroke%20Prevention_Final%20V1.1_4.pdf</a>
BCBS TN	<a href="http://www.bcbst.com/UpcomingMPs/Topics_4-8-16/Percutaneous_Left_Atrial_Append_Clsr_Devices_policy.pdf">http://www.bcbst.com/UpcomingMPs/Topics_4-8-16/Percutaneous_Left_Atrial_Append_Clsr_Devices_policy.pdf</a>
BCBS WNY	<a href="https://securews.bcbswny.com/content/dam/COMMON/Provider/Protocols/P/prov_prot_20226.pdf">https://securews.bcbswny.com/content/dam/COMMON/Provider/Protocols/P/prov_prot_20226.pdf</a>
Blue Shield CA	<a href="https://www.blueshieldca.com/provider/content_assets/documents/download/public/bscpolicy/PercutaneousLeftAtrial.pdf">https://www.blueshieldca.com/provider/content_assets/documents/download/public/bscpolicy/PercutaneousLeftAtrial.pdf</a>
HealthNet	<a href="https://www.healthnet.com/static/general/unprotected/pdfs/national/policies/LeftAtrialAppendageDevices.pdf">https://www.healthnet.com/static/general/unprotected/pdfs/national/policies/LeftAtrialAppendageDevices.pdf</a>
Horizon BCBS-NJ	<a href="https://services3.horizon-bcbsnj.com/hcm/MedPol2.nsf">https://services3.horizon-bcbsnj.com/hcm/MedPol2.nsf</a>
Independence Blue Cross	<a href="http://medpolicy.ibx.com/policies/mpi.nsf/f12d23cb982d59b485257bad00552d87/e35204d0bb53f7ee85257f08004f299d!OpenDocument">http://medpolicy.ibx.com/policies/mpi.nsf/f12d23cb982d59b485257bad00552d87/e35204d0bb53f7ee85257f08004f299d!OpenDocument</a>
Premera Blue Cross	<a href="https://www.premera.com/medicalpolicies/2.02.26.pdf">https://www.premera.com/medicalpolicies/2.02.26.pdf</a>





# The Society for Cardiovascular Angiography and Interventions Foundation

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\*\*\* Transmitted Electronically to [shtap@hca.wa.gov](mailto:shtap@hca.wa.gov)\*\*\*

March 11, 2016

Josh Morse, MPH  
Program Director Health Technology Assessment Program  
P.O. Box 42712  
Olympia, WA 98504-2712

RE: 2016 Prospective HTA Technology Topics – Left Atrial Appendage Closure Device

Dear Mr. Morse:

Thank you for the opportunity to comment on the 2016 Prospective HTA Technology Topics which are posted on the internet at:  
[http://www.hca.wa.gov/hta/Documents/topic\\_select\\_proposed\\_022516.pdf](http://www.hca.wa.gov/hta/Documents/topic_select_proposed_022516.pdf).  
We will restrict our comments to potential topic number 3 on your list “Left Atrial Appendage.”

The Society for Cardiovascular Angiography and Interventions (SCAI) is a 4,600-member professional organization representing invasive and interventional cardiologists in approximately 70 countries. SCAI's mission is to promote excellence in invasive/interventional cardiovascular medicine through physician education and representation, and advancement of quality standards to enhance patient care. SCAI's public education program, SecondsCount, offers comprehensive information about cardiovascular disease. For more information about SCAI and SecondsCount, visit [www.SCAI.org](http://www.SCAI.org) or [www.SecondsCount.org](http://www.SecondsCount.org).

While this is a promising new technology, we believe a new review by the HTA is unnecessary at this point for three reasons:

1. The Centers for Medicare and Medicaid Services (CMS) recently completed a 9 month long coverage review for these devices and posted a National Coverage Analysis at: <https://www.cms.gov/medicare-coverage-database/details/nca->


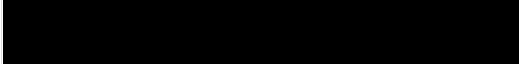


[details.aspx?NCAId=281&TimeFrame=7&DocType=All&bc=AAAAIAAAAAAA  
A%3d%3d&](#). We aren't aware of any deficiencies in CMS's analysis, so we see little potential benefit from a repeated review.

2. The roll out of this device will be carefully monitored and reviewed. The FDA's approval mandates extensive follow-up and reporting (see: [http://www.accessdata.fda.gov/cdrh\\_docs/pdf13/P130013a.pdf](http://www.accessdata.fda.gov/cdrh_docs/pdf13/P130013a.pdf)). Additionally, CMS is requiring that all facilities enroll all their patients in a national, audited registry and that they collect 4 years of follow-up data.
3. The vast majority of patients who will be receiving these devices will be Medicare patients and this means that there will be little financial impact on the state from use of LAAC devices.

We suggest that the HTA's resources be used more effectively in reviewing other procedures or drugs. Thank you once again for the opportunity to provide comments on these proposed list of topics. As always, feel free to contact us for any reason. Wayne Powell, SCAI's Senior Director for Advocacy and Government Relations, can be reached at [wpowell@scai.org](mailto:wpowell@scai.org) or (202)-741-9869.

Sincerely,

James C. Blankenship, MD, MHCM, FSCAI  
President



March 11, 2016

**VIA Electronic Mail to [shtap@hca.wa.gov](mailto:shtap@hca.wa.gov)**

**RE: Potential Health Technology Topics – Non-Pharmacologic Treatments for Migraines/Headaches**

To Whom It May Concern:

The Health Care Authority (HCA) recently proposed topics for future technology assessments. Included in this list is “Non-pharmacologic treatments for migraines/headaches: Includes Botox injections, transcranial magnetic stimulation, nerve destruction, acupuncture and massage. The topic is proposed to determine the safety, efficacy and value of non-drug treatments for migraines and other headaches types”. On behalf of Allergan, Inc., the manufacturer of BOTOX<sup>®</sup> (onabotulinumtoxinA),<sup>1</sup> we encourage HCA to exclude BOTOX<sup>®</sup> from the scope of this review for the following reasons:

- **BOTOX<sup>®</sup> is not a “non-pharmacologic treatment”.** BOTOX<sup>®</sup> is a biological product approved by the U.S. Food and Drug Administration (FDA) under section 351(a) of the Public Health Service Act. If the HCA intends to focus its review solely on non-pharmacologic treatments, BOTOX<sup>®</sup> would fall outside the review’s scope.
- **The Medicaid Drug Rebate Law requires the HCA to cover BOTOX<sup>®</sup> when administered for the treatment of chronic migraine.** BOTOX<sup>®</sup> is FDA-approved for the prophylaxis of headaches in adults with chronic migraine ( $\geq 15$  days per month with a headache last 4 hours a day or longer).<sup>2</sup> (The safety and effectiveness of BOTOX<sup>®</sup> have not been established for the prophylaxis of episodic migraine (14 headache days or fewer per month) in seven placebo-controlled studies.) The Medicaid Drug Rebate Law requires state Medicaid programs to cover FDA-approved indication(s) for any drug or biological product that falls within the scope of a Medicaid Drug Rebate Agreement. As CMS explained in State Release # 51:

*State [action] which denies Medicaid beneficiary access to medically necessary drugs of participating manufacturers conflicts with the mandatory coverage provisions of sections 1902(a)(54) and 1927 of the Social Security Act. Section 1902(a)(54) of the Social Security Act requires States to comply with the applicable requirements of section 1927. Section 1927 requires, among other things, that States permit coverage of medically necessary covered outpatient drugs of manufacturers participating in the drug rebate program. Thus, State*

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<sup>1</sup> **WARNING: DISTANT SPREAD OF TOXIN EFFECT**

Postmarketing reports indicate that the effects of BOTOX and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These may include asthenia, generalized muscle weakness, diplopia, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions, particularly in those patients who have an underlying condition that would predispose them to these symptoms. In unapproved uses, including spasticity in children, and in approved indications, cases of spread of effect have been reported at doses comparable to those used to treat cervical dystonia and spasticity and at lower doses. [See Warnings and Precautions (5.2)].

<sup>2</sup> Adverse reactions reported by  $\geq 2\%$  of BOTOX<sup>®</sup>-treated patients and more frequent than in placebo-treated patients in double-blind, placebo-controlled clinical trials in chronic migraine included headache, migraine, facial paresis, eyelid ptosis, bronchitis, neck pain, musculoskeletal stiffness, muscular weakness, myalgia, musculoskeletal pain, muscle spasms, injection site pain, and hypertension.

**From:** chad@nlhbt.com  
**Sent:** Thursday, March 03, 2016 12:03 PM  
**To:** HCA ST Health Tech Assessment Prog  
**Subject:** re: HCA accepting comments on potential health technology topics

To Whom It May Concern,

We urge you to add mild hyperbaric therapy to the list of reviewed treatments for migraines/headaches. We and many other hyperbaric clinics have great success with this condition. Please feel free to contact us for further information.

Thank you for your consideration,

Chad Redinbo  
253-514-3636

Chad Redinbo  
New Leaf Hyperbarics  
Lacey Clinic  
O: 360-489-0223  
8730 Tallon Lane NE, Suite 104  
Lacey, WA 98516

Tacoma Clinic  
O: 253-212-9211  
6450 Tacoma Mall Blvd, Suite 3  
Tacoma, WA 98409

Eugene Clinic  
O: 541-636-3278  
1200 Executive Parkway, Suite 230  
Eugene, OR 97401

[www.NewLeafHyperbarics.com](http://www.NewLeafHyperbarics.com)

*[action] conflicting with the mandatory coverage provisions of the drug rebate program would not supersede Federal law.*

*Except for those drugs which may be restricted or excluded under section 1927(d)(2), section 1927(d) provides that the State plan must permit coverage of any covered outpatient drug, regardless of its inclusion in the State formulary under section 1927(d)(4), pursuant to a prior authorization system. (...)*

*Therefore, States cannot impose [a requirement] on manufacturers which denies coverage of their drugs under the Medicaid program contrary to the terms of the statute and the national rebate agreement.*

Because Allergan has signed a Medicaid Drug Rebate Agreement, HCA is required to provide coverage for all of BOTOX<sup>®</sup>'s FDA-approved indications, including chronic migraine.

\* \* \* \*

I hope that you have found these comments to be helpful and informative. If you have any questions, please do not hesitate to contact me at 949-677-1512 or via e-mail at [campbell\\_karen@allergan.com](mailto:campbell_karen@allergan.com).

Regards,

Karen L. Campbell, PharmD  
Sr. Medical Scientific Manager  
US Health Outcomes

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<sup>i</sup> The current package labeling includes the following indications for BOTOX<sup>®</sup>:

**1.1 Bladder Dysfunction**

*Overactive Bladder*

BOTOX (onabotulinumtoxinA) for injection is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency, in adults who have an inadequate response to or are intolerant of an anticholinergic medication.

*Detrusor Overactivity associated with a Neurologic Condition*

BOTOX is indicated for the treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition (e.g., SCI, MS) in adults who have an inadequate response to or are intolerant of an anticholinergic medication.

**1.2 Chronic Migraine**

BOTOX is indicated for the prophylaxis of headaches in adult patients with chronic migraine (≥15 days per month with headache lasting 4 hours a day or longer).

*Important limitations*

Safety and effectiveness have not been established for the prophylaxis of episodic migraine (14 headache days or fewer per month) in seven placebo-controlled studies.

**1.3 Spasticity**

*Upper Limb Spasticity*

BOTOX is indicated for the treatment of upper limb spasticity in adult patients, to decrease the severity of increased muscle tone in elbow flexors (biceps), wrist flexors (flexor carpi radialis and flexor carpi ulnaris), finger flexors (flexor digitorum profundus and flexor digitorum sublimis), and thumb flexors (adductor pollicis and flexor pollicis longus).

*Lower Limb Spasticity*

BOTOX is indicated for the treatment of lower limb spasticity in adult patients to decrease the severity of increased muscle tone in ankle and toe flexors (gastrocnemius, soleus, tibialis posterior, flexor hallucis longus, and flexor digitorum longus).

*Important limitations*

Safety and effectiveness of BOTOX have not been established for the treatment of other upper or lower limb muscle groups. Safety and effectiveness of BOTOX have not been established for the treatment of spasticity in pediatric patients under age 18 years. BOTOX has not been shown to improve upper extremity functional abilities, or range of motion at a joint affected by a fixed contracture. Treatment with BOTOX is not intended to substitute for usual standard of care rehabilitation regimens.

**1.4 Cervical Dystonia**

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BOTOX is indicated for the treatment of adults with cervical dystonia, to reduce the severity of abnormal head position and neck pain associated with cervical dystonia.

**1.5 Primary Axillary Hyperhidrosis**

BOTOX is indicated for the treatment of severe primary axillary hyperhidrosis that is inadequately managed with topical agents.

*Important limitations* The safety and effectiveness of BOTOX for hyperhidrosis in other body areas have not been established.

Weakness of hand muscles and blepharoptosis may occur in patients who receive BOTOX for palmar hyperhidrosis and facial hyperhidrosis, respectively. Patients should be evaluated for potential causes of secondary hyperhidrosis (e.g., hyperthyroidism) to avoid symptomatic treatment of hyperhidrosis without the diagnosis and/or treatment of the underlying disease.

Safety and effectiveness of BOTOX have not been established for the treatment of axillary hyperhidrosis in pediatric patients under age 18.

**1.6 Blepharospasm and Strabismus**

BOTOX is indicated for the treatment of strabismus and blepharospasm associated with dystonia, including benign essential blepharospasm or VII nerve disorders in patients 12 years of age and above.

In addition, BOTOX<sup>®</sup> Cosmetic, which has distinct labeling, packaging and NDC-coding, has been approved by the FDA for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients, and for the temporary improvement in the appearance of moderate to severe lateral canthal lines associated with orbicularis oculi activity in adult patients. (See Tab A for a copy of the BOTOX<sup>®</sup> package insert.)

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BOTOX® safely and effectively. See full prescribing information for BOTOX.

**BOTOX (onabotulinumtoxinA) for injection, for intramuscular, intradetrusor, or intradermal use**

Initial U.S. Approval: 1989

### WARNING: DISTANT SPREAD OF TOXIN EFFECT

See full prescribing information for complete boxed warning.

The effects of BOTOX and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults, particularly in those patients who have an underlying condition that would predispose them to these symptoms. (5.2)

### RECENT MAJOR CHANGES

- Indications and Usage, Spasticity (1.3) 1/2016
- Dosage and Administration (2.1, 2.5) 1/2016
- Warnings and Precautions (5.3, 5.10) 1/2016

### INDICATIONS AND USAGE

BOTOX is an acetylcholine release inhibitor and a neuromuscular blocking agent indicated for:

- Treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and frequency, in adults who have an inadequate response to or are intolerant of an anticholinergic medication (1.1)
- Treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition [e.g., spinal cord injury (SCI), multiple sclerosis (MS)] in adults who have an inadequate response to or are intolerant of an anticholinergic medication (1.1)
- Prophylaxis of headaches in adult patients with chronic migraine (≥15 days per month with headache lasting 4 hours a day or longer) (1.2)
- Treatment of spasticity in adult patients (1.3)
- Treatment of cervical dystonia in adult patients, to reduce the severity of abnormal head position and neck pain (1.4)
- Treatment of severe axillary hyperhidrosis that is inadequately managed by topical agents in adult patients (1.5)
- Treatment of blepharospasm associated with dystonia in patients ≥12 years of age (1.6)
- Treatment of strabismus in patients ≥12 years of age (1.6)

**Important limitations:** Safety and effectiveness of BOTOX have not been established for:

- Prophylaxis of episodic migraine (14 headache days or fewer per month) (1.2)
- Treatment of upper or lower limb spasticity in pediatric patients (1.3)
- Treatment of hyperhidrosis in body areas other than axillary (1.5)

### DOSAGE AND ADMINISTRATION

- Follow indication-specific dosage and administration recommendations; Do not exceed a total dose of 400 Units administered in a 3 month interval (2.1)
- See Preparation and Dilution Technique for instructions on BOTOX reconstitution, storage, and preparation before injection (2.2)
- Overactive Bladder: Recommended total dose 100 Units, as 0.5 mL (5 Units) injections across 20 sites into the detrusor (2.3)
- Detrusor Overactivity associated with a Neurologic Condition: Recommended total dose 200 Units, as 1 mL (~6.7 Units) injections across 30 sites into the detrusor (2.3)
- Chronic Migraine: Recommended total dose 155 Units, as 0.1 mL (5 Units) injections per each site divided across 7 head/neck muscles (2.4)
- Upper Limb Spasticity: Select dose based on muscles affected, severity of muscle activity, prior response to treatment, and adverse event history; Electromyographic guidance recommended (2.5)
- Lower Limb Spasticity: Recommended total dose 300 Units to 400 Units divided across ankle and toe muscles (2.5)

### DOSAGE FORMS AND STRENGTHS

Single-use, sterile 100 Units or 200 Units vacuum-dried powder for reconstitution only with sterile, preservative-free 0.9% Sodium Chloride Injection USP prior to injection (3)

### CONTRAINDICATIONS

- Hypersensitivity to any botulinum toxin preparation or to any of the components in the formulation (4.1, 5.4, 6)
- Infection at the proposed injection site (4.2)
- Intradetrusor Injections: Urinary Tract Infection or Urinary Retention (4.3)

### WARNINGS AND PRECAUTIONS

- Potency Units of BOTOX are not interchangeable with other preparations of botulinum toxin products (5.1, 11)
- Spread of toxin effects; swallowing and breathing difficulties can lead to death. Seek immediate medical attention if respiratory, speech or swallowing difficulties occur (5.2, 5.6)
- Potential serious adverse reactions after BOTOX injections for unapproved uses (5.3)
- Concomitant neuromuscular disorder may exacerbate clinical effects of treatment (5.5)
- Use with caution in patients with compromised respiratory function (5.6, 5.7, 5.10)
- Corneal exposure and ulceration due to reduced blinking may occur with BOTOX treatment of blepharospasm (5.8)
- Retrobulbar hemorrhages and compromised retinal circulation may occur with BOTOX treatment of strabismus (5.9)
- Bronchitis and upper respiratory tract infections in patients treated for spasticity (5.10)
- Urinary tract infections in patients treated for OAB (5.12)
- Urinary retention: Post-void residual urine volume should be monitored in patients treated for OAB or detrusor overactivity associated with a neurologic condition who do not catheterize routinely, particularly patients with multiple sclerosis or diabetes mellitus. (5.13)

### ADVERSE REACTIONS

The most common adverse reactions (≥5% and >placebo) are (6.1):

- OAB: urinary tract infection, dysuria, urinary retention
- Detrusor Overactivity associated with a neurologic condition: urinary tract infection, urinary retention
- Chronic Migraine: neck pain, headache
- Spasticity: pain in extremity
- Cervical Dystonia: dysphagia, upper respiratory infection, neck pain, headache, increased cough, flu syndrome, back pain, rhinitis
- Axillary Hyperhidrosis: injection site pain and hemorrhage, non-axillary sweating, pharyngitis, flu syndrome

**To report SUSPECTED ADVERSE REACTIONS, contact Allergan at 1-800-433-8871 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

### DRUG INTERACTIONS

Patients receiving concomitant treatment of BOTOX and aminoglycosides or other agents interfering with neuromuscular transmission (e.g., curare-like agents), or muscle relaxants, should be observed closely because the effect of BOTOX may be potentiated (7)

### USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm. (8.1)
- Pediatric Use: Safety and efficacy are not established in patients under 18 years of age for the prophylaxis of headaches in chronic migraine, treatment of OAB, detrusor overactivity associated with a neurologic condition, spasticity, and axillary hyperhidrosis; in patients under 16 years of age for treatment of cervical dystonia; and in patients under 12 years of age for treatment of blepharospasm and strabismus (8.4)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 1/2016

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\* Sections or subsections omitted from the full prescribing information are not listed.

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## FULL PRESCRIBING INFORMATION

### WARNING: DISTANT SPREAD OF TOXIN EFFECT

Postmarketing reports indicate that the effects of BOTOX and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These may include asthenia, generalized muscle weakness, diplopia, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions, particularly in those patients who have an underlying condition that would predispose them to these symptoms. In unapproved uses, including spasticity in children, and in approved indications, cases of spread of effect have been reported at doses comparable to those used to treat cervical dystonia and spasticity and at lower doses. [See Warnings and Precautions (5.2)]

## 1 INDICATIONS AND USAGE

### 1.1 Bladder Dysfunction

#### *Overactive Bladder*

BOTOX (onabotulinumtoxinA) for injection is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency, in adults who have an inadequate response to or are intolerant of an anticholinergic medication.

#### *Detrusor Overactivity associated with a Neurologic Condition*

BOTOX is indicated for the treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition (e.g., SCI, MS) in adults who have an inadequate response to or are intolerant of an anticholinergic medication.

### 1.2 Chronic Migraine

BOTOX is indicated for the prophylaxis of headaches in adult patients with chronic migraine ( $\geq 15$  days per month with headache lasting 4 hours a day or longer).

#### *Important limitations*

Safety and effectiveness have not been established for the prophylaxis of episodic migraine (14 headache days or fewer per month) in seven placebo-controlled studies.

### 1.3 Spasticity

#### *Upper Limb Spasticity*

BOTOX is indicated for the treatment of upper limb spasticity in adult patients, to decrease the severity of increased muscle tone in elbow flexors (biceps), wrist flexors (flexor carpi radialis and flexor carpi ulnaris), finger flexors (flexor digitorum profundus and flexor digitorum sublimis), and thumb flexors (adductor pollicis and flexor pollicis longus).

#### *Lower Limb Spasticity*

BOTOX is indicated for the treatment of lower limb spasticity in adult patients to decrease the severity of increased muscle tone in ankle and toe flexors (gastrocnemius, soleus, tibialis posterior, flexor hallucis longus, and flexor digitorum longus).

#### *Important limitations*

Safety and effectiveness of BOTOX have not been established for the treatment of other upper or lower limb muscle groups. Safety and effectiveness of BOTOX have not been established for the treatment of spasticity in pediatric patients under age 18 years. BOTOX has not been shown to improve upper extremity functional abilities, or range of motion at a joint affected by a fixed contracture. Treatment with BOTOX is not intended to substitute for usual standard of care rehabilitation regimens.

### 1.4 Cervical Dystonia

BOTOX is indicated for the treatment of adults with cervical dystonia, to reduce the severity of abnormal head position and neck pain associated with cervical dystonia.

### 1.5 Primary Axillary Hyperhidrosis

BOTOX is indicated for the treatment of severe primary axillary hyperhidrosis that is inadequately managed with topical agents.

#### *Important limitations*

The safety and effectiveness of BOTOX for hyperhidrosis in other body areas have not been established. Weakness of hand muscles and blepharoptosis may occur in patients who receive BOTOX for palmar hyperhidrosis and facial hyperhidrosis, respectively. Patients should be evaluated for potential causes of secondary hyperhidrosis (e.g., hyperthyroidism) to avoid symptomatic treatment of hyperhidrosis without the diagnosis and/or treatment of the underlying disease.



Safety and effectiveness of BOTOX have not been established for the treatment of axillary hyperhidrosis in pediatric patients under age 18.

### 1.6 Blepharospasm and Strabismus

BOTOX is indicated for the treatment of strabismus and blepharospasm associated with dystonia, including benign essential blepharospasm or VII nerve disorders in patients 12 years of age and above.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Instructions for Safe Use

The potency Units of BOTOX (onabotulinumtoxinA) for injection are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products and, therefore, units of biological activity of BOTOX cannot be compared to nor converted into units of any other botulinum toxin products assessed with any other specific assay method [*see Warnings and Precautions (5.1) and Description (11)*].

Indication specific dosage and administration recommendations should be followed. When initiating treatment, the lowest recommended dose should be used. In treating adult patients for one or more indications, the maximum cumulative dose should not exceed 400 Units, in a 3 month interval.

The safe and effective use of BOTOX depends upon proper storage of the product, selection of the correct dose, and proper reconstitution and administration techniques. An understanding of standard electromyographic techniques is also required for treatment of strabismus, upper or lower limb spasticity, and may be useful for the treatment of cervical dystonia. Physicians administering BOTOX must understand the relevant neuromuscular and structural anatomy of the area involved and any alterations to the anatomy due to prior surgical procedures and disease, especially when injecting near the lungs.

### 2.2 Preparation and Dilution Technique

Prior to injection, reconstitute each vacuum-dried vial of BOTOX with only sterile, preservative-free 0.9% Sodium Chloride Injection USP. Draw up the proper amount of diluent in the appropriate size syringe (see Table 1, or for specific instructions for detrusor overactivity associated with a neurologic condition see Section 2.3), and slowly inject the diluent into the vial. Discard the vial if a vacuum does not pull the diluent into the vial. Gently mix BOTOX with the saline by rotating the vial. Record the date and time of reconstitution on the space on the label. BOTOX should be administered within 24 hours after reconstitution. During this time period, reconstituted BOTOX should be stored in a refrigerator (2° to 8°C).

**Table 1: Dilution Instructions for BOTOX Vials (100 Units and 200 Units)\*\***

Diluent* Added to 100 Unit Vial	Resulting Dose Units per 0.1 mL	Diluent* Added to 200 Unit Vial	Resulting Dose Units per 0.1 mL
1 mL	10 Units	1 mL	20 Units
2 mL	5 Units	2 mL	10 Units
4 mL	2.5 Units	4 mL	5 Units
8 mL	1.25 Units	8 mL	2.5 Units
10 mL	1 Unit	10 mL	2 Units

\*Preservative-free 0.9% Sodium Chloride Injection, USP Only

\*\*For Detrusor Overactivity associated with a Neurologic Condition Dilution see Section 2.3

Note: These dilutions are calculated for an injection volume of 0.1 mL. A decrease or increase in the BOTOX dose is also possible by administering a smaller or larger injection volume - from 0.05 mL (50% decrease in dose) to 0.15 mL (50% increase in dose).

An injection of BOTOX is prepared by drawing into an appropriately sized sterile syringe an amount of the properly reconstituted toxin slightly greater than the intended dose. Air bubbles in the syringe barrel are expelled and the syringe is attached to an appropriate injection needle. Patency of the needle should be confirmed. A new, sterile needle and syringe should be used to enter the vial on each occasion for removal of BOTOX.

Reconstituted BOTOX should be clear, colorless, and free of particulate matter. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration and whenever the solution and the container permit.

### 2.3 Bladder Dysfunction

#### General

Patients must not have a urinary tract infection (UTI) at the time of treatment. Prophylactic antibiotics, except aminoglycosides, [*see Drug Interactions (7.1)*] should be administered 1-3 days pre-treatment, on the treatment day, and 1-3 days post-treatment to reduce the likelihood of procedure-related UTI.

Patients should discontinue anti-platelet therapy at least 3 days before the injection procedure. Patients on anti-coagulant therapy need to be managed appropriately to decrease the risk of bleeding.

Appropriate caution should be exercised when performing a cystoscopy.

#### *Overactive Bladder*

An intravesical instillation of diluted local anesthetic with or without sedation may be used prior to injection, per local site practice. If a local anesthetic instillation is performed, the bladder should be drained and irrigated with sterile saline before injection.

The recommended dose is 100 Units of BOTOX, and is the maximum recommended dose. The recommended dilution is 100 Units/10 mL with preservative-free 0.9% Sodium Chloride Injection, USP (see Table 1). Dispose of any unused saline.

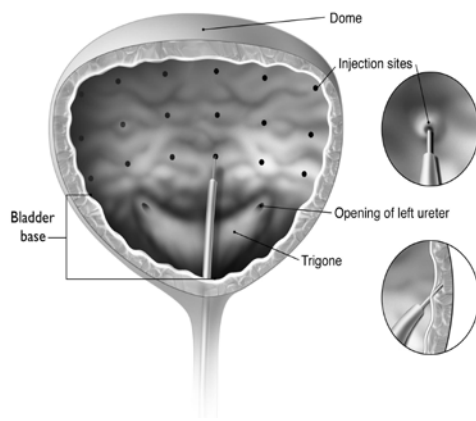
Reconstituted BOTOX (100 Units/10 mL) is injected into the detrusor muscle via a flexible or rigid cystoscope, avoiding the trigone. The bladder should be instilled with enough saline to achieve adequate visualization for the injections, but over-distension should be avoided.

The injection needle should be filled (primed) with approximately 1 mL of reconstituted BOTOX prior to the start of injections (depending on the needle length) to remove any air.

The needle should be inserted approximately 2 mm into the detrusor, and 20 injections of 0.5 mL each (total volume of 10 mL) should be spaced approximately 1 cm apart (see Figure 1). For the final injection, approximately 1 mL of sterile normal saline should be injected so that the remaining BOTOX in the needle is delivered to the bladder. After the injections are given, patients should demonstrate their ability to void prior to leaving the clinic. The patient should be observed for at least 30 minutes post-injection and until a spontaneous void has occurred.

Patients should be considered for reinjection when the clinical effect of the previous injection has diminished (median time until patients qualified for the second treatment of BOTOX in double-blind, placebo-controlled clinical studies was 169 days [~24 weeks]), but no sooner than 12 weeks from the prior bladder injection.

**Figure 1: Injection Pattern for Intradetrusor Injections for Treatment of Overactive Bladder and Detrusor Overactivity associated with a Neurologic Condition**



#### *Detrusor Overactivity associated with a Neurologic Condition*

An intravesical instillation of diluted local anesthetic with or without sedation, or general anesthesia may be used prior to injection, per local site practice. If a local anesthetic instillation is performed, the bladder should be drained and irrigated with sterile saline before injection.

The recommended dose is 200 Units of BOTOX per treatment, and should not be exceeded.

#### 200 Unit Vial of BOTOX

- Reconstitute a 200 Unit vial of BOTOX with 6 mL of preservative-free 0.9% Sodium Chloride Injection, USP and mix the vial gently.
- Draw 2 mL from the vial into each of three 10 mL syringes.
- Complete the reconstitution by adding 8 mL of preservative-free 0.9% Sodium Chloride Injection, USP into each of the 10 mL syringes, and mix gently. This will result in three 10 mL syringes each containing 10 mL (~67 Units in each), for a total of 200 Units of reconstituted BOTOX.
- Use immediately after reconstitution in the syringe. Dispose of any unused saline.

## 100 Unit Vial of BOTOX

- Reconstitute two 100 Unit vials of BOTOX, each with 6 mL of preservative-free 0.9% Sodium Chloride Injection, USP and mix the vials gently.
- Draw 4 mL from each vial into each of two 10 mL syringes. Draw the remaining 2 mL from each vial into a third 10 mL syringe for a total of 4 mL in each syringe.
- Complete the reconstitution by adding 6 mL of preservative-free 0.9% Sodium Chloride Injection, USP into each of the 10 mL syringes, and mix gently. This will result in three 10 mL syringes each containing 10 mL (~67 Units in each), for a total of 200 Units of reconstituted BOTOX.
- Use immediately after reconstitution in the syringe. Dispose of any unused saline.

Reconstituted BOTOX (200 Units/30 mL) is injected into the detrusor muscle via a flexible or rigid cystoscope, avoiding the trigone. The bladder should be instilled with enough saline to achieve adequate visualization for the injections, but over-distension should be avoided.

The injection needle should be filled (primed) with approximately 1 mL of reconstituted BOTOX prior to the start of injections (depending on the needle length) to remove any air.

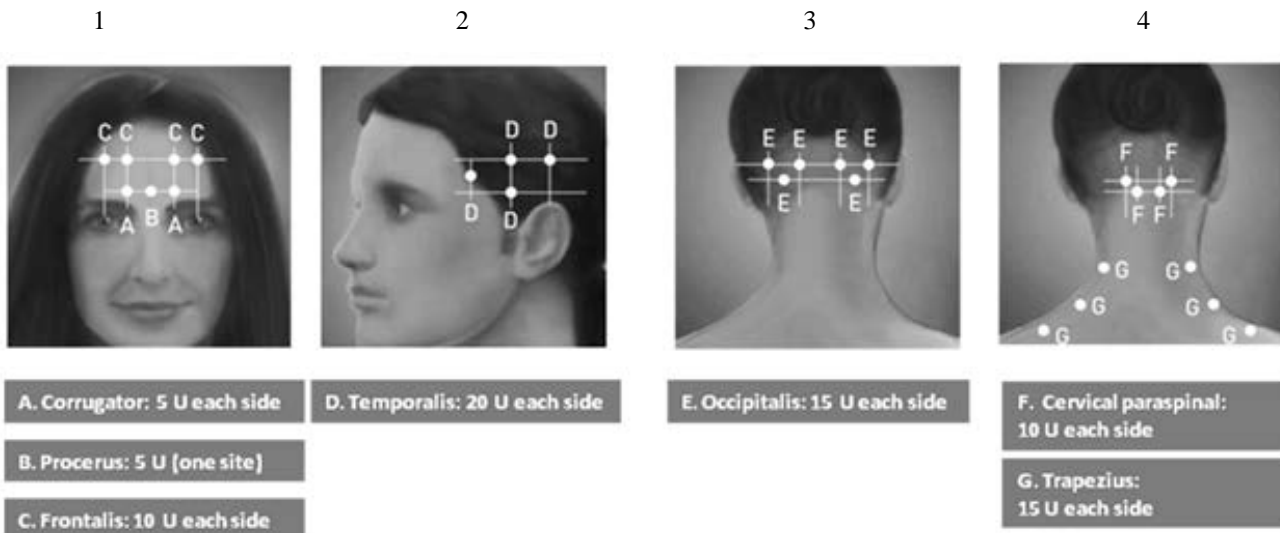
The needle should be inserted approximately 2 mm into the detrusor, and 30 injections of 1 mL (~6.7 Units) each (total volume of 30 mL) should be spaced approximately 1 cm apart (see Figure 1). For the final injection, approximately 1 mL of sterile normal saline should be injected so that the remaining BOTOX in the needle is delivered to the bladder. After the injections are given, the saline used for bladder wall visualization should be drained. The patient should be observed for at least 30 minutes post-injection.

Patients should be considered for re-injection when the clinical effect of the previous injection diminishes (median time to qualification for re-treatment in the double-blind, placebo-controlled clinical studies was 295-337 days [42-48 weeks] for BOTOX 200 Units), but no sooner than 12 weeks from the prior bladder injection.

## 2.4 Chronic Migraine

The recommended dilution is 200 Units/4 mL or 100 Units/2 mL, with a final concentration of 5 Units per 0.1 mL (see Table 1). The recommended dose for treating chronic migraine is 155 Units administered intramuscularly using a sterile 30-gauge, 0.5 inch needle as 0.1 mL (5 Units) injections per each site. Injections should be divided across 7 specific head/neck muscle areas as specified in the diagrams and Table 2 below. A one inch needle may be needed in the neck region for patients with thick neck muscles. With the exception of the procerus muscle, which should be injected at one site (midline), all muscles should be injected bilaterally with half the number of injection sites administered to the left, and half to the right side of the head and neck. The recommended re-treatment schedule is every 12 weeks.

Diagrams 1-4: Recommended Injection Sites (A through G) for Chronic Migraine



**Table 2: BOTOX Dosing by Muscle for Chronic Migraine**

Head/Neck Area	Recommended Dose (Number of Sites <sup>a</sup> )
Frontalis <sup>b</sup>	20 Units divided in 4 sites
Corrugator <sup>b</sup>	10 Units divided in 2 sites
Procerus	5 Units in 1 site
Occipitalis <sup>b</sup>	30 Units divided in 6 sites
Temporalis <sup>b</sup>	40 Units divided in 8 sites
Trapezius <sup>b</sup>	30 Units divided in 6 sites
Cervical Paraspinal Muscle Group <sup>b</sup>	20 Units divided in 4 sites
<b>Total Dose:</b>	<b>155 Units divided in 31 sites</b>

<sup>a</sup> Each IM injection site = 0.1 mL = 5 Units BOTOX

<sup>b</sup> Dose distributed bilaterally

## 2.5 Spasticity

Dosing in initial and sequential treatment sessions should be tailored to the individual based on the size, number and location of muscles involved, severity of spasticity, the presence of local muscle weakness, the patient's response to previous treatment, or adverse event history with BOTOX.

The recommended dilution is 200 Units/4 mL or 100 Units/2 mL with preservative-free 0.9% Sodium Chloride Injection, USP (see Table 1). The lowest recommended starting dose should be used, and no more than 50 Units per site should generally be administered. An appropriately sized needle (e.g., 25-30 gauge) may be used for superficial muscles, and a longer 22 gauge needle may be used for deeper musculature. Localization of the involved muscles with techniques such as needle electromyographic guidance or nerve stimulation is recommended.

Repeat BOTOX treatment may be administered when the effect of a previous injection has diminished, but generally no sooner than 12 weeks after the previous injection. The degree and pattern of muscle spasticity at the time of re-injection may necessitate alterations in the dose of BOTOX and muscles to be injected.

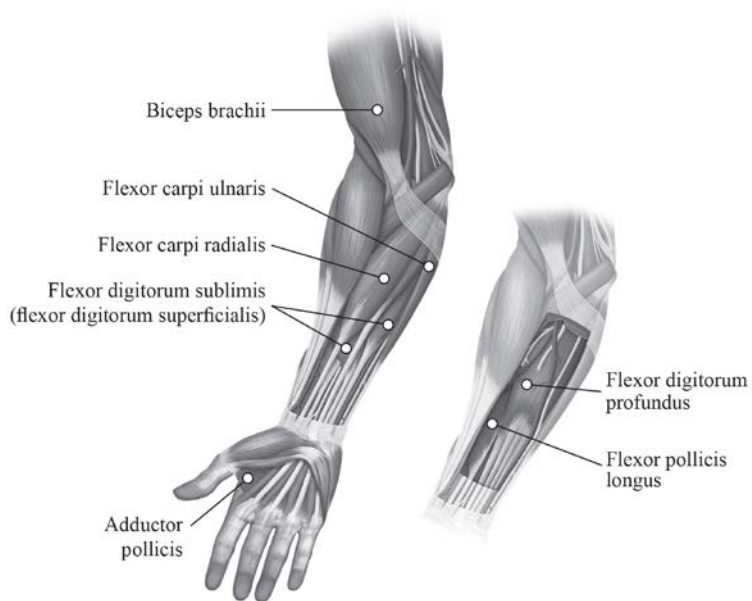
### *Upper Limb Spasticity*

In clinical trials, doses ranging from 75 Units to 400 Units were divided among selected muscles (see Table 3 and Figure 2) at a given treatment session.

**Table 3: BOTOX Dosing by Muscle for Upper Limb Spasticity**

Muscle	Recommended Dose Total Dosage (Number of Sites)
Biceps Brachii	100 Units-200 Units divided in 4 sites
Flexor Carpi Radialis	12.5 Units-50 Units in 1 site
Flexor Carpi Ulnaris	12.5 Units-50 Units in 1 site
Flexor Digitorum Profundus	30 Units-50 Units in 1 site
Flexor Digitorum Sublimis	30 Units-50 Units in 1 site
Adductor Pollicis	20 Units in 1 site
Flexor Pollicis Longus	20 Units in 1 site

**Figure 2: Injection Sites for Upper Limb Spasticity**



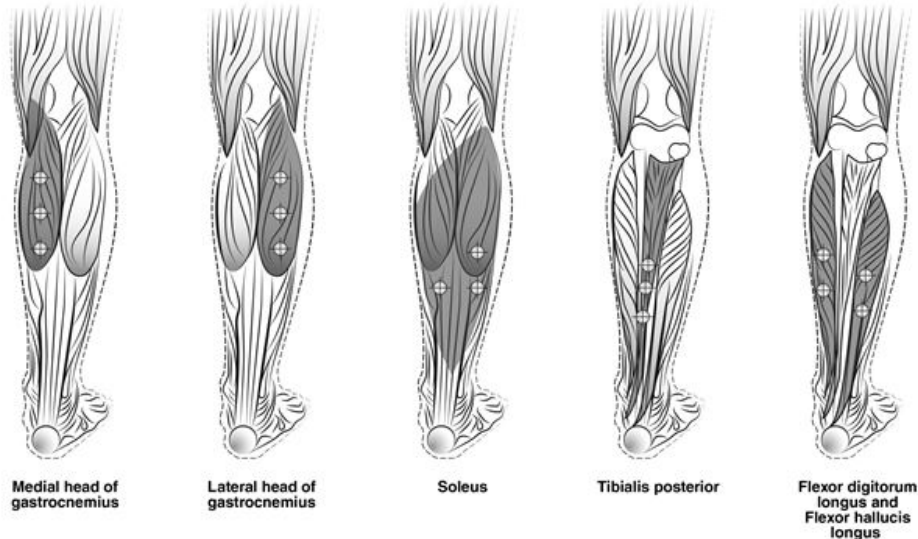
*Lower Limb Spasticity*

The recommended dose for treating lower limb spasticity is 300 Units to 400 Units divided among 5 muscles (gastrocnemius, soleus, tibialis posterior, flexor hallucis longus and flexor digitorum longus) (see Table 4 and Figure 3).

**Table 4: BOTOX Dosing by Muscle for Lower Limb Spasticity**

Muscle	Recommended Dose Total Dosage (Number of Sites)
Gastrocnemius medial head	75 Units divided in 3 sites
Gastrocnemius lateral head	75 Units divided in 3 sites
Soleus	75 Units divided in 3 sites
Tibialis Posterior	75 Units divided in 3 sites
Flexor hallucis longus	50 Units divided in 2 sites
Flexor digitorum longus	50 Units divided in 2 sites

**Figure 3: Injection Sites for Lower Limb Spasticity**



## 2.6 Cervical Dystonia

A double-blind, placebo-controlled study enrolled patients who had extended histories of receiving and tolerating BOTOX injections, with prior individualized adjustment of dose. The mean BOTOX dose administered to patients in this study was 236 Units (25th to 75th percentile range of 198 Units to 300 Units). The BOTOX dose was divided among the affected muscles [see *Clinical Studies (14.5)*].

Dosing in initial and sequential treatment sessions should be tailored to the individual patient based on the patient's head and neck position, localization of pain, muscle hypertrophy, patient response, and adverse event history. The initial dose for a patient without prior use of BOTOX should be at a lower dose, with subsequent dosing adjusted based on individual response. Limiting the total dose injected into the sternocleidomastoid muscle to 100 Units or less may decrease the occurrence of dysphagia [see *Warnings and Precautions (5.2, 5.5, 5.6)*].

The recommended dilution is 200 Units/2 mL, 200 Units/4 mL, 100 Units/1 mL, or 100 Units/2 mL with preservative-free 0.9% Sodium Chloride Injection, USP, depending on volume and number of injection sites desired to achieve treatment objectives (see Table 1). In general, no more than 50 Units per site should be administered using a sterile needle (e.g., 25-30 gauge) of an appropriate length. Localization of the involved muscles with electromyographic guidance may be useful.

Clinical improvement generally begins within the first two weeks after injection with maximum clinical benefit at approximately six weeks post-injection. In the double-blind, placebo-controlled study most subjects were observed to have returned to pre-treatment status by 3 months post-treatment.

## 2.7 Primary Axillary Hyperhidrosis

The recommended dose is 50 Units per axilla. The hyperhidrotic area to be injected should be defined using standard staining techniques, e.g., Minor's Iodine-Starch Test. The recommended dilution is 100 Units/4 mL with 0.9% preservative-free sterile saline (see Table 1). Using a sterile 30 gauge needle, 50 Units of BOTOX (2 mL) is injected intradermally in 0.1 to 0.2 mL aliquots to each axilla evenly distributed in multiple sites (10-15) approximately 1-2 cm apart.

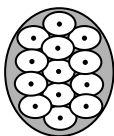
Repeat injections for hyperhidrosis should be administered when the clinical effect of a previous injection diminishes.

### *Instructions for the Minor's Iodine-Starch Test Procedure:*

Patients should shave underarms and abstain from use of over-the-counter deodorants or antiperspirants for 24 hours prior to the test. Patient should be resting comfortably without exercise, hot drinks for approximately 30 minutes prior to the test. Dry the underarm area and then immediately paint it with iodine solution. Allow the area to dry, then lightly sprinkle the area with starch powder. Gently blow off any excess starch powder. The hyperhidrotic area will develop a deep blue-black color over approximately 10 minutes.

Each injection site has a ring of effect of up to approximately 2 cm in diameter. To minimize the area of no effect, the injection sites should be evenly spaced as shown in Figure 4.

**Figure 4: Injection Pattern for Primary Axillary Hyperhidrosis**



Each dose is injected to a depth of approximately 2 mm and at a 45° angle to the skin surface, with the bevel side up to minimize leakage and to ensure the injections remain intradermal. If injection sites are marked in ink, do not inject BOTOX directly through the ink mark to avoid a permanent tattoo effect.

## **2.8      Blepharospasm**

For blepharospasm, reconstituted BOTOX is injected using a sterile, 27-30 gauge needle without electromyographic guidance. The initial recommended dose is 1.25 Units-2.5 Units (0.05 mL to 0.1 mL volume at each site) injected into the medial and lateral pre-tarsal orbicularis oculi of the upper lid and into the lateral pre-tarsal orbicularis oculi of the lower lid. Avoiding injection near the levator palpebrae superioris may reduce the complication of ptosis. Avoiding medial lower lid injections, and thereby reducing diffusion into the inferior oblique, may reduce the complication of diplopia. Ecchymosis occurs easily in the soft eyelid tissues. This can be prevented by applying pressure at the injection site immediately after the injection.

The recommended dilution to achieve 1.25 Units is 100 Units/8 mL; for 2.5 Units it is 100 Units/4 mL (see Table 1).

In general, the initial effect of the injections is seen within three days and reaches a peak at one to two weeks post-treatment. Each treatment lasts approximately three months, following which the procedure can be repeated. At repeat treatment sessions, the dose may be increased up to two-fold if the response from the initial treatment is considered insufficient, usually defined as an effect that does not last longer than two months. However, there appears to be little benefit obtainable from injecting more than 5 Units per site. Some tolerance may be found when BOTOX is used in treating blepharospasm if treatments are given any more frequently than every three months, and is rare to have the effect be permanent.

The cumulative dose of BOTOX treatment for blepharospasm in a 30-day period should not exceed 200 Units.

## **2.9      Strabismus**

BOTOX is intended for injection into extraocular muscles utilizing the electrical activity recorded from the tip of the injection needle as a guide to placement within the target muscle. Injection without surgical exposure or electromyographic guidance should not be attempted. Physicians should be familiar with electromyographic technique.

To prepare the eye for BOTOX injection, it is recommended that several drops of a local anesthetic and an ocular decongestant be given several minutes prior to injection.

The volume of BOTOX injected for treatment of strabismus should be between 0.05-0.15 mL per muscle.

The initial listed doses of the reconstituted BOTOX [*see Dosage and Administration (2.2)*] typically create paralysis of the injected muscles beginning one to two days after injection and increasing in intensity during the first week. The paralysis lasts for 2-6 weeks and gradually resolves over a similar time period. Overcorrections lasting over six months have been rare. About one half of patients will require subsequent doses because of inadequate paralytic response of the muscle to the initial dose, or because of mechanical factors such as large deviations or restrictions, or because of the lack of binocular motor fusion to stabilize the alignment.

### *Initial doses in Units*

Use the lower listed doses for treatment of small deviations. Use the larger doses only for large deviations.

- For vertical muscles, and for horizontal strabismus of less than 20 prism diopters: 1.25 Units-2.5 Units in any one muscle.
- For horizontal strabismus of 20 prism diopters to 50 prism diopters: 2.5 Units-5 Units in any one muscle.
- For persistent VI nerve palsy of one month or longer duration: 1.25 Units-2.5 Units in the medial rectus muscle.

### *Subsequent doses for residual or recurrent strabismus*

- It is recommended that patients be re-examined 7-14 days after each injection to assess the effect of that dose.
- Patients experiencing adequate paralysis of the target muscle that require subsequent injections should receive a dose comparable to the initial dose.
- Subsequent doses for patients experiencing incomplete paralysis of the target muscle may be increased up to two-fold compared to the previously administered dose.
- Subsequent injections should not be administered until the effects of the previous dose have dissipated as evidenced by substantial function in the injected and adjacent muscles.
- The maximum recommended dose as a single injection for any one muscle is 25 Units.

The recommended dilution to achieve 1.25 Units is 100 Units/8 mL; for 2.5 Units it is 100 Units/4 mL (see Table 1).

## **3           DOSAGE FORMS AND STRENGTHS**

Single-use, sterile 100 Units or 200 Units vacuum-dried powder for reconstitution only with sterile, preservative-free 0.9% Sodium Chloride Injection USP prior to injection.

## 4 CONTRAINDICATIONS

### 4.1 Known Hypersensitivity to Botulinum Toxin

BOTOX is contraindicated in patients who are hypersensitive to any botulinum toxin preparation or to any of the components in the formulation [see *Warnings and Precautions (5.4)*].

### 4.2 Infection at the Injection Site(s)

BOTOX is contraindicated in the presence of infection at the proposed injection site(s).

### 4.3 Urinary Tract Infection or Urinary Retention

Intradermal injection of BOTOX is contraindicated in patients with overactive bladder or detrusor overactivity associated with a neurologic condition who have a urinary tract infection. Intradermal injection of BOTOX is also contraindicated in patients with urinary retention and in patients with post-void residual (PVR) urine volume >200 mL, who are not routinely performing clean intermittent self-catheterization (CIC).

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Lack of Interchangeability between Botulinum Toxin Products

The potency Units of BOTOX are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products and, therefore, units of biological activity of BOTOX cannot be compared to nor converted into units of any other botulinum toxin products assessed with any other specific assay method [see *Description (11)*].

### 5.2 Spread of Toxin Effect

Postmarketing safety data from BOTOX and other approved botulinum toxins suggest that botulinum toxin effects may, in some cases, be observed beyond the site of local injection. The symptoms are consistent with the mechanism of action of botulinum toxin and may include asthenia, generalized muscle weakness, diplopia, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death related to spread of toxin effects. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions, and particularly in those patients who have an underlying condition that would predispose them to these symptoms. In unapproved uses, including spasticity in children, and in approved indications, symptoms consistent with spread of toxin effect have been reported at doses comparable to or lower than doses used to treat cervical dystonia and spasticity. Patients or caregivers should be advised to seek immediate medical care if swallowing, speech or respiratory disorders occur.

No definitive serious adverse event reports of distant spread of toxin effect associated with BOTOX for blepharospasm at the recommended dose (30 Units and below), severe primary axillary hyperhidrosis at the recommended dose (100 Units), strabismus, or for chronic migraine at the labeled doses have been reported.

### 5.3 Serious Adverse Reactions with Unapproved Use

Serious adverse reactions, including excessive weakness, dysphagia, and aspiration pneumonia, with some adverse reactions associated with fatal outcomes, have been reported in patients who received BOTOX injections for unapproved uses. In these cases, the adverse reactions were not necessarily related to distant spread of toxin, but may have resulted from the administration of BOTOX to the site of injection and/or adjacent structures. In several of the cases, patients had pre-existing dysphagia or other significant disabilities. There is insufficient information to identify factors associated with an increased risk for adverse reactions associated with the unapproved uses of BOTOX. The safety and effectiveness of BOTOX for unapproved uses have not been established.

### 5.4 Hypersensitivity Reactions

Serious and/or immediate hypersensitivity reactions have been reported. These reactions include anaphylaxis, serum sickness, urticaria, soft tissue edema, and dyspnea. If such a reaction occurs, further injection of BOTOX should be discontinued and appropriate medical therapy immediately instituted. One fatal case of anaphylaxis has been reported in which lidocaine was used as the diluent, and consequently the causal agent cannot be reliably determined.

### 5.5 Increased Risk of Clinically Significant Effects with Pre-Existing Neuromuscular Disorders

Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis or neuromuscular junction disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome) should be monitored when given botulinum toxin. Patients with neuromuscular disorders may be at increased risk of clinically significant effects including generalized muscle weakness, diplopia, ptosis, dysphonia, dysarthria, severe dysphagia and respiratory compromise from therapeutic doses of BOTOX [see *Warnings and Precautions (5.6)*].

### 5.6 Dysphagia and Breathing Difficulties

Treatment with BOTOX and other botulinum toxin products can result in swallowing or breathing difficulties. Patients with pre-existing swallowing or breathing difficulties may be more susceptible to these complications. In most cases, this is a consequence of weakening of muscles in the area of injection that are involved in breathing or oropharyngeal muscles that control swallowing or breathing [see *Warnings and Precautions (5.2)*].



Deaths as a complication of severe dysphagia have been reported after treatment with botulinum toxin. Dysphagia may persist for several months, and require use of a feeding tube to maintain adequate nutrition and hydration. Aspiration may result from severe dysphagia and is a particular risk when treating patients in whom swallowing or respiratory function is already compromised.

Treatment with botulinum toxins may weaken neck muscles that serve as accessory muscles of ventilation. This may result in a critical loss of breathing capacity in patients with respiratory disorders who may have become dependent upon these accessory muscles. There have been postmarketing reports of serious breathing difficulties, including respiratory failure.

Patients with smaller neck muscle mass and patients who require bilateral injections into the sternocleidomastoid muscle for the treatment of cervical dystonia have been reported to be at greater risk for dysphagia. Limiting the dose injected into the sternocleidomastoid muscle may reduce the occurrence of dysphagia. Injections into the levator scapulae may be associated with an increased risk of upper respiratory infection and dysphagia.

Patients treated with botulinum toxin may require immediate medical attention should they develop problems with swallowing, speech or respiratory disorders. These reactions can occur within hours to weeks after injection with botulinum toxin [see *Warnings and Precautions (5.2)*].

### 5.7 Pulmonary Effects of BOTOX in Patients with Compromised Respiratory Status Treated for Spasticity or for Detrusor Overactivity associated with a Neurologic Condition

Patients with compromised respiratory status treated with BOTOX for spasticity should be monitored closely. In a double-blind, placebo-controlled, parallel group study in patients treated for upper limb spasticity with stable reduced pulmonary function (defined as FEV<sub>1</sub> 40-80% of predicted value and FEV<sub>1</sub>/FVC ≤ 0.75), the event rate in change of Forced Vital Capacity ≥15% or ≥20% was generally greater in patients treated with BOTOX than in patients treated with placebo (see Table 5).

**Table 5: Event rate per patient treatment cycle among patients with reduced lung function who experienced at least a 15% or 20% decrease in forced vital capacity from baseline at Week 1, 6, 12 post-injection with up to two treatment cycles with BOTOX or placebo**

	BOTOX 360 Units		BOTOX 240 Units		Placebo	
	≥15%	≥20%	≥15%	≥20%	≥15%	≥20%
Week 1	4%	0%	3%	0%	7%	3%
Week 6	7%	4%	4%	2%	2%	2%
Week 12	10%	5%	2%	1%	4%	1%

Differences from placebo were not statistically significant

In spasticity patients with reduced lung function, upper respiratory tract infections were also reported more frequently as adverse reactions in patients treated with BOTOX than in patients treated with placebo [see *Warnings and Precautions (5.10)*].

In an ongoing double-blind, placebo-controlled, parallel group study in adult patients with detrusor overactivity associated with a neurologic condition and restrictive lung disease of neuromuscular etiology [defined as FVC 50-80% of predicted value in patients with spinal cord injury between C5 and C8, or MS] the event rate in change of Forced Vital Capacity ≥15% or ≥20% was generally greater in patients treated with BOTOX than in patients treated with placebo (see Table 6).

**Table 6: Number and percent of patients experiencing at least a 15% or 20% decrease in FVC from baseline at Week 2, 6, 12 post-injection with BOTOX or placebo**

	BOTOX 200 Units		Placebo	
	≥15%	≥20%	≥15%	≥20%
Week 2	0/12 (0%)	0/12 (0%)	1/11 (9%)	0/11 (0%)
Week 6	2/11 (18%)	1/11 (9%)	0/11 (0%)	0/11 (0%)
Week 12	0/11 (0%)	0/11 (0%)	0/6 (0%)	0/6 (0%)

### 5.8 Corneal Exposure and Ulceration in Patients Treated with BOTOX for Blepharospasm

Reduced blinking from BOTOX injection of the orbicularis muscle can lead to corneal exposure, persistent epithelial defect, and corneal ulceration, especially in patients with VII nerve disorders. Vigorous treatment of any epithelial defect should be employed. This may require protective drops, ointment, therapeutic soft contact lenses, or closure of the eye by patching or other means.

### 5.9 Retrobulbar Hemorrhages in Patients Treated with BOTOX for Strabismus

During the administration of BOTOX for the treatment of strabismus, retrobulbar hemorrhages sufficient to compromise retinal circulation have occurred. It is recommended that appropriate instruments to decompress the orbit be accessible.

#### 5.10 Bronchitis and Upper Respiratory Tract Infections in Patients Treated for Spasticity

Bronchitis was reported more frequently as an adverse reaction in patients treated for upper limb spasticity with BOTOX (3% at 251 Units-360 Units total dose), compared to placebo (1%). In patients with reduced lung function treated for upper limb spasticity, upper respiratory tract infections were also reported more frequently as adverse reactions in patients treated with BOTOX (11% at 360 Units total dose; 8% at 240 Units total dose) compared to placebo (6%). In adult patients treated for lower limb spasticity, upper respiratory tract infections were reported more frequently as an adverse event in patients treated with BOTOX (2% at 300 Units to 400 Units total dose) compared to placebo (1%).

#### 5.11 Autonomic Dysreflexia in Patients Treated for Detrusor Overactivity associated with a Neurologic Condition

Autonomic dysreflexia associated with intradetrusor injections of BOTOX could occur in patients treated for detrusor overactivity associated with a neurologic condition and may require prompt medical therapy. In clinical trials, the incidence of autonomic dysreflexia was greater in patients treated with BOTOX 200 Units compared with placebo (1.5% versus 0.4%, respectively).

#### 5.12 Urinary Tract Infections in Patients with Overactive Bladder

BOTOX increases the incidence of urinary tract infection [see *Adverse Reactions (6.1)*]. Clinical trials for overactive bladder excluded patients with more than 2 UTIs in the past 6 months and those taking antibiotics chronically due to recurrent UTIs. Use of BOTOX for the treatment of overactive bladder in such patients and in patients with multiple recurrent UTIs during treatment should only be considered when the benefit is likely to outweigh the potential risk.

#### 5.13 Urinary Retention in Patients Treated for Bladder Dysfunction

Due to the risk of urinary retention, treat only patients who are willing and able to initiate catheterization post-treatment, if required, for urinary retention.

In patients who are not catheterizing, post-void residual (PVR) urine volume should be assessed within 2 weeks post-treatment and periodically as medically appropriate up to 12 weeks, particularly in patients with multiple sclerosis or diabetes mellitus. Depending on patient symptoms, institute catheterization if PVR urine volume exceeds 200 mL and continue until PVR falls below 200 mL. Instruct patients to contact their physician if they experience difficulty in voiding as catheterization may be required.

The incidence and duration of urinary retention is described below for patients with overactive bladder and detrusor overactivity associated with a neurologic condition who received BOTOX or placebo injections.

#### *Overactive Bladder*

In double-blind, placebo-controlled trials in patients with OAB, the proportion of subjects who initiated clean intermittent catheterization (CIC) for urinary retention following treatment with BOTOX or placebo is shown in Table 7. The duration of post-injection catheterization for those who developed urinary retention is also shown.

**Table 7: Proportion of Patients Catheterizing for Urinary Retention and Duration of Catheterization following an injection in double-blind, placebo-controlled clinical trials in OAB**

Timepoint	BOTOX 100 Units (N=552)	Placebo (N=542)
<b>Proportion of Patients Catheterizing for Urinary Retention</b>		
At any time during complete treatment cycle	6.5% (n=36)	0.4% (n=2)
<b>Duration of Catheterization for Urinary Retention (Days)</b>		
Median	63	11
Min, Max	1, 214	3, 18

Patients with diabetes mellitus treated with BOTOX were more likely to develop urinary retention than those without diabetes, as shown in Table 8.

**Table 8. Proportion of Patients Experiencing Urinary Retention following an injection in double-blind, placebo-controlled clinical trials in OAB according to history of Diabetes Mellitus**

	Patients with Diabetes		Patients without Diabetes	
	BOTOX 100 Units (N=81)	Placebo (N=69)	BOTOX 100 Units (N=526)	Placebo (N=516)
Urinary retention	12.3% (n=10)	0	6.3% (n=33)	0.6% (n=3)

*Detrusor Overactivity associated with a Neurologic Condition*

In double-blind, placebo-controlled trials in patients with detrusor overactivity associated with a neurologic condition, the proportion of subjects who were not using clean intermittent catheterization (CIC) prior to injection and who subsequently required catheterization for urinary retention following treatment with BOTOX or placebo is shown in Table 9. The duration of post-injection catheterization for those who developed urinary retention is also shown.

**Table 9: Proportion of Patients not using CIC at baseline and then Catheterizing for Urinary Retention and Duration of Catheterization following an injection in double-blind, placebo-controlled clinical trials**

Timepoint	BOTOX 200 Units (N=108)	Placebo (N=104)
<b>Proportion of Patients Catheterizing for Urinary Retention</b>		
At any time during complete treatment cycle	30.6% (n=33)	6.7% (n=7)
<b>Duration of Catheterization for Urinary Retention (Days)</b>		
Median	289	358
Min, Max	1, 530	2, 379

Among patients not using CIC at baseline, those with MS were more likely to require CIC post-injection than those with SCI (see Table 10).

**Table 10: Proportion of Patients by Etiology (MS and SCI) not using CIC at baseline and then Catheterizing for Urinary Retention following an injection in double-blind, placebo-controlled clinical trials**

Timepoint	MS		SCI	
	BOTOX 200 Units (N=86)	Placebo (N=88)	BOTOX 200 Units (N=22)	Placebo (N=16)
At any time during complete treatment cycle	31% (n=27)	5% (n=4)	27% (n=6)	19% (n=3)

**5.14 Human Albumin and Transmission of Viral Diseases**

This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) is also considered extremely remote. No cases of transmission of viral diseases or CJD have ever been reported for albumin.

**6 ADVERSE REACTIONS**

The following adverse reactions to BOTOX (onabotulinumtoxinA) for injection are discussed in greater detail in other sections of the labeling:

- Spread of Toxin Effects [see Warnings and Precautions (5.2)]
- Serious Adverse Reactions with Unapproved Use [see Warnings and Precautions (5.3)]
- Hypersensitivity Reactions [see Contraindications (4.1) and Warnings and Precautions (5.4)]
- Increased Risk of Clinically Significant Effects with Pre-Existing Neuromuscular Disorders [see Warnings and Precautions (5.5)]
- Dysphagia and Breathing Difficulties [see Warnings and Precautions (5.6)]
- Pulmonary Effects of BOTOX in Patients with Compromised Respiratory Status Treated for Spasticity or for Detrusor Overactivity associated with a Neurologic Condition [see Warnings and Precautions (5.7)]
- Corneal Exposure and Ulceration in Patients Treated with BOTOX for Blepharospasm [see Warnings and Precautions (5.8)]
- Retrobulbar Hemorrhages in Patients Treated with BOTOX for Strabismus [see Warnings and Precautions (5.9)]
- Bronchitis and Upper Respiratory Tract Infections in Patients Treated for Spasticity [see Warnings and Precautions (5.10)]
- Autonomic Dysreflexia in Patients Treated for Detrusor Overactivity associated with a Neurologic Condition [see Warnings and Precautions (5.11)]
- Urinary Tract Infections in Patients with Overactive Bladder [see Warnings and Precautions (5.12)]

- Urinary Retention in Patients Treated for Bladder Dysfunction [see Warnings and Precautions (5.13)]

## 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

BOTOX and BOTOX Cosmetic contain the same active ingredient in the same formulation, but with different labeled Indications and Usage. Therefore, adverse reactions observed with the use of BOTOX Cosmetic also have the potential to be observed with the use of BOTOX.

In general, adverse reactions occur within the first week following injection of BOTOX and while generally transient, may have a duration of several months or longer. Localized pain, infection, inflammation, tenderness, swelling, erythema, and/or bleeding/bruising may be associated with the injection. Needle-related pain and/or anxiety may result in vasovagal responses (including e.g., syncope, hypotension), which may require appropriate medical therapy.

Local weakness of the injected muscle(s) represents the expected pharmacological action of botulinum toxin. However, weakness of nearby muscles may also occur due to spread of toxin [see Warnings and Precautions (5.2)].

### *Overactive Bladder*

Table 11 presents the most frequently reported adverse reactions in double-blind, placebo-controlled clinical trials for overactive bladder occurring within 12 weeks of the first BOTOX treatment.

**Table 11: Adverse Reactions Reported by  $\geq 2\%$  of BOTOX treated Patients and More Often than in Placebo-treated Patients Within the First 12 Weeks after Intradetrusor Injection, in Double-blind, Placebo-controlled Clinical Trials in Patients with OAB**

Adverse Reactions	BOTOX 100 Units (N=552)	Placebo (N=542)
Urinary tract infection	99 (18%)	30 (6%)
Dysuria	50 (9%)	36 (7%)
Urinary retention	31 (6%)	2 (0%)
Bacteriuria	24 (4%)	11 (2%)
Residual urine volume*	17 (3%)	1 (0%)

\*Elevated PVR not requiring catheterization. Catheterization was required for PVR  $\geq 350$  mL regardless of symptoms, and for PVR  $\geq 200$  mL to  $<350$  mL with symptoms (e.g., voiding difficulty).

A higher incidence of urinary tract infection was observed in patients with diabetes mellitus treated with BOTOX 100 Units and placebo than in patients without diabetes, as shown in Table 12.

**Table 12: Proportion of Patients Experiencing Urinary Tract Infection following an Injection in Double-blind, Placebo-controlled Clinical Trials in OAB according to history of Diabetes Mellitus**

	Patients with Diabetes		Patients without Diabetes	
	BOTOX 100 Units (N=81)	Placebo (N=69)	BOTOX 100 Units (N=526)	Placebo (N=516)
Urinary tract infection (UTI)	25 (31%)	8 (12%)	135 (26%)	51 (10%)

The incidence of UTI increased in patients who experienced a maximum post-void residual (PVR) urine volume  $\geq 200$  mL following BOTOX injection compared to those with a maximum PVR  $<200$  mL following BOTOX injection, 44% versus 23%, respectively. No change was observed in the overall safety profile with repeat dosing during an open-label, uncontrolled extension trial.

### *Detrusor Overactivity associated with a Neurologic Condition*

Table 13 presents the most frequently reported adverse reactions in double-blind, placebo-controlled studies within 12 weeks of injection for detrusor overactivity associated with a neurologic condition.

**Table 13: Adverse Reactions Reported by  $\geq 2\%$  of BOTOX treated Patients and More Frequent than in Placebo-treated Patients Within the First 12 Weeks after Intradermal Injection in Double-blind, Placebo-controlled Clinical Trials**

Adverse Reactions	BOTOX 200 Units (N=262)	Placebo (N=272)
Urinary tract infection	64 (24%)	47 (17%)
Urinary retention	45 (17%)	8 (3%)
Hematuria	10 (4%)	8 (3%)

The following adverse reactions with BOTOX 200 Units were reported at any time following initial injection and prior to re-injection or study exit (median duration of 44 weeks of exposure): urinary tract infections (49%), urinary retention (17%), constipation (4%), muscular weakness (4%), dysuria (4%), fall (3%), gait disturbance (3%), and muscle spasm (2%).

In the MS patients enrolled in the double-blind, placebo-controlled trials, the MS exacerbation annualized rate (i.e., number of MS exacerbation events per patient-year) was 0.23 for BOTOX and 0.20 for placebo.

No change was observed in the overall safety profile with repeat dosing.

#### *Chronic Migraine*

In double-blind, placebo-controlled chronic migraine efficacy trials (Study 1 and Study 2), the discontinuation rate was 12% in the BOTOX treated group and 10% in the placebo-treated group. Discontinuations due to an adverse event were 4% in the BOTOX group and 1% in the placebo group. The most frequent adverse events leading to discontinuation in the BOTOX group were neck pain, headache, worsening migraine, muscular weakness and eyelid ptosis.

The most frequently reported adverse reactions following injection of BOTOX for chronic migraine appear in Table 14.

**Table 14: Adverse Reactions Reported by  $\geq 2\%$  of BOTOX treated Patients and More Frequent than in Placebo-treated Patients in Two Chronic Migraine Double-blind, Placebo-controlled Clinical Trials**

Adverse Reactions by System Organ Class	BOTOX 155 Units-195 Units (N=687)	Placebo (N=692)
Nervous system disorders		
Headache	32 (5%)	22 (3%)
Migraine	26 (4%)	18 (3%)
Facial paresis	15 (2%)	0 (0%)
Eye disorders		
Eyelid ptosis	25 (4%)	2 (<1%)
Infections and Infestations		
Bronchitis	17 (3%)	11 (2%)
Musculoskeletal and connective tissue disorders		
Neck pain	60 (9%)	19 (3%)
Musculoskeletal stiffness	25 (4%)	6 (1%)
Muscular weakness	24 (4%)	2 (<1%)
Myalgia	21 (3%)	6 (1%)
Musculoskeletal pain	18 (3%)	10 (1%)
Muscle spasms	13 (2%)	6 (1%)
General disorders and administration site conditions		
Injection site pain	23 (3%)	14 (2%)
Vascular Disorders		
Hypertension	11 (2%)	7 (1%)

Other adverse reactions that occurred more frequently in the BOTOX group compared to the placebo group at a frequency less than 1% and potentially BOTOX related include: vertigo, dry eye, eyelid edema, dysphagia, eye infection, and jaw pain. Severe worsening of migraine requiring hospitalization occurred in approximately 1% of BOTOX treated patients in Study 1 and Study 2, usually within the first week after treatment, compared to 0.3% of placebo-treated patients.

#### *Upper Limb Spasticity*

The most frequently reported adverse reactions following injection of BOTOX for adult upper limb spasticity appear in Table 15.

**Table 15: Adverse Reactions Reported by  $\geq 2\%$  of BOTOX treated Patients and More Frequent than in Placebo-treated Patients in Adult Upper Limb Spasticity Double-blind, Placebo-controlled Clinical Trials**

Adverse Reactions by System Organ Class	BOTOX 251 Units- 360 Units (N=115)	BOTOX 150 Units- 250 Units (N=188)	BOTOX <150 Units (N=54)	Placebo (N=182)
Gastrointestinal disorder Nausea	3 (3%)	3 (2%)	1 (2%)	1 (1%)
General disorders and administration site conditions Fatigue	4 (3%)	4 (2%)	1 (2%)	0
Infections and infestations Bronchitis	4 (3%)	4 (2%)	0	2 (1%)
Musculoskeletal and connective tissue disorders Pain in extremity Muscular weakness	7 (6%) 0	10 (5%) 7 (4%)	5 (9%) 1 (2%)	8 (4%) 2 (1%)

Twenty two adult patients, enrolled in double-blind placebo controlled studies, received 400 Units or higher of BOTOX for treatment of upper limb spasticity. In addition, 44 adults received 400 Units of BOTOX or higher for four consecutive treatments over approximately one year for treatment of upper limb spasticity. The type and frequency of adverse reactions observed in patients treated with 400 Units of BOTOX were similar to those reported in patients treated for upper limb spasticity with 360 Units of BOTOX.

#### *Lower Limb Spasticity*

The most frequently reported adverse reactions following injection of BOTOX for adult lower limb spasticity appear in Table 16. Two hundred thirty one patients enrolled in a double-blind placebo controlled study (Study 6) received 300 Units to 400 Units of BOTOX, and were compared with 233 patients who received placebo. Patients were followed for an average of 91 days after injection.

**Table 16: Adverse Reactions Reported by  $\geq 2\%$  of BOTOX treated Patients and More Frequent than in Placebo-treated Patients in Adult Lower Limb Spasticity Double-blind, Placebo-controlled Clinical Trial (Study 6)**

Adverse Reactions	BOTOX (N=231)	Placebo (N=233)
Musculoskeletal and connective tissue disorders Arthralgia Back pain Myalgia	8 (3%) 6 (3%) 4 (2%)	2 (1%) 4 (2%) 3 (1%)
Infections and infestations Upper respiratory tract infection	4 (2%)	2 (1%)
General disorders and administration site conditions Injection site pain	5 (2%)	2 (1%)

#### *Cervical Dystonia*

In cervical dystonia patients evaluated for safety in double-blind and open-label studies following injection of BOTOX, the most frequently reported adverse reactions were dysphagia (19%), upper respiratory infection (12%), neck pain (11%), and headache (11%).

Other events reported in 2-10% of patients in any one study in decreasing order of incidence include: increased cough, flu syndrome, back pain, rhinitis, dizziness, hypertonia, soreness at injection site, asthenia, oral dryness, speech disorder, fever, nausea, and drowsiness. Stiffness, numbness, diplopia, ptosis, and dyspnea have been reported.

Dysphagia and symptomatic general weakness may be attributable to an extension of the pharmacology of BOTOX resulting from the spread of the toxin outside the injected muscles [see *Warnings and Precautions* (5.2, 5.6)].

The most common severe adverse reaction associated with the use of BOTOX injection in patients with cervical dystonia is dysphagia with about 20% of these cases also reporting dyspnea [see *Warnings and Precautions* (5.2, 5.6)]. Most dysphagia is reported as mild or moderate in severity. However, it may be associated with more severe signs and symptoms [see *Warnings and Precautions* (5.6)].

Additionally, reports in the literature include a case of a female patient who developed brachial plexopathy two days after injection of 120 Units of BOTOX for the treatment of cervical dystonia, and reports of dysphonia in patients who have been treated for cervical dystonia.

#### *Primary Axillary Hyperhidrosis*

The most frequently reported adverse reactions (3-10% of adult patients) following injection of BOTOX in double-blind studies included injection site pain and hemorrhage, non-axillary sweating, infection, pharyngitis, flu syndrome, headache, fever, neck or back pain, pruritus, and anxiety.

The data reflect 346 patients exposed to BOTOX 50 Units and 110 patients exposed to BOTOX 75 Units in each axilla.

#### *Blepharospasm*

In a study of blepharospasm patients who received an average dose per eye of 33 Units (injected at 3 to 5 sites) of the currently manufactured BOTOX, the most frequently reported adverse reactions were ptosis (21%), superficial punctate keratitis (6%), and eye dryness (6%).

Other events reported in prior clinical studies in decreasing order of incidence include: irritation, tearing, lagophthalmos, photophobia, ectropion, keratitis, diplopia, entropion, diffuse skin rash, and local swelling of the eyelid skin lasting for several days following eyelid injection.

In two cases of VII nerve disorder, reduced blinking from BOTOX injection of the orbicularis muscle led to serious corneal exposure, persistent epithelial defect, corneal ulceration and a case of corneal perforation. Focal facial paralysis, syncope, and exacerbation of myasthenia gravis have also been reported after treatment of blepharospasm.

#### *Strabismus*

Extraocular muscles adjacent to the injection site can be affected, causing vertical deviation, especially with higher doses of BOTOX. The incidence rates of these adverse effects in 2058 adults who received a total of 3650 injections for horizontal strabismus was 17%. The incidence of ptosis has been reported to be dependent on the location of the injected muscles, 1% after inferior rectus injections, 16% after horizontal rectus injections and 38% after superior rectus injections.

In a series of 5587 injections, retrobulbar hemorrhage occurred in 0.3% of cases.

## **6.2 Immunogenicity**

As with all therapeutic proteins, there is a potential for immunogenicity. Formation of neutralizing antibodies to botulinum toxin type A may reduce the effectiveness of BOTOX treatment by inactivating the biological activity of the toxin.

In a long term, open-label study evaluating 326 cervical dystonia patients treated for an average of 9 treatment sessions with the current formulation of BOTOX, 4 (1.2%) patients had positive antibody tests. All 4 of these patients responded to BOTOX therapy at the time of the positive antibody test. However, 3 of these patients developed clinical resistance after subsequent treatment, while the fourth patient continued to respond to BOTOX therapy for the remainder of the study.

One patient among the 445 hyperhidrosis patients (0.2%), two patients among the 380 adult upper limb spasticity patients (0.5%), no patients among 406 migraine patients, no patients among 615 overactive bladder patients, and no patients among 475 detrusor overactivity associated with a neurologic condition patients with analyzed specimens developed the presence of neutralizing antibodies.

The data reflect the patients whose test results were considered positive or negative for neutralizing activity to BOTOX in a mouse protection assay. The results of these tests are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of neutralizing activity to BOTOX with the incidence of antibodies to other products may be misleading.

The critical factors for neutralizing antibody formation have not been well characterized. The results from some studies suggest that BOTOX injections at more frequent intervals or at higher doses may lead to greater incidence of antibody formation. The potential for antibody formation may be minimized by injecting with the lowest effective dose given at the longest feasible intervals between injections.

## **6.3 Post-Marketing Experience**

The following adverse reactions have been identified during post-approval use of BOTOX. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These reactions include: abdominal pain; alopecia, including madarosis; anorexia; brachial plexopathy;

denervation/muscle atrophy; diarrhea; hyperhidrosis; hypoacusis; hypoaesthesia; malaise; paresthesia; peripheral neuropathy; radiculopathy; erythema multiforme, dermatitis psoriasiform, and psoriasiform eruption; strabismus; tinnitus; and visual disturbances.

There have been spontaneous reports of death, sometimes associated with dysphagia, pneumonia, and/or other significant debility or anaphylaxis, after treatment with botulinum toxin [see *Warnings and Precautions (5.4, 5.6)*].

There have also been reports of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including cardiovascular disease. The exact relationship of these events to the botulinum toxin injection has not been established.

New onset or recurrent seizures have also been reported, typically in patients who are predisposed to experiencing these events. The exact relationship of these events to the botulinum toxin injection has not been established.

## **7 DRUG INTERACTIONS**

### **7.1 Aminoglycosides and Other Agents Interfering with Neuromuscular Transmission**

Co-administration of BOTOX and aminoglycosides or other agents interfering with neuromuscular transmission (e.g., curare-like compounds) should only be performed with caution as the effect of the toxin may be potentiated.

### **7.2 Anticholinergic Drugs**

Use of anticholinergic drugs after administration of BOTOX may potentiate systemic anticholinergic effects.

### **7.3 Other Botulinum Neurotoxin Products**

The effect of administering different botulinum neurotoxin products at the same time or within several months of each other is unknown. Excessive neuromuscular weakness may be exacerbated by administration of another botulinum toxin prior to the resolution of the effects of a previously administered botulinum toxin.

### **7.4 Muscle Relaxants**

Excessive weakness may also be exaggerated by administration of a muscle relaxant before or after administration of BOTOX.

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

Pregnancy Category C.

There are no adequate and well-controlled studies in pregnant women. BOTOX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

When BOTOX (4, 8, or 16 Units/kg) was administered intramuscularly to pregnant mice or rats two times during the period of organogenesis (on gestation days 5 and 13), reductions in fetal body weight and decreased fetal skeletal ossification were observed at the two highest doses. The no-effect dose for developmental toxicity in these studies (4 Units/kg) is approximately equal to the maximum recommended human dose of 400 Units on a body weight basis (Units/kg).

When BOTOX was administered intramuscularly to pregnant rats (0.125, 0.25, 0.5, 1, 4, or 8 Units/kg) or rabbits (0.063, 0.125, 0.25, or 0.5 Units/kg) daily during the period of organogenesis (total of 12 doses in rats, 13 doses in rabbits), reduced fetal body weights and decreased fetal skeletal ossification were observed at the two highest doses in rats and at the highest dose in rabbits. These doses were also associated with significant maternal toxicity, including abortions, early deliveries, and maternal death. The developmental no-effect doses in these studies of 1 Unit/kg in rats and 0.25 Units/kg in rabbits are less than the maximum recommended human dose of 400 Units based on Units/kg.

When pregnant rats received single intramuscular injections (1, 4, or 16 Units/kg) at three different periods of development (prior to implantation, implantation, or organogenesis), no adverse effects on fetal development were observed. The developmental no-effect level for a single maternal dose in rats (16 Units/kg) is approximately 2 times the maximum recommended human dose based on Units/kg.

### **8.3 Nursing Mothers**

It is not known whether BOTOX is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when BOTOX is administered to a nursing woman.

### **8.4 Pediatric Use**

#### *Bladder Dysfunction*

Safety and effectiveness in patients below the age of 18 years have not been established.

#### *Prophylaxis of Headaches in Chronic Migraine*



Safety and effectiveness in patients below the age of 18 years have not been established.

#### *Spasticity*

Safety and effectiveness in patients below the age of 18 years have not been established.

#### *Axillary Hyperhidrosis*

Safety and effectiveness in patients below the age of 18 years have not been established.

#### *Cervical Dystonia*

Safety and effectiveness in pediatric patients below the age of 16 years have not been established.

#### *Blepharospasm and Strabismus*

Safety and effectiveness in pediatric patients below the age of 12 years have not been established.

### 8.5 Geriatric Use

Overall, with the exception of Overactive Bladder (see below), clinical studies of BOTOX did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. There were too few patients over the age of 75 to enable any comparisons. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

#### *Overactive Bladder*

Of 1242 overactive bladder patients in placebo-controlled clinical studies of BOTOX, 41.4% (n=514) were 65 years of age or older, and 14.7% (n=182) were 75 years of age or older. Adverse reactions of UTI and urinary retention were more common in patients 65 years of age or older in both placebo and BOTOX groups compared to younger patients (see Table 17). Otherwise, there were no overall differences in the safety profile following BOTOX treatment between patients aged 65 years and older compared to younger patients in these studies.

**Table 17. Incidence of Urinary Tract Infection and Urinary Retention according to Age Group during First Placebo-controlled Treatment, Placebo-controlled Clinical Trials in Patients with OAB**

	<65 Years		65 to 74 Years		≥75 Years	
	<b>BOTOX 100 Units (N=344)</b>	<b>Placebo (N=348)</b>	<b>BOTOX 100 Units (N=169)</b>	<b>Placebo (N=151)</b>	<b>BOTOX 100 Units (N=94)</b>	<b>Placebo (N=86)</b>
<b>Adverse Reactions</b>						
Urinary tract infection	73 (21%)	23 (7%)	51 (30%)	20 (13%)	36 (38%)	16 (19%)
Urinary retention	21 (6%)	2 (0.6%)	14 (8%)	0 (0%)	8 (9%)	1 (1%)

Observed effectiveness was comparable between these age groups in placebo-controlled clinical studies.

## 10 OVERDOSAGE

Excessive doses of BOTOX (onabotulinumtoxinA) for injection may be expected to produce neuromuscular weakness with a variety of symptoms.

Symptoms of overdose are likely not to be present immediately following injection. Should accidental injection or oral ingestion occur or overdose be suspected, the person should be medically supervised for several weeks for signs and symptoms of systemic muscular weakness which could be local, or distant from the site of injection [see *Boxed Warning and Warnings and Precautions (5.2, 5.6)*]. These patients should be considered for further medical evaluation and appropriate medical therapy immediately instituted, which may include hospitalization.

If the musculature of the oropharynx and esophagus are affected, aspiration may occur which may lead to development of aspiration pneumonia. If the respiratory muscles become paralyzed or sufficiently weakened, intubation and assisted respiration may be necessary until recovery takes place. Supportive care could involve the need for a tracheostomy and/or prolonged mechanical ventilation, in addition to other general supportive care.

In the event of overdose, antitoxin raised against botulinum toxin is available from the Centers for Disease Control and Prevention (CDC) in Atlanta, GA. However, the antitoxin will not reverse any botulinum toxin-induced effects already apparent by the time of antitoxin administration. In the event of suspected or actual cases of botulinum toxin poisoning, please contact your local or state Health Department to process a request for antitoxin through the CDC. If you do not receive a response within 30 minutes, please contact the CDC directly at 1-770-488-7100. More information can be obtained at <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5232a8.htm>.

## 11 DESCRIPTION

BOTOX (onabotulinumtoxinA) for injection is a sterile, vacuum-dried purified botulinum toxin type A, produced from fermentation of Hall strain *Clostridium botulinum* type A, and intended for intramuscular, intradetrusor and intradermal use. It is purified from the culture solution by dialysis and a series of acid precipitations to a complex consisting of the neurotoxin, and several accessory proteins. The complex is dissolved in sterile sodium chloride solution containing Albumin Human and is sterile filtered (0.2 microns) prior to filling and vacuum-drying.

The primary release procedure for BOTOX uses a cell-based potency assay to determine the potency relative to a reference standard. The assay is specific to Allergan's products BOTOX and BOTOX Cosmetic. One Unit of BOTOX corresponds to the calculated median intraperitoneal lethal dose (LD<sub>50</sub>) in mice. Due to specific details of this assay such as the vehicle, dilution scheme, and laboratory protocols, Units of biological activity of BOTOX cannot be compared to nor converted into Units of any other botulinum toxin or any toxin assessed with any other specific assay method. The specific activity of BOTOX is approximately 20 Units/nanogram of neurotoxin protein complex.

Each vial of BOTOX contains either 100 Units of Clostridium botulinum type A neurotoxin complex, 0.5 mg of Albumin Human, and 0.9 mg of sodium chloride; or 200 Units of Clostridium botulinum type A neurotoxin complex, 1 mg of Albumin Human, and 1.8 mg of sodium chloride in a sterile, vacuum-dried form without a preservative.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

BOTOX blocks neuromuscular transmission by binding to acceptor sites on motor or sympathetic nerve terminals, entering the nerve terminals, and inhibiting the release of acetylcholine. This inhibition occurs as the neurotoxin cleaves SNAP-25, a protein integral to the successful docking and release of acetylcholine from vesicles situated within nerve endings. When injected intramuscularly at therapeutic doses, BOTOX produces partial chemical denervation of the muscle resulting in a localized reduction in muscle activity. In addition, the muscle may atrophy, axonal sprouting may occur, and extrajunctional acetylcholine receptors may develop. There is evidence that reinnervation of the muscle may occur, thus slowly reversing muscle denervation produced by BOTOX.

When injected intradermally, BOTOX produces temporary chemical denervation of the sweat gland resulting in local reduction in sweating.

Following intradetrusor injection, BOTOX affects the efferent pathways of detrusor activity via inhibition of acetylcholine release.

### 12.3 Pharmacokinetics

Using currently available analytical technology, it is not possible to detect BOTOX in the peripheral blood following intramuscular injection at the recommended doses.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

#### *Carcinogenesis*

Long term studies in animals have not been performed to evaluate the carcinogenic potential of BOTOX.

#### *Mutagenesis*

BOTOX was negative in a battery of in vitro (microbial reverse mutation assay, mammalian cell mutation assay, and chromosomal aberration assay) and in vivo (micronucleus assay) genetic toxicologic assays.

#### *Impairment of Fertility*

In fertility studies of BOTOX (4, 8, or 16 Units/kg) in which either male or female rats were injected intramuscularly prior to mating and on the day of mating (3 doses, 2 weeks apart for males, 2 doses, 2 weeks apart for females) to untreated animals, reduced fertility was observed in males at the intermediate and high doses and in females at the high dose. The no-effect doses for reproductive toxicity (4 Units/kg in males, 8 Units/kg in females) are approximately equal to the maximum recommended human dose of 400 Units on a body weight basis (Units/kg).

### 13.2 Animal Toxicology and/or Pharmacology

In a study to evaluate inadvertent peribladder administration, bladder stones were observed in 1 of 4 male monkeys that were injected with a total of 6.8 Units/kg divided into the prostatic urethra and proximal rectum (single administration). No bladder stones were observed in male or female monkeys following injection of up to 36 Units/kg (~12X the highest human bladder dose) directly to the bladder as either single or 4 repeat dose injections or in female rats for single injections up to 100 Units/kg (~33X the highest human bladder dose).

**14.1 Overactive Bladder (OAB)**

Two double-blind, placebo-controlled, randomized, multi-center, 24-week clinical studies were conducted in patients with OAB with symptoms of urge urinary incontinence, urgency, and frequency (Studies OAB-1 and OAB-2). Patients needed to have at least 3 urinary urgency incontinence episodes and at least 24 micturitions in 3 days to enter the studies. A total of 1105 patients, whose symptoms had not been adequately managed with anticholinergic therapy (inadequate response or intolerable side effects), were randomized to receive either 100 Units of BOTOX (n=557), or placebo (n=548). Patients received 20 injections of study drug (5 units of BOTOX or placebo) spaced approximately 1 cm apart into the detrusor muscle.

In both studies, significant improvements compared to placebo in the primary efficacy variable of change from baseline in daily frequency of urinary incontinence episodes were observed for BOTOX 100 Units at the primary time point of week 12. Significant improvements compared to placebo were also observed for the secondary efficacy variables of daily frequency of micturition episodes and volume voided per micturition. These primary and secondary variables are shown in Tables 18 and 19, and Figures 5 and 6.

**Table 18: Baseline and Change from Baseline in Urinary Incontinence Episode Frequency, Micturition Episode Frequency and Volume Voided Per Micturition, Study OAB-1**

	<b>BOTOX 100 Units (N=278)</b>	<b>Placebo (N=272)</b>	<b>Treatment Difference</b>	<b>p-value</b>
<b>Daily Frequency of Urinary Incontinence Episodes<sup>a</sup></b>				
Mean Baseline	5.5	5.1		
Mean Change <sup>*</sup> at Week 2	-2.6	-1.0	-1.6	
Mean Change <sup>*</sup> at Week 6	-2.8	-1.0	-1.8	
Mean Change <sup>*</sup> at Week 12 <sup>**</sup>	-2.5	-0.9	-1.6 (-2.1, -1.2)	<0.001
<b>Daily Frequency of Micturition Episodes<sup>b</sup></b>				
Mean Baseline	12.0	11.2		
Mean Change <sup>†</sup> at Week 12 <sup>**</sup>	-1.9	-0.9	-1.0 (-1.5, -0.6)	<0.001
<b>Volume Voided per Micturition<sup>b</sup> (mL)</b>				
Mean Baseline	156	161		
Mean Change <sup>†</sup> at Week 12 <sup>**</sup>	38	8	30 (17, 43)	<0.001

\* Least squares (LS) mean change, treatment difference and p-value are based on an ANCOVA model with baseline value as covariate and treatment group and investigator as factors. Last observation carried forward (LOCF) values were used to analyze the primary efficacy variable.

† LS mean change, treatment difference and p-value are based on an ANCOVA model with baseline value as covariate and stratification factor, treatment group and investigator as factors.

\*\* Primary timepoint

<sup>a</sup> Primary variable

<sup>b</sup> Secondary variable

**Table 19: Baseline and Change from Baseline in Urinary Incontinence Episode Frequency, Micturition Episode Frequency and Volume Voided Per Micturition, Study OAB-2**

	<b>BOTOX 100 Units (N=275)</b>	<b>Placebo (N=269)</b>	<b>Treatment Difference</b>	<b>p-value</b>
<b>Daily Frequency of Urinary Incontinence Episodes<sup>a</sup></b>				
Mean Baseline	5.5	5.7		
Mean Change <sup>*</sup> at Week 2	-2.7	-1.1	-1.6	
Mean Change <sup>*</sup> at Week 6	-3.1	-1.3	-1.8	
Mean Change <sup>*</sup> at Week 12 <sup>**</sup>	-3.0	-1.1	-1.9 (-2.5, -1.4)	<0.001
<b>Daily Frequency of Micturition Episodes<sup>b</sup></b>				
Mean Baseline	12.0	11.8		
Mean Change <sup>†</sup> at Week 12 <sup>**</sup>	-2.3	-0.6	-1.7 (-2.2, -1.3)	<0.001
<b>Volume Voided per Micturition<sup>b</sup> (mL)</b>				
Mean Baseline	144	153		
Mean Change <sup>†</sup> at Week 12 <sup>**</sup>	40	10	31 (20, 41)	<0.001

\* LS mean change, treatment difference and p-value are based on an ANCOVA model with baseline value as covariate and treatment group and investigator as factors. LOCF values were used to analyze the primary efficacy variable.

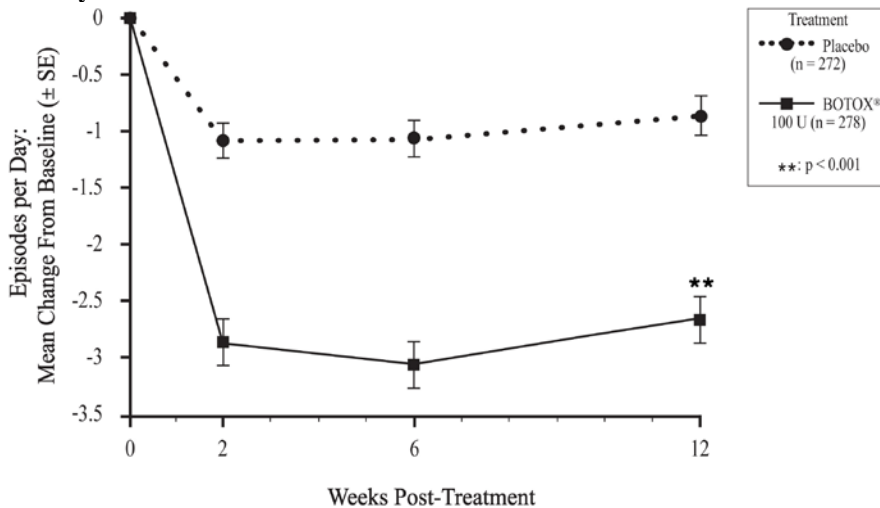
† LS mean change, treatment difference and p-value are based on an ANCOVA model with baseline value as covariate and stratification factor, treatment group and investigator as factors.

\*\* Primary timepoint

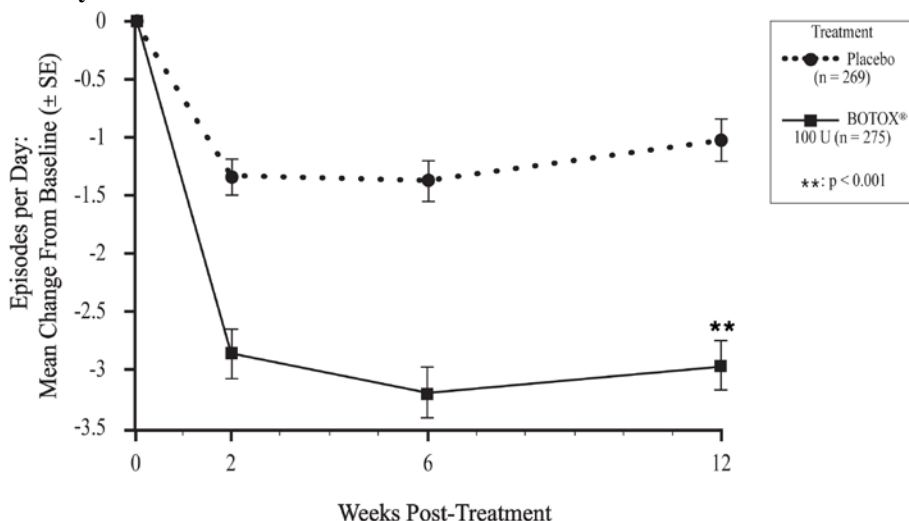
<sup>a</sup> Primary variable

<sup>b</sup> Secondary variable

**Figure 5: Mean Change from Baseline in Daily Frequency of Urinary Incontinence Episodes following intradetrusor injection in Study OAB-1**



**Figure 6: Mean Change from Baseline in Daily Frequency of Urinary Incontinence Episodes following intradetrusor injection in Study OAB-2**



The median duration of response in Study OAB-1 and OAB-2, based on patient qualification for re-treatment, was 19-24 weeks for the BOTOX 100 Unit dose group compared to 13 weeks for placebo. To qualify for re-treatment, at least 12 weeks must have passed since the prior treatment, post-void residual urine volume must have been less than 200 mL and patients must have reported at least 2 urinary incontinence episodes over 3 days.

#### 14.2 Detrusor Overactivity associated with a Neurologic Condition

Two double-blind, placebo-controlled, randomized, multi-center clinical studies were conducted in patients with urinary incontinence due to detrusor overactivity associated with a neurologic condition who were either spontaneously voiding or using catheterization (Studies NDO-1 and NDO-2). A total of 691 spinal cord injury (T1 or below) or multiple sclerosis patients, who had an inadequate response to or were intolerant of at least one anticholinergic medication, were enrolled. These patients were randomized to receive either 200 Units of BOTOX (n=227), 300 Units of BOTOX (n=223), or placebo (n=241).

In both studies, significant improvements compared to placebo in the primary efficacy variable of change from baseline in weekly frequency of incontinence episodes were observed for BOTOX (200 Units) at the primary efficacy time point at week 6. Increases in maximum cystometric capacity and reductions in maximum detrusor pressure during the first involuntary detrusor contraction were also observed. These primary and secondary endpoints are shown in Tables 20 and 21, and Figures 7 and 8.

No additional benefit of BOTOX 300 Units over 200 Units was demonstrated.

**Table 20: Baseline and Change from Baseline in Weekly Urinary Incontinence Episode Frequency, Maximum Cystometric Capacity and Maximum Detrusor Pressure during First Involuntary Detrusor Contraction (cmH2O) Study NDO-1**

	<b>BOTOX 200 Units</b>	<b>Placebo</b>	<b>Treatment Difference*</b>	<b>p-value*</b>
<b>Weekly Frequency of Urinary Incontinence Episodes<sup>a</sup></b>				
N	134	146		
Mean Baseline	32.3	28.3		
Mean Change* at Week 2	-15.3	-10.0	-5.3	—
Mean Change* at Week 6**	-19.9	-10.6	-9.2	p<0.001
Mean Change* at Week 12	-19.8	-8.8	(-13.1, -5.3) -11.0	—
<b>Maximum Cystometric Capacity<sup>b</sup> (mL)</b>				
N	123	129		
Mean Baseline	253.8	259.1		
Mean Change* at Week 6**	135.9	12.1	123.9	p<0.001
			(89.1, 158.7)	
<b>Maximum Detrusor Pressure during First Involuntary Detrusor Contraction<sup>b</sup> (cmH<sub>2</sub>O)</b>				
N	41	103		
Mean Baseline	63.1	57.4		
Mean Change* at Week 6**	-28.1	-3.7	-24.4	—

\* LS mean change, treatment difference and p-value are based on an analysis using an ANCOVA model with baseline weekly endpoint as covariate and treatment group, etiology at study entry (spinal cord injury or multiple sclerosis), concurrent anticholinergic therapy at screening, and investigator as factors. LOCF values were used to analyze the primary efficacy variable.

\*\* Primary timepoint

<sup>a</sup> Primary endpoint

<sup>b</sup> Secondary endpoint

**Table 21: Baseline and Change from Baseline in Weekly Urinary Incontinence Episode Frequency, Maximum Cystometric Capacity and Maximum Detrusor Pressure during First Involuntary Detrusor Contraction (cmH2O) in Study NDO-2**

	<b>BOTOX 200 Units</b>	<b>Placebo</b>	<b>Treatment Difference*</b>	<b>p-value*</b>
<b>Weekly Frequency of Urinary Incontinence Episodes<sup>a</sup></b>				
N	91	91		
Mean Baseline	32.7	36.8		
Mean Change* at Week 2	-18.0	-7.9	-10.1	—
Mean Change* at Week 6**	-19.6	-10.8	-8.8	p=0.003
Mean Change* at Week 12	-19.6	-10.7	(-14.5, -3.0) -8.9	—
<b>Maximum Cystometric Capacity<sup>b</sup> (mL)</b>				
N	88	85		
Mean Baseline	239.6	253.8		
Mean Change* at Week 6**	150.8	2.8	148.0	p<0.001
			(101.8, 194.2)	
<b>Maximum Detrusor Pressure during First Involuntary Detrusor Contraction<sup>b</sup> (cmH<sub>2</sub>O)</b>				
N	29	68		
Mean Baseline	65.6	43.7		
Mean Change* at Week 6**	-28.7	2.1	-30.7	—

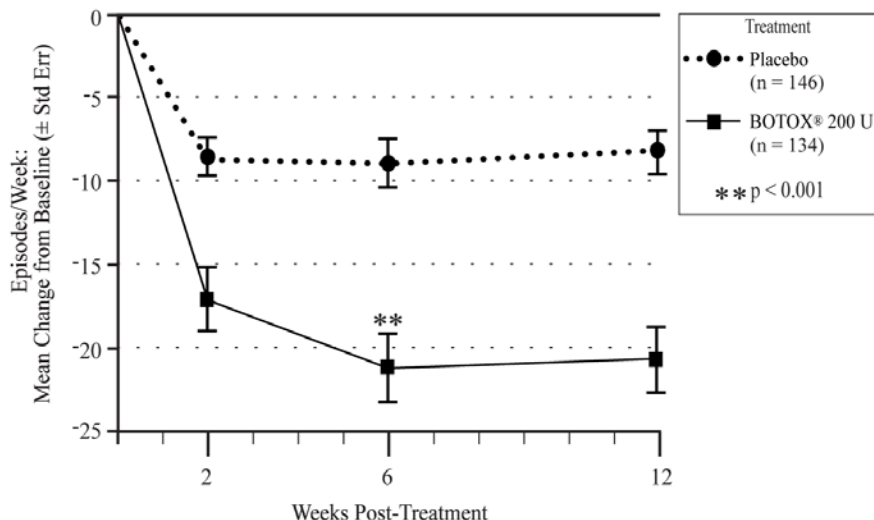
\* LS mean change, treatment difference and p-value are based on an analysis using an ANCOVA model with baseline weekly endpoint as covariate and treatment group, etiology at study entry (spinal cord injury or multiple sclerosis), concurrent anticholinergic therapy at screening, and investigator as factors. LOCF values were used to analyze the primary efficacy variable.

\*\* Primary timepoint

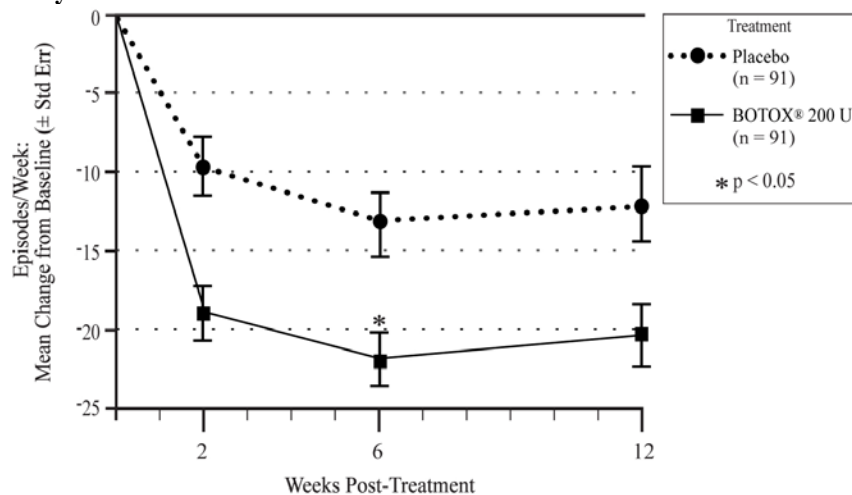
<sup>a</sup> Primary endpoint

<sup>b</sup> Secondary endpoint

**Figure 7: Mean Change from Baseline in Weekly Frequency of Urinary Incontinence Episodes During Treatment Cycle 1 in Study NDO-1**



**Figure 8: Mean Change from Baseline in Weekly Frequency of Urinary Incontinence Episodes During Treatment Cycle 1 in Study NDO-2**



The median duration of response in study NDO-1 and NDO-2, based on patient qualification for re-treatment was 295-337 days (42-48 weeks) for the 200 Units dose group compared to 96-127 days (13-18 weeks) for placebo. Re-treatment was based on loss of effect on incontinence episode frequency (50% of effect in Study NDO-1; 70% of effect in Study NDO-2).

### 14.3 Chronic Migraine

BOTOX was evaluated in two randomized, multi-center, 24-week, 2 injection cycle, placebo-controlled double-blind studies. Study 1 and Study 2 included chronic migraine adults who were not using any concurrent headache prophylaxis, and during a 28-day baseline period had  $\geq 15$  headache days lasting 4 hours or more, with  $\geq 50\%$  being migraine/probable migraine. In both studies, patients were randomized to receive placebo or 155 Units to 195 Units BOTOX injections every 12 weeks for the 2-cycle, double-blind phase. Patients were allowed to use acute headache treatments during the study. BOTOX treatment demonstrated statistically significant and clinically meaningful improvements from baseline compared to placebo for key efficacy variables (see Table 22).

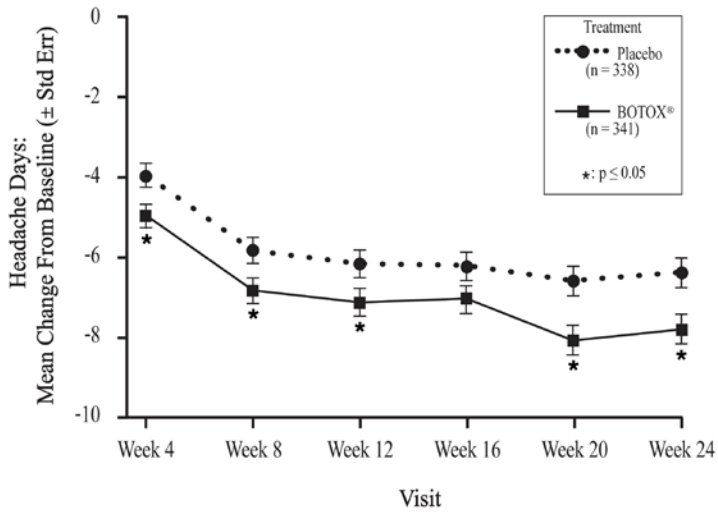
**Table 22: Week 24 Key Efficacy Variables for Study 1 and Study 2**

Efficacy per 28 days	Study 1		Study 2	
	BOTOX (N=341)	Placebo (N=338)	BOTOX (N=347)	Placebo (N=358)
Change from baseline in frequency of headache days	-7.8*	-6.4	-9.2*	-6.9
Change from baseline in total cumulative hours of headache on headache days	-107*	-70	-134*	-95

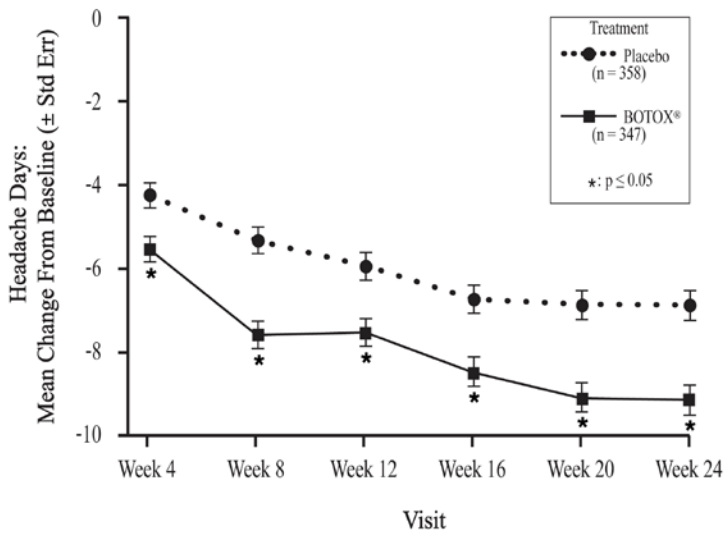
\* Significantly different from placebo ( $p \leq 0.05$ )

Patients treated with BOTOX had a significantly greater mean decrease from baseline in the frequency of headache days at most timepoints from Week 4 to Week 24 in Study 1 (Figure 9), and all timepoints from Week 4 to Week 24 in Study 2 (Figure 10), compared to placebo-treated patients.

**Figure 9: Mean Change from Baseline in Number of Headache Days for Study 1**



**Figure 10: Mean Change from Baseline in Number of Headache Days for Study 2**



## 14.4 Spasticity

### Upper Limb Spasticity

The efficacy of BOTOX for the treatment of upper limb spasticity was evaluated in three randomized, multi-center, double-blind, placebo-controlled studies (Studies 1, 2, and 3). Two additional randomized, multi-center, double-blind, placebo-controlled studies for upper limb spasticity in adults also included the evaluation of the efficacy of BOTOX for the treatment of thumb spasticity (Studies 4 and 5).

Study 1 included 126 patients (64 BOTOX and 62 placebo) with upper limb spasticity (Ashworth score of at least 3 for wrist flexor tone and at least 2 for finger flexor tone) who were at least 6 months post-stroke. BOTOX (a total dose of 200 Units to 240 Units) and placebo were injected intramuscularly (IM) into the flexor digitorum profundus, flexor digitorum sublimis, flexor carpi radialis, flexor carpi ulnaris, and if necessary into the adductor pollicis and flexor pollicis longus (see Table 23). Use of an EMG/nerve stimulator was recommended to assist in proper muscle localization for injection. Patients were followed for 12 weeks.



**Table 23: Study Medication Dose and Injection Sites in Study 1**

<b>Muscles Injected</b>	<b>Volume (mL)</b>	<b>BOTOX (Units)</b>	<b>Number of Injection Sites</b>
<b>Wrist</b>			
Flexor Carpi Radialis	1	50	1
Flexor Carpi Ulnaris	1	50	1
<b>Finger</b>			
Flexor Digitorum Profundus	1	50	1
Flexor Digitorum Sublimis	1	50	1
<b>Thumb</b>			
Adductor Pollicis <sup>a</sup>	0.4	20	1
Flexor Pollicis Longus <sup>a</sup>	0.4	20	1

<sup>a</sup> injected only if spasticity is present in this muscle

The primary efficacy variable was wrist flexors muscle tone at week 6, as measured by the Ashworth score. The Ashworth Scale is a 5-point scale with grades of 0 [no increase in muscle tone] to 4 [limb rigid in flexion or extension]. It is a clinical measure of the force required to move an extremity around a joint, with a reduction in score clinically representing a reduction in the force needed to move a joint (i.e., improvement in spasticity).

Key secondary endpoints included Physician Global Assessment, finger flexors muscle tone, and thumb flexors tone at Week 6. The Physician Global Assessment evaluated the response to treatment in terms of how the patient was doing in his/her life using a scale from -4 = very marked worsening to +4 = very marked improvement. Study 1 results on the primary endpoint and the key secondary endpoints are shown in Table 24.

**Table 24: Primary and Key Secondary Endpoints by Muscle Group at Week 6 in Study 1**

	<b>BOTOX (N=64)</b>	<b>Placebo (N=62)</b>
<b>Median Change from Baseline in Wrist Flexor Muscle Tone on the Ashworth Scale<sup>†a</sup></b>	-2.0*	0.0
<b>Median Change from Baseline in Finger Flexor Muscle Tone on the Ashworth Scale<sup>††b</sup></b>	-1.0*	0.0
<b>Median Change from Baseline in Thumb Flexor Muscle Tone on the Ashworth Scale<sup>††c</sup></b>	-1.0	-1.0
<b>Median Physician Global Assessment of Response to Treatment<sup>††</sup></b>	2.0*	0.0

<sup>†</sup> Primary endpoint at Week 6

<sup>††</sup> Secondary endpoints at Week 6

\* Significantly different from placebo ( $p \leq 0.05$ )

<sup>a</sup> BOTOX injected into both the flexor carpi radialis and ulnaris muscles

<sup>b</sup> BOTOX injected into the flexor digitorum profundus and flexor digitorum sublimis muscles

<sup>c</sup> BOTOX injected into the adductor pollicis and flexor pollicis longus muscles

Study 2 compared 3 doses of BOTOX with placebo and included 91 patients [BOTOX 360 Units (N=21), BOTOX 180 Units (N=23), BOTOX 90 Units (N=21), and placebo (N=26)] with upper limb spasticity (expanded Ashworth score of at least 2 for elbow flexor tone and at least 3 for wrist flexor tone) who were at least 6 weeks post-stroke. BOTOX and placebo were injected with EMG guidance into the flexor digitorum profundus, flexor digitorum sublimis, flexor carpi radialis, flexor carpi ulnaris, and biceps brachii (see Table 25).

**Table 25: Study Medication Dose and Injection Sites in Study 2 and Study 3**

Muscles Injected	Total Dose			Volume (mL) per site	Injection Sites (n)
	BOTOX low dose (90 Units)	BOTOX mid dose (180 Units)	BOTOX high dose (360 Units)		
<b>Wrist</b> Flexor Carpi Ulnaris	10 Units	20 Units	40 Units	0.4	1
Flexor Carpi Radialis	15 Units	30 Units	60 Units	0.6	1
<b>Finger</b> Flexor Digitorum Profundus	7.5 Units	15 Units	30 Units	0.3	1
Flexor Digitorum Sublimis	7.5 Units	15 Units	30 Units	0.3	1
<b>Elbow</b> Biceps Brachii	50 Units	100 Units	200 Units	0.5	4

The primary efficacy variable in Study 2 was the wrist flexor tone at Week 6 as measured by the expanded Ashworth Scale. The expanded Ashworth Scale uses the same scoring system as the Ashworth Scale, but allows for half-point increments.

Key secondary endpoints in Study 2 included Physician Global Assessment, finger flexors muscle tone, and elbow flexors muscle tone at Week 6. Study 2 results on the primary endpoint and the key secondary endpoints at Week 6 are shown in Table 26.

**Table 26: Primary and Key Secondary Endpoints by Muscle Group and BOTOX Dose at Week 6 in Study 2**

	BOTOX low dose (90 Units) (N=21)	BOTOX mid dose (180 Units) (N=23)	BOTOX high dose (360 Units) (N=21)	Placebo (N=26)
<b>Median Change from Baseline in Wrist Flexor Muscle Tone on the Ashworth Scale<sup>†b</sup></b>	-1.5*	-1.0*	-1.5*	-1.0
<b>Median Change from Baseline in Finger Flexor Muscle Tone on the Ashworth Scale<sup>††c</sup></b>	-0.5	-0.5	-1.0	-0.5
<b>Median Change from Baseline in Elbow Flexor Muscle Tone on the Ashworth Scale<sup>††d</sup></b>	-0.5	-1.0*	-0.5 <sup>a</sup>	-0.5
<b>Median Physician Global Assessment of Response to Treatment</b>	1.0*	1.0*	1.0*	0.0

<sup>†</sup> Primary endpoint at Week 6

<sup>††</sup> Secondary endpoints at Week 6

\* Significantly different from placebo ( $p \leq 0.05$ )

<sup>a</sup>  $p=0.053$

<sup>b</sup> Total dose of BOTOX injected into both the flexor carpi radialis and ulnaris muscles

<sup>c</sup> Total dose of BOTOX injected into the flexor digitorum profundus and flexor digitorum sublimis muscles

<sup>d</sup> Dose of BOTOX injected into biceps brachii muscle

Study 3 compared 3 doses of BOTOX with placebo and enrolled 88 patients [BOTOX 360 Units (N=23), BOTOX 180 Units (N=23), BOTOX 90 Units (N=23), and placebo (N=19)] with upper limb spasticity (expanded Ashworth score of at least 2 for elbow flexor tone and at least 3 for wrist flexor tone and/or finger flexor tone) who were at least 6 weeks post-stroke. BOTOX and placebo were injected with EMG guidance into the flexor digitorum profundus, flexor digitorum sublimis, flexor carpi radialis, flexor carpi ulnaris, and biceps brachii (see Table 25).

The primary efficacy variable in Study 3 was wrist and elbow flexor tone as measured by the expanded Ashworth score. A key secondary endpoint was assessment of finger flexors muscle tone. Study 3 results on the primary endpoint at Week 4 are shown in Table 27.

**Table 27: Primary and Key Secondary Endpoints by Muscle Group and BOTOX Dose at Week 4 in Study 3**

	<b>BOTOX low dose (90 Units) (N=23)</b>	<b>BOTOX mid dose (180 Units) (N=21)</b>	<b>BOTOX high dose (360 Units) (N=22)</b>	<b>Placebo (N=19)</b>
<b>Median Change from Baseline in Wrist Flexor Muscle Tone on the Ashworth Scale<sup>†b</sup></b>	-1.0	-1.0	-1.5*	-0.5
<b>Median Change from Baseline in Finger Flexor Muscle Tone on the Ashworth Scale<sup>††c</sup></b>	-1.0	-1.0	-1.0*	-0.5
<b>Median Change from Baseline in Elbow Flexor Muscle Tone on the Ashworth Scale<sup>†d</sup></b>	-0.5	-0.5	-1.0*	-0.5

<sup>†</sup> Primary endpoint at Week 4

<sup>††</sup> Secondary endpoints at Week 4

\* Significantly different from placebo ( $p \leq 0.05$ )

<sup>b</sup> Total dose of BOTOX injected into both the flexor carpi radialis and ulnaris muscles

<sup>c</sup> Total dose of BOTOX injected into the flexor digitorum profundus and flexor digitorum sublimis muscles

<sup>d</sup> Dose of BOTOX injected into biceps brachii muscle

Study 4 included 170 patients (87 BOTOX and 83 placebo) with upper limb spasticity who were at least 6 months post-stroke. In Study 4, patients received 20 Units of BOTOX into the adductor pollicis and flexor pollicis longus (total BOTOX dose =40 Units in thumb muscles) or placebo (see Table 28). Study 5 included 109 patients with upper limb spasticity who were at least 6 months post-stroke. In Study 5, patients received 15 Units (low dose) or 20 Units (high dose) of BOTOX into the adductor pollicis and flexor pollicis longus under EMG guidance (total BOTOX low dose =30 Units, total BOTOX high dose =40 Units), or placebo (see Table 28). The duration of follow-up in Study 4 and Study 5 was 12 weeks.

**Table 28: Study Medication Dose and Injection Sites in Studies 4 and 5**

<b>Muscles Injected</b>	<b>Study 4</b>		<b>Study 5</b>				<b>Number of Injection Sites for Studies 4 and 5</b>
	<b>BOTOX (Units)</b>	<b>Volume (mL)</b>	<b>BOTOX low dose (Units)</b>	<b>BOTOX high dose (Units)</b>	<b>Volume low dose (mL)</b>	<b>Volume high dose (mL)</b>	
<b>Thumb</b>							
Adductor Pollicis	20	0.4	15	20	0.3	0.4	1
Flexor Pollicis Longus	20	0.4	15	20	0.3	0.4	1

The results of Study 4 for the change from Baseline to Week 6 in thumb flexor tone measured by modified Ashworth Scale (MAS) and overall treatment response by Physician Global Assessment at week 6 are presented in Table 29. The MAS uses a similar scoring system as the Ashworth Scale.

**Table 29: Efficacy Endpoints for Thumb Flexors at Week 6 in Study 4**

	<b>BOTOX (N=66)</b>	<b>Placebo (N=57)</b>
<b>Median Change from Baseline in Thumb Flexor Muscle Tone on the modified Ashworth Scale<sup>††a</sup></b>	-1.0*	0.0
<b>Median Physician Global Assessment of Response to Treatment<sup>††</sup></b>	2.0*	0.0

<sup>††</sup> Secondary endpoints at Week 6

\* Significantly different from placebo ( $p \leq 0.001$ )

<sup>a</sup> BOTOX injected into the adductor pollicis and flexor pollicis longus muscles

In Study 5, the results of the change from Baseline to Week 6 in thumb flexor tone measured by modified Ashworth Scale and Clinical Global Impression (CGI) of functional assessment scale assessed by the physician using an 11-point Numeric Rating Scale [-5 worst possible function to +5 best possible function] are presented in Table 30.

**Table 30: Efficacy Endpoints for Thumb Flexors at Week 6 in Study 5**

	<b>BOTOX low dose (30 Units) (N=14)</b>	<b>Placebo low dose (N=9)</b>	<b>BOTOX high dose (40 Units) (N=43)</b>	<b>Placebo high dose (N=23)</b>
<b>Median Change from Baseline in Thumb Flexor Muscle Tone on the modified Ashworth Scale<sup>†††a</sup></b>	-1.0	-1.0	-0.5*	0.0
<b>Median Change from Baseline in Clinical Global Impression Score by Physician<sup>††</sup></b>	1.0	0.0	2.0*	0.0

<sup>††</sup> Secondary endpoint at Week 6

<sup>†††</sup> Other endpoint at Week 6

\* Significantly different from placebo ( $p \leq 0.010$ )

<sup>a</sup> BOTOX injected into the adductor pollicis and flexor pollicis longus muscles

### **Lower Limb Spasticity**

The efficacy and safety of BOTOX for the treatment of lower limb spasticity was evaluated in Study 6, a randomized, multi-center, double-blind, placebo-controlled study. Study 6 included 468 post-stroke patients (233 BOTOX and 235 placebo) with ankle spasticity (modified Ashworth Scale ankle score of at least 3) who were at least 3 months post-stroke. A total dose of 300 Units of BOTOX or placebo were injected intramuscularly and divided between the gastrocnemius, soleus, and tibialis posterior, with optional injection into the flexor hallucis longus, flexor digitorum longus, flexor digitorum brevis, extensor hallucis, and rectus femoris (see Table 31) with up to an additional 100 Units (400 Units total dose). The use of electromyographic guidance or nerve stimulation was required to assist in proper muscle localization for injections. Patients were followed for 12 weeks.

**Table 31: Study Medication Dose and Injection Sites in Study 6**

<b>Muscles Injected</b>	<b>BOTOX (Units)</b>	<b>Number of Injection Sites</b>
<b>Mandatory Ankle Muscles</b>		
Gastrocnemius (medial head)	75	3
Gastrocnemius (lateral head)	75	3
Soleus	75	3
Tibialis Posterior	75	3
<b>Optional Muscles</b>		
Flexor Hallucis Longus	50	2
Flexor Digitorum Longus	50	2
Flexor Digitorum Brevis	25	1
Extensor Hallucis	25	1
Rectus Femoris	100	4

The co-primary endpoints were the average of the change from baseline in modified Ashworth Scale (MAS) ankle score at Week 4 and Week 6, and the average of the Physician Global Assessment of Response (CGI) at Week 4 and Week 6. The CGI evaluated the response to treatment in terms of how the patient was doing in his/her life using a 9-point scale from -4=very marked worsening to +4=very marked improvement).

Statistically significant between-group differences for BOTOX over placebo were demonstrated for the co-primary efficacy measures of MAS and CGI (see Table 32).

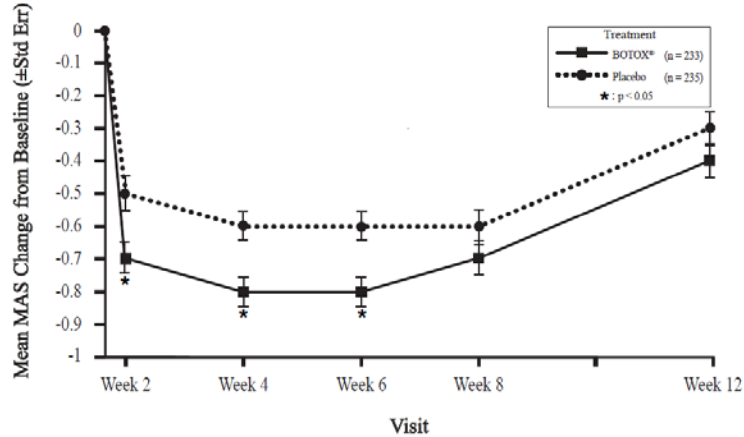
**Table 32: Co-Primary Efficacy Endpoints Results in Study 6 (Intent-to-treat Population)**

	<b>BOTOX 300 to 400 Units (N=233)</b>	<b>Placebo (N=235)</b>
<b>Mean Change from Baseline in Ankle Plantar Flexors on the modified Ashworth Scale</b>		
Week 4 and 6 Average	-0.8*	-0.6
<b>Mean Clinical Global Impression Score by Investigator</b>		
Week 4 and 6 Average	0.9*	0.7

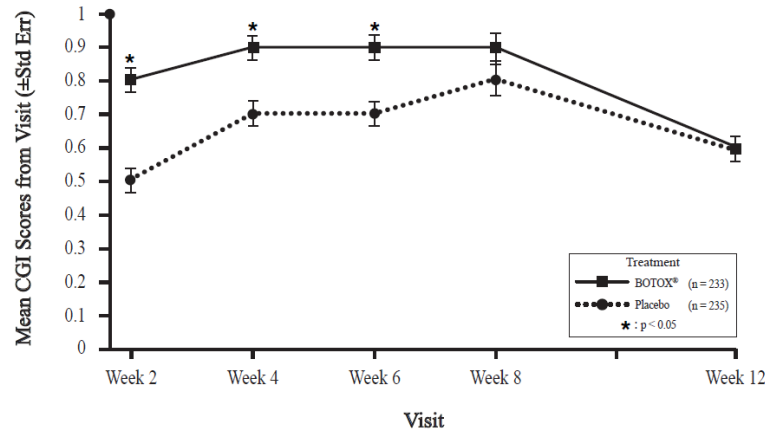
\* Significantly different from placebo ( $p < 0.05$ )

Compared to placebo, significant improvements in MAS change from baseline for ankle plantar flexors (see Figure 11) and CGI (see Figure 12) were observed at Week 2, Week 4, and Week 6 for patients treated with BOTOX.

**Figure 11: Modified Ashworth Scale Ankle Score for Study 6 – Mean Change from Baseline by Visit**



**Figure 12: Clinical Global Impression by Physician for Study 6 – Mean Scores by Visit**



### 14.5 Cervical Dystonia

A randomized, multi-center, double-blind, placebo-controlled study of the treatment of cervical dystonia was conducted. This study enrolled adult patients with cervical dystonia and a history of having received BOTOX in an open label manner with perceived good response and tolerable side effects. Patients were excluded if they had previously received surgical or other denervation treatment for their symptoms or had a known history of neuromuscular disorder. Subjects participated in an open label enrichment period where they received their previously employed dose of BOTOX. Only patients who were again perceived as showing a response were advanced to the randomized evaluation period. The muscles in which the blinded study agent injections were to be administered were determined on an individual patient basis.

There were 214 subjects evaluated for the open label period, of which 170 progressed into the randomized, blinded treatment period (88 in the BOTOX group, 82 in the placebo group). Patient evaluations continued for at least 10 weeks post-injection. The primary outcome for the study was a dual endpoint, requiring evidence of both a change in the Cervical Dystonia Severity Scale (CDSS) and an increase in the percentage of patients showing any improvement on the Physician Global Assessment Scale at 6 weeks after the injection session. The CDSS quantifies the severity of abnormal head positioning and was newly devised for this study. CDSS allots 1 point for each 5 degrees (or part thereof) of head deviation in each of the three planes of head movement (range of scores up to theoretical maximum of 54). The Physician Global Assessment Scale is a 9 category scale scoring the physician's evaluation of the patients' status compared to baseline, ranging from -4 to +4 (very marked worsening to complete improvement), with 0 indicating no change from baseline and +1 slight improvement. Pain is also an important symptom of cervical dystonia and was evaluated by separate assessments of pain frequency and severity on scales of 0 (no pain) to 4 (constant in frequency or extremely severe in intensity). Study results on the primary endpoints and the pain-related secondary endpoints are shown in Table 33.

**Table 33: Efficacy Outcomes of the Phase 3 Cervical Dystonia Study (Group Means)**

	Placebo (N=82)	BOTOX (N=88)	95% CI on Difference
Baseline CDSS	9.3	9.2	
Change in CDSS at Week 6	-0.3	-1.3	(-2.3, 0.3) <sup>[a,b]</sup>
% Patients with Any Improvement on Physician Global Assessment	31%	51%	(5%, 34%) <sup>[a]</sup>
Pain Intensity Baseline	1.8	1.8	
Change in Pain Intensity at Week 6	-0.1	-0.4	(-0.7, -0.2) <sup>[c]</sup>
Pain Frequency Baseline	1.9	1.8	
Change in Pain Frequency at Week 6	-0.0	-0.3	(-0.5, -0.0) <sup>[c]</sup>

<sup>[a]</sup> Confidence intervals are constructed from the analysis of covariance table with treatment and investigational site as main effects, and baseline CDSS as a covariate.

<sup>[b]</sup> These values represent the prospectively planned method for missing data imputation and statistical test. Sensitivity analyses indicated that the 95% confidence interval excluded the value of no difference between groups and the p-value was less than 0.05. These analyses included several alternative missing data imputation methods and non-parametric statistical tests.

<sup>[c]</sup> Confidence intervals are based on the t-distribution.

Exploratory analyses of this study suggested that the majority of patients who had shown a beneficial response by week 6 had returned to their baseline status by 3 months after treatment. Exploratory analyses of subsets by patient sex and age suggest that both sexes receive benefit, although female patients may receive somewhat greater amounts than male patients. There is a consistent treatment-associated effect between subsets greater than and less than age 65. There were too few non-Caucasian patients enrolled to draw any conclusions regarding relative efficacy in racial subsets.

In this study the median total BOTOX dose in patients randomized to receive BOTOX (N=88) was 236 Units, with 25th to 75th percentile ranges of 198 Units to 300 Units. Of these 88 patients, most received injections to 3 or 4 muscles; 38 received injections to 3 muscles, 28 to 4 muscles, 5 to 5 muscles, and 5 to 2 muscles. The dose was divided amongst the affected muscles in quantities shown in Table 34. The total dose and muscles selected were tailored to meet individual patient needs.

**Table 34: Number of Patients Treated per Muscle and Fraction of Total Dose Injected into Involved Muscles**

Muscle	Number of Patients Treated in this Muscle (N=88)	Mean % Dose per Muscle	Mid-Range of % Dose per Muscle*
Splenius capitis/cervicis	83	38	25-50
Sternocleidomastoid	77	25	17-31
Levator scapulae	52	20	16-25
Trapezius	49	29	18-33
Semispinalis	16	21	13-25
Scalene	15	15	6-21
Longissimus	8	29	17-41

\* The mid-range of dose is calculated as the 25th to 75th percentiles.

There were several randomized studies conducted prior to the double-blind, placebo-controlled study, which were supportive but not adequately designed to assess or quantitatively estimate the efficacy of BOTOX.

#### 14.6 Primary Axillary Hyperhidrosis

The efficacy and safety of BOTOX for the treatment of primary axillary hyperhidrosis were evaluated in two randomized, multi-center, double-blind, placebo-controlled studies. Study 1 included adult patients with persistent primary axillary hyperhidrosis who scored 3 or 4 on a Hyperhidrosis Disease Severity Scale (HDSS) and who produced at least 50 mg of sweat in each axilla at rest over 5 minutes. HDSS is a 4-point scale with 1 = “underarm sweating is never noticeable and never interferes with my daily activities”; to 4 = “underarm sweating is intolerable and always interferes with my daily activities”. A total of 322 patients were randomized in a 1:1:1 ratio to treatment in both axillae with either 50 Units of BOTOX, 75 Units of BOTOX, or placebo. Patients were evaluated at 4-week intervals. Patients who responded to the first injection were re-injected when they reported a re-increase in HDSS score to 3 or 4 and produced at least 50 mg sweat in each axilla by gravimetric measurement, but no sooner than 8 weeks after the initial injection.

Study responders were defined as patients who showed at least a 2-grade improvement from baseline value on the HDSS 4 weeks after both of the first two treatment sessions or had a sustained response after their first treatment session and did not receive re-treatment during the study. Spontaneous resting axillary sweat production was assessed by weighing a filter paper held in the axilla over a period of 5 minutes (gravimetric measurement). Sweat production responders were those patients who demonstrated a reduction in axillary sweating from baseline of at least 50% at week 4.

In the three study groups the percentage of patients with baseline HDSS score of 3 ranged from 50% to 54% and from 46% to 50% for a score of 4. The median amount of sweat production (averaged for each axilla) was 102 mg, 123 mg, and 114 mg for the placebo, 50 Units and 75 Units groups respectively.

The percentage of responders based on at least a 2-grade decrease from baseline in HDSS or based on a >50% decrease from baseline in axillary sweat production was greater in both BOTOX groups than in the placebo group (p<0.001), but was not significantly different between the two BOTOX doses (see Table 35).

Duration of response was calculated as the number of days between injection and the date of the first visit at which patients returned to 3 or 4 on the HDSS scale. The median duration of response following the first treatment in BOTOX treated patients with either dose was 201 days. Among those who received a second BOTOX injection, the median duration of response was similar to that observed after the first treatment.

In study 2, 320 adults with bilateral axillary primary hyperhidrosis were randomized to receive either 50 Units of BOTOX (n=242) or placebo (n=78). Treatment responders were defined as subjects showing at least a 50% reduction from baseline in axillary sweating measured by gravimetric measurement at 4 weeks. At week 4 post-injection, the percentages of responders were 91% (219/242) in the BOTOX group and 36% (28/78) in the placebo group, p<0.001. The difference in percentage of responders between BOTOX and placebo was 55% (95% CI=43.3, 65.9).

**Table 35: Study 1 - Study Outcomes**

<b>Treatment Response</b>	<b>BOTOX 50 Units (N=104)</b>	<b>BOTOX 75 Units (N=110)</b>	<b>Placebo (N=108)</b>	<b>BOTOX 50-placebo (95% CI)</b>	<b>BOTOX 75-placebo (95% CI)</b>
<b>HDSS Score change <math>\geq 2</math> (n)<sup>a</sup></b>	55% (57)	49% (54)	6% (6)	49.3% (38.8, 59.7)	43% (33.2, 53.8)
<b>&gt;50% decrease in axillary sweat production % (n)</b>	81% (84)	86% (94)	41% (44)	40% (28.1, 52.0)	45% (33.3, 56.1)

<sup>a</sup> Patients who showed at least a 2-grade improvement from baseline value on the HDSS 4 weeks after both of the first two treatment sessions or had a sustained response after their first treatment session and did not receive re-treatment during the study.

#### **14.7 Blepharospasm**

Botulinum toxin has been investigated for use in patients with blepharospasm in several studies. In an open label, historically controlled study, 27 patients with essential blepharospasm were injected with 2 Units of BOTOX at each of six sites on each side. Twenty-five of the 27 patients treated with botulinum toxin reported improvement within 48 hours. One patient was controlled with a higher dosage at 13 weeks post initial injection and one patient reported mild improvement but remained functionally impaired.

In another study, 12 patients with blepharospasm were evaluated in a double-blind, placebo-controlled study. Patients receiving botulinum toxin (n=8) improved compared with the placebo group (n=4). The effects of the treatment lasted a mean of 12 weeks.

One thousand six hundred eighty-four patients with blepharospasm who were evaluated in an open label trial showed clinical improvement as evaluated by measured eyelid force and clinically observed intensity of lid spasm, lasting an average of 12 weeks prior to the need for re-treatment.

#### **14.8 Strabismus**

Six hundred seventy-seven patients with strabismus treated with one or more injections of BOTOX were evaluated in an open label trial. Fifty-five percent of these patients improved to an alignment of 10 prism diopters or less when evaluated six months or more following injection.

### **16 HOW SUPPLIED/STORAGE AND HANDLING**

BOTOX is supplied in a single-use vial in the following sizes:

100 Units NDC 0023-1145-01

200 Units NDC 0023-3921-02

Vials of BOTOX have a holographic film on the vial label that contains the name “Allergan” within horizontal lines of rainbow color. In order to see the hologram, rotate the vial back and forth between your fingers under a desk lamp or fluorescent light source. (Note: the holographic film on the label is absent in the date/lot area.) If you do not see the lines of rainbow color or the name “Allergan”, do not use the product and contact Allergan for additional information at 1-800-890-4345 from 7:00 AM to 3:00 PM Pacific Time.

#### Storage

Unopened vials of BOTOX should be stored in a refrigerator (2° to 8°C) for up to 36 months. Do not use after the expiration date on the vial. Administer BOTOX within 24 hours of reconstitution; during this period reconstituted BOTOX should be stored in a refrigerator (2° to 8°C). Reconstituted BOTOX should be clear, colorless, and free of particulate matter.

### **17 PATIENT COUNSELING INFORMATION**

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

#### Swallowing, Speaking or Breathing Difficulties, or Other Unusual Symptoms

Advise patients to inform their doctor or pharmacist if they develop any unusual symptoms (including difficulty with swallowing, speaking, or breathing), or if any existing symptom worsens [*see Boxed Warning and Warnings and Precautions (5.2, 5.6)*].

#### Ability to Operate Machinery or Vehicles

Advise patients that if loss of strength, muscle weakness, blurred vision, dizziness, or drooping eyelids occur, they should avoid driving a car or engaging in other potentially hazardous activities.

#### Voiding Symptoms after Bladder Injections

After bladder injections for urinary incontinence, advise patients to contact their physician if they experience difficulties in voiding or burning sensation upon voiding.



**MEDICATION GUIDE**  
**BOTOX<sup>®</sup>**  
**BOTOX<sup>®</sup> Cosmetic**  
**(Boe-tox)**  
**(onabotulinumtoxinA)**  
**for Injection**

**What is the most important information I should know about BOTOX and BOTOX Cosmetic?**  
**BOTOX and BOTOX Cosmetic may cause serious side effects that can be life threatening, including:**

- **Problems breathing or swallowing**
- **Spread of toxin effects**

**These problems can happen hours, days, to weeks after an injection of BOTOX or BOTOX Cosmetic. Call your doctor or get medical help right away if you have any of these problems after treatment with BOTOX or BOTOX Cosmetic:**

**1. Problems swallowing, speaking, or breathing. These problems can happen hours, days, to weeks after an injection of BOTOX or BOTOX Cosmetic** usually because the muscles that you use to breathe and swallow can become weak after the injection. Death can happen as a complication if you have severe problems with swallowing or breathing after treatment with **BOTOX** or **BOTOX Cosmetic**.

- People with certain breathing problems may need to use muscles in their neck to help them breathe. These people may be at greater risk for serious breathing problems with **BOTOX** or **BOTOX Cosmetic**.
- Swallowing problems may last for several months. People who cannot swallow well may need a feeding tube to receive food and water. If swallowing problems are severe, food or liquids may go into your lungs. People who already have swallowing or breathing problems before receiving **BOTOX** or **BOTOX Cosmetic** have the highest risk of getting these problems.

**2. Spread of toxin effects.** In some cases, the effect of botulinum toxin may affect areas of the body away from the injection site and cause symptoms of a serious condition called botulism. The symptoms of botulism include:

- loss of strength and muscle weakness all over the body
- double vision
- blurred vision and drooping eyelids
- hoarseness or change or loss of voice (dysphonia)
- trouble saying words clearly (dysarthria)
- loss of bladder control
- trouble breathing
- trouble swallowing

These symptoms can happen hours, days, to weeks after you receive an injection of **BOTOX** or **BOTOX Cosmetic**.

These problems could make it unsafe for you to drive a car or do other dangerous activities. See "What should I avoid while receiving **BOTOX** or **BOTOX Cosmetic**?"

There has not been a confirmed serious case of spread of toxin effect away from the injection site when **BOTOX** has been used at the recommended dose to treat chronic migraine, severe underarm sweating, blepharospasm, or strabismus, or when **BOTOX Cosmetic** has been used at the recommended dose to treat frown lines and/or crow's feet lines.

### **What are BOTOX and BOTOX Cosmetic?**

**BOTOX** is a prescription medicine that is injected into muscles and used:

- to treat overactive bladder symptoms such as a strong need to urinate with leaking or wetting accidents (urge urinary incontinence), a strong need to urinate right away (urgency), and urinating often (frequency) in adults when another type of medicine (anticholinergic) does not work well enough or cannot be taken.
- to treat leakage of urine (incontinence) in adults with overactive bladder due to neurologic disease when another type of medicine (anticholinergic) does not work well enough or cannot be taken.
- to prevent headaches in adults with chronic migraine who have 15 or more days each month with headache lasting 4 or more hours each day.
- to treat increased muscle stiffness in elbow, wrist, and finger muscles in adults with upper limb spasticity.
- to treat increased muscle stiffness in ankle and toe muscles in adults with lower limb spasticity.
- to treat the abnormal head position and neck pain that happens with cervical dystonia (CD) in adults.
- to treat certain types of eye muscle problems (strabismus) or abnormal spasm of the eyelids (blepharospasm) in people 12 years and older.

**BOTOX** is also injected into the skin to treat the symptoms of severe underarm sweating (severe primary axillary hyperhidrosis) when medicines used on the skin (topical) do not work well enough.

**BOTOX Cosmetic** is a prescription medicine that is injected into muscles and used to improve the look of moderate to severe frown lines between the eyebrows (glabellar lines) in adults for a short period of time (temporary).

**BOTOX Cosmetic** is a prescription medicine that is injected into the area around the side of the eyes to improve the look of crow's feet lines in adults for a short period of time (temporary).

You may receive treatment for frown lines and crow's feet lines at the same time.

It is not known whether **BOTOX** is safe or effective in people younger than:

- 18 years of age for treatment of urinary incontinence
- 18 years of age for treatment of chronic migraine
- 18 years of age for treatment of spasticity
- 16 years of age for treatment of cervical dystonia
- 18 years of age for treatment of hyperhidrosis
- 12 years of age for treatment of strabismus or blepharospasm

**BOTOX Cosmetic** is not recommended for use in children younger than 18 years of age.

It is not known whether **BOTOX** and **BOTOX Cosmetic** are safe or effective to prevent headaches in people with migraine who have 14 or fewer headache days each month (episodic migraine).

It is not known whether **BOTOX** and **BOTOX Cosmetic** are safe or effective for other types of muscle spasms or for severe sweating anywhere other than your armpits.

### **Who should not take BOTOX or BOTOX Cosmetic?**

Do not take **BOTOX** or **BOTOX Cosmetic** if you:

- are allergic to any of the ingredients in **BOTOX** or **BOTOX Cosmetic**. See the end of this Medication Guide for a list of ingredients in **BOTOX** and **BOTOX Cosmetic**.
- had an allergic reaction to any other botulinum toxin product such as *Myobloc*<sup>®</sup>, *Dysport*<sup>®</sup>, or *Xeomin*<sup>®</sup>
- have a skin infection at the planned injection site
- are being treated for urinary incontinence and have a urinary tract infection (UTI)
- are being treated for urinary incontinence and find that you cannot empty your bladder on your own (only applies to people who are not routinely catheterizing)

### **What should I tell my doctor before taking BOTOX or BOTOX Cosmetic?**

**Tell your doctor about all your medical conditions, including if you:**

- have a disease that affects your muscles and nerves (such as amyotrophic lateral sclerosis [ALS or Lou Gehrig's disease], myasthenia gravis or Lambert-Eaton syndrome). See "What is the most important information I should know about **BOTOX** and **BOTOX Cosmetic**?"
- have allergies to any botulinum toxin product
- had any side effect from any botulinum toxin product in the past
- have or have had a breathing problem, such as asthma or emphysema
- have or have had swallowing problems
- have or have had bleeding problems

- have plans to have surgery
- had surgery on your face
- have weakness of your forehead muscles, such as trouble raising your eyebrows
- have drooping eyelids
- have any other change in the way your face normally looks
- have symptoms of a urinary tract infection (UTI) and are being treated for urinary incontinence. Symptoms of a urinary tract infection may include pain or burning with urination, frequent urination, or fever.
- have problems emptying your bladder on your own and are being treated for urinary incontinence
- are pregnant or plan to become pregnant. It is not known if **BOTOX** or **BOTOX Cosmetic** can harm your unborn baby.
- are breast-feeding or plan to breastfeed. It is not known if **BOTOX** or **BOTOX Cosmetic** passes into breast milk.

**Tell your doctor about all the medicines you take**, including prescription and nonprescription medicines, vitamins and herbal products. Using **BOTOX** or **BOTOX Cosmetic** with certain other medicines may cause serious side effects. **Do not start any new medicines until you have told your doctor that you have received BOTOX or BOTOX Cosmetic in the past.**

Especially tell your doctor if you:

- have received any other botulinum toxin product in the last four months
- have received injections of botulinum toxin, such as *Myobloc*<sup>®</sup> (rimabotulinumtoxinB), *Dysport*<sup>®</sup> (abobotulinumtoxinA), or *Xeomin*<sup>®</sup> (incobotulinumtoxinA) in the past. Be sure your doctor knows exactly which product you received.
- have recently received an antibiotic by injection
- take muscle relaxants
- take an allergy or cold medicine
- take a sleep medicine
- take anti-platelets (aspirin-like products) and/or anti-coagulants (blood thinners)

**Ask your doctor if you are not sure if your medicine is one that is listed above.**

Know the medicines you take. Keep a list of your medicines with you to show your doctor and pharmacist each time you get a new medicine.

#### **How should I take BOTOX or BOTOX Cosmetic?**

- **BOTOX** or **BOTOX Cosmetic** is an injection that your doctor will give you.
- **BOTOX** is injected into your affected muscles, skin, or bladder.
- **BOTOX Cosmetic** is injected into your affected muscles.
- Your doctor may change your dose of **BOTOX** or **BOTOX Cosmetic**, until you and your doctor find the best dose for you.
- **Your doctor will tell you how often you will receive your dose of BOTOX or BOTOX Cosmetic injections.**

#### **What should I avoid while taking BOTOX or BOTOX Cosmetic?**

**BOTOX** and **BOTOX Cosmetic** may cause loss of strength or general muscle weakness, vision problems, or dizziness within hours to weeks of taking **BOTOX** or **BOTOX Cosmetic**. **If this happens, do not drive a car, operate machinery, or do other dangerous activities.** See "What is the most important information I should know about **BOTOX** and **BOTOX Cosmetic**?"

#### **What are the possible side effects of BOTOX and BOTOX Cosmetic?**

**BOTOX** and **BOTOX Cosmetic** can cause serious side effects. See "What is the most important information I should know about **BOTOX** and **BOTOX Cosmetic**?"

**Other side effects of BOTOX and BOTOX Cosmetic include:**

- dry mouth
- discomfort or pain at the injection site
- tiredness
- headache
- neck pain
- eye problems: double vision, blurred vision, decreased eyesight, drooping eyelids, swelling of your eyelids, and dry eyes.

- urinary tract infection in people being treated for urinary incontinence
- painful urination in people being treated for urinary incontinence
- inability to empty your bladder on your own and are being treated for urinary incontinence. If you have difficulty fully emptying your bladder after getting **BOTOX**, you may need to use disposable self-catheters to empty your bladder up to a few times each day until your bladder is able to start emptying again.
- allergic reactions. Symptoms of an allergic reaction to **BOTOX** or **BOTOX Cosmetic** may include: itching, rash, red itchy welts, wheezing, asthma symptoms, or dizziness or feeling faint. Tell your doctor or get medical help right away if you are wheezing or have asthma symptoms, or if you become dizzy or faint.

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of **BOTOX** and **BOTOX Cosmetic**. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

#### **General information about BOTOX and BOTOX Cosmetic:**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.

This Medication Guide summarizes the most important information about **BOTOX** and **BOTOX Cosmetic**. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about **BOTOX** and **BOTOX Cosmetic** that is written for healthcare professionals.

#### **What are the ingredients in BOTOX and BOTOX Cosmetic?**

Active ingredient: botulinum toxin type A

Inactive ingredients: human albumin and sodium chloride

Manufactured by: Allergan Pharmaceuticals Ireland a subsidiary of: Allergan, Inc. 2525 Dupont Dr. Irvine, CA 92612

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Patented. See: [www.allergan.com/products/patent\\_notices](http://www.allergan.com/products/patent_notices)



This Medication Guide has been approved by the U.S. Food and Drug Administration.

**Revised: 1/2016**

72309US18

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72511US15





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To the Washington Health Care Authority

Regarding the call for comments on the potential health technologies topics:

Thank you for reviewing and considering the recommendation of non-pharmacologic therapies for migraines and headaches. I am writing to urge you to recommend massage therapy treatments for migraines and headaches.

Below I have cited 17 research articles published in the past five years demonstrating positive results with migraines/headaches and massage therapy. One study from New Zealand documents the most common conditions seen by massage therapists: migraines/headaches are seen by 99% of massage therapists. I also searched the industry fact sheets from the two largest massage therapy associations who regularly conduct surveys on the use of massage therapy. They do not differentiate conditions, but rather cite general acute and chronic pain as one of the primary reasons for seeking massage therapy, ([https://www.amtamassage.org/infocenter/economic\\_industry-fact-sheet.html](https://www.amtamassage.org/infocenter/economic_industry-fact-sheet.html)) and the other cites pain as secondary to stress reduction ([http://www.massagetherapy.com/media/metrics\\_massage\\_clients.php](http://www.massagetherapy.com/media/metrics_massage_clients.php)).

Massage therapy has been found, both anecdotally and in the literature, to reduce pain associated with migraines/headaches, reduce the frequency of headaches, and improve sleep affected by pain associated with migraine/headaches.

Thank you for your consideration,  
Diana L Thompson, LMP  
2<sup>nd</sup> Vice President, AMTA-WA

1.

[Myofascial Trigger Point Release Massage Therapy Relieves Tension-Type Headaches.](#)

Rahim A, Seffinger MA.

J Am Osteopath Assoc. 2016 Jan 1;116(1):55-6. doi: 10.7556/jaoa.2016.009. No abstract available.

PMID: 26745565

[Similar articles](#)

Select item 26472986

2.

[A Randomized Controlled Trial on the Effectiveness of Court-Type Traditional Thai Massage versus Amitriptyline in Patients with Chronic Tension-Type Headache.](#)

Damapong P, Kanchanakhan N, Eungpinichpong W, Putthapitak P, Damapong P.

Evid Based Complement Alternat Med. 2015;2015:930175. doi: 10.1155/2015/930175. Epub 2015 Sep 15.

PMID: 26472986 **Free PMC Article**

[Similar articles](#)

Select item 25607593

3.

[Treating the sequelae of postoperative meningioma and traumatic brain injury: a case of implementation of craniosacral therapy in integrative inpatient care.](#)

Haller H, Cramer H, Werner M, Dobos G.

J Altern Complement Med. 2015 Feb;21(2):110-2. doi: 10.1089/acm.2013.0283. Epub 2015 Jan 21.

PMID: 25607593

[Similar articles](#)

Select item 25329141

4.

[Myofascial trigger point-focused head and neck massage for recurrent tension-type headache: a randomized, placebo-controlled clinical trial.](#)

Moraska AF, Stenerson L, Butryn N, Krutsch JP, Schmiege SJ, Mann JD.

Clin J Pain. 2015 Feb;31(2):159-68. doi: 10.1097/AJP.0000000000000091.

PMID: 25329141 **Free PMC Article**

[Similar articles](#)

Select item 25278005

5.

[Manual therapies for primary chronic headaches: a systematic review of randomized controlled trials.](#)

Chaibi A, Russell MB.

J Headache Pain. 2014 Oct 2;15:67. doi: 10.1186/1129-2377-15-67. Review.

PMID: 25278005 **Free PMC Article**

[Similar articles](#)

Select item 24867852

6.

[Complementary and alternative medicine \(CAM\) use in an Italian cohort of pediatric headache patients: the tip of the iceberg.](#)

Dalla Libera D, Colombo B, Pavan G, Comi G.

Neurol Sci. 2014 May;35 Suppl 1:145-8. doi: 10.1007/s10072-014-1756-y.

PMID: 24867852

[Similar articles](#)

Select item 24738648

7.

[Effects of Thai traditional massage on pressure pain threshold and headache intensity in patients with chronic tension-type and migraine headaches.](#)

Chatchawan U, Eungpinichpong W, Sooktho S, Tiamkao S, Yamauchi J.

J Altern Complement Med. 2014 Jun;20(6):486-92. doi: 10.1089/acm.2013.0176. Epub 2014 Apr 16.

PMID: 24738648

[Similar articles](#)

Select item 24481577

8.

[Use of complementary and alternative medicine by a sample of Turkish primary headache patients.](#)

Karakurum Göksel B, Coşkun Ö, Ucler S, Karatas M, Ozge A, Ozkan S.

Agri. 2014;26(1):1-7. doi: 10.5505/agri.2014.04909.

PMID: 24481577 **Free Article**

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9.

[A pilot study to investigate the short-term effects of specific soft tissue massage on upper cervical movement impairment in patients with cervicogenic headache.](#)

Hopper D, Bajaj Y, Kei Choi C, Jan O, Hall T, Robinson K, Briffa K.

J Man Manip Ther. 2013 Feb;21(1):18-23. doi: 10.1179/2042618612Y.0000000018.

PMID: 24421609 **Free PMC Article**

[Similar articles](#)

Select item 25792906

10.

[Effectiveness of Physical Therapy in Patients with Tension-type Headache: Literature Review.](#)

Victoria Espí-López G, Arnal-Gómez A, Arbós-Berenguer T, González ÁA, Vicente-Herrero T.

J Jpn Phys Ther Assoc. 2014;17(1):31-8. doi: 10.1298/jjpta.17.31.

PMID: 25792906 **Free PMC Article**

[Similar articles](#)

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11.

[Manual treatment for cervicogenic headache and active trigger point in the sternocleidomastoid muscle: a pilot randomized clinical trial.](#)

Bodes-Pardo G, Pecos-Martín D, Gallego-Izquierdo T, Salom-Moreno J, Fernández-de-Las-Peñas C, Ortega-Santiago R.

J Manipulative Physiol Ther. 2013 Sep;36(7):403-11. doi: 10.1016/j.jmpt.2013.05.022. Epub 2013 Jul 8.

PMID: 23845200

[Similar articles](#)

Select item 22920541

12.

[Precipitating and relieving factors of migraine versus tension type headache.](#)

Haque B, Rahman KM, Hoque A, Hasan AT, Chowdhury RN, Khan SU, Alam MB, Habib M, Mohammad QD.

BMC Neurol. 2012 Aug 25;12:82. doi: 10.1186/1471-2377-12-82.

PMID: 22920541 **Free PMC Article**

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13.

[Reduction of current migraine headache pain following neck massage and spinal manipulation.](#)

Noudeh YJ, Vatankhah N, Baradaran HR.

Int J Ther Massage Bodywork. 2012;5(1):5-13. Epub 2012 Mar 31.

PMID: 22553478 **Free PMC Article**

[Similar articles](#)

Select item 21589692

14.

[A descriptive study of the practice patterns of massage new zealand massage therapists.](#)

Smith JM, Sullivan SJ, Baxter GD.

Int J Ther Massage Bodywork. 2011 Mar 30;4(1):18-27.

PMID: 21589692 **Free PMC Article**

[Similar articles](#)

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15.

[Alternative headache treatments: nutraceuticals, behavioral and physical treatments.](#)

Sun-Edelstein C, Mauskop A.

Headache. 2011 Mar;51(3):469-83. doi: 10.1111/j.1526-4610.2011.01846.x. Review.

PMID: 21352222

[Similar articles](#)

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16.

[Manual therapies for migraine: a systematic review.](#)

Chaibi A, Tuchin PJ, Russell MB.

J Headache Pain. 2011 Apr;12(2):127-33. doi: 10.1007/s10194-011-0296-6. Epub 2011 Feb 5. Review.

PMID: 21298314 **Free PMC Article**

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17.

[Benefits of massage-myofascial release therapy on pain, anxiety, quality of sleep, depression, and quality of life in patients with fibromyalgia.](#)

Castro-Sánchez AM, Matarán-Peñarrocha GA, Granero-Molina J, Aguilera-Manrique G, Quesada-Rubio JM, Moreno-Lorenzo C.

Evid Based Complement Alternat Med. 2011;2011:561753. doi: 10.1155/2011/561753.

Epub 2010 Dec 28.

PMID: 21234327 **Free PMC Article**

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Washington  
East Asian Medicine  
Association

March 11, 2016

To Whom It May Concern:

The Washington East Asian Medicine Association strongly supports the topic below for the Health Technology Assessment Committee Review under the Health Care Authority.

**Non- Pharmacologic      Med/High                      Med/High                      Med/High**  
**Treatments for**  
**Migraines/Headaches**

**Policy Context/Reason for selection:** Non-pharmacologic treatments for headaches include Botox injections, transcranial magnetic stimulation, nerve destruction, acupuncture and massage. The topic is proposed to determine the safety, efficacy and value of non-drug treatments for migraines and other headaches types.

Migraine headache is safely and effectively treated by acupuncture. This is documented in several studies, including a recent meta-analysis that compared verum acupuncture to sham acupuncture and found a reduced recurrence rate in the verum group (RR 0.47, 95% CI 0.28 to 0.81; p=0.006, two trials) and no severe adverse events (Yang, Que & Zheng, 2015). And in a recent review of a 2001 Cochrane Review of acupuncture for migraine prophylaxis, authors concluded that “[a]vailable studies suggest that acupuncture is at least as effective as, or possibly more effective than, prophylactic drug treatment, and has fewer adverse effects. Acupuncture should be considered a treatment option for patients willing to undergo this treatment.” (p. 540).

References

Linde K, Allais G, Brinkhaus B, Manheimer E, Vickers A, White AR. (2015). Acupuncture for migraine prophylaxis. Sao Paulo Med J. 2015 Dec;133(6):540. doi: 10.1590/1516-3180.20151336T1.

Yang Y1, Que Q2, Ye X1, Zheng GH (2015). Verum versus sham manual acupuncture for migraine: a systematic review of randomised controlled trials. Acupunct Med. Dec 30. pii: acupmed-2015-010903. doi: 10.1136/acupmed-2015-010903.

Thank you for your consideration.

Sincerely,



Andy McIntyre

Washington East Asian Medicine Association, President





March 7, 2016

Washington State Health Care Authority  
via e-mail: [shtap@hca.wa.gov](mailto:shtap@hca.wa.gov)

RE: Comments – Proposed Technologies for Review – HTA Program  
Proposed Topic: *Skin Substitutes*

Dear HCA Director Teeter:

Thank you for the opportunity to provide comments to the *proposed* technology topic of “skin substitutes.” We align with the goal of requiring “evidence-based criteria and making sure that technology is safe and effective, and that it offers a significant benefit before recommending use to Washington’s state health care programs including Apple Health (Medicaid), the Public Employees Benefits Board (PEBB) Program, and the Department of Labor and Industries workers’ compensation program.”

We assert that new technologies and/or products meet a threshold based on clinical efficacy and published studies as outlined in the *CMS Program Integrity Manual* as it relates specifically to the creation of medical policy for Medicare beneficiaries. We believe this translates to Medicaid program recipients as well.

#### **SCIENCE AND CLINICAL EFFICACY**

A review of the *CMS Program Integrity Manual* indicates the following requirements related to the development of Medicare’s Local Coverage Determination (LCD) policies and scientific and clinical evidence:

#### **CMS Program Integrity Manual – Chapter 13**

##### **13.7.1 - Evidence Supporting LCDs**

***(Rev. 473, Issued: 06-21-13, Effective: 01-15-13, Implementation: 01-15-13)***

Contractor LCDs shall be based on the strongest evidence available. The extent and quality of supporting evidence is key to defending challenges to LCDs. The initial action in gathering evidence to support LCDs shall always be a search of published scientific literature for any available evidence pertaining to the item *or* service in question. In order of preference, LCDs should be based on:

- Published authoritative evidence derived from definitive randomized clinical trials or other definitive studies, and
- General acceptance by the medical community (standard of practice), as supported by sound medical evidence based on:
  - o Scientific data or research studies published in peer-reviewed medical journals;
  - o Consensus of expert medical opinion (i.e., recognized authorities in the field); or
  - o Medical opinion derived from consultations with medical associations or other health care experts.

Acceptance by individual health care providers, or even a limited group of health care providers, normally does not indicate general acceptance by the medical community. Testimonials indicating such limited acceptance, and limited case studies distributed by sponsors with financial interest in the outcome, are not sufficient evidence of general acceptance by the medical community. The broad range of available evidence must be considered and its quality shall be evaluated before a conclusion is reached.

#### **Section 13.1.3: Local Coverage Determinations**

“The LCDs specify under what clinical circumstances *an item or* service is considered to be reasonable and necessary. They are administrative and educational tools to assist providers in submitting correct claims for payment. Contractors publish LCDs to provide guidance to the public and medical community within their jurisdictions. Contractors develop LCDs by considering medical literature, the advice of local medical societies and medical consultants, public comments, and comments from the provider community.” (MiMedx underline) The contractor should adopt LCDs that have been



Please consider the positive impact that the focus on science and clinical efficacy as a coverage requirement for a new technology has on Washington State constituents. This scientific threshold should include clinically proven healing outcomes as evidenced by randomized, controlled trials and published clinical studies for each wound product deemed covered and reimbursed for the afore-mentioned programs in Washington.

Thank you in advance for your review of our comments.

Sincerely,

[Redacted Signature]

Pamela C. McKeown, M.A.  
 Director of Health Policy  
 Office 641-782-5244 | Mobile 612-616-3161  
[pmckeown@mimedx.com](mailto:pmckeown@mimedx.com)

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 Chief Medical Officer  
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[dfetterolf@mimedx.com](mailto:dfetterolf@mimedx.com)

cc: Laura Trivette, Vice President

Enclosure: Appendix

**Appendix**

**Table 1: Clinical Publications**

Product	Study/Publication
Q4101-Apligraf	2 RCTs- one DFU and one VLU; 75 Case Studies
Q4102-Oasis WM	3 RCTs and 5 Case Studies
Q4103-Oasis burn	Not available
Q4104-Integra BMWD	10 Published Studies
Q4105-Integra DRT	11 Studies
Q4106-Dermagraft	1 RCT; 10 articles; 9 case studies
Q4107-Graftjacket	2 Published Studies; 2 Case Studies
Q4108-Integra matrix	Not available
Q4110-Primatrix	9 Studies
Q4111-Gammagraft	10 case studies
Q4115-Alloskin	Not available
Q4117-Hyalomatrix	Not available
Q4118-Matristem	1 Case Study
Q4119-Matristem WM	Case studies
Q4120-Matristem burn	Case studies
Q4121-Theraskin	1 RCT and 1 peer reviewed, case studies
Q4122-Dermacell	2 clinical articles



developed individually or collaboratively with other contractors. The contractor shall ensure that all LCDs are consistent with all statutes, rulings, regulations, and national coverage, payment, and coding policies.”

#### Section 13.5.3: Use of Absolute Words in LCDs

When strong clinical justification exists, (MiMedx underline) contractors may also develop LCDs that contain absolute words such as “is never covered” or “is only covered for”. When phrases with absolute words are clearly stated in LCDs, contractors are not required to make any exceptions or give individual consideration based on evidence. Contractors should create edits/parameters that are as specific and narrow as possible to separate cases that can be automatically denied from those requiring individual review.

Many Medicare Contractors also focus on “science and clinical efficacy” as a basic coverage requirement for Medicare beneficiaries in their written LCDs. Examples from two Medicare Contractors specific to the “science and clinical efficacy” parameter are as follows:

#### NGS (LCD# 33391; effective 10/1/2015)

“Data must include: 1) Use supported by clinical research that appears in at least two well-designed and executed clinical trials that definitively demonstrate safety and effectiveness; or 2) a use that is an accepted standard of medical practice... A product’s use is based on substantial evidence and is reflective of the safety and efficacy of the product as determined in clinical investigations.” (See page 3 of 12).

#### CGS (LCD# 34053; effective 10/1/2015)

“CGS will consider all skin substitute products regulated as Class II or Class III devices as well as those products regulated as HCT/Ps eligible for coverage based upon adequate clinical trial literature that clearly supports their use in wound care therapy. With that in mind, we have determined to cover those which we are satisfied have achieved at least a threshold minimum of literature supporting their efficacy.” (See page 2 of 19).

#### Industry Concern

At an open meeting with one of the Medicare MACs in late 2015, certain wound care groups (e.g. Wound Care Stakeholders and Wound Care Coalition) advocated that CMS should include all skin substitute products as “covered” in written policy (LCDs) based on the argument that physicians need access to all products in the marketplace. However, many of the products in the marketplace with assigned HCPCS “Q” codes have little to no scientific data to support product use (see *Appendix, Table 1*).

#### **MAC Coverage**

The current focus on science and efficacy as a requirement for coverage for skin substitutes is relatively consistent among all MACs, including the retired LCDs from Noridian and WPS. Table 1 (see *Appendix*) is a representation of the products with their related published clinical studies, articles, case studies or white papers. It is clear that very few, if any, of the newer products with assigned HCPCS “Q” codes have randomized controlled trials or published clinical studies; most have case studies, posters or white papers only.

In sum, we are proposing that Washington State HCA align with CMS’ intent to require the development of coverage policy for new technologies based on scientific and clinical evidence, as outlined with the above excerpts from the Medicare *Program Integrity Manual*.

Q4123-Alloskin	Not available
Q4124-Oasis Tri-layer	6 case studies
Q4126-Memoderm	2 case studies
Q4127-Talymed	1 RCT; 6 published studies; case studies
Q4129-Unite biomatrix	Case studies
Q4131-EpiFix	6 RCTs, 23 total published studies
Q4132-Grafix Core	Not available* RCT was only on Grafix Prime (not Core)
Q4133-Grafix Prime	1 RCT*, 3 published studies; *RCT on Grafix Prime Only
Q4134-hMatrix	Not available
Q4135-Mediskin	5 White Papers
Q4136-EZderm	Case studies; clinical evidence summaries
Q4137-Amnioexcel	White paper, case studies, posters
Q4140-Biodfence	Not available
Q4141-Alloskin ac	Not available
Q4148-Neox	8 Case studies, 3 peer reviewed studies
Q4151-AmnioBand	2 posters
Q4152-Dermapure	1 Study (lower limbs)
Q4153-Dermavest	Not available
Q4154-Biovance	3 Case studies; poster
Q4156-Neox	8 Case studies; 3 peer-reviewed study
Q4157-Revitalon	Case studies
Q4158-MariGen	2 studies
Q4159-Affinity	Not available
Q4160-NuShield	Not available

**From:** Radensky, Paul - McDermottPlus <pradensky@mcdermottplus.com>  
**Sent:** Thursday, March 10, 2016 8:30 PM  
**To:** HCA ST Health Tech Assessment Prog  
**Cc:** Schaum, Kathleen (Kathleen.Schaum@smith-nephew.com); Godes, Deborah  
**Subject:** HTA Comments: Skin Substitutes  
**Attachments:** oasis\_ou\_instructions\_for\_use.pdf; oasis\_owm\_instructions\_for\_use.pdf

Dear Ms. Frost Teeter,

On behalf of Smith & Nephew plc, we are pleased to submit comments in response to the 2016 prospective Health Technology Assessment (“HTA”) technology topics which identifies skin substitutes as a potential topic. Smith & Nephew is a diversified advanced medical technology business that markets wound care treatment and prevention products used to treat hard-to-heal wounds, including OASIS® Wound Matrix and OASIS® Ultra Tri-layer Matrix (“OASIS”). The OASIS Matrix products comprise porcine small intestinal submucosa-derived products indicated for the management of partial and full-thickness wounds, pressure ulcers, venous ulcers, chronic vascular ulcers, tunneled, undermined wounds, diabetic ulcers, trauma wounds (abrasions, lacerations, second-degree burns, skin tears), draining wounds, and surgical wounds (donor sites/grafts, post-Mohs’ surgery, post-laser surgery, podiatric, wound dehiscence). The OASIS Matrix products are among the class of cellular and/or tissue-based products for wounds (CTPs) that are commonly referred to as skin substitutes, but which are, in fact, not intended to be substitutes or replacement for skin. CTPs are cellular and/or tissue-based biological products that are intended for use in the management of wounds.

Our comments are provided below to help inform HTA should you decide to move forward with the technology assessment on skin substitutes:

- Evidence by Ulcer Type:** We agree with the position that there are varying levels of clinical evidence on the different types of CTPs. It is important to note that the evidence for and performance of CTPs may vary by type of ulcer and CTPs are typically investigated by type of ulcer. Therefore, we would urge the HTA Program to review the literature by type of ulcer and not mix ulcer types when analyzing or comparing product performance.
- Breadth of Products:** When reviewing the products, we would encourage the HTA to include a broad range of products in this review, including lower cost products, such as the OASIS Matrix products.
- Comparator(s):** When doing the technology assessment, we believe that usual care and other wound healing products are appropriate comparators.
- Outcome(s):** Outcomes are critical and important to assess the safety and effectiveness of the CTPs for the treatment of wounds. When reviewing studies, we recommend that HTA include high quality studies even if the studies do not include all critical outcomes identified by HTA.

In addition, below is a list of references for the OASIS Matrix products that we believe would be appropriate for the HTA to include in its review if it decides to move forward with the technology assessment of skin substitutes. Due to copyright issues, we cannot attach electronic copies of these articles. We are happy to send hard copy reprints, for which we have copyright clearance, to your office.

1. Cazzell SM, Lange DL, Dickerson JE Jr, Slade HB. The Management of Diabetic Foot Ulcers with Porcine Small Intestine Submucosa Tri-Layer Matrix: A Randomized Controlled Trial. *Adv Wound Care*:2015; 4: 1-8. DOI: 10.1089/wound.2015.0645



2. Romanelli M, Dini V, Bertone MS. Randomized comparison of OASIS Wound Matrix versus moist wound dressing in the treatment of difficult-to-heal wounds of mixed arterial/venous etiology. *Adv Skin Wound Care* 2010; 23:34-38.
3. Rando T. Use of a biological extracellular matrix wound therapy to heal complex, chronic wounds. *J Wound Care* 2009;18:70-74.
4. Barendse-Hofmann MG, van Doorn LP, Oskam LP, Steenvoorde P. Extracellular matrix prevents split-skin grafting in selected cases. *J Wound Care* 2007; 16:455-458.
5. Landsman A, Roukis TS, DeFronzo DJ, Agnew P, *et al.* Living cells or collagen matrix: Which is more beneficial in the treatment of diabetic foot ulcers. *Wounds* 2008; 20:111-116.
6. Romanelli M, Dini V, Bertone M, Barbanera S, *et al.* OASIS® wound matrix versus Hyaloskin® in the treatment of difficult-to-heal wounds of mixed arterial/venous aetiology. *Int Wound J* 2007; 4:3-7.
7. O'Donnell TF, Lau J. A systematic review of randomized controlled trials of wound dressings for chronic venous ulcer. *J Vasc Surg* 2006; 44:1118-1125.
8. Niezgoda JA, Van Gils CC, Frykberg RG, Hodde JP, and the OASIS Diabetic Ulcer Study Group. Randomized clinical trial comparing OASIS Wound Matrix to Regranex gel for diabetic ulcers. *Adv Skin Wound Care* 2005; 18:258-266.
9. Mostow EN, Haraway GD, Dalsing M, Hodde JP, *et al.* Effectiveness of an extracellular matrix graft (OASIS Wound Matrix) in the treatment of chronic leg ulcers: a randomized clinical trial. *J Vasc Surg* 2005; 41:837-843.

**Paul Radensky, M.D., J.D.**

Principal



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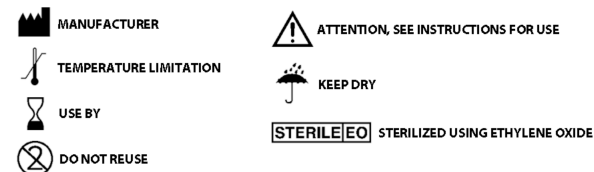
[Website](#) | [vCard](#) | [E-mail](#)

\*\*\*\*\*  
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For more information about our services, please visit <http://www.mcdermottplus.com/>



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Marketed by:

Smith & Nephew, Inc.

Fort Worth, TX 76107

Toll free: 1-800-441-8227

www.smith-nephew.com

COOK<sup>®</sup>

Manufactured by:  
Cook Biotech Incorporated  
West Lafayette, IN 47906



#### INTENDED USE:

OASIS<sup>®</sup> Ultra Tri-Layer Matrix is indicated for the management of wounds including:

- Partial and full-thickness wounds
- Pressure ulcers
- Venous ulcers
- Chronic vascular ulcers
- Tunneled, undermined wounds
- Diabetic ulcers
- Trauma wounds (abrasions, lacerations, second-degree burns, skin tears)
- Draining wounds
- Surgical wounds (donor sites/grafts, post-Moh's surgery, post-laser surgery, podiatric, wound dehiscence)

OASIS<sup>®</sup> Ultra Tri-Layer Matrix is supplied sterile in peel-open packages and is intended for one-time use.

**CAUTION: Federal (U.S.A.) law restricts this device to sale by or on the order of a licensed healthcare practitioner.**

**CONTRAINDICATIONS:** This device is derived from a porcine source and should not be used in patients with known sensitivity to porcine material. This device is not indicated for use in third degree burns.

#### PRECAUTIONS:

- Do not re-sterilize. Discard all open and unused portions of OASIS<sup>®</sup> Ultra Tri-Layer Matrix.
- Device is sterile if the package is dry, unopened and undamaged. Do not use if the package seal is broken.
- The device must be used prior to the expiration date.
- Discard device if mishandling has caused possible damage or contamination.
- OASIS<sup>®</sup> Ultra Tri-Layer Matrix should not be applied until excessive exudate, bleeding, acute swelling, and infection is controlled.

**POTENTIAL COMPLICATIONS:** The following complications are possible. If any of these conditions occur, the device should be removed.

- Infection
- Chronic inflammation (Initial application of wound dressings may be associated with transient, mild, localized inflammation.)
- Allergic reaction
- Excessive redness, pain, swelling, or blistering

**STORAGE:** This device should be stored in a clean, dry location at room temperature.

**STERILIZATION:** This device has been sterilized with ethylene oxide.

#### SUGGESTED INSTRUCTIONS FOR USING OASIS<sup>®</sup> ULTRA TRI-LAYER MATRIX

**NOTE: Always handle OASIS<sup>®</sup> Ultra Tri-Layer Matrix using aseptic technique.**

##### I. Wound Bed Preparation

- A. Prepare the wound bed using standard methods to ensure it is free of exudate and devitalized tissue. An initial excision or debridement of the wound may be necessary to ensure the wound edges contain viable tissue.
- B. Wait for any bleeding to stop before applying OASIS<sup>®</sup> Ultra Tri-Layer Matrix.
- C. Cleanse the wound thoroughly with sterile saline.

##### II. Selection and Preparation of OASIS<sup>®</sup> Ultra Tri-Layer Matrix

- A. Measure the wound and select the appropriate size sheet of dry OASIS<sup>®</sup> Ultra Tri-Layer Matrix. If necessary, the product may be additionally fenestrated or meshed with a scalpel.
- B. Cut the sheet to a size and shape that will cover the entire wound surface and will extend slightly beyond the wound margins.

##### III. Application of OASIS<sup>®</sup> Ultra Tri-Layer Matrix

- A. For ease of handling, apply OASIS<sup>®</sup> Ultra Tri-Layer Matrix by placing it in a dry state over the wound.
- B. Position the dry OASIS<sup>®</sup> Ultra Tri-Layer Matrix to completely contact the entire surface of the wound bed and extend slightly beyond all wound margins. If multiple sheets are necessary to cover the wound, slightly overlap the edges of the sheets.
- C. As required, securely anchor OASIS<sup>®</sup> Ultra Tri-Layer Matrix with physician's preferred fixation method (e.g., STERI-STRIP<sup>™</sup>, tissue sealant, bolsters, dissolvable clips, sutures, staples, or other appropriate fixation method) based on the type of wound, location of wound, patient's mobility, and patient compliance.
- D. Thoroughly rehydrate OASIS<sup>®</sup> Ultra Tri-Layer Matrix by applying sterile saline.
- E. To protect OASIS<sup>®</sup> Ultra Tri-Layer Matrix from adhering to the secondary dressing, apply an appropriate non-adherent primary wound dressing over the OASIS<sup>®</sup> Ultra Tri-Layer Matrix.
- F. Apply an appropriate secondary dressing (multi-layer compression bandage system, total contact cast, or other appropriate dressing) that will manage the wound exudate, keep the OASIS<sup>®</sup> Ultra Tri-Layer Matrix moist, and keep all layers securely in place.

#### IV. Dressing Changes

- A. To prevent damage to the newly incorporating OASIS<sup>®</sup> Ultra Tri-Layer Matrix, only change the primary dressing as necessary, typically every 7 days.
- B. Change secondary dressing as appropriate. Take care to avoid dislodging the OASIS<sup>®</sup> Ultra Tri-Layer Matrix when the secondary dressing is changed.

#### V. Wound Assessment and Wound Bed Preparation for Reapplication of OASIS<sup>®</sup> Ultra Tri-Layer Matrix

- A. Change all dressings every 7 days, or as necessary.

**NOTE:** If a gel forms on the wound surface, do not attempt to forcibly remove it. Successful absorption of OASIS<sup>®</sup> Ultra Tri-Layer Matrix may form a caramel-colored or off-white gel. Do not remove this gel by debridement. This caramelization contains extracellular matrix (ECM), which continues to replace deficient and missing ECM in the wound.

- B. As healing occurs, sections of OASIS<sup>®</sup> Ultra Tri-Layer Matrix may gradually peel. Carefully remove any remaining loose product around the edge as needed.
- C. Gently cleanse the wound surface with sterile saline; leave the ECM gel intact.
- D. Carefully reassess the wound and record healing progression such as wound dimensions, wound depth, wound type, and other relevant information.

#### VI. Reapplication of OASIS<sup>®</sup> Ultra Tri-Layer Matrix and Dressing Changes

- A. Change secondary dressings as needed (See step IV)
- B. If the wound is free of infection and necrosis but not fully epithelialized, reapply newly prepared OASIS<sup>®</sup> Ultra Tri-Layer Matrix over previously absorbed application, (See Steps II and III)
- C. Reapply as needed if OASIS<sup>®</sup> Ultra Tri-Layer Matrix is no longer visible, typically every 7 days.

**NOTE: If excess exudate collects under the sheet, small openings can be cut in the sheet to allow the exudate to drain.**



Rev. 05/14

FP0080-01C

Manufacturer	Attention, see instructions for use
Temperature limit	Keep dry
Use-by date	<b>STERILE</b> <b>EO</b> Sterilized using ethylene oxide
Do not re-use	



Marketed by:  
Smith & Nephew, Inc.

Fort Worth, TX 76107

Toll free: 1-800-441-8227

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**COOK**<sup>®</sup>  
Manufactured by:  
Cook Biotech Incorporated  
West Lafayette, IN 47906



**INTENDED USE:**

OASIS<sup>®</sup> Wound Matrix is indicated for the management of wounds including:

- Partial and full-thickness wounds
- Pressure ulcers
- Venous ulcers
- Chronic vascular ulcers
- Tunneled, undermined wounds
- Diabetic ulcers
- Trauma wounds (abrasions, lacerations, second-degree burns, skin tears)
- Draining wounds
- Surgical wounds (donor sites/grafts, post-Mohs' surgery, post-laser surgery, podiatric, wound dehiscence)

OASIS<sup>®</sup> Wound Matrix is supplied sterile in peel-open packages and is intended for one-time use.

**CAUTION: Federal (U.S.A.) law restricts this device to sale by or on the order of a licensed healthcare practitioner.**

**CONTRAINDICATIONS:** This device is derived from a porcine source and should not be used in patients with known sensitivity to porcine material. This device is not indicated for use in third degree burns.

**PRECAUTIONS:**

- Do not re-sterilize. Discard all open and unused portions of OASIS<sup>®</sup> Wound Matrix.
- Device is sterile if the package is dry, unopened and undamaged. Do not use if the package seal is broken.
- The device must be used prior to the expiration date.
- Discard device if mishandling has caused possible damage or contamination.
- OASIS<sup>®</sup> Wound Matrix should not be applied until excessive exudate, bleeding, acute swelling, and infection is controlled.

**POTENTIAL COMPLICATIONS:** The following complications are possible. If any of these conditions occur, the device should be removed.

- Infection
- Chronic inflammation (Initial application of wound dressings may be associated with transient, mild, localized inflammation.)
- Allergic reaction
- Excessive redness, pain, swelling, or blistering

**STORAGE:** This device should be stored in a clean, dry location at room temperature.

**STERILIZATION:** This device has been sterilized with ethylene oxide.

**SUGGESTED INSTRUCTIONS FOR USING OASIS<sup>®</sup> WOUND MATRIX**

**NOTE: Always handle OASIS<sup>®</sup> Wound Matrix using aseptic technique.**

**I. Wound Bed Preparation**

- Prepare the wound bed using standard methods to ensure it is free of exudate and devitalized tissue. An initial excision or debridement of the wound may be necessary to ensure the wound edges contain viable tissue.
- Wait for any bleeding to stop before applying OASIS<sup>®</sup> Wound Matrix.
- Cleanse the wound thoroughly with sterile saline.

**II. Selection and Preparation of OASIS<sup>®</sup> Wound Matrix**

- Measure the wound and select the appropriate size sheet of dry OASIS<sup>®</sup> Wound Matrix. If necessary, the product may be additionally fenestrated or meshed with a scalpel.
- Cut the sheet to a size and shape that will cover the entire wound surface and will extend slightly beyond the wound margins.

**III. Application of OASIS<sup>®</sup> Wound Matrix**

- For ease of handling, apply OASIS<sup>®</sup> Wound Matrix by placing it in a dry state over the wound.
- Position the dry OASIS<sup>®</sup> Wound Matrix to completely contact the entire surface of the wound bed and extend slightly beyond all wound margins. If multiple sheets are necessary to cover the wound, slightly overlap the edges of the sheets.
- As required, securely anchor OASIS<sup>®</sup> Wound Matrix with physician's preferred fixation method (e.g., STERI-STRIP<sup>™</sup>, tissue sealant, bolsters, dissolvable clips, sutures, staples, or other appropriate fixation method) based on the type of wound, location of wound, patient's mobility, and patient compliance.
- Thoroughly rehydrate OASIS<sup>®</sup> Wound Matrix by applying sterile saline.
- To protect OASIS<sup>®</sup> Wound Matrix from adhering to the secondary dressing, apply an appropriate non-adherent primary wound dressing over the OASIS<sup>®</sup> Wound Matrix.
- Apply an appropriate secondary dressing (multi-layer compression bandage system, total contact cast, or other appropriate dressing) that will manage the wound exudate, keep the OASIS<sup>®</sup> Wound Matrix moist, and keep all layers securely in place.

**IV. Dressing Changes**

- To prevent damage to the newly incorporating OASIS<sup>®</sup> Wound Matrix, only change the primary dressing as necessary, typically every 7 days.
- Change the secondary dressing as appropriate. Take care to avoid dislodging the OASIS<sup>®</sup> Wound Matrix when the secondary dressing is changed.

**V. Wound Assessment and Wound Bed Preparation for Reapplication of OASIS<sup>®</sup> Wound Matrix**

- Change all dressings every 7 days, or as necessary.

**NOTE:** If a gel forms on the wound surface, do not attempt to forcibly remove it. Successful absorption of OASIS<sup>®</sup> Wound Matrix may form a caramel-colored or off-white gel. Do not remove this gel by debridement. This caramelization contains extracellular matrix (ECM), which continues to replace deficient and missing ECM in the wound.

- As healing occurs, sections of OASIS<sup>®</sup> Wound Matrix may gradually peel. Carefully remove any remaining loose products around the edge as needed.
- Gently cleanse the wound surface with sterile saline; leave the ECM gel intact.
- Carefully reassess the wound and record healing progression such as wound dimensions, wound depth, wound type, and other relevant information.

**VI. Reapplication of OASIS<sup>®</sup> Wound Matrix and Dressing Changes**

- Change secondary dressings as needed (see step IV).
- If the wound is free of infection and necrosis but not fully epithelialized, reapply newly prepared OASIS<sup>®</sup> Wound Matrix over previously absorbed application (see steps II and III).
- Reapply OASIS<sup>®</sup> Wound Matrix every 7 days or as needed by repeating previous application steps.

**NOTE: If excess exudate collects under the sheet, small openings can be cut in the sheet to allow the exudate to drain.**

To: Dorothy Frost Teeter, Washington State HCA Director  
From: Dirk Sutherland, Regional Director of Health Policy, Alliqua Biomedical  
Subject: WA HCA proposed technology topics  
Date: March 11, 2016

Hello and thank you for this opportunity to comment on the selection of future Washington State Health Care Authority's Health Technology Assessment topics. Alliqua BioMedical is a provider of advanced wound care solutions. Our products are intended to enhance the wound care practitioner's ability to deal with the challenges in the treatment of complex and/or non-healing wounds".

### **Skin Substitutes Topic**

Alliqua BioMedical manufactures and markets Biovance, a Human Amniotic Membrane Allograft for treatments including complex and/or non-healing wounds.

Alliqua BioMedical believes a technology assessment should be completed identifying products with clinical data demonstrating positive health outcomes for Washington Medicaid beneficiaries allowing access to appropriate, medically necessary use of skin substitutes as is currently available for Washington's Medicare population. Skin substitute products, like Biovance, serve an important role in the treatment of complex and/or non-healing wounds. In April 2015, Noridian removed all HCPCS codes in the Q4xxx range, relating to skin substitutes from their non-covered list stating the following in an article title, "Response to Comments: Non-Covered Services Policy, L35212" (attached to the email this comment was sent with), "Medicare considers "dressings" as generally bundled services that are not paid separately. But Medicare considers "grafts" as separately payable. Over the last decade, the number of skin substitute products on the market has dramatically increased, but utilization still remains relatively low. Consequently, Noridian has decided, at least for the short term, to allow coverage for those products with a HCPCS code in the Q4xxx range. This section is being removed for this LCD."

It is crucial to define the distinction between a "dressing" and a "skin substitute." A dressing is a material that is utilized for covering and protecting a wound, although they can be incorporated into the wound, they help shield the wound against the environment without exerting any direct biological effect in the wound bed. Yet products that maintain a "Q Code" all contain viable or non-viable cells and/or are derived from biological tissue with intrinsic biological activity, are usually not removed from the wound, are uniquely utilized for their biological influence on the healing process – whether they have a positive influence on the healing process without incorporation OR have the ability to stabilize or support healing through incorporation in whole or part into the regenerating tissue. All the products listed in this draft LCD are CTPs and are NOT wound dressings as they promote wound healing by interacting directly or indirectly with the body tissues.

Although complex and/or non-healing wounds are not limited to a specific patient demographic, our experience, speaking with our customers demonstrate a payer mix for these patients that is heavily weighted towards Medicare and Medicaid patients. Skin substitutes have consistently been shown to reduce time to healing and increase complete healing compared to "standard of

care” procedures thus potentially increasing patient quality of life while reducing overall treatment costs to these wounds.

Presently there is not one ideal skin substitute product that provides effective wound healing across the entire spectrum of wound types and patient conditions. It is critical then that practitioners have the ability to utilize their clinical judgment to select the most effective products and treatments for their patients based on the presenting sequelae.

We are aware many payer organizations are currently looking to understand and set guidelines for skin substitute use. One of these organizations is the Blue Cross Blue Shield Association (BCBSA). As a participant in the BCBSA Evidence Street Pilot program I’ve attached the most recent review of their skin substitute policy completed January 2016 for your review. This review includes the BCBSA guidelines presented in a PICO (Population, Interventions, Comparators, Outcomes) format. I hope is helpful for your decision.

### **Additional Topic Recommendation**

Alliqua Biomedical also manufacturers and markets the MIST Therapy system, a Non-Contact Low Frequency Ultrasound system for wound healing. We would like to recommend MIST Therapy as a topic for a HTA review. MIST Therapy has demonstrated in multiple high level studies, a positive impact on health outcomes when treating complex and/or non-healing wounds. Please find attached a clinical summary of available data demonstrating reduced treatment time and increased complete healing rates along with positive outcomes in patient quality of life scores compared to “standard of care” for patients needing treatments for complex and/or non-healing wounds. Reductions in time to heal and complete healing rates for these wounds represent a significant cost avoidance opportunity for the Medicaid population including well documented success treating pressure ulcers. Treatment of pressure ulcers is often initiated in the inpatient setting under a DRG type payment system, however if not available in outpatient setting, continuity of care can be lost resulting in a recurrence and/or re-admittance both of which may result in decreased quality of life and increased cost to the Medicaid population.

As with Skin Substitutes, Washington’s Medicare population currently has access to MIST Therapy when reasonable and medically necessary through Noridian.

Thanks you again for this opportunity to comment.

If you have any questions regarding this comment or would like additional information, please contact Dirk Sutherland using the following contact information.

Kind Regards, Dirk

Dirk Sutherland  
Regional Director of Health Policy  
Alliqua Biomedical  
1010 Stony Hill Road, Suite 200  
Yardley, PA 19067  
Cell (214) 620-4059

## Evidence Summary

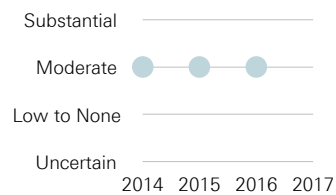
Bio-engineered skin and soft tissue substitutes may be derived from human tissue (autologous or allogeneic), nonhuman tissue (xenographic), synthetic materials, or a composite of these materials. Bio-engineered skin and soft tissue substitutes are being evaluated for a variety of conditions, including breast reconstruction and to aid healing of lower-extremity ulcers and severe burns. Acellular dermal matrix products are also being evaluated in the repair of a variety of soft tissues.

Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"> <li>• With conditions requiring surgical repair</li> </ul>	Interventions of interest are: <ul style="list-style-type: none"> <li>• Bioengineered soft tissue substitutes</li> </ul>	Comparators of interest are: <ul style="list-style-type: none"> <li>• Surgical repair alone</li> </ul>	Relevant outcomes include: <ul style="list-style-type: none"> <li>• Symptoms</li> <li>• Morbid events</li> <li>• Functional outcomes</li> <li>• Quality of life</li> <li>• Treatment-related morbidity</li> </ul>
Individuals: <ul style="list-style-type: none"> <li>• With chronic wounds</li> </ul>	Interventions of interest are: <ul style="list-style-type: none"> <li>• Bioengineered skin substitutes</li> </ul>	Comparators of interest are: <ul style="list-style-type: none"> <li>• Standard wound care</li> </ul>	Relevant outcomes include: <ul style="list-style-type: none"> <li>• Disease-specific survival</li> <li>• Symptoms</li> <li>• Change in disease status</li> <li>• Morbid events</li> <li>• Quality of life</li> </ul>
Individuals: <ul style="list-style-type: none"> <li>• With burns, skin grafts, or traumatic wounds</li> </ul>	Interventions of interest are: <ul style="list-style-type: none"> <li>• Bio-engineered skin substitutes</li> </ul>	Comparators of interest are: <ul style="list-style-type: none"> <li>• Standard wound care</li> </ul>	Relevant outcomes include: <ul style="list-style-type: none"> <li>• Symptoms</li> <li>• Morbid events</li> <li>• Functional outcomes</li> <li>• Quality of life</li> <li>• Treatment-related morbidity</li> </ul>

## Overview by Evidence Review Indications

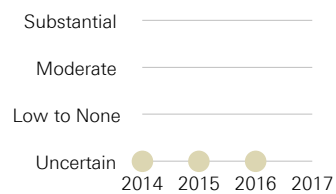
Indication 1: Individuals who have breast reconstruction and are treated with an acellular dermal matrix allograft (eg, AlloDerm, AlloMax, DermaMatrix, FlexHD, Graftjacket).

**The evidence is sufficient to determine qualitatively that the treatment results in a meaningful improvement in the net health outcome.**



Indication 2: Individuals who have parotidectomy and are treated with an acellular dermal matrix allograft.

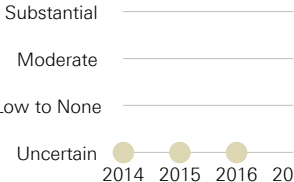
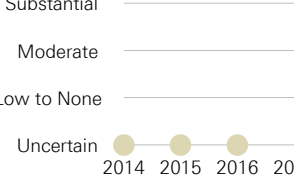
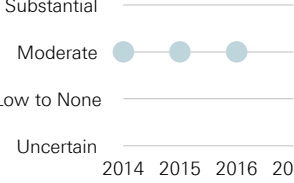
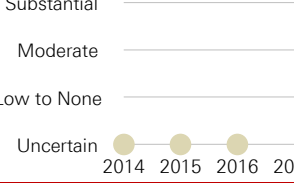
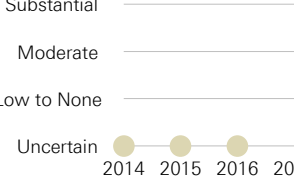
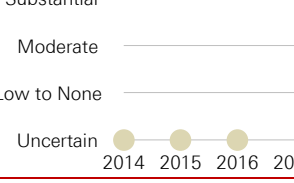
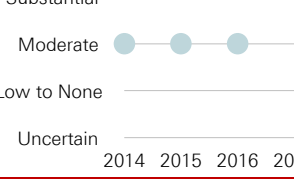
**The evidence is insufficient to determine the effects of the technology on health outcomes.**



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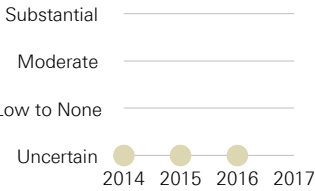
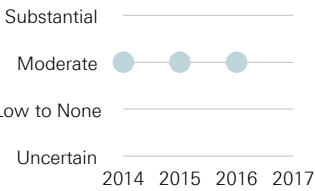
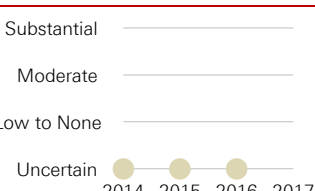
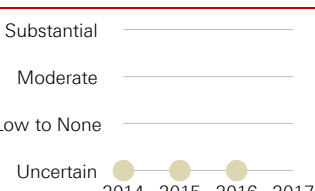
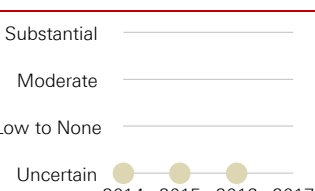
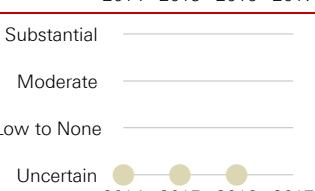
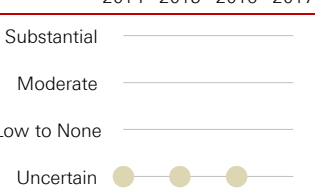
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<p>Indication 3: Individuals who have tendon repair and are treated with an acellular dermal matrix allograft (eg, Graftjacket).</p>	
<p><b>The evidence is insufficient to determine the effects of the technology on health outcomes.</b></p>	
<p>Indication 4: Individuals who have fistula repair and are treated with an acellular dermal matrix allograft.</p>	
<p><b>The evidence is insufficient to determine the effects of the technology on health outcomes.</b></p>	
<p>Indication 5: Individuals with surgical repair of hernias who are treated with any bioengineered soft tissue substitute.</p>	
<p><b>The evidence is sufficient to determine qualitatively that the technology is unlikely to improve the net health outcome.</b></p>	
<p>Indication 6: Individuals who have oral surgery and are treated with an acellular dermal matrix allograft (eg, AlloDerm).</p>	
<p><b>The evidence is insufficient to determine the effects of the technology on health outcomes.</b></p>	
<p>Indication 7: Individuals who have laryngoplasty and are treated with micronized acellular dermal matrix (eg, Cymetra).</p>	
<p><b>The evidence is insufficient to determine the effects of the technology on health outcomes.</b></p>	
<p>Indication 8: Individuals who have tympanoplasty and are treated with an acellular dermal matrix product (eg, AlloDerm).</p>	
<p><b>The evidence is insufficient to determine the effects of the technology on health outcomes.</b></p>	
<p>Indication 9: Individuals with diabetic lower-extremity ulcers who are treated with certain skin and soft tissue substitutes (eg, Apligraf, Dermagraft, Integra Dermal Regeneration Template, Biovance, Epifix, Grafix).</p>	
<p><b>The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.</b></p>	

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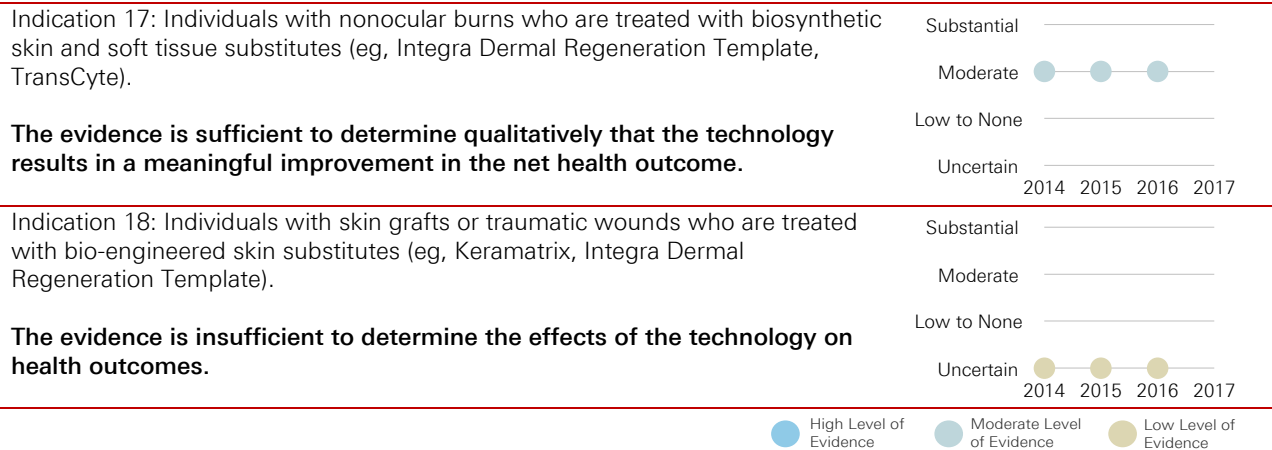
<p>Indication 10: Individuals with diabetic lower-extremity ulcers who are treated with xenogenic skin and soft tissue substitutes (eg, Oasis Wound Matrix, PriMatrix).</p>	
<p><b>The evidence is insufficient to determine the effects of the technology on health outcomes.</b></p>	
<p>Indication 11: Individuals with lower-extremity ulcers due to venous insufficiency who are treated with Apligraf (living cell therapy) or Oasis Wound Matrix (xenogenic collagen scaffold).</p>	
<p><b>The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.</b></p>	
<p>Indication 12: Individuals with lower-extremity ulcers due to venous insufficiency who are treated with Dermagraft (living cell therapy).</p>	
<p><b>The evidence is insufficient to determine the effects of the technology on health outcomes.</b></p>	
<p>Indication 13: Individuals with lower-extremity ulcers due to venous insufficiency who are treated with amniotic membrane (eg, EpiFix) or xenogenic acellular dermal matrix (eg PriMatrix).</p>	
<p><b>The evidence is insufficient to determine the effects of the technology on health outcomes.</b></p>	
<p>Indication 14: Individuals with dystrophic epidermolysis bullosa who are treated with living cell therapy (eg, OrCel).</p>	
<p><b>The evidence is insufficient to determine the effects of the technology on health outcomes.</b></p>	
<p>Indication 15: Individuals with ocular burns who are treated with any bioengineered skin and soft tissue substitutes.</p>	
<p><b>The evidence is insufficient to determine the effects of the technology on health outcomes.</b></p>	
<p>Indication 16: Individuals with nonocular burns who are treated with living cell therapy (eg, Epicel).</p>	
<p><b>The evidence is insufficient to determine the effects of the technology on health outcomes.</b></p>	

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## BACKGROUND

Bio-engineered skin and soft tissue substitutes may be either acellular or cellular. Acellular products (eg, dermis with cellular material removed) contain a matrix or scaffold composed of materials such as collagen, hyaluronic acid, and fibronectin. The various acellular dermal matrix products can differ in a number of ways, including as species source (human, bovine, porcine), tissue source (eg dermis, pericardium, intestinal mucosa), additives (eg antibiotics, surfactants), hydration (wet, freeze dried) and required preparation (multiple rinses, rehydration).

Cellular products contain living cells such as fibroblasts and keratinocytes within a matrix. The cells contained within the matrix may be autologous, allogeneic, or derived from other species (eg, bovine, porcine). Skin substitutes may also be composed of dermal cells, epidermal cells, or a combination of dermal and epidermal cells and may provide growth factors to stimulate healing. Tissue-engineered skin substitutes can be used as either temporary or permanent wound coverings.

There are a large number of potential applications for artificial skin and soft tissue products. One large category is nonhealing wounds, which potentially encompasses diabetic neuropathic ulcers, vascular insufficiency ulcers, and pressure ulcers. A substantial minority of such wounds do not heal adequately with standard wound care, leading to prolonged morbidity and increased risk of mortality. For example, nonhealing lower-extremity wounds represent an ongoing risk for infection, sepsis, limb amputation, and death. Bio-engineered skin and soft tissue substitutes have the potential to improve rates of healing and reduce secondary complications.

The preferred outcomes for the healing of lower-extremity ulcers and burn wounds are the percentage of patients with complete wound healing and the time to complete wound healing.<sup>1</sup> The percentage of patients with 50% wound healing and time to 50% wound healing have also been considered to be appropriate outcomes for these conditions.<sup>2</sup> The percent change in wound area at 4 weeks is predictive of complete healing at 12 weeks in patients with diabetic foot ulcers.<sup>3</sup> Thus, minimal improvement at 30 days can be considered as an indicator that a wound is unlikely to heal in patients with comorbidities that are known to affect wound healing.

Other situations in which bio-engineered skin products might substitute for living skin grafts include certain postsurgical states such as breast reconstruction, in which skin coverage is inadequate for the

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procedure performed, or for surgical wounds in patients with compromised ability to heal. Second- and third-degree burns are another situation in which artificial skin products may substitute for auto- or allografts. Certain primary dermatologic conditions that involve large areas of skin breakdown, such as bullous diseases, may also be conditions in which artificial skin products can be considered as substitutes for skin grafts. Acellular dermal matrix products are also being evaluated in the repair of other soft tissues including rotator cuff repair, following oral and facial surgery, hernias, and a variety of other conditions.

## RATIONALE

This evidence review was developed based on a literature search using MEDLINE in November 2007 for use of an allogeneic tissue-engineered skin substitute (AlloDerm) in breast reconstructive surgery. At the time this review was created, the available data on use of this technology were limited. In particular, there were no comparative studies to evaluate possible changes of the reconstructive time or to evaluate changes in esthetics. In addition, the duration of follow-up was limited, so the impact on longer-term complications such as severe contractures could not be determined. Finally, criteria to determine those who were candidates for use of this procedure had not been established.

In 2011 this evidence review was expanded to address additional bio-engineered skin and soft tissue substitutes and other indications. The most recent literature update was performed through October 30, 2015. Following is a summary of key literature to date.

### Breast Reconstruction

#### AlloDerm

##### *Systematic Reviews*

Two systematic reviews from 2012 found an increased rate of complications with acellular dermal matrix (ADM)-assisted breast reconstruction. One meta-analysis of 16 retrospective studies found a higher likelihood of seroma (pooled odds ratio [OR], 3.9; 95% confidence interval [CI], 2.4 to 6.2), infection (pooled OR=2.7; 95% CI, 1.1 to 6.4) and reconstructive failure (pooled OR=3.0; 95% CI, 1.3 to 6.8) when compared with breast reconstruction using traditional musculofascial flaps.<sup>6</sup> Another meta-analysis that compared 19 studies using ADM (n=2037) with 35 studies using submuscular reconstruction (n=12,847) found an increased risk of total complications (relative risk [RR], 2.05; 95% CI, 1.55 to 2.70), seroma (RR=2.73; 95% CI, 1.67 to 4.46), infection (RR=2.47; 95% CI, 1.71 to 3.57), and reconstructive failure (RR=2.80; 95% CI, 1.76 to 4.45) with ADM.<sup>7</sup> These meta-analyses are limited by the poor quality of included studies and significant heterogeneity.

##### *Randomized Controlled Trials*

In 2012, McCarthy et al reported a multicenter blinded randomized controlled trial (RCT) of AlloDerm in 2-stage expander/implant reconstruction.<sup>8</sup> Seventy patients were randomized to AlloDerm ADM-assisted tissue expander/implant reconstruction or to submuscular tissue expander/implant placement. There were no significant differences between the groups in the primary outcomes of immediate postoperative pain (54.6 AlloDerm and 42.8 control on a 100-point visual analog scale) or pain during the expansion phase (17.0 AlloDerm, 4.6 control), or in the secondary outcome of rate of tissue expansion (91 days AlloDerm, 108 days control) and patient-reported physical well-being. There was no significant difference in adverse events (AEs), although the total number of AEs was small. Phase 2 of the study will evaluate long-term outcomes.

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### ***Controlled Studies***

Preminger et al evaluated the impact of AlloDerm on expansion rates in immediate tissue expander/implant reconstruction in a retrospective matched cohort study.<sup>9</sup> Forty-five patients had reconstruction with AlloDerm and 45 had standard reconstruction. Subjects were matched for expander size ( $\pm 100$  mL), history of irradiation, and indication for mastectomy. There were no significant differences in initial filling volume, mean number of postoperative expansions, mean rate of postoperative tissue expansion, or in the incidence of postoperative complications. Aesthetic outcomes were not addressed. In 2008, Colwell and Breuing reported on 10 patients who had mastopexy with dermal slings; 5 patients were given AlloDerm and 5 were given autologous tissue.<sup>10</sup> Patients maintained projection and breast base width after 6 months to 3 years.

### ***Uncontrolled Studies***

A number of case series have also demonstrated that this approach can provide tissue coverage of implants and tissue expanders.<sup>11,12</sup> AlloDerm has been reported in nipple reconstructive surgery in a case series on 30 nipple reconstructive procedures performed at 1 institution.<sup>13</sup> Use of AlloDerm has also been reported in a small series (n=3) to correct breast implant-related problems (malposition, symmastia, rippling).<sup>14</sup>

### ***Other***

Liu et al reported postoperative complications in breast reconstruction with (n=266) or without (n=204) AlloDerm in 2011.<sup>15</sup> Radiotherapy, body mass index (BMI), intraoperative use of tumescent solution, and medical comorbidities were similar between the 2 groups, but there were twice as many smokers and the implants were larger in the AlloDerm group. There was a trend for a higher rate of major infections that required prosthesis removal in the AlloDerm group (4.9% vs 2.5%, p=0.172) and a statistically significant increase in overall wound infection rate (6.8% vs 2.5%). The overall surgical complication rate was significantly higher in the AlloDerm group (19.5% vs 12.3%). Multivariate analysis indicated that the use of ADM, smoking, higher BMI, higher initial volume, and bigger implant size were associated with a higher overall surgical complication rate. This study is limited by the retrospective analysis and differences between groups at baseline.

Bindingavele et al reviewed charts of 41 patients (65 breasts) who had staged breast reconstruction with acellular cadaveric dermis to report postoperative complication rates.<sup>16</sup> Rates for wound infection, expander removal, hematoma, and seroma were 3.1%, 1.5%, 1.5%, and 4.6%, respectively. The authors concluded that based on low rates of complications and good cosmetic outcomes, the technology should be in the repertoire of plastic surgeons and that follow-up is required to evaluate long-term outcomes.

### **AlloDerm Versus DermaMatrix or FlexHD**

A 2014 retrospective review by Liu et al compared complication rates following breast reconstruction with AlloDerm or FlexHD in 382 consecutive women (547 breasts).<sup>17</sup> Eighty-one percent of the sample was immediate reconstruction; 165 used AlloDerm, and 97 used FlexHD. Mean follow-up was 6.4 months. Compared with breast reconstruction without use of AlloDerm or FlexHD, ADM had a higher rate of delayed healing (20.2% vs 10.3%), although this finding might be related to differences in fill volumes. In univariate analysis, there were no significant differences in complications (return to the operating room, surgical site infection, seroma, hematoma, delayed healing, implant loss) between AlloDerm and FlexHD. In multivariate analysis, there were no significant differences between AlloDerm and FlexHD for the return to the operating room, surgical site infection, seroma, or delayed healing.

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Independent risk factors for implant loss included the use of FlexHD, single-stage reconstruction, and smoking. Another retrospective review from 2013 compared complication rates following use of AlloDerm (n=136) or FlexHD (n=233) in a consecutive series of 255 patients (369 breasts).<sup>18</sup> Total complication rates for the 2 products were similar (19.1% for AlloDerm, 19.3% for FlexHD). Analysis by type of complication showed no significant difference between the 2, and regression analysis controlling for differences in baseline measures found that the type of ADM was not a risk factor for any complication.

Brooke et al conducted a retrospective review of complication rates when AlloDerm (n=49), DermaMatrix (n=110), or FlexHD (n=62) was used for tissue expander breast reconstruction.<sup>19</sup> Clinically significant complications were defined as cellulitis, abscess, seroma, expander leak or puncture, skin necrosis, wound dehiscence, or hematoma. The total clinically significant complication rate was 22% with AlloDerm, 15% with DermaMatrix, and 16% with FlexHD (not significantly different). Infectious complication rates for the 3 products were the same at 10%. When compared with breast reconstruction without an ADM (n=64), there was no significant difference in the total complication rate (17% vs 11%), but there was a trend toward a higher incidence of infectious complications (10% vs 2%, p=0.09)

This small amount of evidence from retrospective comparative studies does not show any difference in outcomes among different types of ADM products.

### **SurgiMend (Fetal Bovine ADM) Versus AlloDerm (Human ADM)**

Butterfield reported a retrospective comparison of 281 patients who underwent breast reconstruction with SurgiMend (79.0%) or AlloDerm (21.0%).<sup>20</sup> AlloDerm was used at the beginning of the study while SurgiMend was used predominantly in the latter period due to ease of use and lower cost; the 2 groups were comparable on patient demographics, risk factors, and concurrent therapy. The rate of seroma, the most prevalent complication, was significantly lower for SurgiMend (8.3%) compared with AlloDerm (15.7%, p=0.044); however, the necrosis rate was higher for SurgiMend (11.1% vs 3.4%, p=0.027), due entirely to a higher minor necrosis rate for SurgiMend (8.8% vs 1.1%). There were no significant differences in complication rates for hematoma, infection, major skin necrosis, or breast implant removal.

### **Section Summary: Breast Reconstruction**

The extensive data from controlled cohorts and case series about the usefulness of this procedure in providing inferolateral support for breast reconstruction supports the use of acellular dermal matrix (ADM) allograft (ie, AlloDerm, AlloMax, DermaMatrix, FlexHD, Graftjacket) in breast reconstruction when there is insufficient tissue expander or implant coverage by the pectoralis major muscle and additional coverage is required; when there is viable but compromised or thin postmastectomy skin flaps that are at risk of dehiscence or necrosis; or when the inframammary fold and lateral mammary folds have been undermined during mastectomy and reestablishment of these landmarks is needed. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

## **Interpositional Graft After Parotidectomy**

### **AlloDerm**

In 2003, Sinha et al reported the use of AlloDerm acellular human dermal matrix as an interpositional physical barrier to prevent the development of Frey syndrome (gustatory sweating) after

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parotidectomy.<sup>21</sup> Thirty patients were divided into 3 groups; it was not described if the assignments were randomized. One group underwent superficial parotidectomy with reconstruction of the defect with AlloDerm, a second group had superficial parotidectomy without placement of an interpositional barrier, and the third group underwent deep-plane rhytidectomy without disruption of the parotid fascia. At minimum 1-year follow-up, there was a subjective incidence of Frey syndrome in 1 patient treated with AlloDerm and 5 patients in group 2. The objective incidence of Frey syndrome, measured with the Minor starch-iodine test, was 2 patients treated with AlloDerm and 8 patients in group 2. None of the patients in group 3 who underwent deep-plane rhytidectomy without disruption of the parotid fascia had subjective or objective Frey syndrome. There were no AEs.

A 2008 publication from Asia compared use of allogeneic ADM (RENOV) in 168 patients who had superficial or partial parotidectomy.<sup>22</sup> Sixty-four patients received an ADM and 104 patients had superficial or partial parotidectomy alone. The size of the graft depended on the amount of tissue required to restore the normal facial contour. The method of assignment to the 2 groups was not described. At a median follow-up of 16 months (range, 11-27), the subjective incidence of Frey syndrome was 2% in the ADM group compared with 61% in controls. Objective assessment, performed in 30 patients randomly selected from each group, found an incidence of Frey syndrome in 2 patients (7%) treated with ADM and 24 patients (80%) in the control group. One patient in the ADM group and 18 patients in the control group developed a parotid fistula.

### DermaMatrix

DermaMatrix is an ADM that differs from AlloDerm in several ways: it can be stored at room temperature (vs refrigerated), it has a shelf-life of 3 years (vs 2 years), and it can be rehydrated in 3 minutes (vs 30 minutes).

Athavale et al evaluated complications of AlloDerm and DermaMatrix in a retrospective review of 100 patients treated between 2001 and 2009 at a single U.S. institution.<sup>23</sup> Exclusion criteria for the study included presence of malignancy on final surgical pathology report, incomplete medical records, previous history of radiotherapy to the head and neck region, and additional procedures to the region of the parotid gland. Initially, only AlloDerm was used; this changed to a 20/80 ratio of AlloDerm/DermaMatrix due to more readily available stock of DermaMatrix. Complications were defined as any outcome that required procedural intervention for resolution (seroma/sialocele formation, infected fluid collection, and/or serosanguinous fluid collection). The authors identified 8 complications in 31 DermaMatrix implants (26%) compared with 5 complications in 69 AlloDerm implants (7%). The complication rate did not differ for total parotidectomies but was higher for DermaMatrix compared with AlloDerm for subtotal parotidectomies (37% vs 8%). Nearly half of all complications were seroma/sialocele formation.

Double-blind RCTs with longer follow-up are needed to evaluate this procedure.

## Tendon Repair

### Graftjacket

In 2012, Barber et al reported an industry-sponsored multicenter RCT of augmentation with Graftjacket acellular human dermal matrix for arthroscopic repair of large (>3 cm) rotator cuff tears involving 2 tendons.<sup>24</sup> Twenty-two patients were randomized to Graftjacket augmentation, and 20 patients were randomized to no augmentation. At a mean follow-up of 24 months (range, 12-38) the American Shoulder and Elbow Surgeons score improved from 48.5 to 98.9 in the Graftjacket group and from 46.0

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to 94.8 in the control group ( $p=0.035$ ). The Constant score improved from 41 to 91.9 in the Graftjacket group and from 45.8 to 85.3 in the control group ( $p=0.008$ ). The University of California, Los Angeles score was not significantly different between the groups. Gadolinium-enhanced magnetic resonance imaging (MRI) scans showed intact cuffs in 85% of repairs in the Graftjacket group and 40% of repairs in the control group. However, no correlation was found between MRI findings and clinical outcomes. Rotator cuff retears occurred in 3 patients (14%) in the Graftjacket group and 9 patients (45%) in the control group. Although these results are promising, additional study with a larger number of patients is needed.

## Fistula Repair

### Acellular Dermal Matrix

A study from Asia compared a xenogeneic ADM (J-I type; J.Y. Life Tissue Engineering, China) with endorectal advancement flap (ERAF) for the treatment of complex anorectal fistula in a randomized study with 90 consecutive patients.<sup>25</sup> Follow-up was performed at 2 days, 2, 4, 6, and 12 weeks, and 5 months after surgery. Success was defined as closure of all external opening, absence of drainage without further intervention, and absence of abscess formation. Success was observed in 82.2% of the ADM group. Fistula recurred in 2 (4.45%) patients in the ADM group compared with 13 (28.89%) patients in the ERAF group. Healing time was reduced (7.5 days vs 24.5 days), and quality of life was rated higher in the ADM group (85.9 vs 65.3). No significant difference was observed in the incontinence and anal deformity rate between the 2 groups. This product is not cleared for marketing in the United States, although the manufacturing process was reported to be similar to Surgisis® AFP™ (Cook Surgical).

### Surgical Repair of Hernias

A 2011 systematic review included 30 level III and level IV articles on ADM for abdominal wall reconstruction.<sup>26</sup> No RCTs or high-quality comparative studies (level I or II) were identified. Examples of the level III studies are described next.

### AlloDerm

Gupta et al compared the efficacy and complications associated with the use of AlloDerm and Surgisis bioactive mesh in 74 patients who underwent ventral hernia repair in 2006.<sup>27</sup> The first 41 procedures were performed using Surgisis Gold 8-ply mesh formed from porcine small intestine submucosa, and the remaining 33 patients had ventral hernia repair with AlloDerm. Patients were seen 7 to 10 days after discharge from the hospital and at 6 weeks. Any signs of wound infection, diastasis, hernia recurrence, changes in bowel habits, and seroma formation were evaluated. The use of the AlloDerm mesh resulted in 8 hernia recurrences (24%). Fifteen of the AlloDerm patients (45%) developed a diastasis or bulging at the repair site. Seroma formation was only a problem in 2 patients.

In 2007, Espinosa-de-los-Monteros et al retrospectively reviewed 39 abdominal wall reconstructions with AlloDerm performed in 37 patients and compared them with 39 randomly selected cases.<sup>28</sup> They reported a significant decrease in recurrence rates when human cadaveric acellular dermis was added as an overlay to primary closure plus rectus muscle advancement and imbrication in patients with medium-sized hernias. However, no differences were observed when adding human cadaveric acellular dermis as an overlay to patients with large-size hernias treated with underlay mesh.

A 2013 study compared AlloDerm with FlexHD for complicated hernia surgery.<sup>29</sup> From 2005 to 2007, AlloDerm was used to repair large (>200 cm<sup>2</sup>) symptomatic complicated ventral hernias that resulted

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from trauma or emergency surgery (N=55). From 2008 to 2010, FlexHD was used to repair large complicated ventral hernias in patients meeting the same criteria (n=40). The 2 groups were comparable at baseline. At 1-year follow-up, all of the AlloDerm patients were diagnosed with hernia recurrence (abdominal laxity, functional recurrence, or true recurrence) requiring a second repair. Eleven patients (31%) in the FlexHD group required a second repair. This comparative study is limited by the use of nonconcurrent comparisons, which is prone to selection bias and does not control for temporal trends in outcomes.

### Reconstructive Tissue Matrix

The PRISM Study Group reported a multicenter double-blinded randomized trial of porcine acellular dermal matrix for parastomal reinforcement in patients undergoing surgery for permanent abdominal wall ostomies.<sup>30</sup> Patients were randomly assigned to undergo standard stoma construction with no reinforcement (n=58) or stoma construction with Reconstructive Dermal Matrix as parastomal reinforcement (n=55). At 24-month follow-up (n=75), the incidence of parastomal hernias was similar for the 2 groups (13.2% of controls, 12.2% of study group).

The limited evidence available at this time does not support the use of AlloDerm in hernia repair or prevention of parastomal hernia.

## Oral Surgery

### AlloDerm

In 2008, Novaes and de Barros described 3 randomized trials from their research group that examined use of ADM in root coverage therapy and alveolar ridge augmentation.<sup>31</sup> Two trials used ADM in both the study and control groups and are not described here. A third trial compared ADM with subepithelial connective tissue graft in 30 gingival recessions (9 patients). At 6 months postsurgery, the ADM showed recession reduction of 1.83 mm while subepithelial connective tissue graft showed recession reduction of 2.10 mm; these were not significantly different.

A nonrandomized cohort study compared AlloDerm with the criterion standard of split-thickness skin grafts in 34 patients who underwent oral cavity reconstruction following surgical removal of tumors.<sup>32</sup> Patients were enrolled after surgical treatment for evaluation at a tertiary care center and divided into 2 cohorts according to the reconstruction method used, which was based on surgeon preference. Twenty-two patients had been treated with AlloDerm, and 12 had been treated with split-thickness skin grafts. The location of the grafts (AlloDerm vs autograft) were on the tongue (54% vs 25%), floor of mouth (9% vs 50%), tongue and floor of mouth (23% vs 8%), buccal (9% vs 0%), or other (5% vs 17%). More patients in the AlloDerm group were treated with radiotherapy (45% vs 17%), and the graft failure rate was higher (14% vs 0%). Radiotherapy had a significantly negative impact for both groups. Histology on a subset of the patients showed increased inflammation, fibrosis, and elastic fibers with split-thickness skin grafts. Functional status and quality of life were generally similar in the 2 groups. Interpretation of these results is limited by the differences between the groups at baseline.

### Laryngoplasty

There are several reports with short-term follow-up of micronized AlloDerm (Cymetra) injection for laryngoplasty. In 2005, Milstein et al reported mean 11.2 month follow-up (range, 1-35) of Cymetra injection in 20 patients with unilateral vocal-fold paralysis.<sup>33</sup> Pre- and postoperative digital voice samples and video stroboscopy were rated on a 4-point scale by a panel of 3 voice experts who were blinded to the pre- or postoperative status. Compared with preoperative measures, Cymetra improved voice quality

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(3.23 to 1.65), glottal closure (3.21 to 1.42), and degree of vocal-fold bowing (2.38 to 1.36). Quality-of-life measures and patients' self-perceptions of vocal quality were also improved. In 5 patients (25%), the effect was temporary, and in 8 patients (40%) who had follow-up of 1 year or longer, the improvement was maintained. Longer-term study in a larger number of patients is needed to determine the durability of this procedure and to evaluate the safety of repeat injections.

### Tympanoplasty

Vos et al reported a retrospective nonrandomized comparison of AlloDerm versus native tissue grafts for type I tympanoplasty in 2005.<sup>34</sup> Included in the study were 108 patients (25 AlloDerm, 53 fascia reconstruction, 30 fascia plus cartilage reconstruction) treated between 2001 and 2004. One surgeon had performed 96% of the AlloDerm tympanoplasties. Operative time was reduced in the AlloDerm group (82 minutes for AlloDerm, 114 minutes for fascial cases, 140 minutes for fascia plus cartilage). There was no significant difference in the success rate of the graft (88% for AlloDerm, 89% for fascia grafts, 96.7% for cartilage plus fascia). There was no significant difference in hearing between the groups at follow-up (time not specified). Longer-term controlled study in a larger number of patients is needed to determine the durability of this procedure.

### Diabetic Lower-Extremity Ulcers

#### Apligraf

In 2001, Veves et al reported on a randomized prospective study on the effectiveness of Apligraf (previously called Graftskin), a living skin equivalent, in treating noninfected nonischemic chronic plantar diabetic foot ulcers.<sup>35</sup> The study involved 24 centers in the United States; 208 patients were randomly assigned to ulcer treatment either with Apligraf (112 patients) or saline-moistened gauze (96 patients, control group). Standard state-of-the-art adjunctive therapy, including extensive surgical débridement and adequate foot off-loading, was provided in both groups. Apligraf was applied at the beginning of the study and weekly thereafter for a maximum of 4 weeks (maximum of 5 applications) or earlier if complete healing occurred. At the 12-week follow-up visit, 63 (56%) Apligraf-treated patients achieved complete wound healing compared with 36 (38%) in the control group ( $p=0.004$ ). The Kaplan-Meier method median time to complete closure was 65 days for Apligraf, significantly lower than the 90 days observed in the control group ( $p=0.003$ ). The rate of adverse reactions was similar between the 2 groups with the exception of osteomyelitis and lower-limb amputations, both of which were less frequent in the Apligraf group. The study concluded that application of Apligraf for a maximum of 4 weeks resulted in a higher healing rate when compared with state-of-the-art treatment and was not associated with any significant AEs. This study was reviewed in a 2001 TEC Assessment, which concluded that Apligraf, in conjunction with good local wound care, met the TEC criteria for the treatment of diabetic ulcers that fail to respond to conservative management.<sup>36</sup>

In 2010, Steinberg et al reported on a study of 72 subjects from Europe and Australia that assessed the safety and efficacy of Apligraf in the treatment of noninfected diabetic foot ulcers.<sup>37</sup> The design and patient population of this study were similar to the 208-subject U.S study (previously described), which led to FDA approval of Apligraf for the treatment of diabetic foot ulcers. For these studies, subjects with a noninfected neuropathic diabetic foot ulcer present for at least 2 weeks were enrolled in these prospective, multicenter, open-label RCTs that compared Apligraf use in conjunction with standard therapy (sharp débridement, standard wound care, off-loading) against standard therapy alone. Pooling of data was performed because of the similarity and consistency of the 2 studies. Efficacy and safety results were consistent across studies independent of mean ulcer duration, which was significantly

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longer in the European study (21 months vs 10 months in the U.S. study). Reported AEs by 12 weeks were comparable across treatment groups in the 2 studies. Efficacy measures demonstrated superiority of Apligraf treatment over control-treated groups in both studies. Combining the data from both studies, 55.2% (80/145) of Apligraf subjects had complete wound closure by 12 weeks, compared with 34.3% (46/134) of control subjects ( $p < 0.001$ ), and Apligraf subjects had a significantly shorter time to complete wound closure ( $p < 0.001$ ). The authors concluded that both the EU and U.S. studies exhibited superior efficacy and comparable safety for subjects treated with Apligraf compared with control subjects, and the studies provide evidence of the benefit of Apligraf in treating diabetic foot ulcer.

In 2010, Kirsner et al reported on analysis of 2517 patients with diabetic neuropathic foot ulcers who were treated between 2001 and 2004.<sup>38</sup> The study was a retrospective analysis using a wound care database; the patients received advanced biological therapy, specifically, Apligraf (446 patients), Regranex, or Procuren. In this study, advanced biological therapy was used, on average, within 28 days from the first wound clinic visit and was associated with a median time to healing of 100 days. Wounds treated with engineered skin (Apligraf) as the first advanced biological therapy were 31.2% more likely to heal than wounds first treated with topical recombinant growth factor ( $p < 0.001$ ) and 40.0% more likely to heal than those first treated with platelet releasate ( $p = 0.01$ ). Wound size, wound grade, duration of wound, and time to initiation of advanced biological therapy affected the time to healing.

### Dermagraft

A pivotal multicenter FDA-regulated trial randomized 314 patients with chronic diabetic ulcers to Dermagraft or control.<sup>39</sup> Over the course of the 12-week study, patients received up to 8 applications of Dermagraft. All patients received pressure-reducing footwear and were encouraged to stay off their study foot as much as possible. At 12 weeks, the median percent wound closure for the Dermagraft group was 91% compared with 78% for the control group. Ulcers treated with Dermagraft closed significantly faster than ulcers treated with conventional therapy. No serious AEs were attributed to Dermagraft. Ulcer infections developed in 10.4% of the Dermagraft patients compared with 17.9% of the control patients. Together, there was a lower rate of infection, cellulitis, and osteomyelitis in the Dermagraft-treated group (19% vs 32.5%). Retrospective analysis of the trial data found a significant reduction in amputation/bone resection rates with Dermagraft (5.5% vs 12.6%,  $p = 0.031$ ).<sup>40</sup> Of the 28 cases of amputation/bone resection, 27 were preceded by ulcer-related infection.

### TheraSkin Versus Dermagraft

Sanders et al reported a small ( $N = 23$ ) industry-funded randomized comparison of TheraSkin (human skin allograft with living fibroblasts and keratinocytes) versus Dermagraft (human-derived fibroblasts cultured on mesh) for diabetic foot ulcers.<sup>41</sup> Wound size at baseline ranged from 0.5 to 18.02 cm<sup>2</sup>; the average wound size was about 5 cm<sup>2</sup> and was similar for the 2 groups ( $p = 0.51$ ). Grafts were applied according to manufacturer's instructions over the first 12 weeks of the study until healing, with an average of 4.4 TheraSkin grafts (every 2 weeks) compared with 8.9 Dermagraft applications (every week). At week 12, complete wound healing was observed in 63.6% of ulcers treated with TheraSkin and 33.3% of ulcers treated with Dermagraft ( $p < 0.049$ ). At 20 weeks, complete wound healing was observed in 90.9% of the TheraSkin-treated ulcers compared with 66.67% of the Dermagraft group ( $p = 0.428$ ). Additional study in a larger number of subjects is needed.

### Graftjacket Regenerative Tissue Matrix

Brigido et al reported a small ( $N = 40$ ) randomized pilot study of Graftjacket compared with conventional treatment for chronic nonhealing diabetic foot ulcers in 2004.<sup>42</sup> Control patients received conventional

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therapy with débridement, wound gel with gauze dressing, and off-loading. Graftjacket patients received surgical application of the scaffold using skin staples or sutures and moistened compressive dressing. A second graft application was necessary after the initial application for all patients in the Graftjacket group. Preliminary 1-month results showed that after a single treatment, ulcers treated with Graftjacket healed at a faster rate than conventional treatment. There were significantly greater decreases in wound length (51% vs 15%), width (50% vs 23%), area (73% vs 34%), and depth (89% vs 25%). All of the grafts incorporated into the host tissue.

In 2009, Reyzelman et al reported an industry-sponsored multicenter randomized study that compared a single application of Graftjacket versus standard of care (SOC) in 86 patients with diabetic foot ulcers.<sup>43</sup> Offloading was performed using a removable cast walker. Ulcer size at presentation was 3.6 cm<sup>2</sup> in the Graftjacket group and 5.1 cm<sup>2</sup> in the control group. Eight patients, 6 in the study group and 2 in the control group, did not complete the trial. At 12 weeks, complete healing was observed in 69.6% of the Graftjacket group and 46.2% of controls. After adjusting for ulcer size at presentation, a statistically significant difference in nonhealing rate was calculated, with odds of healing 2.0 times higher in the study group. Mean healing time was 5.7 weeks versus 6.8 weeks for the control group. The authors did not report if this difference was statistically significant. The median time to healing was 4.5 weeks for Graftjacket (range, 1-12 weeks) and 7.0 weeks for control (range, 2-12 weeks). Kaplan-Meier method survivorship analysis for time to complete healing at 12 weeks showed a significantly lower nonhealing rate for the study group (30.4%) compared with the control group (53.9%). The authors commented that a single application of Graftjacket, as used in this study, is often sufficient for complete healing. This study is limited by the small study population, differences in ulcer size at baseline, and the difference in the percentage of patients censored in each group. Questions also remain about whether the difference in mean time to healing is statistically or clinically significant. Additional trials with a larger number of subjects are needed to evaluate if Graftjacket Regenerative Tissue Matrix improves health outcomes in this population.

### Integra Dermal Regeneration Template

Integra Dermal Regeneration Template is a biosynthetic skin substitute that is FDA approved for life-threatening thermal injury. The Foot Ulcer New Dermal Replacement Study (FOUNDER) multicenter study (32 sites) on Integra Template for chronic nonhealing diabetic foot ulcers was conducted under an FDA-regulated investigational device exemption.<sup>44</sup> A total of 307 patients with at least 1 chronic diabetic foot ulcer were randomized to treatment with Integra Template or a control condition of 0.9% sodium chloride gel. Treatment was given for 16 weeks or until wound closure. There was a modest increase in wound closure with Integra Template (51% vs 32%,  $p=0.001$ ) and a shorter median time to closure (43 days vs 78 days,  $p=0.001$ ). There was a strong correlation between investigator-assessed and computerized planimetry assessment of wound healing ( $r=0.97$ ). Kaplan-Meier analysis showed the greatest difference between groups in wound closure up to 10 weeks, with diminishing differences after 10 weeks. Strengths of the study include adequate power to detect an increase in wound healing of 18%, which was considered to be clinically significant, secondary outcomes of wound closure and time to wound closure by computerized planimetry, and intention-to-treat (ITT) analysis.

### Dehydrated Amniotic Membrane

In 2013, Zelen et al reported an industry-sponsored, non-blinded, RCT comparing use of EpiFix dehydrated amniotic membrane ( $n=13$ ) with SOC (moist wound therapy,  $n=12$ ) for diabetic foot ulcers of at least 4 weeks in duration.<sup>45</sup> EpiFix was applied every 2 weeks if the wound had not healed, with weekly dressing changes comprised of nonadherent dressing, moisture retentive dressing, and a

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compression dressing. Standard moist wound dressing was changed daily. After 4 weeks of treatment, EpiFix-treated wounds had reduced in size by a mean of 97.1% compared with 32.0% for the SOC group. Healing rate, defined as complete epithelialization of the open area of the wound, was 77% for EpiFix compared with 0% for SOC. After 6 weeks of treatment, wounds were reduced by 98.4% with EpiFix treatment compared with -1.8% for SOC. The healing rate was 92% with EpiFix compared with 8% with SOC alone. At the conclusion of the trial, unhealed wounds from the control group were treated with EpiFix.<sup>46</sup> The mean duration of foot ulcers at the beginning of treatment was 19.4 weeks (range, 6.0-54 weeks) for the combined group. Follow-up was available at 9 to 12 months after primary healing in 18 of 22 eligible patients. Examination of these 18 patients found that 17 (94.4%) wounds remained fully healed.

In 2015, Smiell et al reported an industry-sponsored multicenter registry study of Biovance dehydrated amniotic membrane for the treatment of various chronic wound types, including 47 diabetic foot wounds, 20 pressure ulcers, and 89 venous ulcers.<sup>47</sup> This study shows effectiveness of dehydrated amniotic membrane in a real-world setting. The size of the wounds at baseline ranged from less than 2 cm<sup>2</sup> (35.4% of wounds) to over 25 cm<sup>2</sup> (9.0% of wounds). Ninety-eight percent were on the lower extremities. Twenty-eight ulcers had failed prior treatment with advanced biological therapies. For all wound types, 41.6% closed with a mean time to closure of 8 weeks and a mean of 2.4 amniotic membrane applications. In the subgroup of 112 patients who practiced good wound care, including offloading or compression therapy as indicated, 49.6% of wounds achieved closure at a mean of 7.4 weeks. Wounds that had not closed during the observation period decreased in size by a mean of 46.6%.

#### Dehydrated Amniotic Membrane Versus Apligraf

EpiFix (dehydrated amniotic allograft) was compared with Apligraf (living cell therapy) in a multicenter RCT published by Zelen et al in 2015.<sup>48</sup> Sixty patients were randomized to treatment with EpiFix, Apligraf, or standard wound care. Although the patient and site investigator could not be blinded due to differences in products, wound healing was verified by 3 independent physicians who evaluated photographic images. The median wound size was 2.0 cm<sup>2</sup> (range, 1.0-9.0) and the median duration of the index ulcer was 11 weeks (range, 5-54). After 6 weekly treatments, the mean percent wound area healed was 97.1% for EpiFix, 80.9% for Apligraf, and 27.7% for standard care; 95% of wounds had healed in the EpiFix group compared with 45% treated with Apligraf and 35% who received standard wound care ( $p \leq 0.003$ ). The estimated median time to wound closure, based on Kaplan-Meier analysis, was 13 days for EpiFix compared with 49 days for both Apligraf and SOC ( $p \leq 0.001$ ).

In 2015, Kirsner et al reported an industry-sponsored observational study comparing the effectiveness of Apligraf versus EpiFix in a real-world setting.<sup>49</sup> Data was obtained from a wound care-specific database from 3000 wound care facilities. The database included 1458 diabetic ulcers treated for the first time in 2014 with either Apligraf ( $n=994$ ) or EpiFix (464). Using the same criteria used in the 2015 study by Zelen et al (described above), data were included on the treatment of 226 diabetic foot ulcers from 99 wound care centers. Foot wounds were included with size between 1 and 25 cm<sup>2</sup>, duration of 1 year or less, and wound reduction of 20% or less in the 14 days prior to treatment. Although wounds for the 2 groups were comparable at baseline, the rationale for using a particular product was not reported. There were 163 wounds treated with Apligraf (mean, 2.5 applications) and 63 treated with EpiFix (mean, 3.5 applications,  $p=0.003$ ). By week 24, 72% of wounds treated with Apligraf and 47% of wounds treated with EpiFix had closed ( $p=0.01$ ). The median time to closure was 13.3 weeks for Apligraf and 26.0

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weeks for EpiFix ( $p=0.01$ ). This study is limited by the possibility of selection bias in determining treatment assignment.

### Cryopreserved Amniotic Membrane

Grafix cryopreserved amniotic membrane was compared with standard wound care in a multicenter RCT.<sup>50</sup> Strengths of this well-designed study include power analysis, blinded assessment of wound healing, evaluation of wound closure as the primary outcome measure, and ITT analysis. Ninety-seven patients with chronic diabetic foot ulcers were randomized to treatment with Grafix or to standard wound therapy, both administered once a week for up to 12 weeks. Power analysis indicated that 94 patients per arm would be needed for adequate power. However, after prespecified interim analysis at 50% enrollment, the blinded review committee recommended that the trial be stopped due to efficacy of the treatment. ITT analysis from the blinded evaluation phase showed a significant increase in the proportion of patients achieving the primary outcome of wound closure by 12 weeks (62.0% vs 21.3%,  $p<0.001$ ) and a decrease in the median time to complete wound closure (42.0 days vs 69.5 days,  $p=0.019$ ). Safety evaluation found that fewer Grafix-treated patients experienced at least 1 AE (44.0% vs 66.0%,  $p=0.031$ ) and had wound-related infections (18.0% vs 36.2%,  $p=0.044$ ), with a trend toward reduced hospitalization related to infections (6% vs 15%,  $p=0.15$ ).

### Oasis Wound Matrix

Niezgoda et al compared healing rates at 12 weeks for full-thickness diabetic foot ulcers treated with OASIS Wound Matrix, an acellular wound care product, versus Regranex Gel.<sup>51</sup> This was an industry-sponsored, multicenter RCT conducted at 9 outpatient wound care clinics and involved 73 patients with at least 1 diabetic foot ulcer. Patients were randomized to receive either Oasis Wound Matrix ( $n=37$ ) or Regranex Gel ( $n=36$ ) and a secondary dressing. Wounds were cleansed and débrided, if needed, at a weekly visit. The maximum treatment period for each patient was 12 weeks. After 12 weeks of treatment, 18 (49%) Oasis-treated patients had complete wound closure compared with 10 (28%) Regranex-treated patients. Oasis treatment met the noninferiority margin, but did not demonstrate that healing in the Oasis group was statistically superior ( $p=0.055$ ). Post-hoc subgroup analysis showed no significant difference in incidence of healing in patients with type 1 diabetes (33% vs 25%) but showed a significant improvement in patients with type 2 diabetes (63% vs 29%). There was also an increased healing of plantar ulcers in the Oasis group (52% vs 14%). These post-hoc findings are considered hypothesis-generating. Additional study with a larger number of subjects is needed to evaluate the effect of Oasis treatment in comparison with the current SOC.

### PriMatrix

In 2014, Kavros et al reported a prospective multicenter study of PriMatrix (a xenograft fetal bovine dermal collagen matrix) for the treatment of chronic diabetic foot ulcers in 55 patients.<sup>52</sup> The average duration of ulcers before treatment was  $286\pm 353$  days, and the average area was  $4.34\text{ cm}^2$ . Of the 46 patients who completed the study, 76% healed by 12 weeks with an average of 2 applications of PriMatrix. For the ITT population, 64% of wounds healed by 12 weeks.

In 2011, Karr published a retrospective comparison of PriMatrix and Apligraf in 40 diabetic foot ulcers.<sup>53</sup> The first 20 diabetic foot ulcers matching the inclusion and exclusion criteria for each graft were compared. The criteria were: diabetic foot ulcers of 4 weeks in duration; ulcer to at least  $1\text{ cm}^2$  in diameter and to the depth of subcutaneous tissue; healthy tissue at the ulcer; adequate arterial perfusion to heal; and ability to off-load the diabetic ulcer. The products were placed on the wound with clean technique, overlapping the edges of the wound, and secured with sutures or staples. The time to

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complete healing for PriMatrix was 38 days with 1.5 applications compared with 87 days with 2 applications for Apligraf. Although promising, additional study with a larger number of subjects is needed to evaluate the effect of PriMatrix treatment in comparison with the current SOC.

### Section Summary: Diabetic Lower-Extremity Ulcers

RCTs have demonstrated the efficacy of Apligraf, Dermagraft, and Integra Dermal Regeneration Template over the SOC. Several amniotic membrane products have also been shown to improve healing. Additional study with a larger number of subjects is needed to evaluate the effect of Oasis Wound Matrix and PriMatrix treatment in comparison with the current SOC.

## Lower-Extremity Ulcers due to Venous Insufficiency

### Apligraf

Apligraf is a living cell therapy composed of living human keratinocytes and fibroblasts. Falanga et al reported a multicenter randomized trial of Apligraf (human skin equivalent) in 1998.<sup>54</sup> A total of 293 patients with venous insufficiency and clinical signs of venous ulceration were randomized to compression therapy alone or compression therapy and treatment with Apligraf. Apligraf was applied up to a maximum of 5 (mean, 3.3) times per patient during the initial 3 weeks. The primary end points were the percentage of patients with complete healing by 6 months after initiation of treatment and the time required for complete healing. At 6-month follow-up, the percentage of patients healed was increased with Apligraf (63% vs 49%), and the median time to complete wound closure was reduced (61 days vs 181 days). Treatment with Apligraf was found to be superior to compression therapy in healing larger (>1000 mm<sup>2</sup>) and deeper ulcers and ulcers of more than 6 months in duration. There were no symptoms or signs of rejection, and the occurrence of AEs was similar in both groups. This study was reviewed in a 2001 TEC Assessment, which concluded that Apligraf (Graftskin), in conjunction with good local wound care, met the TEC criteria for the treatment of venous ulcers that fail to respond to conservative management.<sup>36</sup>

### Dermagraft

Dermagraft is a living cell therapy composed of cryopreserved human fibroblasts cultured on a bioabsorbable mesh. Dermagraft has been approved by FDA for repair of diabetic foot ulcers. Use of Dermagraft for venous ulcers is an off-label indication. In 2013, Harding et al reported an open-label multicenter RCT that compared Dermagraft plus compression therapy (n=186) versus compression therapy alone (n=180).<sup>55</sup> The study had numerous inclusion/exclusion criteria that restricted the study population to patients who had nonhealing ulcers with compression therapy but had capacity to heal. ITT analysis revealed no significant difference between the 2 groups in the primary outcome measure, the proportion of patients with completely healed ulcers by 12 weeks (34% Dermagraft vs 31% control). Prespecified subgroup analysis revealed a significant improvement in the percent of ulcers healed for ulcers of 12 months or less in duration (52% vs 37%) and for ulcers of 10 cm or less (47% vs 39%). There were no significant differences in the secondary outcomes of time to healing, complete healing by week 24, and percent reduction in ulcer area.

### Oasis Wound Matrix

Oasis Wound Matrix is a xenogeneic collagen scaffold derived from porcine small intestinal mucosa. In 2005, Mostow et al reported an industry-sponsored multicenter (12 sites) randomized trial that compared weekly treatment with Oasis Wound Matrix versus SOC in 120 patients with chronic ulcers due to venous insufficiency that were not adequately responding to conventional therapy.<sup>56</sup> Healing was

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assessed weekly for up to 12 weeks, with follow-up performed after 6 months to assess recurrence. After 12 weeks of treatment, there was a significant improvement in the percentage of wounds healed in the Oasis group (55% vs 34%). After adjusting for baseline ulcer size, patients in the Oasis group were 3 times more likely to achieve healing than those in the group receiving SOC. Patients in the SOC group whose wounds did not heal by the 12th week were given the option to cross over to Oasis treatment. None of the healed patients treated with Oasis wound matrix who were seen for the 6-month follow-up experienced ulcer recurrence.

A research group in Europe has described 2 comparative studies of the Oasis matrix for mixed arterial/venous ulcers. In a 2007 quasirandomized study, Romanelli et al compared the efficacy of 2 extracellular matrix-based products, Oasis and Hyaloskin (extracellular matrix with hyaluronic acid).<sup>57</sup> A total of 54 patients with mixed arterial/venous leg ulcers were assigned to the 2 arms based on order of entry into the study; 50 patients completed the study. Patients were followed up twice a week, and the dressings were changed more than once a week, only when necessary. After 16 weeks of treatment, complete wound closure was achieved in 82.6% of Oasis-treated ulcers compared with 46.2% of Hyaloskin-treated ulcers. Oasis treatment significantly increased the time to dressing change (mean, 6.4 days vs 2.4 days), reduced pain on a 10-point scale (3.7 vs 6.2), and improved patient comfort (2.5 vs 6.7).

In a 2010 trial, Romanelli et al compared Oasis with a moist wound dressing (SOC) in 23 patients with mixed arterial/venous ulcers and 27 patients with venous ulcers.<sup>58</sup> The study was described as randomized, but the method of randomization was not described. After the 8-week study period, patients were followed up monthly for 6 months to assess wound closure. Complete wound closure was achieved in 80% of the Oasis-treated ulcers at 8 weeks, compared with 65% of the SOC group. On average, Oasis-treated ulcers achieved complete healing in 5.4 weeks compared with 8.3 weeks for the SOC group. Treatment with Oasis also increased the time to dressing change (5.2 days vs 2.1 days) and the percentage of granulation tissue formed (65% vs 38%).

### PriMatrix

PriMatrix is a xenogeneic ADM. In 2011, Karr published a retrospective comparison of PriMatrix and Apligraf in 28 venous stasis ulcers.<sup>53</sup> The first 14 venous stasis ulcers matching the inclusion and exclusion criteria for each graft were compared. Criteria were venous stasis ulcers of 4 weeks' duration, at least 1 cm<sup>2</sup> in diameter and to a depth of subcutaneous tissue, with healthy tissue at the ulcer edge, adequate arterial perfusion to heal, and ability to tolerate compression therapy. The products were placed on the wound with clean technique, overlapping the edges of the wound, and secured with sutures or staples. The time to complete healing for PriMatrix was 32 days with 1.3 applications compared with 63 days with 1.7 applications for Apligraf. Although promising, additional study with a larger number of subjects is needed to evaluate the effect of PriMatrix treatment in comparison with the current SOC.

### Dehydrated Amniotic Membrane

In 2014, Serena et al reported an industry-sponsored multicenter open-label RCT that compared EpiFix dehydrated amniotic membrane combined with compression therapy to compression therapy alone for the treatment of venous leg ulcers.<sup>59</sup> Ulcers were included if they were chronic (>1 month in duration); extended through the full thickness of the skin but not down to muscle, tendon, or bone; and had been treated with compression therapy for at least 14 days. A total of 84 participants were enrolled and assigned to a single EpiFix allograft (n=26), 2 allografts (n=27), or compression therapy alone (n=31).

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The primary outcome, the proportion of patients achieving 40% wound closure at 4 weeks, was 62% in the combined EpiFix groups and 32% in the control group ( $p=0.005$ ). During the 4-week study period, 6 patients (11.3%) in the combined EpiFix group and 4 (12.9%) in the control group achieved complete wound closure. Secondary outcomes, which evaluated the use of 1 versus 2 applications of amniotic membrane, showed no significant difference in outcomes (62% vs 63%). Strengths of this study include adequate power and ITT analysis with last observation carried forward. Limitations include the lack of blinding for wound evaluation and use of 40% closure rather than complete closure. A report was published subsequently in 2015 on 44 patients from this RCT (31 had been treated with amniotic membrane) found that wounds with at least 40% wound closure at 4 weeks ( $n=20$ ) had a rate of closure of 80% by 24 weeks; however, this was a retrospective study and didn't take into account additional treatments after the 4-week randomized trial period.<sup>60</sup>

### Section Summary: Lower-Extremity Ulcers due to Venous Insufficiency

RCTs have demonstrated the efficacy of Apligraf and Oasis Wound Matrix over the SOC. Use of these products may be considered medically necessary for lower-extremity ulcers due to venous insufficiency. In a moderately large RCT, Dermagraft was not shown to be more effective than controls in the primary or secondary end points for the entire population and was slightly more effective than controls (an 8%-15% increase in healing) only in subgroups of patients with ulcer duration of 12 months or less or size of 10 cm or less. Given the lack of difference between 1 or 2 applications of EpiFix and the lack of difference between the experimental and control groups in complete wound closure at 4 weeks, additional study is needed. Additional study with a larger number of subjects is also needed to evaluate the effect of PriMatrix treatment in comparison with the current SOC.

### Dystrophic Epidermolysis Bullosa

Dermagraft had been FDA approved by a Humanitarian Device Exemption (HDE) for the treatment of dystrophic epidermolysis bullosa. The manufacturer has since withdrawn Dermagraft from HDE status.

OrCel is approved by an HDE for use in patients with dystrophic epidermolysis bullosa undergoing hand reconstruction surgery, to close and heal wounds created by the surgery, including those at donor sites.

As this is a rare disorder, it is unlikely that there will be RCTs to evaluate whether OrCel improves health outcomes for this condition. Dermagraft is no longer considered medically necessary for this indication, due to the withdrawal of HDE status.

In 2003, Fivenson et al reported the off-label use of Apligraf in 5 patients with recessive dystrophic epidermolysis bullosa who underwent syndactyly release.<sup>61</sup>

Dermagraft, OrCel, and Apligraf are all living cell therapies. Apligraf is a bilayered cell therapy composed of living human keratinocytes and fibroblasts, while OrCel is a bilayered cellular matrix made of bovine collagen in which human dermal cells (fibroblasts and keratinocytes) have been cultured. Dermagraft is composed of cryopreserved human-derived fibroblasts and collagen on a bioabsorbable mesh.

### Ocular Burns

A 2012 Cochrane review evaluated the evidence on amniotic membrane transplantation (AMT) for acute ocular burns.<sup>62</sup> Included in the review was a single RCT from India of 68 patients with acute ocular burns who were randomized to treatment with AMT and medical therapy or medical therapy alone. In the subset of 36 patients with moderate ocular burns who were treated within 7 days, 13 of 20 (65.0%) of control eyes and 14 of 16 (87.5%) of AMT-treated eyes had complete epithelialization by 21 days. There was a trend ( $p=0.09$ ) toward a reduced risk ratio of failure of epithelialization in the treatment group.

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Mean LogMAR (logarithm of the minimum angle of resolution) final visual acuities were 0.06 in the treatment group and 0.38 in the control group. In the subset of patients with severe ocular burns treated within 7 days, 1 of 17 (5.9%) of AMT-treated eyes and 1 of 15 (6.7%) control eyes were epithelialized by day 21. Final visual acuity was 1.77 logMAR in the treated eyes and 1.64 in the control group (not significantly different). The risk of bias was considered to be high because of differences between the groups at baseline and because outcome assessors could not be masked to treatment. The review determined that conclusive evidence supporting the treatment of acute ocular surface burns with AMT is lacking. It should also be noted that the amniotic membrane used in this study was fresh frozen and is not commercially available.

## Nonocular Burns

### Biomembrane

A small (N=46) quasirandomized trial compared treatment with amniotic membrane (Biomembrane) versus polyurethane membrane (Tegaderm) for patients with second- or third-degree burns covering less than 50% total body surface area (BSA).<sup>63</sup> Treatment with amniotic membrane significantly reduced occurrence of infection (4.3%) compared with treatment with polyurethane (13.0%). Pain during dressing was reduced in the group treated with amniotic membrane (43.5% vs 60.9%), while the frequency of healing within the 11- to 20-day follow-up was greater (47.8% vs 39.1%). It was not reported if the evaluators in this quasirandomized study were blinded to treatment condition. In addition, this study did not have a control group treated with medical therapy alone.

### Epicel

Epicel is FDA approved under an HDE for the treatment of deep dermal or full-thickness burns comprising a total BSA of 30% or more. It is unlikely that there will be RCTs to evaluate whether Epicel will improve health outcomes for this condition. One case series described the treatment of 30 severely burned patients with Epicel.<sup>64</sup> The cultured epithelial autografts were applied to a mean of 37% of total BSA. Epicel achieved permanent coverage of a mean of 26% of total BSA, an area greater than that covered by conventional autografts (mean, 25%). Survival was 90% in these severely burned patients.

### EpiFix

Although several small trials from the Middle East and Asia have evaluated locally harvested and processed amniotic membrane, no RCTs were identified with the commercially available EpiFix amniotic membrane.

### Integra Dermal Regeneration Template

A 2013 study compared Integra versus split-thickness skin graft or viscose cellulose sponge (Cellonex), using 3 test sites of 10×5 cm on each of 10 burn patients.<sup>65</sup> The surrounding burn area was covered with meshed autograft. Biopsies were taken from each site on days 3, 7, 14, and 21, and at 3 months and 12 months. The tissue samples were stained and examined for markers of inflammation and proliferation. The Vancouver Scar Scale was used for scar assessment. At 12-month follow-up, the 3 methods resulted in similar clinical appearance, along with similar histologic and immunohistochemical findings.

In 2007, Branski et al reported a randomized trial of Integra compared with a standard autograft-allograft technique in 20 children with an average burn size of 73% total BSA (71% full-thickness burns).<sup>66</sup> Once vascularized (about 14-21 days), the Silastic epidermis was stripped and replaced with thin (0.05-0.13

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mm) epidermal autograft. There were no significant differences between the Integra group and controls in burn size (70% vs 74% total BSA), mortality (40% vs 30%), and length of stay (41 vs 39 days, all respectively). Long-term follow-up revealed a significant increase in bone mineral content and density (24 months) and improved scarring in terms of height, thickness, vascularity, and pigmentation (12 months and 18-24 months) in the Integra group. No differences were observed between the groups in the time to first reconstructive procedure, cumulative reconstructive procedures required during 2 years, and the cumulative operating room time required for these procedures. The authors concluded that Integra can be used for immediate wound coverage in children with severe burns without the associated risks of cadaver skin.

In 2003, Heimbach et al reported a multicenter (13 U.S. burn care facilities) postapproval study involving 222 burn injury patients (36.5% total BSA; range, 1%-95%) who were treated with Integra Dermal Regeneration Template.<sup>67</sup> Within 2 to 3 weeks, the dermal layer regenerated, and a thin epidermal autograft was placed over the wound. The incidence of infection was 16.3%. Mean take rate (absence of graft failure) of Integra was 76.2%; the median take rate was 98%. The mean take rate of epidermal autograft placed over Integra was 87.7%; the median take rate was 95%.

### OrCel

There is limited evidence to support the efficacy of OrCel compared with the SOC for the treatment of split-thickness donor sites. In 2003, Still et al examined the safety and efficacy of bilayered OrCel to facilitate wound closure of split-thickness donor sites in 82 severely burned patients.<sup>68</sup> Each patient had 2 designated donor sites that were randomized to receive a single treatment of either OrCel or the standard dressing (Biobrane-L). The healing time for OrCel sites was significantly shorter than for sites treated with a standard dressing, enabling earlier recropping. OrCel sites also exhibited a nonsignificant trend for reduced scarring. Additional studies are needed to evaluate the effect of this product on health outcomes.

### TransCyte

In 2001, Lukish et al compared 20 consecutive cases of pediatric burns greater than 7% total BSA that underwent wound closure with TransCyte with the previous 20 consecutive burn cases greater than 7% total BSA that received standard therapy.<sup>69</sup> Standard therapy consisted of application of antimicrobial ointments and hydrodébridement. Only 1 child in the TransCyte group required autografting (5%) compared with 7 children in the standard therapy group (35%). Children treated with TransCyte had a statistically significant decreased length of stay compared with those receiving standard therapy (5.9 days vs 13.8 days, respectively).

In 2006, Amani et al compared results from 110 consecutive patients with deep partial-thickness burns who were treated with TransCyte with data from the American Burn Association Patient Registry.<sup>70</sup> Significant differences were found in patients who were treated with dermabrasion and TransCyte compared with the population in the Registry. Patients with 0% to 19.9% total BSA burn treated with dermabrasion and TransCyte had length of stay of 6.1 days versus 9.0 days ( $p < 0.001$ ). Those with 20% to 39.9% total BSA burn had length of stay of 17.5 days versus 25.5 days. Patients who had 40% to 59.9% total BSA burn had length of stay of 31 versus 44.6 days. The authors found this new method of managing patients with partial-thickness burns to be more efficacious and to significantly reduce length of stay compared with traditional management.

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### Traumatic and Surgical Wounds

A 2013 RCT examined the efficacy of Keramatrix keratin dressing on partial-thickness skin graft donor sites.<sup>71</sup> Keramatrix was placed side by side with standard dressing in this within-subject RCT of 26 patients. Split-skin graft donor sites were chosen for the study because they provide uniform thickness wounds for comparisons. Wound healing was assessed as a percent epithelialization, rather than the preferred outcome of percentage of wounds healed and time to complete healing. In patients more than 50 years of age, blinded evaluation found median wound healing of 5% with standard dressing and 10% with Keramatrix (range, 0-100; p=0.023). In patients ages 50 years or younger, median epithelialization was 80% at 7 days (range, 0-100) and there was no significant difference in percent healed between the treatment and control portions of the wound. Study in a larger number of patients/wounds with complicating factors is needed.

Use of Integra Dermal Regeneration Template has been reported in small case series (<20 patients) for the treatment of severe wounds with exposed bone, joint and/or tendon.<sup>72-74</sup> No controlled trials were identified.

### Other

In addition to indications previously reviewed, off-label uses of bio-engineered skin substitutes have included pressure ulcers, inflammatory ulcers such as pyoderma gangrenosum and vasculitis, scleroderma digital ulcers, postkeloid removal wounds, genetic conditions, and variety of other conditions.<sup>75</sup> In addition, products that have been FDA approved/cleared for 1 indication (eg, lower-extremity ulcers) have been used off-label in place of other FDA approved/cleared products (eg, for burns).<sup>76</sup> No controlled trials were identified for these indications. Therefore, they are considered investigational.

### Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 1.

**Table 1. Summary of Key Trials**

NCT No.	Trial Name	Planned Enrollment	Completion Date
<b>Ongoing</b>			
NCT02120755 <sup>a</sup>	A Randomized Comparison of AmnioClear™ Human Allograft Amniotic Membrane vs. Moist Wound Dressing in the Treatment of Diabetic Wounds	60	Unknown
NCT02399826 <sup>a</sup>	A Prospective, Randomized, Comparative Parallel Study of Amniotic Membrane Graft in the Management of Diabetic Foot Ulcers	40	Jan 2016
NCT02609594 <sup>a</sup>	A Multi-center Randomized Controlled Clinical Trial Evaluating Two Application Regimens of Amnioband Dehydrated Human Amniotic Membrane and Standard of Care vs. Standard of Care Alone in the Treatment of Venous Leg Ulcers	240	Dec 2016

NCT: national clinical trial.

<sup>a</sup> Denotes industry-sponsored or cosponsored trial.

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## Summary of Evidence

### **Surgical Repair**

The evidence on bioengineered soft-tissue substitutes for individuals undergoing surgical repair includes randomized controlled trials (RCTs). Relevant outcomes are symptoms, morbid events, functional outcomes, quality of life, and treatment-related morbidity. Overall, there are a limited number of soft-tissue substitutes, and the evidence is limited for any specific product. Following is a description of the evidence for specific indications.

#### ***Breast Reconstruction***

The extensive data from controlled cohorts and case series about the usefulness of this procedure in providing inferolateral support for breast reconstruction supports the use of acellular dermal matrix (ADM) allograft (ie, AlloDerm, AlloMax, DermaMatrix, FlexHD, Graftjacket) in breast reconstruction when there is insufficient tissue expander or implant coverage by the pectoralis major muscle and additional coverage is required; when there is viable but compromised or thin postmastectomy skin flaps that are at risk of dehiscence or necrosis; or when the inframammary fold and lateral mammary folds have been undermined during mastectomy and reestablishment of these landmarks is needed. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

#### ***Interpositional Graft After Parotidectomy***

Two lower quality controlled trials were identified that demonstrated a reduction in the incidence of Frey syndrome with use of an interpositional ADM allograft. Neither study described the method of group assignment or blinding of patients and assessors. The evidence is insufficient to determine the effects of the technology on health outcomes.

#### ***Tendon Repair***

One small RCT was identified that found improved outcomes with Graftjacket ADM allograft for rotator cuff repair. Although these results are promising, additional study with a larger number of subjects is needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

#### ***Fistula Repair***

One RCT was identified that used an ADM allograft that has not been cleared for marketing in the United States. The evidence is insufficient to determine the effects of the technology on health outcomes.

#### ***Surgical Repair of Hernias***

The limited evidence available does not support the efficacy of any tissue-engineered skin substitute for surgical repair of hernias. The evidence is sufficient to determine qualitatively that the technology is unlikely to improve the net health outcome.

#### ***Oral Surgery***

Use of an ADM allograft (AlloDerm) has been reported for root coverage therapy and oral cavity reconstruction following surgical removal of tumors. Although AlloDerm may possibly result in less scar contracture, results to date have not shown an improvement over the standard of care. The evidence is insufficient to determine the effects of the technology on health outcomes.

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### *Laryngoplasty*

The effect of micronized ADM (eg, Cymetra) in laryngoplasty has been reported in case series. Longer term controlled study in a larger number of patients is needed to determine the durability of this procedure and to evaluate the safety of repeat injections. The evidence is insufficient to determine the effects of the technology on health outcomes.

### *Tympanoplasty*

AlloDerm ADM has been compared with native tissue grafts in a non-RCT. There was no significant difference in the success rate of the graft (88% for AlloDerm, 89% for fascia grafts, 96.7% for cartilage plus fascia), and there was no significant difference in hearing between the groups at follow-up. Longer-term controlled study in a larger number of patients is needed to determine the durability of this procedure. The evidence is insufficient to determine the effects of the technology on health outcomes.

### **Chronic Wounds**

The evidence on bioengineered skin substitutes for individuals with chronic wounds includes RCTs. Relevant outcomes include disease-specific survival, symptoms, change in disease status, morbid events, and quality of life. Overall, the number of bio-engineered skin substitutes is large, but the evidence is limited for any specific product. Relatively few products have been compared with the standard of care, and then only for some indications. Some comparative trials have been identified for use in lower-extremity ulcers (diabetic or venous) and for treatment of burns. In these trials, there is a roughly 15% to 20% increase in the rate of healing. Several other products/indications are supported by a U.S. Food and Drug Administration (FDA) humanitarian device exemption. Following is a description of the evidence for specific indications.

#### *Diabetic Lower-Extremity Ulcers*

- RCTs have demonstrated the efficacy of Apligraf, Dermagraft (ADM), and Integra Dermal Regeneration Template (biosynthetic) over the standard of care. Several amniotic membrane products have also been shown to improve healing. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.
- Additional study with a larger number of subjects is needed to evaluate the effect of xenogenic skin substitutes (eg Oasis Wound Matrix and PriMatrix) in comparison with the current standard of care. The evidence is insufficient to determine the effects of the technology on health outcomes.

#### *Lower-Extremity Ulcers due to Venous Insufficiency*

- RCTs have demonstrated the efficacy of Apligraf ADM and xenogenic Oasis Wound Matrix over the standard of care. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.
- In a moderately large RCT, Dermagraft ADM was not shown to be more effective than controls in the primary or secondary end points for the entire population and was slightly more effective than controls (an 8%-15% increase in healing) only in subgroups of patients with ulcer duration of 12 months or less or size of 10 cm or less. The evidence is insufficient to determine the effects of the technology on health outcomes.
- In a randomized comparison of EpiFix amniotic membrane versus standard of care that used a primary outcome measure of 40% wound healing, there was no difference between 1 or 2 applications of EpiFix and no difference between the experimental and controls groups in

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complete wound closure at 4 weeks. Additional study is needed. Additional study with a larger number of subjects is also needed to evaluate the effect of the xenogenic PriMatrix skin substitute in comparison with the current standard of care. The evidence is insufficient to determine the effects of the technology on health outcomes.

### **Burns, Skin Grafts, and Traumatic Wounds**

The evidence on bio-engineered soft-tissue substitutes for individuals with burns, skin grafts, and traumatic wounds includes RCTs. Relevant outcomes are symptoms, morbid events, functional outcomes, quality of life, and treatment-related morbidity. Overall, there are a limited number of soft-tissue substitutes, and the evidence is limited for any specific product. Following is a description of the evidence for specific indications.

#### ***Dystrophic Epidermolysis Bullosa***

OrCel (living cell therapy) has received approval via a Humanitarian Device Exemption. As this is a rare disorder, it is unlikely that there will be RCTs. The evidence is insufficient to determine the effects of the technology on health outcomes.

#### ***Ocular Burns***

The evidence is insufficient to determine the effects of the technology on health outcomes.

#### ***Nonocular Burns***

Epicel (living cell therapy) is FDA-approved under a humanitarian device exemption for the treatment of deep dermal or full-thickness burns comprising a total body surface area of 30% or more. The evidence is insufficient to determine the effects of the technology on health outcomes.

Comparative studies have demonstrated improved outcomes for the biosynthetic skin substitutes Integra Dermal Regeneration Template and TransCyte for the treatment of burns. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

#### ***Traumatic and Surgical Wounds***

Keramatrix (xenogenic skin substitute) was compared with standard of care in a small RCT for healing of skin graft donor sites. Results overall are equivocal. Study in a larger number of patients/wounds is needed. Use of biosynthetic Integra Dermal Regeneration Template has been reported in small case series (<20 patients) for the treatment of severe wounds with exposed bone, joint, and/or tendon. Controlled trials are needed to evaluate this product/indication. The evidence is insufficient to determine the effects of the technology on health outcomes.

## **SUPPLEMENTAL INFORMATION**

### **Practice Guidelines and Position Statements**

#### **American Society of Plastic Surgeons and Wound Healing Society**

Review of the literature for 2013 guidelines from the American Society of Plastic Surgeons (ASPS) found that evidence suggests that the use of ADM, although increasingly common in postmastectomy expander/implant breast reconstruction, can result in increased risk of complications in the presence of certain risk factors.<sup>77</sup> ASPS notes that cellular dermal matrix is currently used to increase soft tissue coverage, support the implant pocket, improve contour, and reduce pain with expansion. However,

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evidence to support these improved surgical outcomes are limited. Some evidence suggests that use of ADM is associated with increased postoperative complications, specifically related to infection and seroma. Overall, ASPS found that evidence on ADM products in postmastectomy expander/implant breast reconstruction is varied and conflicting, and gave a grade C recommendation based on level III evidence that surgeons should evaluate each clinical case individually and objectively determine the use of ADM.

In 2006, ASPS endorsed guidelines from the Wound Healing Society (WHS) on the treatment of arterial insufficiency ulcers.<sup>78</sup> The guidelines state that extracellular matrix replacement therapy appears to be promising for mixed ulcers and may have a role as an adjuvant agent in arterial ulcers, but further study is required (level IIIC). “Despite the existence of animal studies, case series, and a small number of random control trials to support biomaterial use for pressure ulcers, diabetic ulcers, and venous ulcers; there are no studies specifically on arterial ulcers. Therefore, studies in arterial ulcers must be conducted before the recommendation can be made.”

ASPS endorsed guidelines from WHS on the treatment of venous ulcers in 2006.<sup>79</sup> The guidelines state that various skin substitutes or biologically active dressings are emerging that provide temporary wound closure and serve as a source of stimuli (eg, growth factors) for healing of venous ulcers. Guideline #7b.1 states that there is evidence that a bilayered artificial skin (biologically active dressing), used in conjunction with compression bandaging, increases the chance of healing a venous ulcer compared with compression and a simple dressing (level I).

ASPS also endorsed guidelines from WHS on the treatment of diabetic ulcers in 2006.<sup>80</sup> The guidelines state that healthy living skin cells assist in healing diabetic foot ulcers by releasing therapeutic amounts of growth factors, cytokines, and other proteins that stimulate the wound bed. Guideline 7.2.2 states that living skin equivalents may be of benefit in healing diabetic foot ulcers (level I).

The 2007 guidelines from ASPS on chronic wounds of the lower extremity state that maintaining a moist environment, while simultaneously removing soluble factors detrimental to wound healing, might logically provide optimal conditions for wound healing.<sup>81</sup> Classic dressings include gauze, foam, hydrocolloid, and hydrogels. Fluid-handling mechanisms include absorption, gelling, retention, and vapor transmission. Bioactive dressings include topical antimicrobials, bio-engineered composite skin equivalent, bilaminar dermal regeneration template, and recombinant human growth factor.

### **National Institute for Health and Care Excellence**

In 2015, the U.K.’s National Institute for Health and Care Excellence (NICE) published clinical guidelines on the prevention and management of diabetic foot problems.<sup>82</sup> NICE recommends that clinicians consider dermal or skin substitutes as an adjunct to standard care when treating diabetic foot ulcers, only when healing has not progressed and on the advice of the multidisciplinary foot care service.

### **American College of Foot and Ankle Surgeons**

The 2006 clinical consensus statement [previously called clinical practice guideline] on diabetic foot disorders from the American College of Foot and Ankle Surgeons states that bio-engineered tissues have been shown to significantly increase complete wound closure in venous and diabetic foot ulcers.<sup>83</sup> Tissue-engineered skin substitutes can function both as biologic dressings and as delivery systems for growth factors and extracellular matrix components through the activity of live human fibroblasts contained in their dermal elements. Currently, 2 bio-engineered tissues have been approved to treat diabetic foot ulcers in the United States: Apligraf and Dermagraft; both have demonstrated efficacy in

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RCTs. Apligraf has been shown to significantly reduce the time to complete wound closure in venous and diabetic ulcers. Regenerative tissue matrix (Graftjacket) is used in diabetic foot ulcers, although it had not undergone any RCTs at the time of this guideline. This allograft skin is minimally processed to remove epidermal and dermal cells while preserving the bioactive components and structure of dermis. This results in a framework that supports cellular repopulation and vascularization. Oasis, composed of structural cellular components and growth factors used to promote natural tissue remodeling, completed a randomized trial that showed noninferiority to becaplermin gel in the healing of diabetic foot ulcers. Integra Dermal Regeneration Template, a collagen-chondroitin sponge overlaid with silicone originally developed for burns, has been shown to be ideally suited to chronic and pathologic wounds.

### **Infectious Diseases Society of America**

The 2012 guidelines from the Infectious Diseases Society of America state that for selected diabetic foot wounds that are slow to heal, clinicians might consider using bio-engineered skin equivalents (weak recommendation, moderate evidence), growth factors (weak, moderate), granulocyte colony-stimulating factors (weak, moderate), hyperbaric oxygen therapy (strong, moderate), or negative pressure wound therapy (weak, low).<sup>84</sup> It is emphasized that none of these measures have been shown to improve resolution of infection and that they are expensive, not universally available, may require consultation with experts, and reports supporting their utility are mostly flawed.

### **Agency for Healthcare Research and Quality**

A 2012 Technology Assessment from the Agency for Healthcare Research and Quality does not make a formal recommendation for bio-engineered skin and soft tissue substitutes.<sup>4</sup> The Assessment notes that autologous tissue grafting is an invasive and painful procedure and often the extent of damaged skin is too large to be covered by autologous tissue graft alone. A variety of skin substitutes and alternatives are designed to replace the damaged epithelial and dermal layers of skin, and many of the conditions and biological factors needed in the healing process may be provided by the substitute skin products.

### **U.S. Preventive Services Task Force Recommendations**

Not applicable.

### **Medicare National Coverage**

Centers for Medicare and Medicaid Services (CMS) has issued the following national coverage determination: Porcine (pig) skin dressings are covered, if reasonable and necessary for the individual patient as an occlusive dressing for burns, donor sites of a homograft, and decubiti and other ulcers.<sup>85</sup>

Since 2014, CMS no longer distinguishes between different skin substitutes and will classify them as either high cost or low cost.<sup>86</sup> CMS will package skin substitutes of the same class into the associated surgical procedures for hospital outpatient departments and ambulatory surgical centers. A separate payment might be made if the item is furnished on a different date of service as the primary service.

### **Regulatory Status**

There are a large number of artificial skin products that are commercially available or in development. The following summary of commercially available skin substitutes describes those products that have substantial relevant evidence on efficacy. Information on other artificial skin and soft tissue substitutes that are available in the United States may be found in a 2012 Technology Assessment from the Agency for Healthcare Research and Quality.<sup>4</sup>

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### Acellular Dermal Matrix

Allograft acellular dermal matrix (ADM) products derived from donated human skin tissue are supplied by U.S. AATB-compliant tissue banks using the standards of the American Association of Tissue Banks (AATB) and U.S. Food and Drug Administration (FDA) guidelines. The processing removes the cellular components (ie, epidermis and all viable dermal cells) that can lead to rejection and infection. ADM products from human skin tissue are regarded as minimally processed and not significantly changed in structure from the natural material; FDA classifies it as banked human tissue and therefore, does not require FDA approval.

- AlloDerm® (LifeCell Corp.) is an ADM (allograft) tissue-replacement product that is created from native human skin and processed so that the basement membrane and cellular matrix remain intact. Originally, AlloDerm required refrigeration and rehydration before use. It is currently available in a ready-to-use product that is stored at room temperature. An injectable micronized form of AlloDerm (Cymetra) is also available.
- AlloMax™ Surgical Graft (Bard Davol) is an acellular non-cross-linked human dermis allograft. (AlloMax was previously marketed as NeoForm™.)
- FlexHD® (Ethicon) is an acellular hydrated dermis derived from donated human allograft skin. The Musculoskeletal Transplant Foundation acquires and processes the tissue.
- DermACELL™ (LifeNet Health) is an allogeneic ADM processed with proprietary technologies MATRACELL® and PRESERVON®.
- DermaMatrix™ (Synthes) is a freeze-dried ADM (allograft) derived from donated human skin tissue. DermaMatrix Acellular Dermis is processed by the Musculoskeletal Transplant Foundation® (MTF®).
- DermaPure™ (Tissue Regenix Wound Care) is a single-layer decellularized human dermal allograft for the treatment of acute and chronic wounds.
- Graftjacket® Regenerative Tissue Matrix (also called Graftjacket Skin Substitute, KCI) is an acellular regenerative tissue matrix that has been processed from human skin supplied from U.S. tissue banks. The allograft is minimally processed to remove the epidermal and dermal cells, while preserving dermal structure. Graftjacket Xpress® is an injectable product.

FDA product code: FTM, OXF.

### Xenogenic

Keramatrix® (Keraplast Research) is an open-cell foam comprised of freeze-dried keratin that is acellular animal-derived. In 2009, it was cleared for marketing by FDA through the 510(k) marketing process under the name of Keratec. The wound dressings are indicated in the management of the following types of dry, light, and moderately exuding partial and full-thickness wounds, pressure (stage I-IV) and venous stasis ulcers, ulcers caused by mixed vascular etiologies, diabetic ulcers, donor sites, and grafts.

Helicoll (Encol) is an acellular collagen matrix from bovine dermis. In 2004, it was cleared by FDA through the 510(k) process for topical wound management that includes partial and full-thickness wounds, pressure ulcers, venous ulcers, chronic vascular ulcers, diabetic ulcers, trauma wounds (eg, abrasions, lacerations, second-degree burns, skin tears), and surgical wounds including donor sites/grafts.

Permacol™ (Covidien) is xenogenic and composed of cross-linked porcine dermal collagen. Cross-linking improves the tensile strength and long-term durability, but decreases pliability.

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PriMatrix™ (TEI Biosciences) is a xenogeneic ADM processed from fetal bovine dermis. It was cleared for marketing by FDA through the 510(k) process for partial- and full-thickness wounds; diabetic, pressure, and venous stasis ulcers; surgical wounds; and tunneling, draining, and traumatic wounds. FDA product code: KGN.

SurgiMend® PRS (TEI Biosciences) is a xenogeneic ADM processed from fetal bovine dermis. This product is currently undergoing an FDA-regulated investigational device exemption (IDE) trial for breast reconstruction.

Strattice™ Reconstructive Tissue Matrix (LifeCell Corp.) is a xenogenic non-cross-linked porcine-derived ADM. There are pliable and firm versions, which are stored at room temperature and come fully hydrated.

OASIS™ Wound Matrix (Cook Biotech) is a xenogeneic collagen scaffold derived from porcine small intestinal mucosa. In 2000, it was cleared for marketing by FDA through the 510(k) process for the management of partial- and full-thickness wounds including pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled undermined wounds, surgical wounds, trauma wounds, and draining wounds. FDA Product code: KGN.

### Amniotic Membrane

Amniotic membrane consists of 2 conjoined layers, the amnion and chorion, and forms the innermost lining of the amniotic sac or placenta.<sup>5</sup> It is harvested immediately after birth, cleaned, sterilized, and either fresh frozen or dehydrated. Human amniotic membrane is considered to be minimally processed and not significantly changed in structure from the natural material; FDA classifies it as banked human tissue and, therefore, it does not require FDA approval. Amniotic membrane sheet products include Affinity™ (NuTech Medical), AlloWrap™ (AlloSource), AmnioBand and GUARDIAN (Musculoskeletal Transplant Foundation), AmnioGraft® (Bio-Tissue), BioDfence™ and BioDDryFlex® (both from BioD), Biovance® (*Alliqua Biomedical*), Dermavest™ and Plurivest™ (Aedicell), EpiFix® (dehydrated- MiMedix) Neox®1000 (Amniox® Medical), Grafix® Prime and Grafix® Core (cryopreserved, Osiris), NuShield™ (NuTech Medical), Revitalon™ (previously known as AmnioClear, Medline Industries). Injectable amniotic membrane products, such as AmnioFix® (MiMedix), are discussed in evidence review 7.01.149.

### Living Cell Therapy

Apligraf® (Organogenesis) is a bilayered living cell therapy composed of an epidermal layer of living human keratinocytes and a dermal layer of living human fibroblasts. Apligraf® is supplied as needed, in one size, with a shelf-life of 10 days. In 1998, it was approved by FDA for use in conjunction with compression therapy for the treatment of noninfected, partial- and full-thickness skin ulcers due to venous insufficiency and in 2001 for full-thickness neuropathic diabetic lower-extremity ulcers nonresponsive to standard wound therapy. FDA product code: FTM.

Dermagraft® (Organogenesis) is composed of cryopreserved human-derived fibroblasts and collagen derived from newborn human foreskin and cultured on a bioabsorbable polyglactin mesh scaffold. Dermagraft has been approved by FDA for repair of diabetic foot ulcers. FDA product code: PFC.

TheraSkin® (Soluble Systems) is a cryopreserved human skin allograft composed of living fibroblasts and keratinocytes and an extracellular matrix in epidermal and dermal layers. TheraSkin® is derived from human skin allograft in compliance with the AATB and FDA guidelines. It is considered a minimally processed human cell, tissue, and cellular- and tissue-based product (HCT/P) by the FDA.

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Epicel® (Genzyme Biosurgery) is a cultured epithelial autograft and is FDA-approved under an HDE for the treatment of deep dermal or full-thickness burns comprising a total body surface area of 30% or more. It may be used in conjunction with split-thickness autografts or alone in patients for whom split-thickness autografts may not be an option due to the severity and extent of their burns. FDA product code: OCE.

OrCel™ (Forticell Bioscience; formerly Composite Cultured Skin) is an absorbable allogeneic bilayered cellular matrix, made of bovine collagen, in which human dermal cells have been cultured. It was approved by FDA premarket approval for healing donor site wounds in burn victims and under an HDE for use in patients with recessive dystrophic epidermolysis bullosa undergoing hand reconstruction surgery to close and heal wounds created by the surgery, including those at donor sites. FDA product code: ODS.

### Biosynthetic

Biobrane®/Biobrane-L (Smith and Nephew) is a biosynthetic wound dressing constructed of a silicon film with a nylon fabric partially imbedded into the film. The fabric creates a complex 3-dimensional structure of trifilament thread, which chemically binds collagen. Blood/sera clot in the nylon matrix, adhering the dressing to the wound until epithelialization occurs. FDA product code: FRO.

Integra® Dermal Regeneration Template (marketed as Omnigraft Dermal Regeneration Matrix, Integra LifeSciences) is a bovine, collagen/glycosaminoglycan dermal replacement covered by a silicone temporary epidermal substitute. It was approved by FDA for use in postexcisional treatment of life-threatening full-thickness or deep partial-thickness thermal injury where sufficient autograft is not available at the time of excision or not desirable because of the physiologic condition of the patient. Integra™ Matrix Wound Dressing and Integra™ meshed Bilayer Wound Matrix are substantially equivalent skin substitutes approved by FDA through the 510(k) process for other indications. Integra® Bilayer Wound Matrix (Integra LifeSciences) is designed to be used in conjunction with negative pressure wound therapy. The meshed bilayer provides a flexible wound covering and allows drainage of wound exudate. FDA product code: MDD.

TransCyte™ (Advanced Tissue Sciences) consists of human dermal fibroblasts grown on nylon mesh, combined with a synthetic epidermal layer and was approved by FDA in 1997. TransCyte is intended to be used as a temporary covering over burns until autografting is possible. It can also be used as a temporary covering for some burn wounds that heal without autografting.

### Synthetic

Suprathel® (PolyMedics Innovations) is a synthetic copolymer membrane fabricated from a tripolymer of polylactide, trimethylene carbonate, and s-caprolactone. It is used to provide temporary coverage of superficial dermal burns and wounds. Suprathel® is covered with gauze and a dressing that is left in place until the wound has healed.

## REFERENCES

1. U.S. Food and Drug Administration. Guidance for industry: Chronic cutaneous ulcer and burn wounds. 2006; <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071324.pdf>. Accessed December 23, 2015.
2. European Wound Management Association. Outcomes in controlled and comparative studies on non-healing wounds: recommendations to improve the quality of evidence in wound management. *J Wound Care* 2010; 19(6): 239-268. Accessed December 23, 2015.

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3. Sheehan P, Jones P, Caselli A, et al. Percent change in wound area of diabetic foot ulcers over a 4-week period is a robust predictor of complete healing in a 12-week prospective trial. *Diabetes Care*. Jun 2003;26(6):1879-1882. PMID 12766127
4. Snyder DL, Sullivan N, Schoelles KM. Skin Substitutes for Treating Chronic Wounds. Research conducted by the ECRI Institute Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract Number: HHS 290-2007-10063). 2012; [http://www.ahrq.gov/research/findings/ta/skinsubs/HCPRO610\\_skinsubst-final.pdf](http://www.ahrq.gov/research/findings/ta/skinsubs/HCPRO610_skinsubst-final.pdf). Accessed November, 2014.
5. Zelen CM, Snyder RJ, Serena TE, et al. The Use of Human Amnion/Chorion Membrane in the Clinical Setting for Lower Extremity Repair: A Review. *Clin Podiatr Med Surg*. Jan 2015;32(1):135-146. PMID 25440424
6. Ho G, Nguyen TJ, Shahabi A, et al. A systematic review and meta-analysis of complications associated with acellular dermal matrix-assisted breast reconstruction. *Ann Plast Surg*. Apr 2012;68(4):346-356. PMID 22421476
7. Kim JY, Davila AA, Persing S, et al. A meta-analysis of human acellular dermis and submuscular tissue expander breast reconstruction. *Plast Reconstr Surg*. Jan 2012;129(1):28-41. PMID 22186498
8. McCarthy CM, Lee CN, Halvorson EG, et al. The use of acellular dermal matrices in two-stage expander/implant reconstruction: a multicenter, blinded, randomized controlled trial. *Plast Reconstr Surg*. Nov 2012;130(5 Suppl 2):57S-66S. PMID 23096987
9. Preminger BA, McCarthy CM, Hu QY, et al. The influence of AlloDerm on expander dynamics and complications in the setting of immediate tissue expander/implant reconstruction: a matched-cohort study. *Ann Plast Surg*. May 2008;60(5):510-513. PMID 18434824
10. Colwell AS, Breuing KH. Improving shape and symmetry in mastopexy with autologous or cadaveric dermal slings. *Ann Plast Surg*. Aug 2008;61(2):138-142. PMID 18650604
11. Salzberg CA. Nonexpansive immediate breast reconstruction using human acellular tissue matrix graft (AlloDerm). *Ann Plast Surg*. Jul 2006;57(1):1-5. PMID 16799299
12. Breuing KH, Colwell AS. Inferolateral AlloDerm hammock for implant coverage in breast reconstruction. *Ann Plast Surg*. Sep 2007;59(3):250-255. PMID 17721209
13. Garramone CE, Lam B. Use of AlloDerm in primary nipple reconstruction to improve long-term nipple projection. *Plast Reconstr Surg*. May 2007;119(6):1663-1668. PMID 17440338
14. Baxter RA. Intracapsular allogenic dermal grafts for breast implant-related problems. *Plast Reconstr Surg*. Nov 2003;112(6):1692-1696; discussion 1697-1698. PMID 14578804
15. Liu AS, Kao HK, Reish RG, et al. Postoperative complications in prosthesis-based breast reconstruction using acellular dermal matrix. *Plast Reconstr Surg*. May 2011;127(5):1755-1762. PMID 21228744
16. Bindingavele V, Gaon M, Ota KS, et al. Use of acellular cadaveric dermis and tissue expansion in postmastectomy breast reconstruction. *J Plast Reconstr Aesthet Surg*. 2007;60(11):1214-1218. PMID 17459797
17. Liu DZ, Mathes DW, Neligan PC, et al. Comparison of outcomes using AlloDerm versus FlexHD for implant-based breast reconstruction. *Ann Plast Surg*. May 2014;72(5):503-507. PMID 23636114
18. Seth AK, Persing S, Connor CM, et al. A comparative analysis of cryopreserved versus prehydrated human acellular dermal matrices in tissue expander breast reconstruction. *Ann Plast Surg*. Jun 2013;70(6):632-635. PMID 23429218
19. Brooke S, Mesa J, Uluer M, et al. Complications in tissue expander breast reconstruction: a comparison of AlloDerm, DermaMatrix, and FlexHD acellular inferior pole dermal slings. *Ann Plast Surg*. Oct 2012;69(4):347-349. PMID 22868313
20. Butterfield JL. 440 Consecutive immediate, implant-based, single-surgeon breast reconstructions in 281 patients: a comparison of early outcomes and costs between SurgiMend fetal bovine and AlloDerm human cadaveric acellular dermal matrices. *Plast Reconstr Surg*. May 2013;131(5):940-951. PMID 23629076
21. Sinha UK, Saadat D, Doherty CM, et al. Use of AlloDerm implant to prevent frey syndrome after parotidectomy. *Arch Facial Plast Surg*. Jan-Feb 2003;5(1):109-112. PMID 12533152
22. Ye WM, Zhu HG, Zheng JW, et al. Use of allogenic acellular dermal matrix in prevention of Frey's syndrome after parotidectomy. *Br J Oral Maxillofac Surg*. Dec 2008;46(8):649-652. PMID 18547692

---

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23. Athavale SM, Phillips S, Mangus B, et al. Complications of alloderm and dermamatrix for parotidectomy reconstruction. *Head Neck*. Jan 2012;34(1):88-93. PMID 21469246
24. Barber FA, Burns JP, Deutsch A, et al. A prospective, randomized evaluation of acellular human dermal matrix augmentation for arthroscopic rotator cuff repair. *Arthroscopy*. Jan 2012;28(1):8-15. PMID 21978432
25. ba-bai-ke-re AMM, Wen H, Huang HG, et al. Randomized controlled trial of minimally invasive surgery using acellular dermal matrix for complex anorectal fistula. *World J Gastroenterol*. Jul 14 2010;16(26):3279-3286. PMID 20614483
26. Zhong T, Janis JE, Ahmad J, et al. Outcomes after abdominal wall reconstruction using acellular dermal matrix: A systematic review. *J Plast Reconstr Aesthet Surg*. May 28 2011. PMID 21624851
27. Gupta A, Zahriya K, Mullens PL, et al. Ventral herniorrhaphy: experience with two different biosynthetic mesh materials, Surgisis and Alloderm. *Hernia*. Oct 2006;10(5):419-425. PMID 16924395
28. Espinosa-de-los-Monteros A, de la Torre JI, Marrero I, et al. Utilization of human cadaveric acellular dermis for abdominal hernia reconstruction. *Ann Plast Surg*. Mar 2007;58(3):264-267. PMID 17471129
29. Bochicchio GV, De Castro GP, Bochicchio KM, et al. Comparison Study of Acellular Dermal Matrices in Complicated Hernia Surgery. *J Am Coll Surg*. Oct 2013;217(4):606-613. PMID 23973102
30. Fleshman JW, Beck DE, Hyman N, et al. A prospective, multicenter, randomized, controlled study of non-cross-linked porcine acellular dermal matrix fascial sublay for parastomal reinforcement in patients undergoing surgery for permanent abdominal wall ostomies. *Dis Colon Rectum*. May 2014;57(5):623-631. PMID 24819103
31. Novaes AB, Jr., de Barros RR. Acellular dermal matrix allograft. The results of controlled randomized clinical studies. *J Int Acad Periodontol*. Oct 2008;10(4):123-129. PMID 19055225
32. Girod DA, Sykes K, Jorgensen J, et al. Acellular dermis compared to skin grafts in oral cavity reconstruction. *Laryngoscope*. Nov 2009;119(11):2141-2149. PMID 19650133
33. Milstein CF, Akst LM, Hicks MD, et al. Long-term effects of micronized Alloderm injection for unilateral vocal fold paralysis. *Laryngoscope*. Sep 2005;115(9):1691-1696. PMID 16148719
34. Vos JD, Latev MD, Labadie RF, et al. Use of AlloDerm in type I tympanoplasty: a comparison with native tissue grafts. *Laryngoscope*. Sep 2005;115(9):1599-1602. PMID 16148702
35. Veves A, Falanga V, Armstrong DG, et al. Graftskin, a human skin equivalent, is effective in the management of noninfected neuropathic diabetic foot ulcers: a prospective randomized multicenter clinical trial. *Diabetes Care*. Feb 2001;24(2):290-295. PMID 11213881
36. Blue Cross and Blue Shield Technology Evaluation Center. Graftskin for the treatment of skin ulcers. *TEC Assessments*. 2001;Volume 16, Tab 12.
37. Steinberg JS, Edmonds M, Hurley DP, Jr., et al. Confirmatory data from EU study supports Apligraf for the treatment of neuropathic diabetic foot ulcers. *J Am Podiatr Med Assoc*. Jan-Feb 2010;100(1):73-77. PMID 20093548
38. Kirsner RS, Warriner R, Michela M, et al. Advanced biological therapies for diabetic foot ulcers. *Arch Dermatol*. Aug 2010;146(8):857-862. PMID 20713816
39. Marston WA, Hanft J, Norwood P, et al. The efficacy and safety of Dermagraft in improving the healing of chronic diabetic foot ulcers: results of a prospective randomized trial. *Diabetes Care*. Jun 2003;26(6):1701-1705. PMID 12766097
40. Frykberg RG, Marston WA, Cardinal M. The incidence of lower-extremity amputation and bone resection in diabetic foot ulcer patients treated with a human fibroblast-derived dermal substitute. *Adv Skin Wound Care*. Jan 2015;28(1):17-20. PMID 25407083
41. Sanders L, Landsman AS, Landsman A, et al. A prospective, multicenter, randomized, controlled clinical trial comparing a bioengineered skin substitute to a human skin allograft. *Ostomy Wound Manage*. Sep 2014;60(9):26-38. PMID 25211605
42. Brigido SA, Boc SF, Lopez RC. Effective management of major lower extremity wounds using an acellular regenerative tissue matrix: a pilot study. *Orthopedics*. Jan 2004;27(1 Suppl):s145-149. PMID 14763548
43. Reyzelman A, Crews RT, Moore JC, et al. Clinical effectiveness of an acellular dermal regenerative tissue matrix compared to standard wound management in healing diabetic foot ulcers: a prospective, randomised, multicentre study. *Int Wound J*. Jun 2009;6(3):196-208. PMID 19368581

---

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44. Driver VR, Lavery LA, Reyzelman AM, et al. A clinical trial of Integra Template for diabetic foot ulcer treatment. *Wound Repair Regen.* Nov 12 2015;23(6):891-900. PMID 26297933
45. Zelen CM, Serena TE, Denoziere G, et al. A prospective randomised comparative parallel study of amniotic membrane wound graft in the management of diabetic foot ulcers. *Int Wound J.* Jun 7 2013. PMID 23742102
46. Zelen CM, Serena TE, Fetterolf DE. Dehydrated human amnion/chorion membrane allografts in patients with chronic diabetic foot ulcers: a long term follow-up study. *Wound Medicine* 2014;4:1-4.
47. Smiell JM, Treadwell T, Hahn HD, et al. Real-world Experience With a Decellularized Dehydrated Human Amniotic Membrane Allograft. *Wounds.* Jun 2015;27(6):158-169. PMID 26061491
48. Zelen CM, Gould L, Serena TE, et al. A prospective, randomised, controlled, multi-centre comparative effectiveness study of healing using dehydrated human amnion/chorion membrane allograft, bioengineered skin substitute or standard of care for treatment of chronic lower extremity diabetic ulcers. *Int Wound J.* Dec 2015;12(6):724-732. PMID 25424146
49. Kirsner RS, Sabolinski ML, Parsons NB, et al. Comparative effectiveness of a bioengineered living cellular construct vs. a dehydrated human amniotic membrane allograft for the treatment of diabetic foot ulcers in a real world setting. *Wound Repair Regen.* Sep 2015;23(5):737-744. PMID 26100572
50. Lavery LA, Fulmer J, Shebetka KA, et al. The efficacy and safety of Grafix((R)) for the treatment of chronic diabetic foot ulcers: results of a multi-centre, controlled, randomised, blinded, clinical trial. *Int Wound J.* Oct 2014;11(5):554-560. PMID 25048468
51. Niezgodna JA, Van Gils CC, Frykberg RG, et al. Randomized clinical trial comparing OASIS Wound Matrix to Regranex Gel for diabetic ulcers. *Adv Skin Wound Care.* Jun 2005;18(5 Pt 1):258-266. PMID 15942317
52. Kavros SJ, Dutra T, Gonzalez-Cruz R, et al. The use of PriMatrix, a fetal bovine acellular dermal matrix, in healing chronic diabetic foot ulcers: a prospective multicenter study. *Adv Skin Wound Care.* Aug 2014;27(8):356-362. PMID 25033310
53. Karr JC. Retrospective comparison of diabetic foot ulcer and venous stasis ulcer healing outcome between a dermal repair scaffold (PriMatrix) and a bilayered living cell therapy (Apligraf). *Adv Skin Wound Care.* Mar 2011;24(3):119-125. PMID 21326023
54. Falanga V, Margolis D, Alvarez O, et al. Rapid healing of venous ulcers and lack of clinical rejection with an allogeneic cultured human skin equivalent. Human Skin Equivalent Investigators Group. *Arch Dermatol.* Mar 1998;134(3):293-300. PMID 9521027
55. Harding K, Sumner M, Cardinal M. A prospective, multicentre, randomised controlled study of human fibroblast-derived dermal substitute (Dermagraft) in patients with venous leg ulcers. *Int Wound J.* Apr 2013;10(2):132-137. PMID 23506344
56. Mostow EN, Haraway GD, Dalsing M, et al. Effectiveness of an extracellular matrix graft (OASIS Wound Matrix) in the treatment of chronic leg ulcers: a randomized clinical trial. *J Vasc Surg.* May 2005;41(5):837-843. PMID 15886669
57. Romanelli M, Dini V, Bertone M, et al. OASIS wound matrix versus Hyaloskin in the treatment of difficult-to-heal wounds of mixed arterial/venous aetiology. *Int Wound J.* Mar 2007;4(1):3-7. PMID 17425543
58. Romanelli M, Dini V, Bertone MS. Randomized comparison of OASIS wound matrix versus moist wound dressing in the treatment of difficult-to-heal wounds of mixed arterial/venous etiology. *Adv Skin Wound Care.* Jan 2010;23(1):34-38. PMID 20101114
59. Serena TE, Carter MJ, Le LT, et al. A multicenter, randomized, controlled clinical trial evaluating the use of dehydrated human amnion/chorion membrane allografts and multilayer compression therapy vs. multilayer compression therapy alone in the treatment of venous leg ulcers. *Wound Repair Regen.* Nov-Dec 2014;22(6):688-693. PMID 25224019
60. Serena TE, Yaakov R, DiMarco D, et al. Dehydrated human amnion/chorion membrane treatment of venous leg ulcers: correlation between 4-week and 24-week outcomes. *J Wound Care.* Nov 2015;24(11):530-534. PMID 26551645
61. Fivenson DP, Scherschun L, Cohen LV. Apligraf in the treatment of severe mitten deformity associated with recessive dystrophic epidermolysis bullosa. *Plast Reconstr Surg.* Aug 2003;112(2):584-588. PMID 12900618
62. Clare G, Suleman H, Bunce C, et al. Amniotic membrane transplantation for acute ocular burns. *Cochrane Database Syst Rev.* 2012;9:CD009379. PMID 22972141

---

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63. Adly OA, Moghazy AM, Abbas AH, et al. Assessment of amniotic and polyurethane membrane dressings in the treatment of burns. *Burns*. Aug 2010;36(5):703-710. PMID 20004061
64. Carsin H, Ainaud P, Le Bever H, et al. Cultured epithelial autografts in extensive burn coverage of severely traumatized patients: a five year single-center experience with 30 patients. *Burns*. Jun 2000;26(4):379-387. PMID 10751706
65. Lagus H, Sarlomo-Rikala M, Bohling T, et al. Prospective study on burns treated with Integra(R), a cellulose sponge and split thickness skin graft: comparative clinical and histological study--randomized controlled trial. *Burns*. Dec 2013;39(8):1577-1587. PMID 23880091
66. Branski LK, Herndon DN, Pereira C, et al. Longitudinal assessment of Integra in primary burn management: a randomized pediatric clinical trial. *Crit Care Med*. Nov 2007;35(11):2615-2623. PMID 17828040
67. Heimbach DM, Warden GD, Luterman A, et al. Multicenter postapproval clinical trial of Integra dermal regeneration template for burn treatment. *J Burn Care Rehabil*. Jan-Feb 2003;24(1):42-48. PMID 12543990
68. Still J, Glat P, Silverstein P, et al. The use of a collagen sponge/living cell composite material to treat donor sites in burn patients. *Burns*. Dec 2003;29(8):837-841. PMID 14636761
69. Lukish JR, Eichelberger MR, Newman KD, et al. The use of a bioactive skin substitute decreases length of stay for pediatric burn patients. *J Pediatr Surg*. Aug 2001;36(8):1118-1121. PMID 11479839
70. Amani H, Dougherty WR, Blome-Eberwein S. Use of Transcyte and dermabrasion to treat burns reduces length of stay in burns of all size and etiology. *Burns*. Nov 2006;32(7):828-832. PMID 16997480
71. Davidson A, Jina NH, Marsh C, et al. Do functional keratin dressings accelerate epithelialization in human partial thickness wounds? A randomized controlled trial on skin graft donor sites. *Eplasty*. 2013;13:e45. PMID 24058716
72. Helgeson MD, Potter BK, Evans KN, et al. Bioartificial dermal substitute: a preliminary report on its use for the management of complex combat-related soft tissue wounds. *J Orthop Trauma*. Jul 2007;21(6):394-399. PMID 17620998
73. Taras JS, Sapienza A, Roach JB, et al. Acellular dermal regeneration template for soft tissue reconstruction of the digits. *J Hand Surg Am*. Mar 2010;35(3):415-421. PMID 20138715
74. Weigert R, Choughri H, Casoli V. Management of severe hand wounds with Integra(R) dermal regeneration template. *J Hand Surg Eur Vol*. Mar 2011;36(3):185-193. PMID 21078866
75. Lazic T, Falanga V. Bioengineered skin constructs and their use in wound healing. *Plast Reconstr Surg*. Jan 2011;127 Suppl 1:75S-90S. PMID 21200276
76. Saffle JR. Closure of the excised burn wound: temporary skin substitutes. *Clin Plast Surg*. Oct 2009;36(4):627-641. PMID 19793557
77. American Society of Plastic Surgeons. Evidence-Based Clinical Practice Guideline: Breast Reconstruction with Expanders and Implants. 2013; <http://www.plasticsurgery.org/Documents/medical-professionals/health-policy/evidence-practice/breast-reconstruction-expanders-with-implants-guidelines.pdf>. Accessed November, 2014.
78. Hopf HW, Ueno C, Aslam R, et al. Guidelines for the treatment of arterial insufficiency ulcers. *Wound Repair Regen* 2006; 14(6):693-710. 2007/01/04:<http://www.plasticsurgery.org/For-Medical-Professionals/Legislation-and-Advocacy/Health-Policy-Resources/Endorsed-Guidelines-Developed-by-Other-Medical-Societies/Wound-Healing-Society-.html>. Accessed November, 2014.
79. Robson MC, Cooper DM, Aslam R, et al. Guidelines for the treatment of venous ulcers. *Wound Repair Regen* 2006; 14(6): 649-62. 2006; 2007/01/04:<http://www.plasticsurgery.org/For-Medical-Professionals/Legislation-and-Advocacy/Health-Policy-Resources/Endorsed-Guidelines-Developed-by-Other-Medical-Societies/Wound-Healing-Society-.html>. Accessed November, 2014.
80. Steed DL, Attinger C, Colaizzi T, et al. Guidelines for the treatment of diabetic ulcers. *Wound Repair Regen* 2006; 14(6):680-92. 2006; 2007/01/04:<http://www.plasticsurgery.org/For-Medical-Professionals/Legislation-and-Advocacy/Health-Policy-Resources/Endorsed-Guidelines-Developed-by-Other-Medical-Societies/Wound-Healing-Society-.html>. Accessed November, 2014.
81. American Society of Plastic Surgeons (ASPS). Evidence-based Clinical Practice Guideline: Chronic Wounds of the Lower Extremity. 2007; <http://www.plasticsurgery.org/Documents/medical-professionals/health->

---

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- policy/evidence-practice/Evidence-based-Clinical-Practice-Guideline-Chronic-Wounds-of-the-Lower-Extremity.pdf. Accessed November, 2014.
82. National Institute for Health and Care Excellence (NICE). NICE Clinical Guideline NG19. Diabetic Foot Problems: Prevention and Management. 2015; <https://www.nice.org.uk/guidance/ng19/evidence>. Accessed December 22, 2015.
  83. Frykberg RG, Zgonis T, Armstrong DG, et al. Diabetic foot disorders. A clinical practice guideline (2006 revision). *J Foot Ankle Surg* 2006; 45 (5 Suppl):S1-66.  
[http://www.acfas.org/uploadedFiles/Healthcare\\_Community/Education\\_and\\_Publications/Clinical\\_Practice\\_Guidelines/DiabeticCPG-small.pdf](http://www.acfas.org/uploadedFiles/Healthcare_Community/Education_and_Publications/Clinical_Practice_Guidelines/DiabeticCPG-small.pdf). Accessed November, 2014.
  84. Lipsky BA, Berendt AR, Cornia PB, et al. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. *Clin Infect Dis*. 2012 Jun;54(12):e132-173. 2012; [http://www.idsociety.org/uploadedFiles/IDSA/Guidelines-Patient\\_Care/PDF\\_Library/2012%20Diabetic%20Foot%20Infections%20Guideline.pdf](http://www.idsociety.org/uploadedFiles/IDSA/Guidelines-Patient_Care/PDF_Library/2012%20Diabetic%20Foot%20Infections%20Guideline.pdf). Accessed November, 2014.
  85. Centers for Medicare and Medicaid Services (CMS). Porcine skin and gradient pressure dressing. 270.5. <http://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=139&ncdver=1&bc=AgAAQAAAAAAAA&>. Accessed November, 2014.
  86. Centers for Medicare and Medicaid Services (CMS). CMS issues hospital outpatient department and ambulatory surgical center policy and payment changes for 2014. 2013; <http://www.cms.gov/Newsroom/MediaReleaseDatabase/Fact-Sheets/2013-Fact-Sheets-Items/2013-11-27-3.html>. Accessed November, 2014.

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Contractor Information Table

<b>Contractor Name</b> <a href="#">Noridian Healthcare Solutions, LLC opens in new window</a>	<b>Contract Number</b> 01112	<b>Contract Type</b> A and B MAC	<b>Jurisdiction</b> J - E
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General Information

General Article Information Table

<b>Article ID</b> A54305	<b>Jurisdiction</b> California - Northern
<b>Original ICD-9 Article ID</b>	<b>Original Effective Date</b> 07/09/2015
<b>Article Title</b> Response to Comments: Non-Covered Services Policy, L35212	<b>Retirement Date</b> ANTICIPATED 01/09/2016
<b>Article Type</b> Response to Comments	

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## Article Guidance

### Article Text:

Noridian’s Response to Provider Recommendations (for comment period ending 07/11/2014):

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### Response to Comments

COMMENT	RESPONSE
Lariat and other left atrial interventions. We received fifteen comments regarding use of the Lariat device for left atrial closure to prevent embolic disease. Of these, most were testimonials on the use of this device, but copies of published studies were not provided.	Since the comment period ended, another device, Watchman, has received FDA approval and Noridian, in conjunction with other contractors are studying these interventions to determine coverage. At this time, we will leave 0281T as non-covered. In addition, until new codes are issued indication that these are separate procedures, the descriptor “resection/ligation of atrial appendage” shall remain in Group 2 as a component of another service.

<p>Decision-DX UM. We received nine comments regarding the Decision-DX UM test for uveal melanoma. Most of the letters were testimonials, but one letter was accompanied by supportive literature.</p>	<p>Noridian will consider coverage on a case-by-case basis provided that the patient has a confirmed diagnosis of uveal melanoma, has no evidence for metastasis, the test is performed only once for the beneficiary, and the beneficiary's information has been entered in the appropriate registry.</p>
<p>Skin Substitutes. We received 13 comments regarding various skin substitutes mostly one known as Grafix.</p>	<p>Medicare considers "dressings" as generally bundled services that are not paid separately. But Medicare considers "grafts" as separately payable. Over the last decade, the number of skin substitute products on the market has dramatically increased, but utilization still remains relatively low. Consequently, Noridian has decided, at least for the short term, to allow coverage for those products with a HCPCS code in the Q4xxx range. This section is being removed for this LCD.</p>
<p>83698, PLA2 Test. We received 23 comments on the test for lipoprotein associated phospholipase with mixed advice. Many commenters provided testimonials on the usefulness of this test, some on its lack of usefulness. Three comments were substantial with references included.</p>	<p>Noridian's review of these references indicates that this test is not used in guiding therapy. The primary therapy that could be affected by the results of this test is statin therapy for hypercholesterolemia. Current national guidelines offer no role for this test in initiating, monitoring or adjusting statin therapy.</p>
<p>82172. We received five comments regarding coverage for apolipoprotein including two with extensive references which we reviewed.</p>	<p>Like the lipoprotein associated phospholipase, the clinical utility for this test remains unproven. The most recent national guidelines for management of hypercholesterolemia do not include a role for these assays.</p>
<p>Procalcitonin 84145. One person provided a testimonial on the usefulness of procalcitonin assays. The comment included two pertinent papers regarding the relationship between sepsis and procalcitonin.</p>	<p>This LCD affects services paid in outpatient settings and does not affect services performed during an inpatient hospital stay. The studies included with this comment involved persons evaluated during acute hospitals stays, so would not be affected by this LCD. [N.B. not for publication: Recent articles have been less supportive of the role for procalcitonin]</p>
<p>Ova-1. Three persons commented on the usefulness of the OVA-1 genetic test and provided references to published studies.</p>	<p>Since the publication of this draft, Noridian has worked with Palmetto GBA and is using the coverage determinations promulgated by the MolDx program at Palmetto. Coverage of the Ova-1 test, coded with 81503, has been considered by the MolDx program, so will be removed</p>

<p>Prolaris. One comment was received on the clinical utility of Prolaris assay accompanied by numerous supporting articles.</p>	<p>from this LCD to avoid duplicated efforts. This assay is being removed from this policy and a separate LCD has been promulgated.</p>
<p>Argus II. We received two comments regarding coverage insertion of the ARGUS-II retinal device. This is currently billed with the Category III CPT Code 0100T.</p>	<p>While this technology is an exciting technical achievement the Noridian medical directors have carefully reviewed the published studies and do not see sufficient evidence to support coverage at this time. The studies fail to provide measurable evidence for an improvement in the patient's activities of daily living. We understand that additional studies may be in progress and may provide additional data when they become available.</p>
<p>SI-Fusion. Three comments regarded percutaneous sacroiliac fusion. All three were testimonials and did not include copies of published studies.</p>	<p>For 2014, CPT issued a new Category I code for this service and is grouped with the open procedure for a similar service. Noridian has removed this service from the Non-covered services LCD, but is concerned that this procedure has limited usefulness and may develop an LCD dealing with both procedures.</p>
<p>0042T. One testimonial was received regarding CT cerebral perfusion analysis, but was accompanied by no published studies or references.</p>	<p>This was insufficient information for coverage.</p>
<p>QST. We received two comments supporting the use of QST test (0106T-0110T). One of the comments included a single reference to a published paper.</p>	<p>Upon review of that single published study, we do not think that the clinical utility of this study has been demonstrated. Therefore this service shall remain non-covered.</p>
<p>Knee Osteochondral Grafts (27415, 27416, 29866, 29868). One comment provided extensive literature regarding osteochondral grafting procedures.</p>	<p>There is impressive published literature on this service, but Medicare claims data indicate that less than 30 of these procedures are performed annually on Medicare beneficiaries. Consequently, we will remove these services from the Non-covered services LCD for the present time.</p>
<p>Transforaminal US Guided Interventions (0228T, 0229T, 0230T, 0231T). One comment reported on the use of ultrasound guided transforaminal injections and was accompanied by four abstracts.</p>	<p>These procedures are usually performed under fluoroscopy. The published abstracts indicate that ultrasound guidance may offer some utility and this contractor had previously allowed coverage based on these scanty reports. So these services will be removed from this LCD.</p>

Artificial Disc (22856, 22861). One comment asked for coverage of total disc arthroplasty (cervical) and revisions for the lumbar disc arthroplasty providing numerous references.

These are rarely performed procedures in the Medicare population with less than 150 in 2013 and fewer than that in prior years. At this time we do not believe that there are sufficient data regarding the long term safety and efficacy for general coverage.

Laboratory Developed Tests. One comment regarded non-coverage of non-FDA approved tests.

This LCD does not provide a blanket non-coverage of laboratory approved tests nor of tests not cleared or reviewed by the FDA. The language in the Indications and Limitations Section provide examples of reasons for coverage. Most of the laboratory developed assays that have caused concern lately are those tests considered by the MoDx project which is a separate initiative and is not related to the LCD.





## CLINICAL SUMMARY

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Many of the wound care products available today have limited clinical evidence to support their use. A decision was made early on to invest in high quality clinical evidence that supports the appropriate use of MIST Therapy to assist medical professionals in their wound care treatment decisions.

## CLINICAL EVIDENCE LEVEL I-III SUMMARY

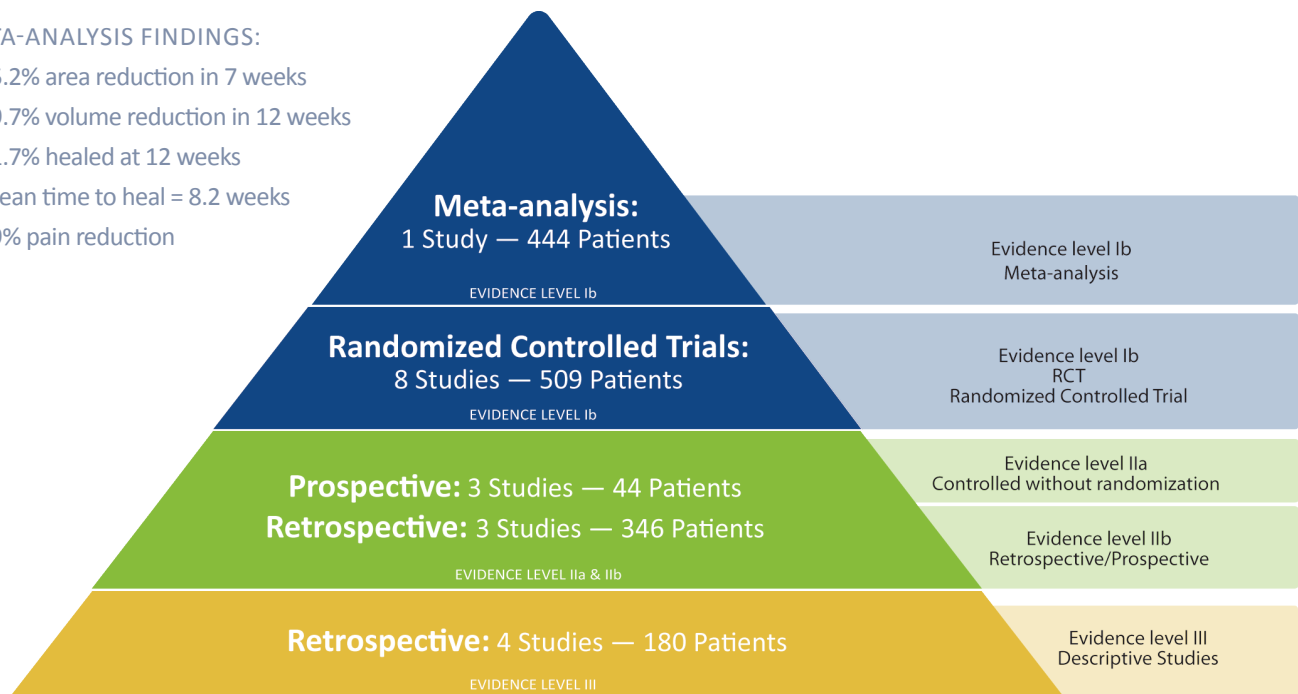
MIST Therapy was introduced into the market in late 2004 and has been investigated in a variety of Level I-III Clinical Studies including one (1) meta-analysis, eight (8) randomized controlled trials, two (2) prospective, six (6) retrospective, and two (2) observational studies.

Few wound care technologies have the clinical evidence to support a meta-analysis. In the meta-analysis using only MIST Therapy ultrasound clinical data, eight (8) peer-reviewed studies with consistent designs for treatment and control wound groups were pooled to review the effects of MIST Therapy on healing time, wound size, volume, and pain. The authors concluded that “MIST Therapy demonstrates remarkable consistency of reduction in wound area, volume, pain and healing times across a wide range of wounds.”

### SUMMARY OF MIST THERAPY LEVEL I-III CLINICAL DATA

#### META-ANALYSIS FINDINGS:

- 85.2% area reduction in 7 weeks
- 79.7% volume reduction in 12 weeks
- 41.7% healed at 12 weeks
- Mean time to heal = 8.2 weeks
- 79% pain reduction



The results of these Level I-III studies demonstrate accelerated wound healing in patients with multiple comorbidities. When compared to standard of care results, MIST Therapy provides nearly twice the healing in the same period of time as traditional Standard of Care (SOC). See tables on following pages for more details.



**TABLE OF CLINICAL EVIDENCE LEVEL I STUDY DETAILS - META-ANALYSIS**

LEVEL OF EVIDENCE	PUBLICATION AUTHOR JOURNAL	WOUND POPULATION	MEASUREMENT	MIST RESULT	SOC RESULT	TREATMENT DURATION	STATISTICS
I b	Noncontact Low-Frequency Ultrasound Therapy in the Treatment of Chronic Wounds: A Meta-Analysis Driver VR, Yao M, Miller CJ Wound Regeneration and Repair 2011	N* = 444 (463 wounds)	Wound Closure (N=429)	41.7%	**24%	12 weeks	95% CI (Confidence Interval)
			Wound Area Reduction (N=188)	85.2% reduction	Not reported	Mean 7 weeks	95% CI
		Diabetic Foot, Ischemic, Neuropathic, Venous, Multifactorial Etiology, Pressure, Surgical, Traumatic	Wound Volume Reduction (N=278)	79.7% reduction	Not reported	Mean 12 weeks	95% CI
			Pain Reduction (N=139)	79% reduction	Not reported	From Baseline	Not reported

**TABLE OF CLINICAL EVIDENCE LEVEL I STUDY DETAILS - RANDOMIZED CONTROL TRIALS**

LEVEL OF EVIDENCE	PUBLICATION AUTHOR JOURNAL	WOUND POPULATION	MEASUREMENT	MIST RESULT	SOC RESULT	TREATMENT DURATION	STATISTICS
I b <b>NEW</b>	A Prospective, Randomized, Controlled Trial Comparing the Effects of Noncontact, Low-Frequency Ultrasound to Standard Care in Healing Venous Leg Ulcers Gibbons GW, Orgill DP, Serena TE, Novoung A, O'Connell JB, Li WW, Driver VR Ostomy and Wound Management 2015	N= 112 Enrolled N = 81 Randomized	Mean % Wound Area Reduction	61.6% reduction	45% reduction	4 weeks	p=0.02
		Venous Leg Ulcers	Pain VAS Measurement	80% reduction	20% reduction		p=0.01
I b <b>NEW</b>	A Prospective, Randomized, Controlled Trial Comparing the Effects of Noncontact, Low-Frequency Ultrasound to Standard Care in Healing Split Thickness Donor Sites Prather JL, Tummel EK, Patel AB, Smith DJ, Gould LJ Journal of American College of Surgeons 2015	N=33 Enrolled N = 27 Randomized	Time to first "no drainage"	12.1 days	21.3 days	NA	p=0.04
			Time to 2 consecutive visits with no drainage	16.1 days	28.1 days		p=0.02
		Split-Thickness Donor Sites	Time to Adjudicated Fully Epithelialized	18.2 days	27.5 days		p=0.03
			Recidivism at 6 weeks	8%	45%		p=0.06
I b <b>NEW</b>	Noncontact Low-Frequency Ultrasound Therapy Compared with UK Standard of Care for Venous Leg Ulcers in a Single-Centre, Assessor-Blinded Randomized Control Trial White J, Ivins N, Wilkes A, Carolan-Rees G, Harding KG International Wound Journal 2015	N=47 Enrolled N = 36 Randomized	Wound Area	47% reduction	39% reduction	Study population too small to demonstrate statistical significance	p=0.565
		Venous Leg Ulcers	Pain	-14.4 points	-5.3 points		p=0.078

\*Total patient population from 8 studies = 519 (444 treated with MIST), 538 wounds (463 treated with MIST)

\*\*Margolis meta-analysis of standard of care treatments for DFU's was discussed in the article and used for comparison to MIST results.

*Level I Study Details continued on next page*

**TABLE OF CLINICAL EVIDENCE LEVEL I STUDY DETAILS - RANDOMIZED CONTROL TRIALS CONTINUED**

LEVEL OF EVIDENCE	PUBLICATION AUTHOR JOURNAL	WOUND POPULATION	MEASUREMENT	MIST RESULT	SOC RESULT	TREATMENT DURATION	STATISTICS
I b	Comparison of High-Frequency and MIST Ultrasound Therapy for the Healing of Venous Leg Ulcers Beheshti A, Shafigh Y, Parsa H, Zangivand A. Advances in Clinical and Experimental Medicine 2014	N=90	Wound Area Reduction	63.7% at 4 months	46.4% at 4 months	12 weeks followed by SOC	p=0.01
	Venous Leg Ulcers	Mean Time to Healing in Months	5.7	8.13	p<0.0001		
		Pain Reduction	55.4% reduction at 4 months	33.7% reduction at 4 months	p<0.0001		
I b	High-Frequency and Noncontact Low-Frequency Ultrasound Therapy for Venous Leg Ulcer Treatment: A Randomized, Controlled Study Olyaie M, Rad FS, Elahifar MA, Garkaz A, Mahsa G Ostomy and Wound Management 2013	N = 90	Wound Area Reduction	72.8% at 4 months	55.4% at 4 months	12 weeks followed by SOC	p=0.04
	Venous Leg Ulcers	Mean Time to Healing in Months	6.65	8.5	p<0.05		
		Pain Reduction	47.1% reduction at 4 months	17.7% reduction at 4 months	p=0.001		
I b	A Pilot Study Evaluating Noncontact Low Frequency Ultrasound on Diabetic Foot Ulcers and Underlying Molecular Mechanisms Yao M, Hasturk H, Kantarci A, Gu G, Garcia-Lavin S, Fabbi M, Park N, Hayashi, H, Attala K, French M, Driver V International Wound Care Journal 2012	N = 12	Wound Area Reduction	86% reduction	39% reduction	4 weeks	p<0.05
	Diabetic Foot Ulcers						
I b	Treatment of Ischemic Wounds with Noncontact, Low-Frequency Ultrasound: The Mayo Clinic Experience, 2004-2006 Kavros SJ, Miller JL, Hanna SW Advances in Skin & Wound Care 2007	N = 70	>50% Wound Area Reduction	63% achieved >50% reduction	29% achieved >50% reduction	12 weeks	p<0.001
	Ischemic, Neuropathic, Venous, Multifactorial						
I b	Ultrasound Therapy for Recalcitrant Diabetic Foot Ulcers: Results of a Randomized, Double-Blind, Controlled Multicenter Study Ennis WJ, Formann P, Mozen N, Massey J, Conner-Kerr T, Meneses P Ostomy & Wound Management 2005	N = 55	Wound Closure	40.7%	14.3%	12 weeks	p<0.0366
	Diabetic Foot Ulcers						

**TABLE OF CLINICAL EVIDENCE LEVEL II STUDY DETAILS**

LEVEL OF EVIDENCE	PUBLICATION AUTHOR JOURNAL	WOUND POPULATION	MEASUREMENT	MIST RESULT	SOC RESULT	TREATMENT DURATION	STATISTICS
II a	A Prospective Pilot Study of Ultrasound Therapy Effectiveness in Refractory Venous Leg Ulcers  Escandon J, Vivas AC, Perez R, Kirsner R, Davis S  International Wound Journal 2012	N = 10  Venous Leg Ulcers	Wound Area Reduction	45% reduction	Failure to improve in previous 30 days	4 weeks	p<0.0039
II a	The Impact of Noncontact, Nonthermal, Low-Frequency Ultrasound on Bacterial Counts in Experimental and Chronic Wounds  Serena T, Lee SK, Lam K, Attar P, Meneses P, Ennis W  Ostomy Wound Management 2009	N = 11  Pressure Ulcers (Stage III)	Wound Volume Reduction  Wound Area Reduction	20% reduction  26% reduction	NA	2 weeks	Not reported
II b	Effects of Noncontact Low-Frequency Ultrasound on Healing of Suspected Deep Tissue Injury: A Retrospective Analysis  Honaker JS, Forston MR, Davis EA, Wiesner MW, Morgan JA  International Wound Care Journal 2012	N = 85 (127 DTIs)  Deep Tissue Injuries (Pressure Ulcers)	Wound Evolution/Resolution at hospital discharge  Severity Scale Assessment	Resolved 18% Stage II 62% DTI 5% Stage III, IV unstageable 15%	2% 20% 30% 48%	10 MIST Treatments over 21 days	Not reported  p<0.000
II b	Expedited Wound Healing with Noncontact, Low-Frequency Ultrasound Therapy in Chronic Wounds: A Retrospective Analysis  Kavros SJ, Liedl DA, Boon, AJ, Miller JL, Hobbs JA, Andrews KL  Advances in Skin and Wound Care 2008	N = 210  Ischemic, Venous, Neuropathic, Multifactorial	Wound Closure	53% in mean of 147 days	32% in mean of 134 days	SOC followed by 12 weeks MIST treatment then SOC	p = 0.0009
II b	Use of Noncontact Low-Frequency Ultrasound in the Treatment of Chronic Foot and Leg Ulcerations  Kavros SJ, Schenck EC  J of American Podiatric Medical Assn 2007	N = 51  Chronic Lower Leg and Foot Ulcers, Multifactorial, Arterial, Diabetic	Wound Closure  Wound Volume Reduction	51%  94.9±9.8% reduction	0% patients were treated with SOC prior to starting MIST  37.3±18.6% reduction	MIST mean 5.5±2.8 weeks  SOC mean 9.8±5.5 weeks	p<0.05  p<0.0001
II b	Evaluation of Clinical Effectiveness of MIST Ultrasound Therapy for the Healing of Chronic Wounds  Ennis WJ, Valdes W, Gainer M, Meneses P.  Advances in Skin and Wound Care 2006	N = 23 (29 wounds)  Diabetic, Ischemic, Venous, Pressure, Post-operative, Inflammatory	Wound Closure	MIST only 69%  MIST assisted* 73.3%	<15% area reduction in 2 week prior to MIST	6.82 weeks  10.47 weeks	Not reported  Not reported

\*addition of Apligraf

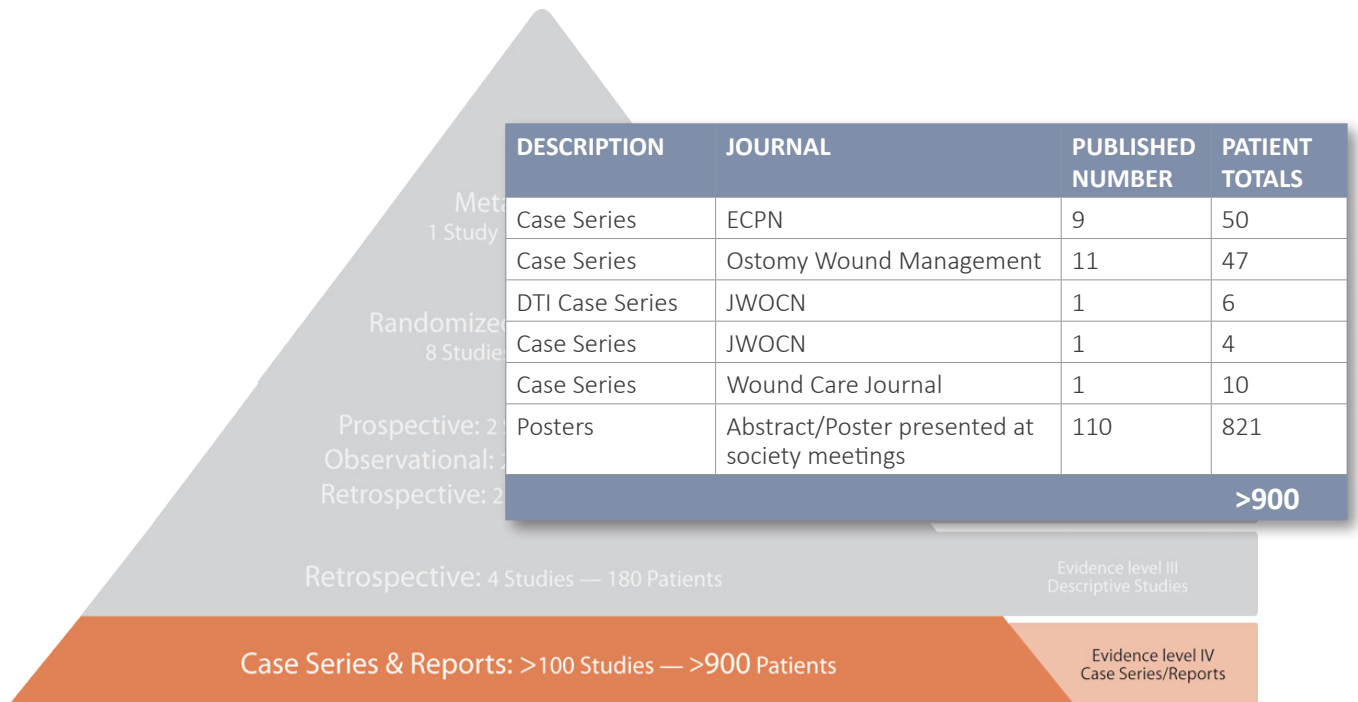
**TABLE OF CLINICAL EVIDENCE LEVEL III STUDY DETAILS**

LEVEL OF EVIDENCE	PUBLICATION AUTHOR JOURNAL	WOUND POPULATION	MEASUREMENT	MIST RESULT	SOC RESULT	TREATMENT DURATION	STATISTICS
III	Adjuvant Use of Acoustic Pressure Wound Therapy* for Treatment of Chronic Wounds  Cole PS, Quisberg J, Melin MM  J Wound Ostomy Continence Nursing 2009	N = 41 (52 wounds)	Wound Closure	38%	<15% wound area reduction in 2 weeks prior to MIST	Mean 6.8 weeks	Not reported
			Wound Area Reduction	88% reduction		Mean 7.6 weeks	p<0.0001
		Wound Volume Reduction	100% reduction				p<0.0001
		Pressure, Venous, Arterial, Surgical, Traumatic, other	Pain VAS Measurement	2.9 reduction	NA		p<0.0001
III	A Retrospective Analysis of Acoustic Pressure Wound Therapy: Effects on the Healing Progression of Chronic Wounds  Haan J, Lucich S  J American College of Certified Wound Specialists 2009	N = 48 (50 wounds)	Wound Closure	24%	<15% wound area reduction in 2 weeks prior to MIST	Mean 4.2 weeks	Not reported
		Pressure, Venous, Arterial, Surgical, Traumatic, Neuropathic, other	Wound Area Reduction	92% reduction		Mean 5.5 weeks	p<0.0001
				Pain VAS Measurement	1.8 reduction	NA	
III	Noncontact Ultrasound Therapy for Adjunctive Treatment of Nonhealing Wounds: Retrospective Analysis  Bell AL, Cavorsi J  PT Journal 2008	N = 76	Wound Closure	18%	<15% reduction in 2 weeks prior to MIST	Median 3.6 weeks	Not reported
			Wound Area Reduction	79% reduction		Median 4.3 weeks	p<0.0001
		Pressure, Venous (28), Arterial, Surgical/Traumatic (25), other	Pain VAS Measurement	1.8 reduction	NA		p=0.001
III	The Effect of Noncontact, Low-Intensity, Low-Frequency Therapeutic Ultrasound on Lower-Extremity Chronic Wound Pain: A Retrospective Chart Review  Gehling ML, Samies JH  Ostomy Wound Management 2007	N = 15  Venous, Ischemia, Sickle cell	Pain VAS Measurement	80% reduction  (8.07±1.91 to 1.67±1.76) VAS	Baseline	2-4 weeks	p = 0.0003

\*Acoustic Pressure Wound Therapy = Noncontact Low Frequency Ultrasound = MIST Therapy  
VAS Measurement = Visual Analog Scale used to assess pain- 10 point numeric pain scale

## CLINICAL EVIDENCE LEVEL IV SUMMARY - PUBLISHED CASE SERIES AND REPORTS

Over 900 patients have been studied in peer reviewed case series/reports showing successful outcomes with MIST Therapy across all care settings.



These cases include patients with a wide variety of wound types including:

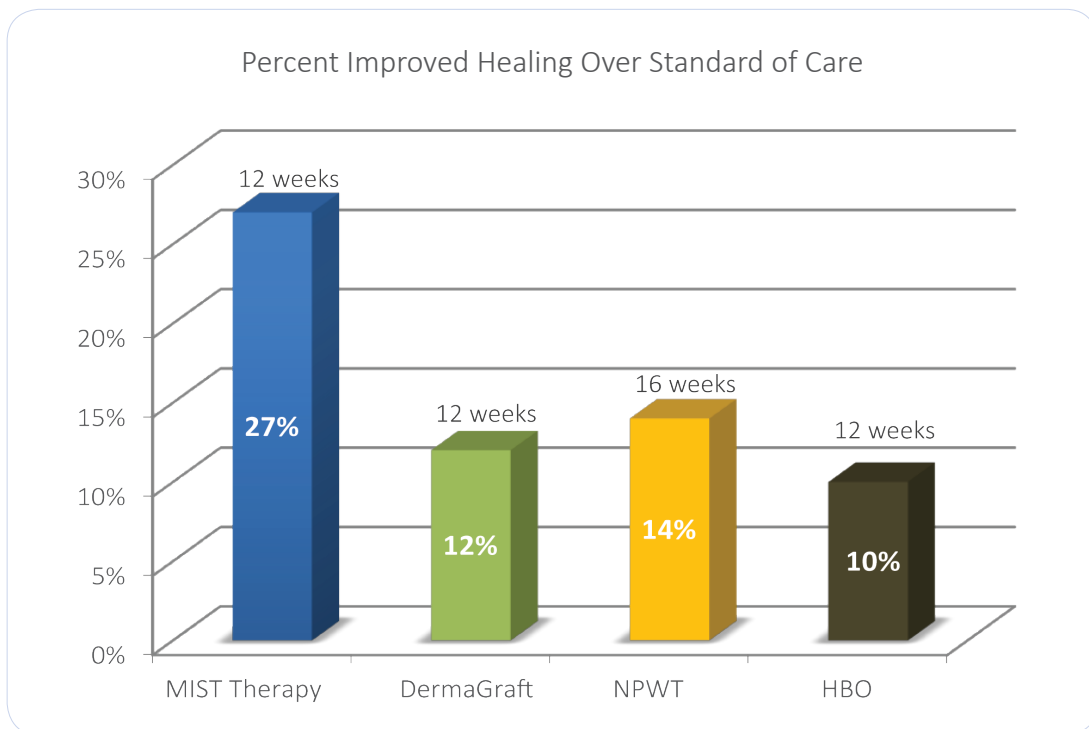
- Amputation Incisions
- Arterial Ulcers
- Burns
- Calciphylaxis
- Graft Preparation
- Deep Tissue Injuries
- Dehisced Wounds
- Diabetic Ulcers
- Donor Sites
- Exposed Tendons
- Fungal
- IV Infiltrates
- Medical Device Induced Wounds
- Necrotizing Fasciitis
- Perirectal Abscess
- Pilonidal Cysts
- Pressure Ulcers
- Pyoderma Gangrenosum
- Sickle Cell
- Surgical Wounds
- Traumatic Wounds
- Undermining/Tunnels
- Vascular Ulcers
- Wound Matrix Product

**As wound care specialists have gained a better understanding MIST Therapy's mechanism of action, the versatility of the system has allowed them to apply this technology to a number of challenging wound types.**

## MIST THERAPY COMPARED TO OTHER ADVANCED WOUND CARE TREATMENTS

It can be difficult to compare one advanced wound care treatment to another as very little comparative data exists today. In addition, many of the studies that exist have been completed in different patient populations with different wound types.

To evaluate how MIST Therapy compared to other advanced wound care treatments, we looked at randomized control trials in a single wound type- diabetic foot ulcers (all studies compared treatment arm to standard of care). To control for differences in patient populations, we evaluated the difference in healing rates between the treatment group and the control group.



	Weeks Treated	Treatment Group % healed	Control Group % healed	Difference	Study
<b>MIST Therapy</b>	<b>12</b>	<b>41.7%</b>	<b>14.3%</b>	<b>27.4%</b>	Ennis 2005, Celleration MIST Therapy (n=55)
DermaGraft	12	30%	18%	12%	Marston 2003, Smith and Nephew- Dermagraft (n=314)
NPWT	16	43%	29%	14%	Blume 2008, KCI- VAC (n=342)
HBO	12	12%	2%	10%	Londahl 2010, Independent Study (n=94)

**All of the advanced wound care treatments demonstrated faster healing rates in the same period of time when compared to the standard of care arm. However, MIST Therapy provided twice the benefit when compared to the other advanced wound care treatments.**

**From:** Hughes, Jeff <HUGH.HUGHES@integralife.com>  
**Sent:** Friday, March 11, 2016 11:27 AM  
**To:** HCA ST Health Tech Assessment Prog  
**Subject:** Evidence based criteria provided for policy review of Skin Substitutes submitted 3 11 2016  
**Attachments:** Washington State HCA Omnigraft support materials and FOUNDER Study.pdf;  
Washington State Health Care Authority Request .pdf

Dear Policy Review Team at Washington State Health Care Authority,

Thank you for allowing the comments as your team undertakes reviewing 6 technology topics. This evidence based requests falls within one of the six policies open for review, Skin Substitutes. Two pdf are attached for your review.

- 1) The request introduces you to Integra's Omnigraft. This January 7, 2016 PMA approved skin substitute is back by the FOUNDER study which is the largest single study in this category with 307 patients from 32 centers across the US.
- 2) The Support materials include the FOUNDER study, the FDA PMA approval and announcement and more.

This category is documented to have poor data, an expensive platform with many products requiring 5, 8 and even 10 applications. The Founder study on average, healed patients in 1.9 applications with 72 % of those healing, healing in one. We are optimistic that this type of study and information changes the paradigm of skin substitutes and that you find it worthy of payment in the State of Washington.

Best regards,

**Jeff Hughes**  
**Director of Reimbursement**  
Payer Access  
Integra LifeSciences Corporation  
OTT Division, Tissue Technology Business  
311 Enterprise Dr, Plainsboro, NJ 08536

262-225-1300 cell

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March 11, 2016

Washington State Health Care Authority

[shtap@hcs.wa.gov](mailto:shtap@hcs.wa.gov)

Provide Evidence Based Criteria for  
Request for Consideration and Addition to

**Skin substitutes:** Various skin substitute products are available for treatment of complex and/or non-healing wounds. The level of evidence available varies for different products, and the safety, efficacy and value of the products are uncertain. The reason for proposing this topic is to identify and review the available evidence to determine coverage for products that are demonstrated to be safe and effective for treatment of wounds.

Open for Comment thru March 11, 2016

Dear Washington State Health Care Authority Policy Review Committee,

I am writing on behalf of Integra LifeSciences to request a reconsideration of the above-referenced Medical Policy in order to expand coverage to include two Integra LifeSciences products, Integra<sup>®</sup> Dermal Regeneration Template (IDRT) and Integra<sup>®</sup> Omnigraft<sup>™</sup> Dermal Regeneration Matrix (Omnigraft<sup>™</sup>) which were recently approved by the FDA for the treatment of diabetic foot ulcers. I have enclosed with this letter both the communication Integra LifeSciences received from the FDA approving these products for the treatment of diabetic foot ulcers, and the clinical evidence that FDA considered in making this determination as supporting documentation for this request.

As you can see from these materials, FDA expanded the approved indications for the Integra LifeSciences' product, IDRT, which has been on the market since 1996 for the treatment of burns, based on the results of a large multi-center, randomized, controlled clinical trial. Because Integra LifeSciences will be also provide IDRT under the name Omnigraft<sup>™</sup>, we are asking that you add both of these products as covered under **Medically Necessary Skin Substitutes**.



## Specific Coverage Request

Integra LifeSciences requests that the **Skin Substitute policy** be revised to include coverage of IDRT and Omnigraft™ for the treatment of diabetic foot ulcers.

IDRT is an advanced, acellular, bilayer matrix specifically engineered for dermal regeneration. On the market since 1996, it is the only FDA-approved product indicated for the treatment of third degree burns and the reconstruction of scar contracture with a dermal regeneration claim.<sup>1</sup>

On January 7, 2016, FDA added an additional indication for use via PMA Supplement to IDRT based on the clinical results of a large multi-center, randomized, controlled clinical trial (the Foot Ulcer New Dermal Replacement Study (FOUNDER) Study). This study evaluated the safety and efficacy of IDRT for the treatment of non-healing chronic diabetic foot ulcers. The FDA indications for use now read as follows:

- Integra® Dermal Regeneration Template is indicated for: the postexcisional treatment of life-threatening full-thickness or deep partial-thickness thermal injuries where sufficient autograft is not available at the time of excision or not desirable due to the physiological condition of the patient; repair of scar contractures when other therapies have failed or when donor sites for repair are not sufficient or desirable due to the physiological condition of the patient; and treatment of partial and full-thickness neuropathic diabetic foot ulcers that are greater than six weeks in duration with no capsule, tendon or bone exposed, when used in conjunction with standard diabetic ulcer care.

Because Integra will also provide IDRT under a new product label, Omnigraft™, FDA approved this product with the following indication:

- Integra® Omnigraft™ Dermal Regeneration Matrix is indicated for use in the treatment of partial and full-thickness neuropathic diabetic foot ulcers that are greater than six weeks in duration, with no capsule, tendon or bone exposed, when used in conjunction with standard diabetic ulcer care.

### *The FOUNDER Study*

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<sup>1</sup> Integra Dermal Regeneration Template® is a skin replacement product originally approved by FDA in 1996 under a PMA supported by a controlled clinical trial and an extensive post-approval study. Based on these studies, it is indicated for the treatment of burns (FDA PMA #P900033) and the repair of scar contracture (FDA PMA #P900033S8).

The FOUNDER study provides the most significant published results on the use of skin substitutes to treat diabetic foot ulcers to date. The study is unmatched in the wound care area in terms of the strength of its study design, and the study results are both direct and conclusive. Per the description in the policy review announcement, *“Various skin substitute products are available for treatment of complex and/or non-healing wounds. The level of evidence available varies for different products, and the safety, efficacy and value of the products are uncertain. The reason for proposing this topic is to identify and review the available evidence to determine coverage for products that are demonstrated to be safe and effective for treatment of wounds.”*

It is our goal that the evidence, quality and outcomes of the FOUNDER study merit inclusion for payment in the State of Washington as efficacious to quickly close diabetic foot ulcers with less applications resulting in an economic win for the patients that you serve.

Key aspects of the FOUNDER study’s design include the following:

- *Large, Multi-Center RCT.* The FOUNDER study, published in the *Wound Healing and Tissue Regeneration* Journal, which served as the clinical basis for FDA approval, is the largest multi-center, randomized controlled clinical trial of its kind designed to evaluate the safety and effectiveness of a cellular and/or tissue-based product for the treatment of diabetic foot ulcers. It included **32 sites from across the United States**, and it involved **307 subjects** with Type II diabetes and at least one diabetic foot ulcer.
- *14-Day Run-In Period.* In contrast to some previous trials of diabetic foot ulcer treatments that had no run-in period or a run-in period of 7 days, eligible patients were first required to complete a 14-day run-in period during which time they were treated with the standard of care regimen. This ensured that the study **evaluated the most difficult to heal diabetic foot ulcers**.
- *Computerized Planimetry.* Third party computerized planimetry was used as an independent assessment method to confirm wound closure and wound size.
- *Generalizability.* Despite strict inclusion and exclusion criteria, any bias against generalizability was minimized by enrolling and randomizing subjects from 32 academic and private practice sites across the US to ensure that study participants represent patients with chronic diabetic foot ulcers from a heterogeneous population. Further, a full range of age groups were represented in the study, which would cover the Medicaid population.

**Key outcomes of the FOUNDER study include the following:**

- **Higher Relative Wound Closure.** Diabetic foot ulcers treated with IDRT/Omnigraft™ achieved a 125% relative improvement in closure compared to standard of care at 12 weeks
- **Faster Time to Healing.** Patients treated with IDRT/Omnigraft™ healed 5 weeks faster than patients in the control group who received standard of care.
- **Rapid Wound Closure Rate.** Patients who received IDRT/Omnigraft™ experienced a 50% faster wound size reduction compared to the control group.
- **Single Application.** Of the wounds that healed, 96% of those treated with IDRT, Omnigraft™ healed with three or less applications with 72% healing in one application. In contrast, studies of cell-based products and minimally processed human tissue allografts required an average of 4-6 applications. This factor alone stands out compared to the majority of products in this category that require 5, 8 and even 10 applications. (see AHRQ report 2012)
- **Improved Quality of Life.** Patients treated with IDRT/Omnigraft™ experienced a significant improvement in Physical Functioning and a decrease in Bodily Pain over standard of care (as defined by SF-36). This is the first skin substitute study to include quality of life.

We at Integra LifeSciences appreciate your timely review of this request and stand ready to provide additional information you might need to move forward. We hope that you find these materials sufficient to act favorably on our request to add IDRT and Omnigraft™ as covered for the treatment of diabetic foot ulcers in the State of Washington Skin Substitute policy.

Please contact either myself or Donna Cartwright directly if you have any questions concerning this request. We would be available to schedule a conference call or meeting with you to discuss this submission. Thank you for your consideration of this request.

Sincerely,

*H. J. Hughes*

Jeff Hughes  
Integra LifeSciences Corporation  
Reimbursement Services  
262-225-1300  
[Hugh.hughes@integralife.com](mailto:Hugh.hughes@integralife.com)

*Donna Cartwright*

Donna Cartwright  
Integra LifeSciences Corporation  
Reimbursement Services  
609-936-2265  
[Donna.Cartwright@integralife.com](mailto:Donna.Cartwright@integralife.com)

Attachment:

- Supporting Documents for IDRT and Omnigraft for DFUs
  - **Bookmark 1** - FDA Omnigraft Press Release
  - **Bookmark 2** - FDA PMA Approval Letter for Omnigraft
  - **Bookmark 3** - FDA Summary of Safety and Effectiveness Data
  - **Bookmark 4** - Omnigraft IFU/Package Insert
  - **Bookmark 5** - Published RCT for Integra Omnigraft Template for Diabetic Foot Ulcer Treatment **The FOUNDER Study**
  - **Bookmark 6** - Executive Summary of Diabetic Foot Ulcer Trial and Protocol
  - **Bookmark 7** - Bibliography

**U.S. Food and Drug Administration**  
Protecting and Promoting *Your* Health

## FDA News Release

# FDA approves Integra Omnigraft Dermal Regeneration Matrix to treat diabetic foot ulcers

## For Immediate Release

January 7, 2016

## Release

[Español \(/NewsEvents/Newsroom/ComunicadosdePrensa/ucm481258.htm\)](#)

The U.S. Food and Drug Administration today approved a new indication for the Integra Omnigraft Dermal Regeneration Matrix (Omnigraft) to treat certain diabetic foot ulcers. The matrix device, which is made of silicone, cow collagen, and shark cartilage, is placed over the ulcer and provides an environment for new skin and tissue to regenerate and heal the wound.

An estimated 29 million people in the United States have been diagnosed with diabetes, according to the Centers for Disease Control and Prevention, and about 25 percent of them will experience a foot ulcer during their lifetime. Chronic diabetic foot ulcers are associated with tissue and bone infections and result in 50,000 amputations each year.

“We are excited to see a new innovation in diabetes care with the potential to improve the number of foot ulcers that heal,” said William Maisel, M.D., M.P.H., acting director of the Office of Device Evaluation in the FDA’s Center for Devices and Radiological Health. “Healing of these painful and debilitating ulcers is essential for patients to resume walking and other daily activities.”

The FDA first approved Integra Dermal Regeneration Template (which the company now also calls Omnigraft) in 1996 for the treatment of life threatening burn injuries when the use of a patient’s own skin for a graft was not possible. In 2002, Integra Dermal Regeneration Template was approved for a new indication to treat patients undergoing reconstructive surgery for burn scars when they cannot have skin grafts. Now, Omnigraft is approved to treat certain diabetic foot ulcers that last for longer than six weeks and do not involve exposure of the joint capsule, tendon or bone, when used in conjunction with standard diabetic ulcer care.

Omnigraft's new indication is based on a clinical study that demonstrated that the matrix device improved ulcer healing compared to standard diabetic foot ulcer care, which includes cleaning and covering the wound with a surgical bandage and keeping weight off of the foot with the ulcer. In the study, 51 percent of patients treated with Omnigraft had healed ulcers after 16 weeks compared to 32 percent of patients treated with standard diabetic foot ulcer care alone.

Adverse events observed in the clinical trial included infections, increased pain, swelling, nausea, and new or worsening ulcers.

Omnigraft should not be used in patients with allergies to cow (bovine) collagen or chondroitin (cartilage from any source) since serious allergic reactions may occur. Omnigraft should also not be used on infected wounds.

Omnigraft is manufactured by Integra LifeSciences Corporation of Plainsboro, New Jersey.

The FDA, an agency within the U.S. Department of Health and Human Services, protects the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices. The agency also is responsible for the safety and security of our nation's food supply, cosmetics, dietary supplements, products that give off electronic radiation, and for regulating tobacco products.

###

#### Inquiries

#### Media

✉ [Eric Pahon \(mailto:eric.pahon@fda.hhs.gov\)](mailto:eric.pahon@fda.hhs.gov)

☎ 240-402-4177

#### Consumers

☎ 888-INFO-FDA

#### Related Information

- [FDA: Medical Devices \(/MedicalDevices/default.htm\)](/MedicalDevices/default.htm)
- [FDA: Diabetes Information \(/ForPatients/Illness/Diabetes/default.htm\)](/ForPatients/Illness/Diabetes/default.htm)

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Food and Drug Administration  
10903 New Hampshire Avenue  
Document Control Center – WO66-G609  
Silver Spring, MD 20993-0002

January 07, 2016

Integra LifeSciences Corporation  
Ms. Diana M. Bordon  
Director, Regulatory Affairs  
311Enterprise Drive  
Plainsboro, New Jersey 08536

Re: P900033/s042  
Integra Omnigraft Dermal Regeneration Matrix  
Integra Dermal Regeneration Template  
Filed: February 2, 2015  
Amended: April 3 and 17, October 2, and December 23, 2015  
Procode: MGR

Dear Ms. Bordon:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) supplement for the Integra Omnigraft Dermal Regeneration Matrix (a.k.a. Omnigraft) and Integra Dermal Regeneration Template. Integra Omnigraft Dermal Regeneration Matrix is indicated for use in the treatment of partial and full-thickness neuropathic diabetic foot ulcers that are greater than six weeks in duration, with no capsule, tendon or bone exposed, when used in conjunction with standard diabetic ulcer care and Integra Dermal Regeneration Template is indicated for the postexcisional treatment of life-threatening full-thickness or deep partial-thickness thermal injuries where sufficient autograft is not available at the time of excision or not desirable due to the physiological condition of the patient; repair of scar contractures when other therapies have failed or when donor sites for repair are not sufficient or desirable due to the physiological condition of the patient; and treatment of partial and full-thickness neuropathic diabetic foot ulcers that are greater than six weeks in duration with no capsule, tendon or bone exposed, when used in conjunction with standard diabetic ulcer care. We are pleased to inform you that the PMA supplement is approved. You may begin commercial distribution of the device as modified in accordance with the conditions of approval described below.

The sale and distribution of this device are restricted to prescription use in accordance with 21 CFR 801.109 and under section 515(d)(1)(B)(ii) of the Federal Food, Drug, and Cosmetic Act (the act). FDA has determined that this restriction on sale and distribution is necessary to provide reasonable assurance of the safety and effectiveness of the device. Your device is therefore a restricted device subject to the requirements in sections 502(q) and (r) of the act, in addition to the many other FDA requirements governing the manufacture, distribution, and marketing of devices.



Expiration dating for this device has been established and approved at 2 years at 36-86°F (2-30°C).

Continued approval of this PMA is contingent upon the submission of periodic reports, required under 21 CFR 814.84, at intervals of one year (unless otherwise specified) from the date of approval of the original PMA. Two copies of this report, identified as "Annual Report" and bearing the applicable PMA reference number, should be submitted to the address below. The Annual Report should indicate the beginning and ending date of the period covered by the report and should include the information required by 21 CFR 814.84. This is a reminder that as of September 24, 2014, class III devices are subject to certain provisions of the final UDI rule. These provisions include the requirement to provide a UDI on the device label and packages (21 CFR 801.20), format dates on the device label in accordance with 21 CFR 801.18, and submit data to the Global Unique Device Identification Database (GUDID) (21 CFR 830 Subpart E). Additionally, 21 CFR 814.84 (b)(4) requires PMA annual reports submitted after September 24, 2014, to identify each device identifier currently in use for the subject device, and the device identifiers for devices that have been discontinued since the previous periodic report. It is not necessary to identify any device identifier discontinued prior to December 23, 2013. For more information on these requirements, please see the UDI website, <http://www.fda.gov/udi>.

In addition to the above, and in order to provide continued reasonable assurance of the safety and effectiveness of the device, the Annual Report must include, separately for each model number (if applicable), the number of devices sold and distributed during the reporting period, including those distributed to distributors. The distribution data will serve as a denominator and provide necessary context for FDA to ascertain the frequency and prevalence of adverse events, as FDA evaluates the continued safety and effectiveness of the device.

Before making any change affecting the safety or effectiveness of the device, you must submit a PMA supplement or an alternate submission (30-day notice) in accordance with 21 CFR 814.39. All PMA supplements and alternate submissions (30-day notice) must comply with the applicable requirements in 21 CFR 814.39. For more information, please refer to the FDA guidance document entitled, "Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process" ([www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089274.htm](http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089274.htm)).

You are reminded that many FDA requirements govern the manufacture, distribution, and marketing of devices. For example, in accordance with the Medical Device Reporting (MDR) regulation, 21 CFR 803.50 and 21 CFR 803.52, you are required to report adverse events for this device. Manufacturers of medical devices, including in vitro diagnostic devices, are required to report to FDA no later than 30 calendar days after the day they receive or otherwise becomes aware of information, from any source, that reasonably suggests that one of their marketed devices:

1. May have caused or contributed to a death or serious injury; or
2. Has malfunctioned and such device or similar device marketed by the manufacturer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

Additional information on MDR, including how, when, and where to report, is available at [www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm](http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm).

In accordance with the recall requirements specified in 21 CFR 806.10, you are required to submit a written report to FDA of any correction or removal of this device initiated by you to: (1) reduce a risk to health posed by the device; or (2) remedy a violation of the act caused by the device which may present a risk to health, with certain exceptions specified in 21 CFR 806.10(a)(2). Additional information on recalls is available at [www.fda.gov/Safety/Recalls/IndustryGuidance/default.htm](http://www.fda.gov/Safety/Recalls/IndustryGuidance/default.htm).

CDRH does not evaluate information related to contract liability warranties. We remind you; however, that device labeling must be truthful and not misleading. CDRH will notify the public of its decision to approve your PMA by making available, among other information, a summary of the safety and effectiveness data upon which the approval is based. The information can be found on the FDA CDRH Internet HomePage located at [www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/PMAApprovals/default.htm](http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/PMAApprovals/default.htm). Written requests for this information can also be made to the Food and Drug Administration, Dockets Management Branch, (HFA-305), 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. The written request should include the PMA number or docket number. Within 30 days from the date that this information is placed on the Internet, any interested person may seek review of this decision by submitting a petition for review under section 515(g) of the act and requesting either a hearing or review by an independent advisory committee. FDA may, for good cause, extend this 30-day filing period.

Failure to comply with any post-approval requirement constitutes a ground for withdrawal of approval of a PMA. The introduction or delivery for introduction into interstate commerce of a device that is not in compliance with its conditions of approval is a violation of law.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form. Final printed labeling that is identical to the labeling approved in draft form will not routinely be reviewed by FDA staff when accompanied by a cover letter stating that the final printed labeling is identical to the labeling approved in draft form. If the final printed labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment.

All required documents should be submitted in six copies, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

U.S. Food and Drug Administration  
Center for Devices and Radiological Health  
PMA Document Control Center – WO66-G609  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002

If you have any questions concerning this approval order, please contact Charles N. Durfor, Ph.D. at (301) 796-6970.

Sincerely yours,

for Binita S. Ashar, M.D., M.B.A., F.A.C.S.  
Director  
Division of Surgical Devices  
Office of Device Evaluation  
Center for Devices and Radiological Health

## SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

### I. General Information

Device Generic Name: Interactive Wound Dressing

Device Trade Name: Integra Dermal Regeneration Template  
Integra Omnigraft Dermal Regeneration Matrix

Device Procode: MGR

Applicant: Integra LifeSciences Corporation  
311 Enterprise Drive  
Plainsboro, NJ 08536, USA

Date of Panel Recommendation: None

Premarket Approval Application Number: P900033/S042

Date of FDA Notice of Approval: January 7, 2016

Expedited: Not applicable

The original PMA (P900033), Integra Dermal Regeneration Template (Integra Template) was approved for postexcisional treatment of life-threatening full-thickness or deep partial-thickness thermal injuries where sufficient autograft is not available at the time of excision or not desirable due to the physiological condition of the patient. Subsequently Integra Template was approved for the repair of scar contractures when other therapies have failed or when donor sites for repair are not sufficient or desirable due to the physiological condition of the patient (P900033/S008). The SSEDs to support these Indications for Use are available on the CDRH website and are incorporated by reference. The purpose of this supplement, S042, is to add a new Indication for Use, i.e., the treatment of partial and full-thickness neuropathic diabetic foot ulcers that are greater than six weeks in duration, with no capsule, tendon or bone exposed, when used in conjunction with standard diabetic ulcer care. Integra Template will also be marketed as Integra Omnigraft Dermal Regeneration Matrix (Omnigraft), specifically for the indication in the treatment of partial and full-thickness neuropathic diabetic foot ulcers that are greater than six weeks in duration, with no capsule, tendon or bone exposed, when used in conjunction with standard diabetic ulcer care.

### II. INDICATION FOR USE

Integra<sup>®</sup> Omnigraft Dermal Regeneration Matrix is indicated for use in the treatment of partial and full-thickness neuropathic diabetic foot ulcers that are greater than six weeks in duration, with no capsule, tendon or bone exposed, when used in conjunction with

standard diabetic ulcer care.

Integra<sup>®</sup> Dermal Regeneration Template is indicated for the postexcisional treatment of life-threatening full-thickness or deep partial-thickness thermal injuries where sufficient autograft is not available at the time of excision or not desirable due to the physiological condition of the patient; repair of scar contractures when other therapies have failed or when donor sites for repair are not sufficient or desirable due to the physiological condition of the patient; and treatment of partial and full-thickness neuropathic diabetic foot ulcers that are greater than six weeks in duration with no capsule, tendon or bone exposed, when used in conjunction with standard diabetic ulcer care.

### **III. CONTRAINDICATIONS**

- This device should not be used in patients with known sensitivity to bovine collagen or chondroitin materials.
- Integra template should not be used on clinically diagnosed infected wounds.

### **IV. WARNINGS AND PRECAUTIONS**

The Warnings and Precautions can be found in the Integra Dermal Regeneration Template and Integra Omnigraft Dermal Regeneration Matrix labeling.

### **V. DEVICE DESCRIPTION**

Integra Template, available in meshed and non-meshed configurations, is an advanced bilayer matrix for dermal regeneration. The dermal replacement layer consists of a porous, three-dimensional matrix, comprised of bovine collagen and chondroitin-6-sulfate (C6S) that is designed with a controlled porosity and defined degradation rate. The temporary epidermal layer is made of a thin polysiloxane (silicone) layer to provide immediate wound coverage and control moisture loss from the wound.

Integra Template is provided sterile and non-pyrogenic. The inner foil pouch and product should be handled using sterile technique. Integra Template should not be re-sterilized.

### **VI. ALTERNATIVE PRACTICES AND PROCEDURES**

The current standard of care for partial and full-thickness neuropathic diabetic foot ulcers is sharp debridement, moist wound therapy with daily wound care dressings, offloading, and infection control. For diabetic foot ulcers that are non-responsive to conventional therapy, alternative practices include skin substitutes, cellular or tissue derived products, or surgical alternatives such as arterial bypass grafting where vascular supply is insufficient and skin grafts.

### **VII. MARKETING HISTORY**

Integra Template was first granted FDA Premarket Approval for use in life-threatening thermal injuries under PMA P900033 on March 1, 1996. On April 19, 2002, PMA

P900033 Supplement 008 was approved for an expanded indication for use (i.e., repair of scar contractures).

Integra Template was granted CE Mark approval in the European Union on March 20, 1998. The Integra product line is currently approved for marketing in the United States, European Union, Canada, Mexico, Argentina, Brazil, Colombia, Costa Rica, Peru, South Africa, Turkey, United Arab Emirates, Saudi Arabia, Israel, Egypt, Serbia, Jordan, Japan, New Zealand, Australia, and Singapore for use in partial and full thickness wounds and reconstructive surgery.

#### **VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH**

The safety of Integra Template for the treatment of partial and full-thickness neuropathic diabetic foot ulcers greater than six weeks in duration with no capsule, tendon or bone exposed, when used in conjunction with standard diabetic ulcer care was evaluated in a premarket clinical trial. Potential adverse events (e.g., complications) associated with the device and diabetic foot ulcer care, as reported in the clinical trial, include infection, worsening of ulcer, pain in extremity, cellulitis, osteomyelitis, edema peripheral, excoriation, upper respiratory tract infection, blister, influenza, pneumonia, vomiting, hypoglycemia, ingrown nail, urinary tract infection, erythema, cardiac failure congestive, pyrexia, diarrhea, hypertension, ulcer recurrence, local swelling, skin maceration, application site erosion, contusion, decubitus ulcer, nasopharyngitis, constipation, gastroesophageal reflux disease, diabetic neuropathy, dizziness, asthma, cough, dyspnea, sinusitis, chest pain, hypotension, renal failure, blood glucose decreased, blood pressure increased, anxiety, arthralgia, laceration, abscess limb, gastritis, balance disorder, drug hypersensitivity, nail avulsion, sepsis, gout, muscle spasms, musculoskeletal pain, skin fissures, headache, coronary artery disease, visual impairment, anemia, localized infection, gangrene, diabetic ketoacidosis, limb injury, cataract, hyperlipidemia, skin ulcer, paronychia, skin infection, soft tissue infection, hypoesthesia, pulmonary embolism, and skin papilloma .

For the specific adverse events that occurred in the clinical study, please see Section X below.

#### **IX. SUMMARY OF PRECLINICAL STUDIES**

The preclinical testing performed in the original P900033 application was adequate to support the safety and effectiveness of the device for the treatment of partial and full-thickness neuropathic diabetic foot ulcers greater than six weeks in duration with no capsule, tendon or bone exposed, when used in conjunction with standard diabetic ulcer care. No additional preclinical studies were submitted in this Panel Track Supplement.

#### **X. SUMMARY OF PRIMARY CLINICAL STUDY**

The sponsor, i.e., Integra LifeSciences Corporation performed a clinical study to establish a reasonable assurance of safety and effectiveness for Integra Template for the treatment of partial and full-thickness neuropathic diabetic foot ulcers greater than six weeks in

duration with no capsule, tendon or bone exposed and no tunneling undermining or sinus tracts, when used in conjunction with standard diabetic ulcer care.

#### **A. Study Design**

Patients were enrolled and treated between April 1, 2010 and June 5, 2014. The database for this PMA reflects data collected through June 10, 2014 and includes 307 subjects who were randomized and received either Integra Template or Control treatment. There were 32 investigational sites \.

The clinical study IDRT/DFU US 2009-3 was a prospective, multi-center open-label, randomized (stratification by ulcer size) concurrently controlled pivotal clinical trial of subjects with partial or full thickness diabetic foot ulcers located distal to the malleolus with controlled diabetes and without significant compromise of arterial circulation. Subjects who met the entry criteria were enrolled in the two week Pre-Treatment Phase and followed while they received standard of care treatment (e.g., wound debridement, moist wound therapy with 0.9% Sodium Chloride gel) for the study ulcer, and appropriate secondary dressings as well as nutritional support and offloading/protective devices.

The primary safety endpoint was the incidence of adverse events recorded during the 16 week Treatment Phase and three monthly visits of the Follow-up Phase. Evaluations also included serum chemistry measurement (i.e., serum creatinine, blood urea nitrogen (BUN), serum glucose, HbA1c, pre-albumin and CBC with differential) at Pre-Treatment and the end of the Treatment Phase.

The primary effectiveness endpoint was the percentage of subjects with complete closure of the study ulcer as assessed by the Investigator, during the Treatment Phase.

##### **1. Clinical Inclusion and Exclusion Criteria:**

Enrollment in IDRT/DFU US 2009-3 was limited to consented patients who met the following inclusion criteria: male or female of any race 18 years of age or older, females of childbearing potential with a negative urine pregnancy test result at baseline and practicing a reliable method of contraception throughout the study. All subjects were also required to have: Type I or Type II diabetes, HbA1c < 12%, a diabetic foot ulcer (DFU) that met all of the following criteria (i.e., full-thickness neuropathic DFU located distal to the malleolus (ankle) excluding ulcers between the toes, a minimum 2 cm margin between the qualifying ulcer and any other ulcer on the target foot, ulcer size  $\geq 1 \text{ cm}^2$  and  $\leq 12 \text{ cm}^2$ , Wagner grade 1 or 2, depth  $\leq 5 \text{ mm}$  with no capsule, tendon or bone exposed and no tunneling undermining or sinus tracts and baseline ulcer duration at least 30 days at screening visit). Subjects also needed to have the ability to maintain the required offloading and applicable dressing changes as well as adequate vascular perfusion as defined by one of the following: (ABI  $\geq 0.65$  and  $\leq 1.2$ , Toe pressure  $> 50 \text{ mm Hg}$ , TcpO<sub>2</sub>  $> 40 \text{ mm Hg}$  or Doppler ultrasound consistent with adequate blood flow).

Patients were not permitted to enroll in IDRT/DFU US 2009-3 if they met any of the following exclusion criteria: suspected or confirmed signs of gangrene or wound infection on any part of the affected limb (subjects with wound infection at the Screening visit could be treated and subsequently re-screened for participation in the study after eradication of infection), history of hypersensitivity to bovine collagen and/or chondroitin, pregnant at the time of treatment, previously treated under this clinical study protocol, participated in another clinical study involving a device or a systematically administered investigational study drug or treatment within 30 days of randomization, currently receiving (within 30 days of the randomization visit) or was scheduled to receive medication within 30 days which was known to interfere with or affect the rate and quality of wound healing (e.g., steroid, immunosuppressive therapy, autoimmune disease therapy, allergenic therapy, cytostatic therapy), any of the following unstable conditions or circumstances that could interfere with treatment regimen compliance: the ability to perform required dressing changes, ability to comply with the treatment visit schedule, mental incapacity or current substance abuse, excessive lymphedema which could interfere with wound healing, active Charcot foot or Charcot foot with bony prominence that could inhibit wound healing, ulcers secondary to a disease other than diabetes, osteomyelitis with necrotic soft bone (if the Investigator suspected the presence of osteomyelitis, the diagnosis required confirmation by plain film X-ray), Chopart amputation, a history of bone cancer or metastatic disease of the affected limb, radiation therapy to the foot, or chemotherapy within the 12 months prior to randomization, treatment with wound dressings that included growth factors, engineered tissues, or skin substitutes (e.g., Regranex, Dermagraft, Apligraf, GraftJacket, OASIS, PriMatrix, or Matristem) within 30 days of randomization or was scheduled to receive these during the study, treated with hyperbaric oxygen within 5 days of Screening or was scheduled to receive this therapy during the study, a non-study ulcer that required a treatment other than moist wound therapy (i.e., the Standard of Care identified under this study), a history of or any of the following intercurrent illnesses or conditions that could compromise the safety of the subject or the normal wound healing process: end stage renal disease, immunosuppression, severe malnutrition, liver disease, aplastic anemia, scleroderma, acquired immune deficiency disease (AIDS) or Human Immunodeficiency Virus (HIV) positive, connective tissue disorder or exacerbation of sickle cell anemia, an employee or relative or any member of the Investigational site or the Sponsor or at the end of the Run-in period, and prior to Randomization, any of the following conditions: did not continue to meet the entrance criteria (inclusion and exclusion) above, or the size of the study ulcer, following debridement, had decreased by more than 30% from the baseline assessment measured at Screening.

2. Follow-up Schedule

Prior to randomization, subjects entered a two week Screening/Run-in (Pre-Treatment) Phase during which subjects were treated with debridement and Standard of Care for diabetic foot ulcers. After the two-week Run-in period,



subjects whose ulcer size had decreased less than 30% and who continued to meet the eligibility criteria were randomized to either Active Treatment (Integra Template plus Standard of Care) or Control Treatment (Standard of Care) for the Treatment Phase of the study. During the Treatment Phase, subjects were treated and evaluated weekly for up to 16 weeks or until the study ulcer completely healed. Four weeks after either the study ulcer was confirmed completely healed or the final Treatment Visit (week 16), subjects entered the 12-week Follow-up Phase. During the Follow-up Phase, subjects attended monthly visits for safety and effectiveness outcomes, such as ulcer recurrence, adverse events and a Quality of Life Questionnaire.

### 3. Clinical Endpoints

The primary safety objective was to evaluate Integra Template safety through weekly assessments during the 16 week Treatment Phase and monthly visits during the three month Follow-up Phase. Evaluations included both monitoring for adverse events and changes in serum chemistry parameters (i.e., serum creatinine, blood urea nitrogen, serum glucose, HbA1c, pre-albumin and CBC with differential).

The primary effectiveness endpoint was the percentage of subjects with complete wound closure as assessed by the Investigator during the 16 week Treatment Phase. In the primary effectiveness analysis, the Last Observation Carried Forward principle was used for post-baseline time points with missing assessments. All subjects that discontinued before 100% wound closure during the Treatment Phase were not replaced and were considered treatment failures for the primary and secondary endpoint evaluations. Covariate analyses in the Intent-to-Treat population assessed the correlation of factors on ulcer healing and the robustness of the primary analysis, (i.e., baseline ulcer size, location and age, gender, baseline HbA1c, insulin use at baseline, diabetes type, race, smoking history, and baseline BMI).

The following additional effectiveness endpoints were evaluated during the Treatment Phase: 1) percentage of subjects with complete wound closure (assessed by computerized planimetry), 2) time to complete wound closure (assessed by the Investigator), 3) time to complete wound closure (assessed by computerized planimetry), 4) the rate of wound closure (assessed by computerized planimetry), 5) the incidence of study ulcer recurrence, determined during the Follow-up Phase, and 6) changes in the Quality of Life metrics, evaluated throughout the study.

## **B. Accountability of PMA Cohort**

As illustrated in Table 1, 545 subjects were screened and 307 subjects were randomized to treatment.

Table 1 – Subject Disposition

Event	Integra	Control
Subjects screened	545	
Subjects randomized	307	
Subjects not randomized	238 (44%)	
Randomized Subjects	154	153
Completing Treatment Phase	128 (83.1%)	117 (76.5%)
Withdrawn during Treatment	26	36
Completed Follow-up	106 (68.8%)	82 (53.6%)
Withdrawn during Follow-up	22	35

The reasons that 238 subjects were enrolled and screened, but not randomized to treatment were: 83/238 (35%) had an ulcer heal more than 30% during the run-in period, 43/238 (18%) had ulcers that did not meet the size criteria, 31/238 (13%) had HbA1c greater than 12%, 21/238 (9%) had other reasons, 19/238 (8%) had an ongoing infection, 14/238 (6%) were non-compliant, 10/238 (4%) had a history of intercurrent illness/condition, 7/238 (3%) had osteomyelitis, 5/238 (2%) had an ulcer depth greater than 5mm, and 5/238 (2%) withdrew consent.

At the conclusion of the Treatment Phase of the trial, 128/154 (83.1%) of the Integra and 117/153 (76.5%) of the Control subjects remained on study. At the conclusion of the Treatment and Follow-Up Phases of the study, 106/154 (68.8%) Integra and 82/153 (53.6%) Control subjects completed the trial. The ramifications of the loss of 48/154 (31.2%) of the Integra and 71/153 (46.4%) of the Control subjects (or a total of 119/307 (38.8%) of the study participants is discussed below in the Other Analyses Section.

### C. Study Population Demographics and Baseline Parameters

The baseline demographics in the Integra and Control arms were comparable for all parameters including, but not limited to, severity and type of diabetes, gender, race, age, and ulcer size area (Table 2).

Table 2 – ITT Baseline Population Demographics and Baseline Characteristics

Characteristic	Statistic	Integra (N = 154)	Control (N = 153)	Total (N = 307)
Age (years)	Mean (SD)	55.8 (10.6)	57.3 (9.7)	56.5 (10.1)
	Median	56.0	57.0	57.0
	Min, Max	31.0, 82.0	28.0, 82.0	28.0, 82.0
Gender	Male, n (n/N%)	118 (76.6)	114 (74.5)	232 (75.6)
	Female, n (n/N%)	36 (23.4)	39 (25.5)	75 (24.4)
Race	American Indian/Alaskan Native, n (n/N%)	0 (0.0)	2 (1.3)	2 (0.6)
	Asian, n (n/N%)	1 (0.6)	2 (1.3)	3 (1.0)
	Black Or African American, n (n/N%)	28 (18.2)	34 (22.1)	62 (20.1)

	Native Hawaiian or Pacific Islander, n (n/N%)	1 (0.6)	0 (0.0)	1 (0.3)
	Caucasian, n (n/N%)	118 (76.6)	111 (72.1)	229 (74.4)
	Other, n (n/N%)	6 (3.9)	5 (3.2)	11 (3.6)
Ethnicity	Not Hispanic/Latino, n (n/N%)	108 (70.1)	116 (75.8)	224 (73.0)
	Hispanic or Latino, n (n/N%)	46 (29.9)	37 (24.2)	83 (27.0)
Weight (kg)	Mean (SD)	107 (23.3)	107 (28.9)	107 (26.2)
	Median	105	103	104
	Min, Max	63.5, 178	52.2, 221	52.2, 221
Height (cm)	Mean (SD)	178 (9.4)	177 (12.2)	177 (10.9)
	Median	178	180	178
	Min, Max	154, 196	132, 203	132, 203
BMI (kg/m <sup>2</sup> )	Mean (SD)	34.0 (7.2)	34.1 (8.4)	34.0 (7.8)
	Median	33.8	32.1	33.0
	Min, Max	21.4, 58.9	19.9, 62.4	19.9, 62.4
Tobacco Product Use	Yes, n (n/N%)	28 (18.2)	19 (12.4)	47 (15.3)
	No, n (n/N%)	126 (81.8)	134 (87.6)	260 (84.7)
Diabetes Mellitus Type	Type 1, n (n/N%)	4 (2.6)	13 (8.5)	17 (5.5)
	Type 2, n (n/N%)	150 (97.4)	140 (91.5)	290 (94.5)
Use Of Insulin at Baseline	Yes, n (n/N%)	30 (19.5)	37 (24.2)	67 (21.8)
	No, n (n/N%)	124 (80.5)	116 (75.8)	240 (78.2)
Age Of Study Ulcer (Days)	n	154	153	307
	Mean (SD)	308 (491)	303 (418)	305 (455)
	Median	126	152	140
	Min, Max	31.0, 4501	32.0, 2059	31.0, 4501
% Reduction in Ulcer Area Size Between Screening & First Treatment Application	Mean (SD)	-14 (38.0)	-17 (65.9)	-16 (53.7)
	Median	-3.4	-1.6	-2.0
	Min, Max	-228, 29.2	-565, 28.6	-565, 29.2
Baseline Study Ulcer Size (cm <sup>2</sup> )	Mean (SD)	3.53 (2.5)	3.65 (2.6)	3.59 (2.6)
	Median	2.6	2.6	2.6
	Min, Max	1.0, 11.5	1.0, 10.8	1.0, 11.5
Location of Study Ulcer	Plantar, n (n/N %)	126 (81.8)	127 (83.0)	253 (82.4)
	Dorsal, n (n/N %)	28 (18.1)	25 (16.3)	53 (17.3)
	Medial, n (n/N %)	0	1 (0.7)	1 (0.3)
Wagner Grade	Grade 1, n (n/N %)	45 (29.2)	37 (24.2)	82 (26.7)
	Grade 2, n (n/N %)	109 (70.8)	116 (75.8)	225 (73.3)

*Number of Integra Template Applications* – The median number of Integra Template applications was one (i.e., 92/154 (59.7%) subjects required a single Integra Template application). Table 3 provides a summary of the number of subjects and the number

of Integra Template applications required. Reapplications were at the discretion of the investigator. The most common reasons for reapplications were non-adherence with fluid accumulation and infection.

Table 3 – Summary of Subjects with Applications of Integra Template

No. of Applications	No. Integra Subjects N = 154 n (n/N %)
1	92 (59.7)
2	33 (21.4)
3	12 (7.8)
4	5 (3.2)
5	5 (3.2)
6	2 (1.3)
7	2 (1.3)
11	2 (1.3)
15	1 (0.6)

*Offloading of the Study Ulcer* – DFU offloading is a well-recognized method of promoting wound closure. Subject compliance in ulcer offloading was assessed via subject diary review and subject interviews. In this analysis, high levels of overall subject offloading compliance were observed for both Integra (i.e., mean = 21.6 hours/day) and Control subjects (i.e., mean = 20.9 hours / day). Given the limited number of subjects with low offloading compliance (i.e., 8/154 Integra and 11/153 Control subjects offloaded 0-14 hours / day), no significant correlation could be made between offloading compliance with incidence of healing, time to wound healing, and subject discontinuation.

#### D. Safety and Effectiveness Results

##### 1. Safety Results

All Adverse Events (AEs) – 101/154 (65.6%) of Integra and 115/153 (75.2%) of Control subjects reported an AE. A total of 798 AEs were reported, with 444/798 (55.6%) AEs in Control subjects and 354/798 (44.4%) AEs in Integra subjects.

All AEs that were reported in the study at an incidence of greater than or equal to 1% in either cohort are presented in Table 4. This table reflects AEs that were both attributed and not attributed to treatment. They are also listed in descending order according to their frequency in the Integra cohort. There were no unanticipated AEs in the trial.

Table 4 – Adverse Events (Reported in  $\geq 1\%$  of Subjects) by MEDRA Preferred Term

Adverse event (Preferred Term)	Integra N = 154 Subjects n (n/N%)	Control N = 153 subjects n (n/N%)
Diabetic foot infection	23 (14.9)	23 (15.0)
Diabetic foot	22 (14.3)	31 (20.3)

Pain in extremity	14 (9.1)	20 (13.1)
Cellulitis	13 (8.4)	13 (8.5)
Osteomyelitis	9 (5.8)	19 (12.4)
Edema peripheral	7 (4.5)	7 (4.6)
Nausea	7 (4.5)	3 (2.0)
Condition aggravated	6 (3.9)	14 (9.2)
Excoriation	6 (3.9)	7 (4.6)
Upper respiratory tract infection	6 (3.9)	6 (3.9)
Blister	6 (3.9)	6 (3.9)
Influenza	5 (3.2)	3 (2.0)
Wound	4 (2.6)	6 (3.9)
Pneumonia	4 (2.6)	3 (2.0)
Vomiting	4 (2.6)	2 (1.3)
Hypoglycemia	4 (2.6)	1 (0.7)
Ingrowing nail	4 (2.6)	1 (0.7)
Urinary tract infection	3 (1.9)	6 (3.9)
Erythema	3 (1.9)	4 (2.6)
Cardiac failure congestive	3 (1.9)	4 (2.6)
Pyrexia	3 (1.9)	3 (2.0)
Application site pain	3 (1.9)	2 (1.3)
Diarrhea	3 (1.9)	2 (1.3)
Hypertension	3 (1.9)	2 (1.3)
Disease recurrence	3 (1.9)	1 (0.7)
Local swelling	3 (1.9)	1 (0.7)
Skin maceration	3 (1.9)	1 (0.7)
Application site erosion	3 (1.9)	0
Contusion	3 (1.9)	0
Decubitus ulcer	2 (1.3)	4 (2.6)
Nasopharyngitis	2 (1.3)	2 (1.3)
Constipation	2 (1.3)	2 (1.3)
Gastroesophageal reflux disease	2 (1.3)	2 (1.3)
Diabetic neuropathy	2 (1.3)	2 (1.3)
Dizziness	2 (1.3)	2 (1.3)
Asthma	2 (1.3)	2 (1.3)
Cough	2 (1.3)	2 (1.3)
Dyspnea	2 (1.3)	2 (1.3)
Pain	2 (1.3)	2 (1.3)
Sinusitis	2 (1.3)	1 (0.7)
Chest pain	2 (1.3)	1 (0.7)
Hypotension	2 (1.3)	0
Renal failure	2 (1.3)	0
Blood glucose decreased	2 (1.3)	0
Blood pressure increased	2 (1.3)	0
Anxiety	2 (1.3)	0
Arthralgia	1 (0.6)	6 (3.9)
Laceration	1 (0.6)	5 (3.3)
Abscess limb	1 (0.6)	4 (2.6)
Gastritis	1 (0.6)	3 (2.0)
Balance disorder	1 (0.6)	3 (2.0)
Drug hypersensitivity	1 (0.6)	3 (2.0)
Nail avulsion	1 (0.6)	2 (1.3)
Sepsis	1 (0.6)	2 (1.3)

Gout	1 (0.6)	2 (1.3)
Muscle spasms	1 (0.6)	2 (1.3)
Musculoskeletal pain	1 (0.6)	2 (1.3)
Skin fissures	1 (0.6)	2 (1.3)
Headache	1 (0.6)	2 (1.3)
Coronary artery disease	1 (0.6)	2 (1.3)
Visual impairment	1 (0.6)	2 (1.3)
Anemia	1 (0.6)	2 (1.3)
Localized infection	0	4 (2.6)
Gangrene	0	3 (2.0)
Diabetes mellitus	0	3 (2.0)
Diabetic ketoacidosis	0	3 (2.0)
Limb injury	0	3 (2.0)
Cataract	0	3 (2.0)
Hyperlipidemia	0	2 (1.3)
Skin ulcer	0	2 (1.3)
Paronychia	0	2 (1.3)
Skin infection	0	2 (1.3)
Soft tissue infection	0	2 (1.3)
Hypoesthesia	0	2 (1.3)
Pulmonary embolism	0	2 (1.3)
Skin papilloma	0	2 (1.3)

*Serious Adverse Events (SAEs)* – 38/154 (24.7%) of the Integra and 55/153 (35.9%) of the Control subjects reported a SAE. The incidence of serious infections and infestations was 27/154 (17.5%) in the Integra and 40/153 (26.1%) in the Control cohorts. Osteomyelitis was the most common SAE infection (i.e., 8/154 (5.2%) of the Integra and 15/153 (9.8%) of the Control subjects).

*Adverse Events potentially related to treatment (TRAE)* - occurred in 7/154 (4.5%) of the Integra and 8/153 (5.2%) of the Control subjects. In the Integra group, the 11 TRAE incidences were: diabetic foot infections (3.2%; 5/154), application site cellulitis (0.6%; 1/154), cellulitis (0.6%; 1/154), infected skin ulcer (0.6%; 1/154), sepsis (0.6%; 1/154), application site erythema (0.6%; 1/154), and excoriation (0.6%; 1/154). Four incidences, occurring in two subjects, were also Serious Adverse Events (i.e., sepsis, diabetic foot infection, cellulitis, and infected skin ulcer). These serious, potentially related AEs resulted in the two Integra subjects being withdrawn from the clinical trial. In the Control group, the 17 TRAEs were: application site odor (0.7%; 1/153), arthralgia (0.7%; 1/153), condition aggravated (1.3%; 2/153), dermatitis atopic (0.7%; 1/153), diabetic foot (1.3%; 2/153), laceration (0.7%; 1/153), neuropathic arthropathy (0.7%; 1/153), edema peripheral (0.7%; 1/153), osteomyelitis (0.7%; 1/153), pain in extremity (0.7%; 1/153), skin papilloma (0.7%; 1/153), urinary tract infection (0.7%; 1/153), and wound (0.7%; 1/153). None of the 17 potentially related AEs in the Control group were considered Serious Adverse Events; however, one subject in the Control group was withdrawn from the clinical trial due to a potentially related adverse event (i.e. osteomyelitis). All other Integra and Control subjects who

withdrew from the clinical trial due to AEs had events that were judged unlikely or not related to the study treatment.

*Patient Death* – Four Control subjects and zero Integra subjects died during the study. All deaths were judged unrelated to the Study Treatment.

*Chemical Labs* – Serum Chemistry Values for all Subjects (i.e., range, mean and median values) were comparable between the two treatment groups at both baseline and the end of treatment. None of the subjects in this trial had the treatment discontinued or the trial terminated due to laboratory abnormalities. Changes in the serum chemistry that were deemed clinically significant by the Investigators were reported as adverse events. One Integra and one Control subject experienced SAEs reported as hypoglycemia. None of these events were judged related to the Study Treatment.

## 2. Effectiveness results

### **Primary Effectiveness Endpoint**

The primary effectiveness endpoint was complete closure of the study ulcer, as assessed by the investigator, during the 16-week Treatment Phase. 79/154 (51.3%) of the Integra and 49/153 (32.0%) of the Control subjects achieved 100% complete closure of the study ulcer. This 19.3% treatment difference was statistically significant (p-value = 0.0007).

### **Secondary Effectiveness Outcomes**

*Complete Wound Closure – Computerized Planimetry* – During the Treatment Phase, 77/154 (50.0%) of the Integra and 48/153 (31.4%) of the Control subjects achieved 100% complete wound closure as assessed by Computerized Planimetry. The treatment difference of 18.6% was statistically significant (p=0.0010) and a strong agreement with the Primary Effectiveness endpoint was observed.

*Time to Complete Wound Closure – Investigator’s Assessment* – The Kaplan-Meier results for the Investigator Assessment of time to complete wound closure demonstrated that: 1) approximately 50% of the IDRT subjects achieved complete wound closure by day 85, whereas only 32% of the Control subjects achieved complete wound closure at the end of the Treatment Phase (Day 112); 2) a 49 day difference existed in the time needed to achieve complete healing for 25% of all subjects (i.e., 43 days for IDRT and 92 days for Control subjects); and 3) the median time to complete wound closure for Integra subjects (43 days) was 35 days shorter than Control subjects (78 days).

*Time to Complete Wound Closure – Computerized Planimetry* – Results similar to the Investigator Assessment of time to complete wound closure were observed,

i.e., 1) 99 days were required for approximately 50% of the IDRT subjects to achieve complete wound closure; 2) a 49 day difference existed in the time needed to achieve complete healing in 25% of all subjects (i.e., 43 days for IDRT and 92 days for Control subjects ); and 3) the median time to complete wound closure for Integra subjects (43 days) was 35 days shorter than Control subjects (78 days).

*Rate of Wound Size Reduction* – The rate of wound healing (% healed/week) or rate of wound size reduction was measured via planimetric assessment (during the Treatment Phase) and calculated with the following formula:

$$\text{Rate (\% healed/week)} = \frac{7 * [(\text{Baseline wound size}) - (\text{Post-baseline wound size})]}{[(\text{Baseline wound size}) * (\text{days in clinical trial})]}$$

The average wound size at baseline was 3.53 cm<sup>2</sup> for Integra and 3.65 cm<sup>2</sup> for Control subjects. The rate of wound size reduction observed at the end of the Treatment Phase for Integra and Control subjects was 7.15% healed/week and 4.81% healed/week, respectively (p=0.0115).

*Incidence of Ulcer Recurrence* – 15/79 (19.0%) of the healed Integra and 13/49 (26.5%) of the healed Control subjects experienced ulcer recurrence during the study. The difference was not statistically significant.

*Change in Baseline Quality of Life Metrics at the End of Treatment* – Integra subjects showed significant improvements in: 1) the Physical Functioning for daily activities of walking, climbing stairs, bending, bathing, carrying groceries, and moderate to vigorous activities and 2) the Reduction in the Bodily Pain (and/or limitations of normal work activities due to pain) Modules of the Quality of Life Questionnaire SF-36v2 Health Survey, compared to Control subjects. No significant differences between treatment groups were observed for the other Modules in the Quality of Life Questionnaire SF-36v2 Health Survey (i.e., General Health, Social Functioning, Role Emotional, Mental Health or Vitality).

### 3. Subgroup Analyses

*Covariate Analyses* – Two factors in the ITT Population, i.e., baseline wound size (p = 0.0009) and study ulcer age (p = 0.0014), were significant contributing factors to ulcer healing. Diabetes Mellitus Type, baseline HbA1c, race, baseline BMI, wound location (left or right foot), tobacco use, age, ethnicity, Wagner Grade, ulcer location (plantar/dorsal/medial), insulin use, or gender were not significant factors to wound healing. All analysis models for the primary and secondary endpoints were adjusted for the baseline wound size and the baseline age of ulcer.



*Fenestrated vs. Non-Fenestrated Integra Template* – Fenestrating and meshing (at a 1:1 ratio) of Integra Template was permitted (at the discretion of the investigator) to allow for drainage in the presence of exudate or hematoma. Based on CRF review: 1) no subjects received meshed Integra Template, 2) 122 subjects had fenestrated Integra Template applied at one or more visits, 3) 33 subjects received neither meshed nor fenestrated Integra Template, 4) one subject had both fenestrated and non-cut Integra Template at different visits and is counted in both subgroups, 5) 65/122 (53.28%) of the subjects receiving fenestrated Integra Template achieved complete wound closure, 6) 14/33 (42.42%) of the subjects receiving non-fenestrated Integra Template achieved wound closure, and 7) 32.03% of the Control group achieved wound closure.

*Poolability of Sites* – Site poolability was assessed prior to pooling the data from the different investigational sites. The results of this analysis demonstrated that the effect of site was not statistically significant and the overall results for complete wound closure were not site-dependent.

*Subject Withdrawal from the Study* – The reasons for subject withdrawal/discontinuation from the Treatment, and Study (i.e., Treatment + Follow-up Phases) are presented in Tables 5 and 6, respectively.

Table 5 – Reasons for Subject Withdrawal from Treatment Phase

Premature Termination Reason	<b>Integra</b> N = 154 n (n/N %)	<b>Control</b> N = 153 n (n/N %)	<b>Total</b> N = 307 n (n/N %)
Adverse Event	13 (8.4%)	16 (10.5%)	29 (9.4%)
Investigator’s decision	8 (5.2%)	8 (5.2%)	16 (5.2%)
Subject withdrew consent	1 (0.6%)	6 (3.9%)	7 (2.3%)
Protocol violation	2 (1.3%)	2 (1.3%)	4 (1.3%)
Lost-to-follow-up	1 (0.6%)	2 (1.3%)	3 (1.0%)
Other	1 (0.6%)	2 (1.3%)	3 (1.0%)
<b>Total</b>	<b>26 (16.9%)</b>	<b>36 (23.5%)</b>	<b>62 (20.2%)</b>

Table 6 – Reasons for Subject Withdrawal from Study (Treatment + Follow-up Phases)

Premature Termination Reason	<b>Integra</b> N = 154 n (n/N %)	<b>Control</b> N = 153 n (n/N %)	<b>Total</b> N = 307 n (n/N %)
Adverse Event	13 (8.4%)	25 (16.3%)	38 (12.4%)
Investigator’s decision	14 (9.1%)	16 (10.5%)	30 (9.8%)
Lost-to-follow-up	9 (5.8%)	11 (7.2%)	20 (6.5%)
Other	6 (3.9%)	7 (4.6%)	13 (4.2%)
Subject withdrew	3 (1.9%)	9 (5.9%)	12 (3.9%)

consent			
Protocol violation	3 (1.9%)	3 (2.0%)	6 (2.0%)
Total	48 (31.2%)	71 (46.4%)	119 (38.8%)

The impact of subject withdrawals on the validity of the clinical study was analyzed as discussed below.

*Demographics of the Withdrawn Population* were compared and no evidence of selection bias in subject withdrawal was observed. These analyses included comparisons of the following factors for Integra and Control cohorts who withdrew during the Treatment Phase: 1) baseline study ulcer size, 2) the mean wound size reduction during the two week Run-In period, 3) the proportion of plantar to dorsal wounds and 4) baseline ulcer severity (i.e., ratio of Grade 1 to Grade 2 ulcers). The average baseline ulcer duration of Control subjects who withdrew during the Treatment Phase was longer than Integra subjects (i.e., a mean value of 254 days for Integra and 368 days for Control subjects).

Based on the computerized planimetry assessment prior to subject withdrawal during the treatment phase, a majority of withdrawals were due to the lack of treatment effectiveness in both groups, and the observed higher percentage of withdrawal in the control group appeared to be a reflection of the inferior performance of the Control treatment as compared to the Integra treatment. Also, no significant association between the treatment groups and subject discontinuation was observed for: 1) subjects with a history of lower extremity amputation and discontinuation during the Treatment Phase, 2) subjects with a history of cellulitis and discontinuation during the Treatment Phase, 3) subjects without a history of lower extremity infection and discontinuation during the Treatment Phase, 4) subjects with an additional ulcer at study entry and discontinuation during the Treatment Phase, 5) subjects with a prior history of foot surgery and discontinuation during the Treatment Phase, 6) the time that a subject remained on study prior to withdrawal, 7) the number of subjects who withdrew from the study during the Treatment Phase and experienced at least one major protocol deviation, 8) the amount of daily offloading or 9) the frequency of AEs and SAEs in both treatment cohorts. Therefore, the loss of these subjects did not significantly alter the evaluation of device safety or effectiveness.

#### **E. Financial Disclosure**

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 35 Principal Investigators and 80 Sub-Investigators at sites that randomized subjects. None of the Principal or Sub Investigators had disclosable

financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

**XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION**

- **Relevant Post Market Experience**

Since March 01, 1996, Integra Template has been sold for the treatment of life-threatening full-thickness or deep partial-thickness thermal injuries, and since April 19, 2002 Integra Template has also been sold for the repair of scar contractures. Integra Bilayer Matrix Wound Dressing (which has the same composition as Integra Template) was cleared on August 14, 2002 for the management of partial and full thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, surgical wounds (donor sites / grafts, post-Moh’s surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree burns, and skin tears) and draining wounds. Integra Wound Matrix Dressing (which contains the same dermal layer, but not the silicone layer of Integra Template), was cleared on September 10, 2002 for the same indications as the Integra Bilayer Matrix Wound Dressing. Integra Wound Matrix (Thin) (which has the same, but thinner composition as Integra Wound Matrix Dressing) was cleared on February 9, 2012 for management of wounds including: partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (donor sites/grafts, post-Moh's surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree bums, skin tears) and draining wounds.

Since 1996, 111 clinical Medical Device Reports (MDRs) were submitted to the sponsor, and these are summarized in Table 7.

Table 7 – Summary of Clinical MDRs of Integra Product Family Since 1996

<b>MDR Category</b>	<b>Total MDRs</b>
Infection	60
Poor Take/Dislodgment	18
Allergic Reaction	6
Autograft Lost	4
Wound Dehiscence	4
Regeneration of Granulous Skin	3
Death*	3
No Autograft Take	3
Non healing Wound	2
Matrix Calcification	2
Septic Shock	1
Hematoma	1
Fever	1
Hypertrophic Scarring	1
Bulging of Graft	1
Factor 5 Deficiency**	1
<b>Total</b>	<b>111</b>

\* The three deaths that Integra filed as MDRs were deemed by the physicians who reported the complaints to be unrelated to the Integra template.

\*\* Integra investigators determined that Factor 5 Deficiency could not have been caused by the Integra product. The complaint was filed because a physician thought that the product could have caused the deficiency based on his research that bovine thrombin has been known to cause the deficiency. However, Integra products do not contain bovine thrombin.

## **XII. PANEL RECOMMENDATIONS**

Pursuant to section 515(c)(2) of the Food, Drug and Cosmetic Act (the Act) as amended by the Safe Medical Devices Act of 1990, this PMA supplement was not referred to the General and Plastic Surgery Panel and FDA advisory panel for review and recommendation. This is because the information in this PMA supplement substantially duplicates information previously reviewed by this panel.

## **XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES**

### **A. Effectiveness Conclusions**

Assessment of product effectiveness is based on the results of Pivotal Clinical Trial IDRT/DFU US 2009-3. The submitted data provided a reasonable assurance that the device is effective for the treatment of partial and full-thickness neuropathic diabetic foot ulcers that are greater than six weeks in duration, with no capsule, tendon or bone exposed, when used in conjunction with standard diabetic ulcer care. The specific conclusions are:

- The study met the pre-specified primary effectiveness criterion of complete study ulcer closure, (as assessed by the investigator during the 16-week treatment period). 79/154 (51.3%) of the Integra and 49/153 (32.0%) of the Control subjects achieved complete wound closure. This 19.3% treatment difference was statistically significant (p-value = 0.0007). 245/307 (79.8%) of the subjects were evaluated for this primary effectiveness endpoint.
- The study met the following pre-specified secondary effectiveness endpoints. Specifically, Integra Template was statistically superior in the: 1) percentage of subjects with complete study ulcer closure, as assessed by computerized planimetry, (i.e., 77/154 (50.0%) of the Integra vs 48/153 (31.4%);) of the Control subjects, p=0.0010); 2) the time to complete wound closure as assessed by the Investigator (i.e., the median time to complete wound closure for Integra subjects (43 days) was 35 days shorter than Control subjects (78 days); 3) the time to complete wound closure as assessed by computerized planimetry; (i.e., the same results were observed by computerized planimetry and Investigator assessment); and 4) the wound closure rate as assessed by computerized planimetry (i.e., the average rate of wound size reduction was 7.15% (Integra) and 4.81% (Control) healed/week), p=0.0115.

- The incidence of ulcer recurrence, although not statistically significant, was less in the healed Integra Template cohort 15/79 (19.0%) than the healed Control subject cohort 13/49 (26.5%).
- Omnigraft subjects showed improvement in the Physical Functioning for Daily Activities and Reduction in the Bodily Pain modules of the Quality of Life Questionnaire SF-36v2 Health Survey questionnaire. No significant differences between treatment groups were observed for General Health, Social Functioning, Role Emotional, Mental Health or Vitality Modules of this questionnaire.
- Review of baseline demographics and wound conditions, indicated that the two cohorts were well balanced. With the exception of baseline ulcer size and baseline ulcer age, no other study covariate (i.e., Diabetes Mellitus Type, baseline HbA1c, race, baseline BMI, wound location (left or right foot), tobacco use, patient age (continuous), patient age (cutoff 65 years), ethnicity, Wagner Grade, Insulin use, gender, and ulcer location (plantar/dorsal/medial) influenced the clinical effectiveness outcomes measured. This observation is consistent with previous clinical studies of diabetic neuropathic foot ulcers.

## **B. Safety Conclusions**

The adverse effects of the device are based on data collected in the Pivotal Study IDRT/DFU US 2009-3 to support PMA approval, as described above, as well as an evaluation of the Post Market Surveillance reports. The submitted data provided a reasonable assurance that the device is safe for the treatment of partial and full-thickness neuropathic diabetic foot ulcers that are greater than six weeks in duration, with no capsule, tendon or bone exposed, when used in conjunction with standard diabetic ulcer care. The specific conclusions are:

- Safety assessments included clinical visits during the two week Pre-Treatment Phase, weekly assessments during the 16 week Treatment Phase, and monthly assessments during the three month Follow-up Phase. Serum chemistry parameters were also determined at baseline and the end of the Treatment Phase.
- 101/154 (65.6%) of the Integra and 115/153 (75.2%) of the Control subjects reported an adverse event (AE). Of the total 798 AEs reported in the study, 354/798 (44.4%) occurred in Integra and 444/798 (55.6%) occurred in Control subjects. Integra subjects experienced fewer AEs than Control subjects.
- 38/154 (24.7%) of the Integra and 55/153 (35.9%) of the Control subjects reported a serious adverse event (SAE). Integra subjects experienced fewer SAEs than Control subjects.
- Adverse Events that were potentially related to treatment (TRAE) occurred in 7/154 (4.5%) of the Integra and 8/153 (5.2%) of the Control subjects. In the Integra group, the TRAEs were: diabetic foot infections (3.2%; 5/154), application

site cellulitis (0.6%; 1/154), cellulitis (0.6%; 1/154), infected skin ulcer (0.6%; 1/154), sepsis (0.6%; 1/154), application site erythema (0.6%; 1/154), and excoriation (0.6%; 1/154). In the Control group, the TRAEs were: application site odor (0.7%; 1/153), arthralgia (0.7%; 1/153), condition aggravated (1.3%; 2/153), dermatitis atopic (0.7%; 1/153), diabetic foot (1.3%; 2/153), laceration (0.7%; 1/153), neuropathic arthropathy (0.7%; 1/153), edema peripheral (0.7%; 1/153), osteomyelitis (0.7%; 1/153), pain in extremity (0.7%; 1/153), skin papilloma (0.7%; 1/153), urinary tract infection (0.7%; 1/153), and wound (0.7%; 1/153).

- The most common AE in the study was infection. 56/154 (36.4%) of Integra subjects experienced an infection or infestation, 26/56 (46.4%) of these subjects healed and 11/56 (19.6%) of these subjects went on to amputation. 74/153 (48.4%) of Control subjects experienced an infection or infestation, 19/74 (25.7%) of these subjects healed and 16/74 (21.6%) of these subjects went on to amputation. The incidence of SAEs infections and infestations was 27/154 (17.5%) in the Integra and 40/153 (26.1%) in the Control cohorts. Osteomyelitis was the most common SAE infection. This SAE occurred in 8/154 (5.2%) of the Integra and 15/153 (9.8%) of the Control subjects.
- Four Control subjects died during the study of causes unrelated to study treatment. No patient deaths occurred in the Integra cohort.
- Recognizing the limitations associated with reviewing safety information in the Integra LifeSciences Corporation Postmarketing Safety database, it appears that the types and incidence of adverse events observed with Integra (and similar products) are reported at a low level and do not raise any concerns for the proposed indication for use. Since the product has been on the market in various forms since 1996, it is also unlikely that further post market experience will provide different information as to safety of the device. Furthermore, there is no reason to expect that “real-world” experience will differ. Thus, the safety profile of Integra Template in seriously burned patients for the past 19 years was an important consideration.

### **C. Benefit-Risk Conclusion**

The impact of diabetic foot ulcers (DFU) on individuals and society is significant. Failure to respond to local wound care in DFU will usually result in amputation. If wound closure can be achieved, it is likely to delay the need for surgical intervention and offer other benefits such as improvements in: productivity, mental outlook, social interactions, and time at work, as well as decreased mortality.

The benefits of Omnigraft observed in this study were improved ulcer healing rates and patient condition. The risks associated with this product are well known and no new or unexpected risks were identified during the trial in this population. The safety and efficacy of this product in this population was superior to standard of care.

In conclusion, given the available information above, the data demonstrate that for treatment of partial and full-thickness neuropathic diabetic foot ulcers that are greater than six weeks in duration with no capsule, tendon or bone exposed, when used in conjunction with standard diabetic ulcer care, that the probable benefits outweigh the probable risks when used in accordance with the indications for use.

**D. Overall Conclusion**

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use.

**XIV. CDRH Decision**

CDRH issued an approval order on January 7, 2016.

**XV. Approval Specifications**

Directions for Use: See product labeling.

Hazard to Health from Use of the Device: See Indications, Contraindications, Warnings, and Precautions, Adverse Reactions in the device labeling.

Postapproval Requirement and Restrictions: See the approval order.

# Omnigraft™

Dermal Regeneration Matrix



Instructions for Use



# Integra® Omnigraft™

## Dermal Regeneration Matrix

### DESCRIPTION

Integra® Omnigraft™ Dermal Regeneration Matrix (Omnigraft) is an advanced bilayer matrix for dermal regeneration. The dermal replacement layer consists of a porous, three-dimensional matrix, comprised of bovine collagen and chondroitin-6-sulfate (C6S) that is designed with a controlled porosity and defined degradation rate. The temporary epidermal layer is made of a thin polysiloxane (silicone) layer to provide immediate wound coverage and control moisture loss from the wound.

Omnigraft, also marketed as Integra® Dermal Regeneration Template, is provided sterile and non-pyrogenic. The inner foil pouch and product should be handled using sterile technique. Omnigraft should not be re-sterilized.

### INDICATIONS

Integra® Omnigraft Dermal Regeneration Matrix is indicated for use in the treatment of partial and full-thickness neuropathic diabetic foot ulcers that are greater than six weeks in duration, with no capsule, tendon or bone exposed, when used in conjunction with standard diabetic ulcer care.

Integra® Dermal Regeneration Template is indicated for: the postexcisional treatment of life-threatening full-thickness or deep partial-thickness thermal injuries where sufficient autograft is not available at the time of excision or not desirable due to the physiological condition of the patient; repair of scar contractures when other therapies have failed or when donor sites for repair are not sufficient or desirable due to the physiological condition of the patient; and treatment of partial and full-thickness neuropathic diabetic foot ulcers that are greater than six weeks in duration with no capsule, tendon or bone exposed, when used in conjunction with standard diabetic ulcer care.

### CONTRAINDICATIONS

- Omnigraft should not be used in patients with known sensitivity to bovine collagen or chondroitin materials.
- Omnigraft should not be used on clinically diagnosed infected wounds.

### WARNINGS

Debridement or excision must be done thoroughly to remove any remaining necrotic tissue that may delay healing or cause infection. Omnigraft will not incorporate into a wound bed of nonviable tissue. Leaving any remaining nonviable tissue may create an environment for bacterial growth.

### PRECAUTIONS

- The following complications are possible with the use of wound treatments. The product should be removed if any of these conditions occur: infection, chronic inflammation (initial application of wound products may be associated with transient, mild, localized inflammation), allergic reaction, excessive redness, pain, or swelling.
- Do not re-sterilize. Discard all opened and unused portions of Omnigraft.
- Omnigraft is sterile if the package is unopened and undamaged. Do not use if the package seal is broken.
- Discard Omnigraft if mishandling has caused possible damage or contamination.

- There have been no clinical studies evaluating Omnigraft in pregnant women. Caution should be exercised before using Omnigraft in pregnant women. Such use should occur only when the anticipated benefit clearly outweighs the risk.
- Do not use enzymatic debridement agents when cleaning out the wound.
- Omnigraft should be applied on the day of debridement. Delaying the application of Omnigraft may substantially impair the take of the material to the wound bed.
- Hemostasis must be achieved prior to applying Omnigraft. Inadequate control of bleeding will interfere with the incorporation of Omnigraft.
- Appropriate bolstering techniques should be used so Omnigraft maintains intimate contact with the wound bed.
- Keep the dressings dry and avoid contact with water at all times.
- Omnigraft must NOT be excised off the wound.
- Caution must be employed to not remove the newly formed dermal tissue when removing the silicone layer.
- Placing the patient in hydrotherapy immersion may interfere with proper incorporation of Omnigraft and cause premature separation of the silicone layer and non-adherence to the wound bed.
- Appropriate offloading techniques to minimize pressure and shearing should be used to reduce the risk of mechanical dislodgement.

### ADVERSE EVENTS

#### a) Neuropathic Diabetic Foot Ulcer Clinical Trial

All adverse events at a frequency of  $\geq 1\%$  in either cohort that were observed in the clinical trial evaluating Omnigraft for the treatment of partial and full-thickness neuropathic diabetic foot ulcers that are greater than six weeks in duration, with no capsule, tendon or bone exposed, when used in conjunction with standard diabetic ulcer care are presented in Table 1. This table includes adverse events that were both attributed to and not attributed to treatment. The adverse events are listed in descending order according to their frequency in the Omnigraft cohort.

**Table 1: Adverse Events Reported in Greater than 1% of Patients in the Diabetic Foot Ulcer Study**

Adverse Event	Omnigraft N = 154 Patients n (n/N%)	Control N = 153 Patients n (n/N%)
Diabetic foot infection	23 (14.9)	23 (15.0)
Diabetic foot*	22 (14.3)	31 (20.3)
Pain in extremity	14 (9.1)	20 (13.1)
Cellulitis	13 (8.4)	13 (8.5)
Osteomyelitis	9 (5.8)	19 (12.4)
Edema peripheral	7 (4.5)	7 (4.6)
Nausea	7 (4.5)	3 (2.0)
Condition aggravated	6 (3.9)	14 (9.2)
Excoriation	6 (3.9)	7 (4.6)
Upper respiratory tract infection	6 (3.9)	6 (3.9)

Adverse Event	Omnigraft N = 154 Patients n (n/N%)	Control N = 153 Patients n (n/N%)
Blister	6 (3.9)	6 (3.9)
Influenza	5 (3.2)	3 (2.0)
Wound	4 (2.6)	6 (3.9)
Pneumonia	4 (2.6)	3 (2.0)
Vomiting	4 (2.6)	2 (1.3)
Hypoglycemia	4 (2.6)	1 (0.7)
Ingrown nail	4 (2.6)	1 (0.7)
Urinary tract infection	3 (1.9)	6 (3.9)
Erythema	3 (1.9)	4 (2.6)
Cardiac failure congestive	3 (1.9)	4 (2.6)
Pyrexia	3 (1.9)	3 (2.0)
Application site pain	3 (1.9)	2 (1.3)
Diarrhea	3 (1.9)	2 (1.3)
Hypertension	3 (1.9)	2 (1.3)
Disease recurrence	3 (1.9)	1 (0.7)
Local swelling	3 (1.9)	1 (0.7)
Skin maceration	3 (1.9)	1 (0.7)
Application site erosion	3 (1.9)	—
Contusion	3 (1.9)	—
Decubitus ulcer	2 (1.3)	4 (2.6)
Nasopharyngitis	2 (1.3)	2 (1.3)
Constipation	2 (1.3)	2 (1.3)
Gastro-esophageal reflux disease	2 (1.3)	2 (1.3)
Diabetic neuropathy	2 (1.3)	2 (1.3)
Dizziness	2 (1.3)	2 (1.3)
Asthma	2 (1.3)	2 (1.3)
Cough	2 (1.3)	2 (1.3)
Dyspnea	2 (1.3)	2 (1.3)
Pain	2 (1.3)	2 (1.3)
Sinusitis	2 (1.3)	1 (0.7)
Chest pain	2 (1.3)	1 (0.7)
Hypotension	2 (1.3)	—
Renal failure	2 (1.3)	—
Blood glucose decreased	2 (1.3)	—
Blood pressure increased	2 (1.3)	—
Anxiety	2 (1.3)	—

Adverse Event	Omnigraft N = 154 Patients n (n/N%)	Control N = 153 Patients n (n/N%)
Arthralgia	1 (0.6)	6 (3.9)
Laceration	1 (0.6)	5 (3.3)
Abscess limb	1 (0.6)	4 (2.6)
Gastritis	1 (0.6)	3 (2.0)
Balance disorder	1 (0.6)	3 (2.0)
Drug hypersensitivity	1 (0.6)	3 (2.0)
Nail avulsion	1 (0.6)	2 (1.3)
Sepsis	1 (0.6)	2 (1.3)
Gout	1 (0.6)	2 (1.3)
Muscle spasms	1 (0.6)	2 (1.3)
Musculoskeletal pain	1 (0.6)	2 (1.3)
Skin fissures	1 (0.6)	2 (1.3)
Headache	1 (0.6)	2 (1.3)
Coronary artery disease	1 (0.6)	2 (1.3)
Visual impairment	1 (0.6)	2 (1.3)
Anemia	1 (0.6)	2 (1.3)
Localized infection	—	4 (2.6)
Gangrene	—	3 (2.0)
Diabetes mellitus	—	3 (2.0)
Diabetic ketoacidosis	—	3 (2.0)
Limb injury	—	3 (2.0)
Cataract	—	3 (2.0)
Hyperlipidemia	—	2 (1.3)
Skin ulcer	—	2 (1.3)
Paronychia	—	2 (1.3)
Skin infection	—	2 (1.3)
Soft tissue infection	—	2 (1.3)
Hypoesthesia	—	2 (1.3)
Pulmonary embolism	—	2 (1.3)
Skin papilloma	—	2 (1.3)

\*Diabetic foot includes new, worsening, and recurring ulcers.

Serious Adverse Events (SAE): 38/154 (24.7%) of the Omnigraft and 55/153 (35.9%) of the Control subjects reported a SAE. The incidence of serious infections and infestations was 27/154 (17.5%) in the Omnigraft and 40/153 (26.1%) in the Control cohorts. Osteomyelitis was the most common SAE infection (i.e., 8/154 (5.2%) of the Omnigraft and 15/153 (9.8%) of the Control subjects). Four Control and zero Omnigraft subjects died during the study.

Adverse Events potentially related to treatment (TRAE) occurred in 7/154 (4.5%) of the Omnigraft and 8/153 (5.2%) of the Control subjects. In the Omnigraft group, the TRAEs were: diabetic foot infections (3.2%; 5/154), application site cellulitis (0.6%; 1/154), cellulitis (0.6%; 1/154), infected skin ulcer (0.6%; 1/154), sepsis (0.6%; 1/154), application site erythema (0.6%; 1/154), and excoriation (0.6%; 1/154). In the Control group, the TRAEs were: application site odor (0.7%; 1/153), arthralgia (0.7%; 1/153), condition aggravated (1.3%; 2/153), dermatitis atopic (0.7%; 1/153), diabetic foot (1.3%; 2/153), laceration (0.7%; 1/153), neuropathic arthropathy (0.7%; 1/153), edema peripheral (0.7%; 1/153), osteomyelitis (0.7%; 1/153), pain in extremity (0.7%; 1/153), skin papilloma (0.7%; 1/153), urinary tract infection (0.7%; 1/153), and wound (0.7%; 1/153).

#### b) U.S. Burn Clinical Trials

Omnigraft, evaluated under the marketed trade name of Integra® Dermal Regeneration Template (Integra template), has been found to be well tolerated in 4 prospective clinical trials involving 444 burn patients. There were no reports of clinically significant immunological or histological responses to the implantation of Integra template. There were no reports of rejection of Integra template.

Adverse events in the Postapproval study were similar to those observed in the previous clinical trials and are common in populations of critically ill burn patients regardless of type of treatment used. There were no trends noted. There were 6 adverse events which were rated by the investigator as being related. These events were all single occurrences except for sepsis (2). These adverse events occurred in less than 1% of the safety population.

**Table 2: Adverse Events Reported in Greater than 1% of Patients in the Postapproval Study**

Adverse Event	Postapproval Study N = 216 Patients n/N (%)
Sepsis	50/216 (23.1%)
Death	30/216 (13.9%)
Infection	6/216 (2.8%)
Thrombophlebitis	6/216 (2.8%)
Kidney Failure	6/216 (2.8%)
Necrosis	5/216 (2.3%)
Hemorrhage	5/216 (2.3%)
Heart Arrest	4/216 (1.9%)
Apnea	4/216 (1.9%)
Pneumonia	4/216 (1.9%)
Allergic Reaction	3/216 (1.4%)
Fever	3/216 (1.4%)
Multisystem Failure	3/216 (1.4%)
Atrial Fibrillation	3/216 (1.4%)
Gastrointestinal Hemorrhage	3/216 (1.4%)
Kidney Abnormal Function	3/216 (1.4%)

Adverse events reported in less than 1% of the population were as follows: enlarged abdomen, accidental injury, hypothermia, peritonitis, hypotension, peripheral vascular disorder, arrhythmia, cardiomyopathy, cardiovascular disorder, congestive heart failure, pulmonary embolism, dyspnea, aspiration pneumonia, hypoxia, pleural effusion, respiratory distress syndrome, cholecystitis, gastro intestinal perforation, hepatorenal syndrome, ingested obstruction, and pancreatitis.

**Table 3: Adverse Events Reported in Greater than 1% of Patients in Previous Studies**

Adverse Events	Multi-center N=149 Patients n/N (%)	Anatomic Site N=59 Patients n/N (%)	Meshed vs. Sheet N=20 Patients n/N (%)
Death	37/149 (24.8%)	19/59 (32.2%)	3/20 (15%)
Sepsis	17/149 (11.4%)	4/59 (6.8%)	1/20 (5.0%)
Apnea	13/149 (8.7%)	5/59 (8.5%)	0/20 (0.0%)
Pneumonia	10/149 (6.7%)	0/59 (0.0%)	0/20 (0.0%)
Heart Arrest	7/149 (4.7%)	6/59 (10.2%)	0/20 (0.0%)
Kidney Failure	5/149 (3.4%)	4/59 (6.8%)	0/20 (0.0%)
Respiratory Distress	3/149 (2.0%)	0/59 (0.0%)	0/20 (0.0%)
Infection	2/149 (1.3%)	0/59 (0.0%)	0/20 (0.0%)
Lung Disease	2/149 (1.3%)	0/59 (0.0%)	0/20 (0.0%)
Dyspnea	1/149 (0.7%)	1/59 (1.7%)	0/20 (0.0%)
Adrenal Insufficiency	1/149 (0.7%)	0/59 (0.0%)	0/20 (0.0%)
Agitation	1/149 (0.7%)	0/59 (0.0%)	0/20 (0.0%)
Convulsion	1/149 (0.7%)	0/59 (0.0%)	0/20 (0.0%)
Hematemesis	1/149 (0.7%)	0/59 (0.0%)	0/20 (0.0%)
Hemoptysis	1/149 (0.7%)	0/59 (0.0%)	0/20 (0.0%)
Liver Cirrhosis	1/149 (0.7%)	0/59 (0.0%)	0/20 (0.0%)
Nonadherence	1/149 (0.7%)	0/59 (0.0%)	0/20 (0.0%)
Shock	1/149 (0.7%)	0/59 (0.0%)	0/20 (0.0%)
Skin Discoloration	1/149 (0.7%)	0/59 (0.0%)	0/20 (0.0%)
Asystole	0/149 (0.0%)	0/59 (0.0%)	1/20 (5.0%)
Cerebral Artery Infarct	0/149 (0.0%)	1/59 (1.7%)	0/20 (0.0%)
Metastatic Ovarian Cancer	0/149 (0.0%)	1/59 (1.7%)	0/20 (0.0%)
Peritonitis	0/149 (0.0%)	1/59 (1.7%)	0/20 (0.0%)
Sarcoidosis	0/149 (0.0%)	0/59 (0.0%)	1/20 (5.0%)
Third Degree Burn	0/149 (0.0%)	1/59 (1.7%)	0/20 (0.0%)
Multisystem Failure	0/149 (0.0%)	3/59 (5.1%)	0/20 (0.0%)

The adverse events directly related to the use of Integra template were: wound fluid accumulation, positive wound cultures, and clinical wound infection.

In these clinical trials, data were collected regarding wound infection. The consequences of infection at sites treated with Integra template included partial or complete loss of take (incorporation into the wound bed) of Integra template. Infection rates in sites treated with Integra template in the three clinical trials supporting the PMA ranged from 14 to 55%. The overall infection rate for the Postapproval Study was 16.3%.

### c) Scar Contracture Reconstruction Study

The following adverse events were reported in a Reconstructive Surgery Study involving 20 patients with 30 anatomical sites and a Retrospective Contracture Reconstruction Survey involving 89 patients and 127 anatomic sites.

**Table 4: Adverse Events Reported in Greater than 1% of Patients in the Reconstructive Contracture Surgery Study and Retrospective Contracture Reconstruction Survey**

Adverse Events	Reconstructive Surgery Study N = 30 Sites n/N (%)	Retrospective Contracture Reconstruction Survey N = 127 Sites n/N (%)
Infection	0/30 (0.0%)	26/127 (20.5%)
Fluid under Silicone Layer	0/30 (0.0%)	18/127 (14.2%)
Partial graft loss (Integra)	0/30 (0.0%)	2/127 (1.6%)
Failure to take (Integra)	0/30 (0.0%)	8/127 (6.3%)
Shearing/ Mechanical shift (loss of Integra)	1/30 (3.3%)	6/127 (4.7%)
Hematoma	5/30 (16.7%)	3/127 (2.3%)
Granulation tissue formation	0/30 (0.0%)	4/127 (3.1%)
Delayed Healing	0/30 (0.0%)	1/127 (0.8%)
Separation of the Silicone Layer	0/30 (0.0%)	1/127 (0.8%)
Seroma	0/30 (0.0%)	1/127 (0.8%)
Pruritis	0/30 (0.0%)	1/127 (0.8%)
Epidermal autograft loss >15%	2/30 (6.7%)	7/127 (5.5%)
Epidermal autograft loss <15%	7/30 (23.3%)	9/127 (7.1%)

There were no infections reported in the Reconstructive Surgery Study and the reported infection rate was 20.5% in the Retrospective Contracture Reconstruction Survey. No deaths were reported.

### d) Postmarket Surveillance

Table 5 lists the 111 clinical Medical Device Reports (MDRs) that occurred since 1996 with Integra.

**Table 5: Summary of Clinical MDRs of Integra® Product Family Since 1996**

MDR Category	Total MDRs
Infection	60
Poor Take/Dislodgment	18
Allergic Reaction	6
Autograft Lost	4
Wound Dehiscence	4
Regeneration of Granulous Skin	3
Death*	3
No Autograft Take	3
Non healing Wound	2
Matrix Calcification	2
Septic Shock	1
Hematoma	1
Fever	1
Hypertrophic Scarring	1
Bulging of Graft	1
Factor 5 Deficiency**	1
<b>Total</b>	<b>111</b>

\* The three deaths that Integra filed as MDRs were deemed by the physicians who reported the complaints to be unrelated to the Integra template.

\*\* Integra investigators determined that Factor 5 Deficiency could not have been caused by the Integra product. The complaint was filed because a physician thought that the product could have caused the deficiency based on his research that bovine thrombin has been known to cause the deficiency. Integra products do not contain bovine thrombin and could not have caused the Factor 5 Deficiency.

## SUMMARY OF CLINICAL STUDIES

### a) Neuropathic Diabetic Foot Ulcer Clinical Trial

Clinical Trial IDRT/DFU US 2009-3 was a prospective, multi-center (32 sites), open-label, randomized (stratification by ulcer size) concurrently controlled pivotal study in subjects with partial or full thickness diabetic foot ulcers located distal to the malleolus with controlled diabetes and without significant compromise of arterial circulation. Subjects who met the entry criteria were enrolled in a two-week Pre-Treatment Phase while they received standard of care treatment for their study ulcer. Subjects who continued to meet the entry criteria after the Pre-Treatment Phase (e.g., an ulcer whose size decreased less than 30%) were randomized to a 16 week Treatment Phase with either: Omnigrift + Standard of Care (Treatment) or Standard of Care alone (Control). At the conclusion of the Treatment Phase subjects underwent three additional monthly visits in the Follow-up Phase to monitor open or healed ulcer status.

The primary effectiveness endpoint was the percentage of subjects with complete study ulcer closure as assessed by the Investigator, during the 16 week Treatment Phase.

The primary safety endpoint was the incidence of adverse events recorded during the study (i.e., the Pre-Treatment, Treatment and Follow-up Phases). Safety evaluations also included assessment of serum chemistry values at Pre-Treatment Phase and the end of Treatment Phase visits.

### Study Population Demographics and Baseline Parameters

The baseline demographics in the Omnigraft and Control arms were comparable for all parameters evaluated (Table 6).

**Table 6: ITT Baseline Population Demographics and Baseline Characteristics**

Characteristic	Statistic	Omnigraft (N = 154)	Control (N = 153)	Total (N = 307)
Age (years)	Mean (SD)	55.8 (10.6)	57.3 (9.7)	56.5 (10.1)
	Median	56.0	57.0	57.0
	Min, Max	31.0, 82.0	28.0, 82.0	28.0, 82.0
Gender	Male, n (n/N%)	118 (76.6)	114 (74.5)	232 (75.6)
	Female, n (n/N%)	36 (23.4)	39 (25.5)	75 (24.4)
Race	American Indian/Alaskan Native, n (n/N%)	0 (0.0)	2 (1.3)	2 (0.6)
	Asian, n (n/N%)	1 (0.6)	2 (1.3)	3 (1.0)
	Black Or African American, n (n/N%)	28 (18.2)	34 (22.1)	62 (20.1)
	Native Hawaiian or Pacific Islander, n (n/N%)	1 (0.6)	0 (0.0)	1 (0.3)
	Caucasian, n (n/N%)	118 (76.6)	111 (72.1)	229 (74.4)
	Other, n (n/N%)	6 (3.9)	5 (3.2)	11 (3.6)
Ethnicity	Not Hispanic/Latino, n (n/N%)	108 (70.1)	116 (75.8)	224 (73.0)
	Hispanic or Latino, n (n/N%)	46 (29.9)	37 (24.2)	83 (27.0)
Weight (kg)	Mean (SD)	107 (23.3)	107 (28.9)	107 (26.2)
	Median	105	103	104
	Min, Max	63.5, 178	52.2, 221	52.2, 221
Height (cm)	Mean (SD)	178 (9.4)	177 (12.2)	177 (10.9)
	Median	178	180	178
	Min, Max	154, 196	132, 203	132, 203
BMI (kg/m <sup>2</sup> )	Mean (SD)	34.0 (7.2)	34.1 (8.4)	34.0 (7.8)
	Median	33.8	32.1	33.0
	Min, Max	21.4, 58.9	19.9, 62.4	19.9, 62.4
Tobacco	Yes, n (n/N%)	28 (18.2)	19 (12.4)	47 (15.3)
Product Use	No, n (n/N%)	126 (81.8)	134 (87.6)	260 (84.7)
Diabetes Mellitus Type	Type 1, n (n/N%)	4 (2.6)	13 (8.5)	17 (5.5)
	Type 2, n (n/N%)	150 (97.4)	140 (91.5)	290 (94.5)
Use Of Insulin at Baseline	Yes, n (n/N%)	30 (19.5)	37 (24.2)	67 (21.8)
	No, n (n/N%)	124 (80.5)	116 (75.8)	240 (78.2)
Age Of Study Ulcer (Days)	N	154	153	307
	Mean (SD)	308 (491)	303 (418)	305 (455)
	Median	126	152	140
	Min, Max	31.0, 4501	32.0, 2059	31.0, 4501

Characteristic	Statistic	Omnigraft (N = 154)	Control (N = 153)	Total (N = 307)
% Reduction in Ulcer Area Size Between Screening & First Treatment Application	Mean (SD)	-14 (38.0)	-17 (65.9)	-16 (53.7)
	Median	-3.4	-1.6	-2.0
	Min, Max	-228, 29.2	-565, 28.6	-565, 29.2
Baseline Study Ulcer Size (cm <sup>2</sup> )	Mean (SD)	3.53 (2.5)	3.65 (2.6)	3.59 (2.6)
	Median	2.6	2.6	2.6
	Min, Max	1.0, 11.5	1.0, 10.8	1.0, 11.5
Location of Study Ulcer	Plantar, n (n/N %)	126 (81.8)	127 (83.0)	253 (82.4)
	Dorsal, n (n/N %)	28 (18.1)	25 (16.3)	53 (17.3)
	Medial, n (n/N %)	0	1 (0.7)	1 (0.3)
Wagner Grade	Grade 1, n (n/N %)	45 (29.2)	37 (24.2)	82 (26.7)
	Grade 2, n (n/N %)	109 (70.8)	116 (75.8)	225 (73.3)

## Results

545 subjects were screened and 307 patients were randomized to treatment (i.e., 154 Omnigraft and 153 Control subjects).

### Effectiveness

The primary effectiveness endpoint was complete study ulcer closure during the 16-week Treatment Phase, as assessed by the Investigator. 79/154 (51.3%) of the Omnigraft and 49/153 (32.0%) of the Control subjects achieved 100% complete closure of the study ulcer ( $p = 0.0007$ ).

Clinically significant improvements in patient outcome were also observed in the following secondary effectiveness endpoints: 1) complete wound closure via computerized planimetry, 2) time to complete wound closure (by both Investigator and computerized planimetry assessments), and 3) the rate of wound size reduction per week. Similar to the primary endpoint, when assessed by computerized planimetry, 77/154 (50.0%) of the Omnigraft and 48/153 (31.4%) of the Control subjects achieved 100% complete closure of the study ulcer ( $p=0.0010$ ). For subjects that healed, the median time to wound closure was 43 and 78 days for the Omnigraft and Control cohorts, respectively (by both Investigator and computerized planimetry assessments). At the final treatment visit, the average rate of wound closure (by the planimetry assessments) was 7.15% and 4.81% for the Omnigraft and Control cohorts, respectively ( $p=0.0115$ ).

Omnigraft subjects showed improvement in the Physical Functioning for Daily Activities and Reduction in the Bodily Pain modules of the Quality of Life Questionnaire SF-36v2 Health Survey questionnaire. No significant differences between treatment groups were observed for General Health, Social Functioning, Role Emotional, Mental Health or Vitality Modules of this questionnaire.

15/79 (19.0%) of the Omnigraft and 13/49 (26.5%) of Control subjects experienced ulcer recurrence during the study. The difference was not statistically significant.

### Additional Analyses

Number of Omnigraft Applications – Table 7 provides a summary of the number of subjects and the number of Omnigraft applications required. Reapplications were at the discretion of the investigator.

**Table 7: Summary of Omnigraft Applications**

No. of Applications	No. Omnigraft Subjects N = 154 n (n/N %)
1	92 (59.7)
2	33 (21.4)
3	12 (7.8)
4	5 (3.2)
5	5 (3.2)
6	2 (1.3)
7	2 (1.3)
11	2 (1.3)
15	1 (0.6)

### Covariate Analyses

Baseline wound size and study ulcer age were significant factors for ulcer healing. Diabetes Mellitus Type, baseline HbA1c, race, baseline BMI, wound location (left or right foot), tobacco use, age, ethnicity, Wagner Grade, ulcer location (plantar/dorsal/medial), insulin use, or gender were not significant factors for wound healing.

At the conclusion of the Pre-Treatment and Treatment Phases of the trial, 128/154 (83.1%) of the Omnigraft and 117/153 (76.5%) of the Control subjects remained on study. 106/154 (68.8%) Omnigraft and 82/153 (53.6%) Control subjects completed the trial through follow-up. Based on the computerized planimetry assessment prior to subject withdrawal during the treatment phase, a majority of withdrawals were due to the lack of treatment effectiveness in

both groups, and the observed higher percentage of withdrawal in the control group appeared to be a reflection of the inferior performance of the Control treatment as compared to the Omingraft treatment. Also, no significant association between the treatment groups and subject discontinuation was observed for: 1) subjects with a history of lower extremity amputation and discontinuation during the Treatment Phase, 2) subjects with a history of cellulitis and discontinuation during the Treatment Phase, 3) subjects without a history of lower extremity infection and discontinuation during the Treatment Phase, 4) subjects with an additional ulcer at study entry and discontinuation during the Treatment Phase, 5) subjects with a prior history of foot surgery and discontinuation during the Treatment Phase, 6) the time that a subject remained on study prior to withdrawal, 7) the number of subjects who withdrew from the study during the Treatment Phase and experienced at least one major protocol deviation, 8) the amount of daily offloading or 9) the frequency of AEs and SAEs in both treatment cohorts. Therefore, the loss of these subjects did not significantly alter the evaluation of device safety and effectiveness.

## b) Burn Studies

Integra template has been evaluated in over 1,200 wound sites in 444 burn patients in a series of 4 studies:

- Multi-center Safety and Efficacy Clinical Trial (Pivotal)
- Anatomic Site Study
- Meshed vs. Sheet Integra template Study
- Postapproval Study

Demographic, safety and effectiveness data for Integra template are summarized in the table below.

**Table 8: Summary of Burn Clinical Trial Results**

Variable		Multi-center Study	Anatomical Site Study	Meshed vs. Sheet Study	Postapproval Study
Year		1983-1989	1985-1992	1989-1992	1997-2000
Number of Patients	N	149	59	20	216
Number of Wound Sites		207	130	59	841
Age (years)	Mean ± SD	32.0 ± 21.5	49.2 ± 21.2	30.1 ± 15.6	34.7 ± 23.9
	Range	<1 - 88	19 - 93	4 - 59	<1 - 87
Gender	Male, n (%)	112 (75.2%)	33 (55.9%)	16 (80%)	151 (69.9%)
	Female, n (%)	37 (24.8%)	26 (44.1%)	4 (20%)	65 (30.1%)
Race	Caucasian, n (%)	98 (65.8%)	56 (94.9%)	14 (70.0%)	151 (69.9%)
	Black, n (%)	32 (21.5%)	0 (0.0%)	6 (30.0%)	38 (17.6%)
	Hispanic, n (%)	15 (10.1%)	3 (5.1%)	0 (0.0%)	20 (9.2%)
	American Indian, n (%)	3 (2.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
	Asian, n (%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	4 (1.8%)
	Other, n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.9%)
% BSA Total Burn	Mean ± SD	45.7 ± 18.6	49.8 ± 24.6	53.6 ± 19.4	36.5 ± 24.7
	Range	14.5 - 88.5	1 - 97	30 - 90	<1 - 95
% BSA Full-Thickness	Mean ± SD	31.8 ± 20.8	42.5 ± 24.0	35.4 ± 22.4	27.9 ± 24.4
	Range	0 - 88.5	1 - 95	0 - 78	0 - 95
% Inhalation Injury	%	42%	62.50%	50%	45%
Take	Mean	65.1%*	77.60%	80.60%	76.20%
	Median	80%*	95%	100%	98%
Infection	%	55%	14%	25%	16.30%
Mortality	%	24.80%	32%	15%	13.90%

\*Paired comparative wound sites

### ***Multi-center Safety and Efficacy Clinical Trial (Burn Pivotal Study)***

In the pivotal multi-center clinical trial, 149 patients (with 207 total wound sites) were evaluated for safety and 106 patients (with 136 comparative wound sites) were included in an assessment of efficacy. The demographic profile was: mean age 32.0, age range <1 to 88 years, gender: 112 males and 37 females and a mean %TBSA burn of 45.7% with a range of 14.5%-88.5%. Take, which was defined as the median fractional area of the wound site to support epidermal growth, was the main efficacy variable and was bimodally distributed. In the multi-center trial, Integra template had successful take (take >10%) in 69% of the wound sites (94 of 136). For this group of wound sites with successful take, the mean take was 81%, and the median take was 90%. Over 80% of the wound sites in this successful take group had greater than 60% take. Integra template failed to take (take ≤10%) in 31% of the wound sites (42 of 136 comparative wound sites). For this group, the mean take was 1.7% and the median take was 0%.

The Integra template neodermis provided a viable surface for the successful transplantation of thin, meshed and spread epidermal autograft. The take of epidermal autograft was bimodally distributed. In the multi-center trial, epidermal autograft had successful take (take >10%) in 90.5% of the sites (95 of 105 comparative wound sites). For this group of wound sites with successful take, the mean was 84% and the median take was 90%. Over 80% of the wound sites in this successful take group had greater than 65% take. Epidermal autograft failed to take (take ≤10%) in 9.5% of the sites (10 of 105 comparative wound sites). For this group, the mean take was 1.7% take and the median take was 0%.

No significant difference was seen between the total time for burn healing for wounds treated with Integra template and for wounds treated with temporary wound covers. The healing time of thin epidermal autograft on the Integra template neodermis was comparable to that of conventional autograft. Donor sites for thin epidermal autograft healed faster and allowed for more cycles of reharvesting than conventional donor sites.

### ***Histological Evaluation***

Three hundred thirty-six serial biopsies were obtained from 131 patients participating in the multi-center clinical trial ranging from 7 days to 2 years after application of Integra template. A histological study of the wound healing in the burned areas was conducted. An intact dermis was achieved with regrowth of apparently normal reticular and papillary dermis. No scar formation appeared in the biopsies of patients examined.

### ***Anatomic Site Study***

In the noncomparative single-center anatomic site study, 59 patients (130 wound sites) were evaluated for safety and 41 patients (104 wound sites) were evaluated for efficacy parameters. The demographic profile was: mean age, 49.2, age range 19-93 years, gender: 33 males and 26 females and a mean %TBSA burn of 49.8% with a range of 1%-97%. The mean take of Integra template was 77.6%, and the median take was 95%. The mean take of the epidermal autograft was 77.8% and the median take was 85%. Median take was similar for the various anatomic locations evaluated. However, the small number of patients and noncomparative nature of the study prevented conclusions from being made.

### ***Meshed vs. Sheet Study***

A pilot study was conducted on 20 patients (59 wound sites) to compare 2:1 meshed (but not expanded) and sheet Integra template. The demographic profile was: mean age, 30.1, age range 4-59 years,

gender: 16 males and 4 females and a mean % TBSA Burn of 53.6% with a range of 30-90%. The mean take of Integra template in this study was 80.6% and the median take was 100%, while the mean take for the epidermal autograft was 86.5% and the median take was 95%. However, due to the small number of patients and study design, statistical conclusions could not be drawn.

### ***Postapproval Study***

A Postapproval Study of Integra template evaluated the safety and effectiveness in 216 patients, 841 wound sites. There were 222 patients enrolled in the study, however 6 patients did not meet entry criteria (3 did not sign the patient informed consent form, 3 did not receive Integra template) resulting in 216 patients entered into the study. The demographic profile was: mean age 34.7, age range 4 months to 87 years, gender: 151 males and 65 females and a mean %TBSA burn of 36.5% with a range of <1% to 95%. Effectiveness was measured by graft take. Overall mean percent take for Integra template was 76.2% and the median percent take for Integra template was 98%. The mean take of epidermal autograft was 87.4% with median take of 95%. The rate of infection in the study patients was 16.3% (13.2% superficial and 3.1% invasive). Patient mortality was 13.9%. Data analysis indicated that mortality was related to patient age, percent total body surface area burned, presence of inhalation injury, and presence of infection at a non-Integra template treated wound site. Invasive infection at an Integra template wound site was not a significant risk factor for mortality.

## **c) Scar Contracture Reconstruction Studies**

### ***Reconstructive Surgery Study***

This study evaluated the clinical and histologic outcomes in 20 consecutive patients (30 anatomic sites) whose scars and contractures were treated with Integra template. Patients' mean age was 27.6 years, with an age range of 4-54 years. Patient follow-up ranged from 3 to 24 months. The mean take was derived from the adverse event data and was calculated to be 94.2% for Integra template and 86.3% for epidermal autograft. Efficacy was evaluated using the Vancouver Burn Scar Assessment scale by an independent review panel, a visual analog scale of patient satisfaction and histological evaluations of patient biopsies. The Vancouver Burn Scar Assessment scale ranges from 0 (normal) to 15. The mean preoperative Vancouver Burn Scar Assessment was 13.3 and the mean postoperative score was 9.0. For the patient satisfaction assessments, patients or their parents completed a questionnaire at least 3 months after the second stage of the reconstruction. A visual analog scale was used in which a score of 0%=preoperative scar and a score of 100%=normal skin with no scar. Patients/parents reported mean scores of 72% for range of movement, 62% for softness, 59% for appearance, 27% for pruritis and 14% for dryness.

### ***Retrospective Contracture Reconstruction Survey***

This survey requested information from physicians already using Integra template on the use of the product for contracture reconstruction. Information was received from 13 of 19 physicians surveyed who reported on 89 patients and 127 anatomic sites. The demographic profile for the reported patients was: mean age 24.8, age range <1 to 72, gender 52 males and 37 females. The safety results of this survey are provided in tabular form in the adverse event section.



## INFORMATION FOR USE

Omnigraft is indicated for use in the treatment of partial and full-thickness neuropathic diabetic foot ulcers that are greater than six weeks in duration, with no capsule, tendon or bone exposed, when used in conjunction with standard diabetic ulcer care.

## INSTRUCTIONS FOR USE

### Sharp Debridement

1. Using aseptic technique, prepare the wound bed using standard methods to ensure the wound is free of debris and necrotic tissue.
2. Sharp debridement must be made to the level of viable tissue. Meticulous hemostasis needs to be achieved to prevent hematoma or excessive fluid accumulation. Omnigraft should not be applied over infected or deteriorating wounds until the underlying issue has been resolved.

### Cleansing

1. Cleanse the wound thoroughly using a neutral, non-irritating, and non-toxic solution such as sterile saline or sterile water.

### Product Preparation

1. To minimize the risk of infection, change your gloves following debridement and cleansing and before handling Omnigraft. A fresh set of sterile instruments are required for Omnigraft placement, shaping, and cutting.
2. Using aseptic technique, open the outer pouch and remove the inner foil pouch. Place the foil pouch flat on a sterile surface to open it. While holding the tab, remove the product from the pouch and peel off the protective plastic sheets.
3. Rinse the product with a sterile saline solution for at least 2 minutes. Carefully remove the tab from the product. Keep product in the basin until application.

**NOTE:** Before the application, Omnigraft can be pie crusted or fenestrated but must not be expanded. Fenestrations may improve the ability of the matrix to conform to irregular surfaces and may improve contact with the wound bed.

### Product Application

1. Trim Omnigraft to size and apply immediately following wound bed preparation. The product should overlap the edges of the wound by 2mm. Any air bubbles should be carefully removed by moving them to the edge of the sheet using a gentle rolling motion to achieve intimate contact with the wound bed.

**NOTE:** It is critical that the collagen layer be in direct contact with the prepared wound bed. The silicone layer, identified by the black threads, must be placed away from the wound bed. Do not apply upside down; the black threads must be clearly visible. The black threads do not have to be placed in a certain orientation.

2. Omnigraft should be firmly secured using surgical staples or sutures so the product maintains intimate contact with the wound bed.
3. Appropriate bolstering may be used so Omnigraft maintains intimate contact with the wound bed.
4. After bolstering, use appropriate dressings to maintain product adherence and protect the wound area. The optimum secondary dressing is determined by wound location, size, depth, and user preference.

### Post Application Care

1. Clinicians should change the dressings weekly without disturbing Omnigraft. Frequency of dressing changes will be dependent upon the volume of exudate produced, the type of dressing used, and the clinician's need to inspect the wound bed for signs of infection or healing.

**NOTE:** Ensure that Omnigraft maintains intimate contact with the wound bed at all times. Be careful not to disturb Omnigraft.

**NOTE:** Use a 15 blade scalpel to make an incision if hematoma or excess exudate exists.

2. Use an offloading device for patients following the application of Omnigraft to reduce shearing forces and to protect the wound site from future re-injury, especially on the plantar aspect of the foot.

### Removal of Silicone Layer

1. If the edges of the silicone layer have separated from the wound site, the separated silicone can be trimmed.

**NOTE:** The silicone layer of Omnigraft may be removed when the collagen layer has been replaced by neodermis, usually 14 to 21 days after application.

2. The clinician must be careful when removing the silicone layer. The silicone layer can usually be removed using only forceps. Generally, it should peel off easily. Difficulties in removal may indicate that the neodermis formation is incomplete.

**Caution:** Do not remove the newly formed neodermal tissue when removing the silicone layer. Omnigraft must not be excised off the wound.

**Caution:** If bleeding occurs, or if patient complains of excessive pain, stop and wait 1 to 2 additional days. Forced removal may result in wound re-injury.

**NOTE:** It is recommended to always offload the ulcer until the wound has closed. To minimize recurrence, continue to offload to prevent future re-injury per the treating clinician's protocol.

## POTENTIAL POST APPLICATION PROBLEMS

### *Wound Infection*

Wounds having excessive discharge may require more frequent dressing changes and may require the use of appropriate antimicrobial intervention. The dressings should be removed and wound sites inspected for infection. Appropriate diagnostic and therapeutic procedures should be followed.

### *Hematoma*

Areas of hematoma should be monitored and aspirated or excised as required. New Omnigraft may be applied to the excised sites.

### *Poor Incorporation of Omnigraft*

If Omnigraft is not incorporated into the wound bed, carefully remove the product and examine the wound bed. Areas of poor Omnigraft incorporation may be treated by reapplication of the product.

### *Premature Silicone Layer Separation*

If the silicone layer separates from the wound bed after new dermal formation begins, only the loose area of the silicone layer needs to be removed.

## PATIENT COUNSELING INFORMATION

Patients receiving Omnigraft should be counseled that: Omnigraft is to be used in combination with good ulcer care including an offloading device, optimal metabolic control, and proper nutrition. Once the ulcer has healed, ulcer prevention practices should be implemented including regular visits to the appropriate treating clinician. Patients should be given the patient brochure to remind them of this information.

## TREATMENT OF DIABETES

Omnigraft does not address the underlying pathophysiology of diabetic foot ulcers. The patient's diabetes should be managed according to standard medical practice.

## SINGLE USE DEVICE

Omnigraft is supplied in a single-use package and is guaranteed to be sterile and non-pyrogenic unless opened or damaged. The product is intended for use as an absorbable implant and is not to be reused. Any attempt to re-sterilize or reuse the product/components will damage the matrix and impair its ability to function as intended. All unused pieces must be discarded.

## HOW SUPPLIED

Omnigraft is available in the following sizes:

Integra® Omnigraft™ Dermal Regeneration Matrix		
Product Codes	Size	Quantity
DFU4041	4 cm x 4 cm	1 unit/box
DFU7071	7 cm x 7 cm	1 unit/box

The bilayer sheets consist of collagen with an outer removable silicone layer, which is identified by black suture markers to ensure proper placement of the sheets on the wound bed.

## STORAGE

Store flat at room temperature: +2°C (+36°F) to +30°C (+86°F).













## DISPOSAL

Product to be disposed according to institutional procedures.

## PRODUCT INFORMATION DISCLOSURE

INTEGRA LIFESCIENCES CORPORATION HAS EXERCISED REASONABLE CARE IN THE SELECTION OF MATERIALS AND THE MANUFACTURE OF THESE PRODUCTS. INTEGRA LIFESCIENCES EXCLUDES ALL WARRANTIES, WHETHER EXPRESSED OR IMPLIED, INCLUDING BUT NOT LIMITED TO, ANY IMPLIED WARRANTIES OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE. INTEGRA LIFESCIENCES SHALL NOT BE LIABLE FOR ANY INCIDENTAL OR CONSEQUENTIAL LOSS, DAMAGE, OR EXPENSE, DIRECTLY OR INDIRECTLY ARISING FROM USE OF THIS PRODUCT. INTEGRA LIFESCIENCES NEITHER ASSUMES NOR AUTHORIZES ANY PERSON TO ASSUME FOR IT ANY OTHER OR ADDITIONAL LIABILITY OR RESPONSIBILITY IN CONNECTION WITH THESE PRODUCTS.

## SYMBOLS USED ON LABELING

	Do not re-use
	This product is not manufactured with Natural Rubber Latex
	Do not re-sterilize
	Do not use if package is damaged
	Expiration date (YYYY-MM-DD)
	Sterilized using irradiation
	Lot number
	Consult Instructions for Use
	Temperature Limitation
	Manufacturer
	Catalog number
	Caution: Federal (USA) law restricts this device to sale by or on the order of a physician or practitioner



# A clinical trial of Integra Template for diabetic foot ulcer treatment

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## Abstract

Individuals with diabetes mellitus are at an increased risk of developing a diabetic foot ulcer (DFU). This study evaluated the safety and efficacy of Integra Dermal Regeneration Template (IDRT) for the treatment of nonhealing DFUs. The Foot Ulcer New Dermal Replacement Study was a multicenter, randomized, controlled, parallel group clinical trial conducted under an Investigational Device Exemption. Thirty-two sites enrolled and randomized 307 subjects with at least one DFU. Consented patients were entered into the 14-day run-in phase where they were treated with the standard of care (0.9% sodium chloride gel) plus a secondary dressing and an offloading/protective device. Patients with less than 30% reepithelialization of the study ulcer after the run-in phase were randomized into the treatment phase. The subjects were randomized to the control treatment group (0.9% sodium chloride gel;  $n = 153$ ) or the active treatment group (IDRT,  $n = 154$ ). The treatment phase was 16 weeks or until confirmation of complete wound closure (100% reepithelialization of the wound surface), whichever occurred first. Following the treatment phase, all subjects were followed for 12 weeks. Complete DFU closure during the treatment phase was significantly greater with IDRT treatment (51%) than control treatment (32%;  $p = 0.001$ ) at sixteen weeks. The median time to complete DFU closure was 43 days for IDRT subjects and 78 days for control subjects in wounds that healed. The rate of wound size reduction was 7.2% per week for IDRT subjects vs. 4.8% per week for control subjects ( $p = 0.012$ ). For the treatment of chronic DFUs, IDRT treatment decreased the time to complete wound closure, increased the rate of wound closure, improved components of quality of life and had less adverse events compared with the standard of care treatment. IDRT could greatly enhance the treatment of nonhealing DFUs.

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Trial Registration: [clinicaltrials.gov](http://clinicaltrials.gov)  
Identifier: NCT01060670.

Currently, there are 387 million individuals worldwide living with diabetes mellitus including 29 million Americans. Diabetics have up to a 25% lifetime risk of developing a diabetic foot ulcer (DFU).<sup>1-3</sup> Once an ulcer develops, healing is often slow and challenging even for those with proper treatment. A meta-analysis of studies involving the standard of care for DFUs demonstrated only a 24% healing rate at 12 weeks.<sup>4</sup> A high proportion of DFUs become infected (61%)<sup>5</sup> and approximately 15% of DFUs result in lower extremity amputation.<sup>6,7</sup> However, an estimated 44–85% of these amputations can be prevented with improved foot care programs.<sup>8</sup> DFUs are responsible for more hospitalizations than any other complication of diabetes, ranging in costs from \$9 to \$13 billion in addition to the costs

associated with diabetes itself.<sup>9</sup> Substantial morbidity rates also adversely impact the physical and mental quality of life of those afflicted.<sup>10</sup> Studies using quality of life questionnaires showed that patients with a nonhealing DFU report significantly lower scores compared with diabetic patients without DFUs.<sup>11,12</sup> As a result of the complexity to treat these wounds, nonhealing DFUs inflict an economic burden on the healthcare system and considerably impair a patient's quality of life.

The standard of care for DFUs is sharp debridement, daily wound care dressings, offloading, and infection control.<sup>13</sup> However, the majority of DFUs that undergo this treatment do not heal completely and are considered to be nonresponsive to conventional therapy if the DFUs have not shown

marked improvement over a 4-week period.<sup>4</sup> For these non-healing chronic DFUs, there have been a number of cellular- and/or tissue-based products (CTPs) that have been evaluated in multicenter, randomized, controlled clinical trials and have demonstrated varying degrees of success.<sup>14–17</sup> The products evaluated in these trials consist of cell-based products and minimally processed human tissue allografts.

Integra Dermal Regeneration Template (IDRT; marketed as Omnigraft Dermal Regeneration Matrix) is based on Integra's Dermal Regeneration Matrix (IDRM) Technology which is an advanced, acellular, bilayer matrix specifically engineered for dermal regeneration.<sup>18</sup> The dermal replacement layer was designed with a controlled porosity and degradation rate and consists of a three-dimensional matrix of collagen and the glycosaminoglycan, chondroitin-6-sulfate. The temporary epidermal layer is made of silicone to provide mechanical protection and act as a barrier for bacterial contamination.

The IDRM Technology has been previously evaluated in four prospective clinical trials for the treatment of third degree burns and the reconstruction of scar contracture involving 444 subjects and over 1,200 wound sites.<sup>19\*</sup> In addition, products using IDRM Technology have been pre-market approved and 510(k) cleared by the Food and Drug Administration (FDA).<sup>†</sup> The IDRM Technology has been on the market since 1996 and has a long history of safe and effective use in third degree burns, scar reconstruction, and acute and chronic wounds. The primary goal of the Foot Ulcer New Dermal Replacement Study (FOUNDER), conducted under an Investigational Device Exemption (IDE), was to evaluate the safety and efficacy of IDRT for the treatment of nonhealing chronic DFUs.

## METHODS

### Trial design and subjects

The FOUNDER Study was a multicenter, randomized, controlled clinical trial with two parallel groups that was designed based on guidelines from the FDA for developing products for the treatment of chronic cutaneous ulcers.<sup>20</sup> Thirty-two sites enrolled and randomized subjects. Key inclusion criteria included confirmed type I or type II diabetes with a hemoglobin A1c  $\leq 12\%$ , patients aged 18 or older, presence of a full-thickness neuropathic ulcer located distal to the malleolus, study ulcer duration greater than 30 days, ulcer area between 1 and 12 cm<sup>2</sup> postdebridement, and adequate vascular perfusion as defined by ankle-brachial index  $\geq 0.65$  and  $\leq 1.2$  or toe pressure  $> 50$  mmHg or TcPO<sub>2</sub>  $> 40$  mmHg or doppler ultrasound consistent with adequate blood flow to the affected extremity. The main exclusion criteria were active infection including osteomyelitis, exposed capsule, tendon, or bone, and reduction of wound  $\geq 30\%$  during the screening period (Table 1). The study was divided into three phases:

screening/run-in, randomization/treatment, and follow-up (Figure 1).

### Screening/run-in phase

After providing written consent and prior to randomization, subjects entered the screening/run-in phase. During this phase, a series of screening assessments and a 14-day run-in period with the standard of care treatment were performed to determine eligibility. During the first day of the run-in phase, the following procedures were performed: infection and exudate assessment, sharp debridement of the study ulcer, measure of the deepest dimension of the study ulcer (postdebridement), photograph of the study ulcer (predebridement and postdebridement), study ulcer tracing for planimetric assessment (postdebridement), and standard of care treatment. Additional assessments performed during the run-in phase were location and duration of the study ulcer, subject demographics, medical history, medication usage and therapies, physical examination, height and weight, neuropathic assessments, laboratory assessments, and a vascular perfusion assessment. The standard of care treatment was applied in the outpatient setting and consisted of sharp debridement followed by the application of moist wound therapy consisting of 0.9% sodium chloride gel plus a secondary dressing consisting of a nonadherent foam dressing, an outer gauze wrap, and an offloading/protective device, Active Offloading Walker (boot and/or shoe). Although there is no "gold standard" for moist wound therapy, the American Society of Plastic Surgeons recommends maintaining a moist wound environment.<sup>21</sup> Saline gauze and/or gels have been used as the standard of care for the control groups in previous clinical trials.<sup>22–27</sup> Subjects were instructed on the standard of care treatment that included daily dressing changes. For subjects having more than one qualifying DFU, the study ulcer was designated at the discretion of the site investigator. Nonstudy ulcers were only treated with the standard of care.

### Randomization/treatment phase

On completion of the run-in period, the subjects were evaluated to determine whether they continued to satisfy the eligibility criteria applied during the screening phase. The study ulcer was debrided using sharp debridement prior to the first treatment. In addition, planimetric assessment was performed on digitized acetate tracings to objectively quantify wound closure. Computerized planimetry was conducted in a blinded manner by a central laboratory. Subjects whose study ulcer healed less than 30% during the run-in period were randomized using a software algorithm at a central location in mixed blocks of 2 and 4 in a 1 : 1 ratio to the active or control treatment. Randomization was stratified by study site and wound size ( $\leq 3$  cm<sup>2</sup> vs.  $> 3$  cm<sup>2</sup>). The assigned treatment began on the day of randomization and the treatment phase lasted until the subject had 100% wound closure or for up to 16 weeks.

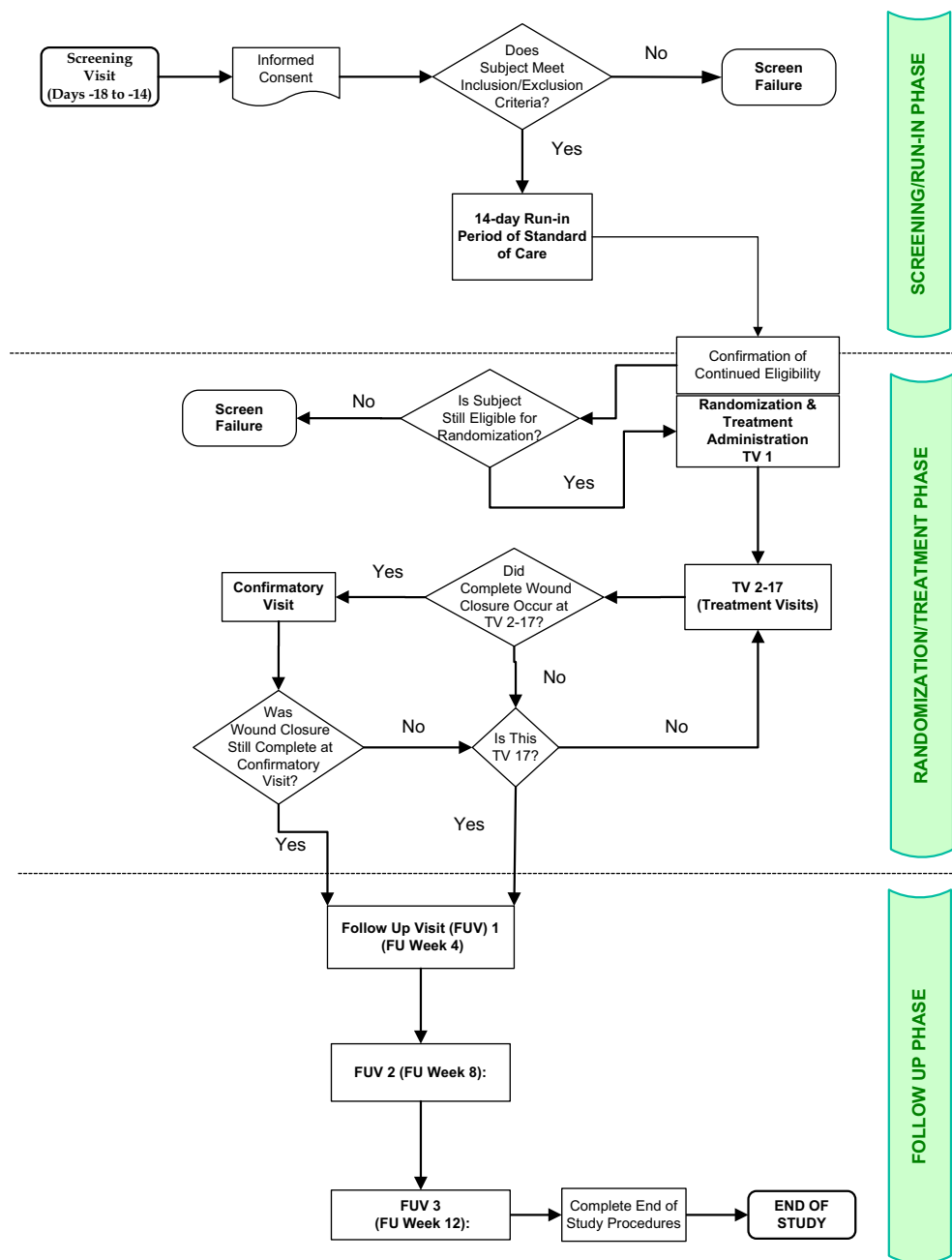
The control treatment was standard of care and the active treatment was IDRT. The standard of care treatment applied during the treatment phase was identical to the standard of care treatment applied during the screening/run-in phase. The control group subjects (or a trained caregiver) performed once-daily dressing changes.

\*LifeSciences I. Premarket Approval Number: P900033. Integra Artificial Skin, Dermal Regeneration Template. Approval Date: Mar 1, 1996.

†Marketed as Integra<sup>®</sup> Omnigraft<sup>™</sup> Dermal Regeneration Matrix, Integra<sup>®</sup> Derma-build<sup>™</sup> Wound Matrix, Integra<sup>®</sup> Dermal Regeneration Template, Integra<sup>®</sup> Meshed Dermal Regeneration Template, Integra<sup>®</sup> Bilayer Wound Matrix, Integra<sup>®</sup> Meshed Bilayer Wound Matrix.

**Table 1.** Trial inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria	
1) 18 years of age or older	1) Suspected or confirmed signs/symptoms of gangrene or wound infection on any part of the affected limb	11) Osteomyelitis with necrotic soft bone
2) Type 1 or type 2 diabetes mellitus	2) History of hypersensitivity to bovine collagen and/or chondroitin	12) Chopart amputation
3) Glycosylated hemoglobin (HbA <sub>1c</sub> ) ≤12%	3) Pregnancy	13) History of bone cancer or metastatic disease of the affected limb, radiation therapy to the foot, or chemotherapy within the 12 months prior to randomization
4) Negative serum pregnancy test at screening for female participants of child-bearing potential	4) Previous treatment under this clinical study protocol	14) Treatment with wound dressings that include growth factors, engineered tissues, or skin substitutes within 30 days of randomization or scheduled to receive such treatment during the study
5) Adequate vascular perfusion of the affected limb	5) Participation in another clinical trial involving a device or systematically administered investigational study drug or treatment within 30 days of the randomization visit	15) Treatment with hyperbaric oxygen within 5 days of screening or scheduled to receive this treatment during the study
6) Willing and able to maintain the required off-loading (as applicable for the location of the ulcer) and applicable dressing changes	6) Receiving or scheduled to receive a medication or treatment which, in the opinion of the Investigator, was known to interfere with, or affect the rate and quality of, wound healing	16) Nonstudy ulcer requiring treatment that could not be treated during the study with moist wound therapy
7) At least one DFU that met the following criteria: <ul style="list-style-type: none"> <li>a) Ulcer was diagnosed as a full-thickness neuropathic DFU that was located distal to the malleolus (excluding ulcers between the toes but including those of the heel),</li> <li>b) Minimum 2-cm margin between the qualifying study ulcer and any other ulcers on the specified foot (postdebridement),</li> <li>c) Area ≥1 square centimeter (cm<sup>2</sup>) and ≤12 cm<sup>2</sup> (postdebridement at the time of randomization),</li> <li>d) Wagner grade 1 or 2, e) depth ≤5 mm with no exposed capsule, tendon or bone and no tunneling, undermining or sinus tracts,</li> <li>e) Duration of the study ulcer was at least 30 days at the time of the screening visit.</li> </ul>	7) Any unstable condition or circumstance that could interfere with treatment regimen compliance (e.g., ability to perform required dressing changes, ability to comply with treatment visit schedule, mental incapacity, current substance abuse)	17) History of or intercurrent illnesses or conditions (other than diabetes) that would compromise the safety of the subject, or the normal wound healing process (i.e., end stage renal disease, immunosuppression, etc.)
	8) Excessive lymphedema that could interfere with wound healing	18) Employees or relatives of any member of the Investigational site or the sponsor
	9) Unstable Charcot foot or Charcot with bony prominence	19) Size of the study ulcer following debridement decreased by more than 30% during the run-in period
	10) Ulcers secondary to a disease other than diabetes	



**Figure 1.** Description of study phases. [Color figure can be viewed in the online issue, which is available at [wileyonlinelibrary.com](http://wileyonlinelibrary.com).]

For the active treatment group, IDRT was applied in the outpatient setting. Fenestrating and meshing of the IDRT was permitted to allow for drainage and in the presence of exudating wounds or hematomas. The IDRT was applied to the debrided wound, trimmed to size and secured with sutures or staples, and covered with a secondary dressing. The silicone layer of IDRT was removed when the collagen layer was replaced by new tissue, typically 14–21 days after application. Reapplication of IDRT was per-

formed at the discretion of the investigator. The secondary dressing changes for the active treatment group were performed weekly by site personnel.

The subjects’ wounds were evaluated weekly during the treatment phase or until wound closure. If criteria for complete wound closure were met, the participant returned for a confirmation visit 1 week later. Confirmation of wound closure was confirmed at a second consecutive study visit.

### Follow-up phase

After completing the treatment phase, all subjects were followed for the 12-week follow-up phase with clinic visits every 4 weeks. The first visit of the follow-up phase was 4 weeks after the confirmation visit or the final visit of the treatment phase for subjects who did not achieve wound closure. All subjects were monitored for ulcer recurrence and safety. Subjects whose wounds did not completely heal continued treatment within their assigned group and were additionally monitored for wound closure.

### Off-loading

The sponsor provided participants in both groups with an appropriate off-loading/protective device (Active Offloading Walker, boot, and/or shoe) throughout the screening/run-in and treatment phases. Participants who did not achieve complete closure during the 16-week treatment phase continued to use the off-loading device throughout the follow-up phase. For participants who did achieve complete closure during the treatment phase, use of the off-loading device was recommended for an additional 6 weeks. Participants were instructed to wear the off-loading/protective device at all times, except during sleeping, bathing, or showering. Compliance information on the use of the off-loading device was collected by the study staff at each visit via diary review and participant interviews.

### Baseline ulcer measurements

The DFU location was documented according to foot (left or right), surface (plantar, dorsal, or medial), and area (forefoot, midfoot, or hindfoot). Ulcer depth and size were measured. Duration of the DFU at screening was determined based on the days elapsed between first documented diagnosis of the DFU and the date of the informed consent signing.

### Outcome assessment

The primary endpoint was the percentage of subjects with complete closure of the study ulcer, as assessed by the Investigator, during the treatment phase. Complete wound closure was defined as 100% reepithelialization of the wound surface with no discernable exudate and without drainage or dressing requirements. Secondary endpoints included: (1) percentage of subjects with complete wound closure of the study ulcer, as assessed by computerized planimetry, during the treatment phase; (2) time to complete wound closure, as assessed by the Investigator; (3) time to complete wound closure, as assessed by computerized planimetry, (4) rate of wound closure, as assessed by computerized planimetry, (5) incidence of ulcer recurrence at the site of the study ulcer during the follow-up phase; and (6) change in Quality of Life metrics from baseline to 16 weeks assessed by the Short Form Health Survey (SF-36). The number and type of adverse events (AEs) were also collected and categorized.

### Statistical analysis

A sample size of 296 subjects in the randomization/treatment phase was needed to have 80% power to detect a clinically meaningful difference of 18% (46% in the active

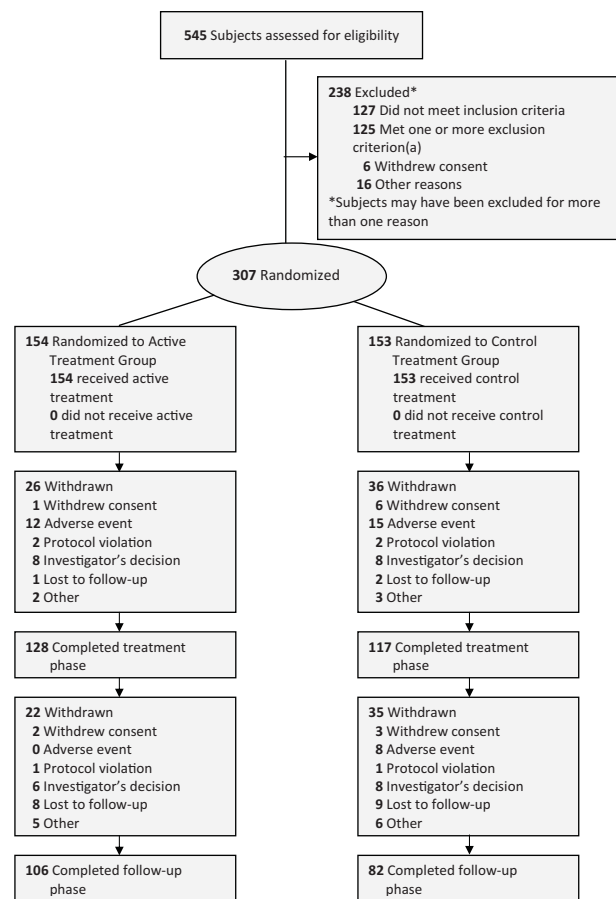
group vs. 28% in the control group) for the primary outcome using a two-sided 0.05 level test and assuming a 20% dropout rate.

For all primary and secondary efficacy outcomes, the intent-to-treat cohort was used and for the safety analyses, any subjects receiving treatment after randomization were included. Appropriate descriptive statistics, including proportion for binary outcomes and means and medians for continuous outcomes, were calculated by treatment group. Between-group comparison in baseline characteristics assessed for balance between study groups in variables that were potentially associated with healing. Individual baseline variables showing between-group imbalance with *p*-value less than 0.05 were included in all models for covariate adjusted estimates to demonstrate the robustness of the primary analyses.

For the primary outcome, the treatment groups were compared for complete wound closure, as determined by the investigator, at 16 weeks postrandomization using the logistic regression model, adjusting for baseline ulcer size strata. The type I (alpha) error rate was set at 0.05. Those with no postbaseline assessments were considered as not healed in the primary analysis (the last observation was carried forward for subjects without follow-up data). An odds ratio (OR) was estimated from the model in which an OR significantly greater than 1 provided evidence for a greater healing percentage in the active group vs. the control group. To adjust for between-site differences, a mixed-effects logistic regression with random intercepts for sites was preferred, but due to some sites having a small number of patients, the OR estimate from the mixed-effects logistic regression model was not reliable, and hence, the final OR was based on the logistic regression model. The robustness of the final OR estimate was checked by estimating it from both the mixed-effects logistic regression model and from a logistic regression model with sites as fixed effects.

For secondary outcomes, the treatment groups were compared using a Closed Test procedure to maintain the type I error rate at 0.05. The secondary outcome of complete wound closure, as assessed by computerized planimetry (0 cm<sup>2</sup>), was compared in the same way as the primary outcome. Time to complete wound closure as assessed by the Investigator and by computerized planimetry were each analyzed using a Cox regression model adjusting for baseline ulcer size strata, and hazard ratios (HRs) and their 95% confidence intervals are calculated based on the model. The model was adjusted for within-site correlation, and proportional hazard assumption was checked using the interaction term of time by active group indicator. Rate of wound closure was assessed using weekly assessed wound size by planimetry as a dependent variable using a linear mixed-effects regression model. The model included site as random-effects to adjust for between-site differences, and patient as random effects nested within site to adjust for within-patient correlation from weekly measurements. Incidence of ulcer recurrence during the follow-up phase was compared using the same analytic approach as the primary outcome.

Post hoc analyses of the individual components of the quality of life metric at the end of the treatment phase were performed using linear mixed-effects regression with both baseline and end of treatment phase quality of life as



**Figure 2.** Description of subjects assessed for participation in the FOUNDER Study.

the dependent variable, and the interaction of intervention group indicator by 16-week indicator tested for the treatment efficacy. The rate of AEs was compared between treatment groups using logistic regression. Statistical analyses were performed using SAS 9.3.

## RESULTS

### Study subjects

From April 2010 to November 2013, 545 patients with DFUs were assessed for study eligibility. The intent-to-treat sample consisted of 307 subjects; 154 subjects randomized to the active treatment group and 153 subjects randomized to the control treatment group (Figure 2). The overall withdrawal rate after randomization but during the treatment phase was 20% (62/307). There was no difference between the active and control groups in withdrawal from the study ( $p = 0.15$ ).

Table 2 describes the baseline patient characteristics and the study wound characteristics. No statistically significant difference was found in any baseline variable. Subjects in either the active or the control group had similar wound characteristics in terms of size at the end of the run-in

period, ulcer age at enrollment, and ulcer location. Because neither the patient nor the wound characteristics showed imbalances between treatment groups, covariate adjustments were not made for any comparisons between treatment groups.

Complete closure of the study ulcer during the treatment phase (16 weeks), as defined by the investigator, was significantly greater in the active group (51%; 79/154) in comparison to the control group (32%; 49/153,  $p = 0.001$ ). Similar results were found when wound closure was assessed by computerized planimetry: 50% (77/154) in the active group and 31% (48/153) in the control group ( $p = 0.001$ ). The odds of complete wound closure determined at the end of the treatment phase were 2.2 times greater (95% CI = 1.4, 3.5;  $p = 0.001$ ) for the active group compared with the control group. Analysis using planimetric data to assess wound closure was consistent with an OR of 2.2 (95% CI = 1.3, 3.5;  $p = 0.001$ ). When complete wound closure as defined by the Investigator was assessed at 12 weeks, the results were again significantly different between the two groups (45% active (70/154) vs. 20% control (31/153);  $p < 0.001$ ). The odds of complete wound closure at 12 weeks were 3.3 times greater (95% CI = 2.0, 5.4;  $p < 0.001$ ) for the active group compared with the control group. The median number of applications per patient, including the initial application, for the active group was 1 (range 1–15).

Time to complete wound closure as assessed by the Investigator is shown using Kaplan–Meier curves (Figure 3) by treatment group. For those wounds that healed, the median time to complete closure of the wound was 43 days for the active group and 78 days for the control group. Cox regression model showed a significant nonproportional hazards over time between the two treatment groups, as indicated by a significant interaction of time by active group ( $p = 0.001$ ). On graphical examination of the hazards and Schoenfeld residuals by the treatment group, the best fitting model estimated the HR to show three times higher likelihood of complete wound closure in the active group compared with the control group during the first ten weeks (HR = 3.13, 95% CI = 2.34, 4.20,  $p < 0.001$ ), followed by no difference between groups as indicated by HR not different from 1 after week 10 (HR = 0.84; 95% CI = 0.49, 1.44,  $p = 0.53$ ) or equivalently, a significant 73% reduction in the HR of wound closure after week 10 (HR = 0.27, 95% CI = 0.14, 0.50;  $p < 0.001$ ). The HR estimate was similar based on time to complete ulcer closure from planimetric assessment since the Investigator assessment of weeks to complete wound closure correlated highly with computerized planimetry assessment ( $r = 0.97$ ,  $p < 0.0001$ ).

The weekly wound size during the treatment phase by treatment group is shown in Figure 4. The rate of reduction in wound size was 7.2% per week for the active group vs. 4.8% per week for the control group ( $p = 0.012$ ). The percentage of subjects with ulcer recurrence at the completion of the follow-up phase was 19% for the active group and 26% for the control group ( $p = 0.32$ ). Quality of life data showed significant improvements in Physical Functioning ( $p = 0.047$ ) and Bodily Pain ( $p = 0.033$ ) for the active group compared with the control group.

The majority of AEs in both groups were mild. There were significantly more subjects with severe AEs (15.6%



**Table 2.** Baseline patient characteristics

	Active treatment group (n = 154)	Control treatment group (n = 153)	Total (n = 307)	p Value*
Patient characteristic				
Age <sup>†</sup> (mean ± SD)	55.8 ± 10.6	57.3 ± 9.7	56.5 ± 10.1	0.18
Male (%)	118 (76.6)	114 (74.5)	232 (75.6)	0.67
Caucasian <sup>#</sup> (%)	118 (76.6)	111 (72.5)	229 (74.4)	0.41
Black or African-American <sup>#</sup> (%)	28 (18.2)	34 (22.2)	62 (20.2)	0.46
Hispanic or Latino <sup>#</sup> (%)	46 (29.9)	37 (24.2)	83 (27.0)	0.26
Use tobacco (%)	28 (18.2)	19 (12.4)	47 (15.3)	0.16
Body mass index (mean ± SD)	34.0 ± 7.2	34.1 ± 8.4	34.0 ± 7.8	0.90
HbA <sub>1c</sub> (%; mean ± SD)	8.0 ± 1.8 (64 mmol/mol)	8.2 ± 1.9 (66 mmol/mol)	8.2 ± 1.7 (66 mmol/mol)	0.50
Study wound characteristics				
Size at end of run-in (cm <sup>2</sup> , mean ± SD)	3.53 ± 2.5	3.65 ± 2.7	3.59 ± 2.6	0.71
Ulcer age at enrollment:				
Days ± SD	308 ± 491	303 ± 418	305 ± 455	0.93
Median (IQR)	126 (288)	152 (224)	140 (266)	0.69
Wagner grade 2 (%)	109 (70.8)	116 (75.8)	225 (73.3)	0.32 <sup>‡</sup>
Location <sup>§</sup>				
Dorsal (%)	28 (18.2)	25 (16.5)	53 (17.3)	
Plantar (%)	126 (81.8)	127 (83.6)	253 (82.7)	0.69
Area				
Calcaneal (%)	0	2 (1.3)	2 (0.7)	
Forefoot (%)	109 (70.8)	93 (60.8)	202 (65.8)	
Midfoot (%)	33 (21.4)	40 (26.1)	73 (23.8)	
Hindfoot (%)	12 (7.8)	18 (11.7)	30 (9.8)	0.16

\*Based on chi-square tests for categorical variables and *t* tests for continuous variables.

<sup>†</sup>Medicare-age patients (age 65 or older) represent 18.2% (28/154) of the active group population and 20.3% (31/153) of the control group population.

<sup>‡</sup>Compares Wagner Grade 2 vs. Wagner Grade 1.

<sup>§</sup>One participant randomized to the standard care group whose study ulcer was in the medial location is not included in this tabulation.

<sup>#</sup>Subjects with multiple races are counted per each race.

SD, standard deviation; IQR, interquartile range.

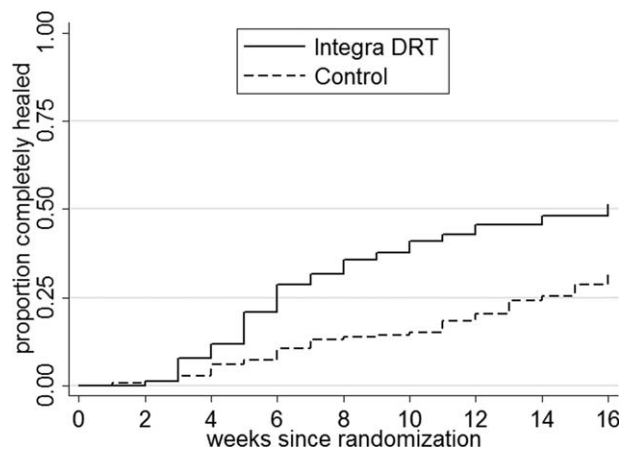
in active and 26.8% in control group;  $p = 0.016$ ) and moderate AEs (31.8% in active and 42.5% in control group;  $p = 0.053$ ) in the control group compared with the active group. The AEs potentially related to study treatment were similar in both treatment groups (7/154 (4.5%) in the active group vs. 8/153 (5.2%) in the control group).

## DISCUSSION

This multicenter, randomized, controlled trial demonstrated that for the treatment of chronic DFUs, an increased percentage of subjects achieved complete wound closure when treated with IDRT compared with the standard of care. Additionally, IDRT decreased the time to complete wound closure, improved components of quality of life, and attained a lower percentage of patients with severe AEs compared with the standard of care. The

assessment of health-related quality of life as an outcome is something that other DFU clinical trials involving a cellular- and/or tissue-based product have not evaluated. Limitations in mobility, difficulty performing activities of daily living, and increased reliance on caregivers are a few examples of how DFUs deleteriously affect quality of life.

This study has several strengths, including a large sample size. In addition, the majority of IDRT-treated patients required only one application of the product. This is in contrast to studies of cell-based products and minimally processed human tissue allografts that required an average of 4–6 applications.<sup>14,17</sup> During the 14-day run-in period in this study, only patients having DFUs that healed less than 30% were randomized into the clinical trial. Thus, this study evaluated not only chronic DFUs but also the most difficult to heal DFUs. The wound closure results at

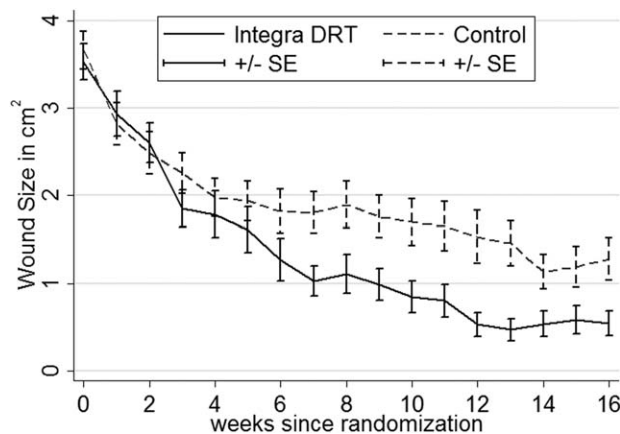


**Figure 3.**  $p < 0.001$  from log-rank test of equality of healing function between the two groups.

12 weeks were similar to those of other multicenter, randomized, controlled studies that assessed outcomes at 12 weeks.<sup>14,15,28</sup>

In DFUs, the rate of wound closure is important because the risk for developing complications increases the longer the wound stays open. Based on the median time to healing, the IDRT group healed 5 weeks faster than the control group. Additionally, the average wound size reduction per week was 50% faster in the IDRT group compared with the control group. As a result of the faster time to wound closure with IDRT, the cost of hospitalization caused by DFU-related complications such as infection and/or amputation can be reduced.

The chronic wound environment provides challenges such as a prolonged inflammatory response and elevated protease activity that damages or disrupts the extracellular matrix and as a result cannot support wound healing.<sup>29</sup> Therefore, collagen-based matrices are thought to be beneficial because of their ability to replace the absent or dysfunctional extracellular matrix<sup>30</sup> and to reduce proteases.<sup>31</sup> It has been further demonstrated that this advanced, bioengineered, acellular matrix minimizes or prevents an



**Figure 4.** Weekly wound size during the treatment phase by treatment group.

inflammatory or immunogenic response that may arise from cell-based products.<sup>15,16,29,32</sup>

One of the limitations of this study and all other DFU studies involving CTPs is that the study was not double-blinded. This bias was overcome by the use of third-party blinded computerized planimetry to confirm wound closure and wound size. Computerized planimetry is considered to be an optimal independent assessment method.<sup>33–35</sup> Despite strict inclusion and exclusion criteria, any bias against generalizability was minimized by enrolling and randomizing subjects from 32 academic and private practice sites across the United States to ensure that study participants represent patients with chronic DFUs from a heterogeneous population. Furthermore, the demographics of this study population were comparable to the demographics of previous multicenter, randomized, controlled clinical studies evaluating CTPs for the treatment of DFUs.<sup>14–17</sup>

This study represents an advanced, bioengineered, acellular matrix that successfully met its primary outcome in a multicenter, randomized, controlled trial. The dermal replacement layer, consisting of collagen and chondroitin-6-sulfate, has been shown to promote dermal regeneration and vascularization in previous clinical studies.<sup>36,37</sup> The new collagen that was formed was indistinguishable from normal dermal collagen.<sup>36,37</sup> The silicone layer provides durability and a moisture flux rate that is comparable to normal epidermis by allowing the wound environment to remain moist. The silicone layer also provides immediate wound closure and acts as a physical barrier to bacterial contamination.<sup>18</sup> In this study, once the silicone layer was removed, the dermal layer promoted reepithelialization of the wound to achieve complete wound closure. IDRT is also ready to use off the shelf in contrast to cell-based products that require additional steps to prepare the product for use.<sup>18</sup> Cell-based products also need multiple reapplications in treating a DFU whereas this study demonstrated that reapplications of IDRT are generally not necessary. These design features of IDRT translate to clinical benefits that are ideal for the treatment of chronic, hard-to-heal DFUs. In this study evaluating CTPs for the treatment of DFUs, IDRT demonstrated safety and efficacy including improvements in quality in life with a single application in the outpatient setting. The safe and effective use of IDRT in the inpatient setting has also been demonstrated previously in clinical trials evaluating its use for the treatment of third degree burns and scar contracture reconstruction. IDRT was designed to maintain a moist wound environment while promoting dermal regeneration and reepithelialization. The history of safe and effective use of IDRM Technology, which has been studied in nearly 600 subjects in various clinical trials for multiple indications in the inpatient and outpatient settings, demonstrates that IDRT could play an important role in the treatment of chronic, hard-to-heal DFUs.

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## Conflicts of Interest

Vickie R. Driver: Dr. Driver reports grants from Integra Lifesciences outside the submitted work; Lawrence A. Lavery: Dr. Lavery reports grants from Integra during the conduct of the study; Alexander M. Reyzelman: Dr. Reyzelman reports personal fees from Integra during the conduct of the study; Timothy G. Dutra: Dr. Dutra reports personal fees from Integra during the conduct of the study; nonfinancial support from Integra, outside the submitted work; Cyaandi R. Dove, DPM: Dr. Dove reports personal fees from Integra during the conduct of the study; personal fees from Integra outside the submitted work; Sandra V. Kotsis, MPH: None; H. Myra Kim: Dr. Kim reports grants from Integra LifeSciences Corporation; Kevin C. Chung: Dr. Chung reports grants from Integra LifeSciences Corporation.

## References

- Boulton A, Armstrong D. *Diabetic foot and ulceration: epidemiology and pathophysiology*. London: Taylor & Francis, 2005.
- Boulton AJ. The diabetic foot. *Medicine* 2010; 38: 644–8.
- Snyder RJ, Kirsner RS, Wariner RA, 3rd, Lavery LA, Hanft JR, Sheehan P. Consensus recommendations on advancing the standard of care for treating neuropathic foot ulcers in patients with diabetes. *Ostomy Wound Manage* 2010; 56 (4 Suppl.): S1–24.
- Margolis DJ, Kantor J, Berlin JA. Healing of diabetic neuropathic foot ulcers receiving standard treatment: a meta-analysis. *Diabetes Care* 1999; 22: 692–5.
- Lavery LA, Armstrong DG, Wunderlich RP, Mohler MJ, Wendel CS, Lipsky BA. Risk factors for foot infections in individuals with diabetes. *Diabetes Care* 2006; 29: 1288–93.
- Ramsey SD, Newton K, Blough D, McCulloch DK, Sandhu N, Reiber GE, et al. Incidence, outcomes, and cost of foot ulcers in patients with diabetes. *Diabetes Care* 1999; 22: 382–7.
- Sanders LJ. Diabetes mellitus: prevention of amputation. *J Am Podiatr Med Assoc* 1994; 84: 322–8.
- Bild DE, Selby JV, Sinnock P, Browner WS, Braveman P, Showstack JA. Lower-extremity amputation in people with diabetes. Epidemiology and prevention. *Diabetes Care* 1989; 12: 24–31.
- Rice JB, Desai U, Cummings AK, Birnbaum HG, Skornicki M, Parsons NB. Burden of diabetic foot ulcers for medicare and private insurers. *Diabetes Care* 2014; 37: 651–8.
- Armstrong DG, Lavery LA, Wrobel JS, Vileikyte L. Quality of life in healing diabetic wounds: does the end justify the means? *J Foot Ankle Surg* 2008; 47: 278–82.
- Ribu L, Hanestad BR, Moum T, Birkeland K, Rustoen T. A comparison of the health-related quality of life in patients with diabetic foot ulcers, with a diabetes group and a nondiabetes group from the general population. *Qual Life Res* 2007; 16: 179–89.
- Goodridge D, Trepman E, Sloan J, et al. Quality of life of adults with unhealed and healed diabetic foot ulcers. *Foot Ankle Int* 2006; 27: 274–80.
- The University of Michigan Medical School, The University of Michigan Health System's Educational Services for Nursing, Barry University School of Podiatric Medicine. The standard of care for evaluation and treatment of diabetic foot ulcers. 2010. Available at [http://www.woundcarenurses.org/uploads/7/6/6/7/7667574/diabetic\\_ulcers.pdf](http://www.woundcarenurses.org/uploads/7/6/6/7/7667574/diabetic_ulcers.pdf) (accessed May 29, 2014).
- Veves A, Falanga V, Armstrong DG, Sabolinski ML. Graftskin, a human skin equivalent, is effective in the management of noninfected neuropathic diabetic foot ulcers: a prospective randomized multicenter clinical trial. *Diabetes Care* 2001; 24: 290–5.
- Marston WA, Hanft J, Norwood P, Pollak R. The efficacy and safety of Dermagraft in improving the healing of chronic diabetic foot ulcers: results of a prospective randomized trial. *Diabetes Care* 2003; 26: 1701–5.
- Reyzelman A, Crews RT, Moore JC, et al. Clinical effectiveness of an acellular dermal regenerative tissue matrix compared to standard wound management in healing diabetic foot ulcers: a prospective, randomised, multicentre study. *Int Wound J* 2009; 6: 196–208.
- Lavery LA, Fulmer J, Shebetka KA, et al. The efficacy and safety of Grafix<sup>®</sup> for the treatment of chronic diabetic foot ulcers: results of a multi-centre, controlled, randomised, blinded, clinical trial. *Int Wound J* 2014; 11: 554–60.
- Yannas IV, Burke JF. Design of an artificial skin. I. Basic design principles. *J Biomed Mater Res* 1980; 14: 65–81.
- Heimbach DM, Warden GD, Luterma A, et al. Multicenter postapproval clinical trial of Integra dermal regeneration template for burn treatment. *J Burn Care Rehabil* 2003; 24: 42–8.
- U.S. Department of Health & Human Services Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), Center for Devices and Radiological Health (CDRH). FDA Guidance for Industry: Chronic Cutaneous Ulcer and Burn Wounds-Developing Products for Treatment. June 2006 Clinical/Medical. Available at: <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071324.pdf>, (accessed May 29, 2014).
- American Society of Plastic Surgeons. Evidence-based Clinical Practice Guideline: Chronic Wounds of the Lower Extremity. 2007; 1–21.
- Steed DL. Clinical evaluation of recombinant human platelet-derived growth factor for the treatment of lower extremity diabetic ulcers. Diabetic Ulcer Study Group. *J Vasc Surg* 1995; 21: 71–8; discussion 79–81.
- Steed DL, Goslen JB, Holloway GA, Malone JM, Bunt TJ, Webster MW. Randomized prospective double-blind trial in healing chronic diabetic foot ulcers. CT-102 activated platelet supernatant, topical versus placebo. *Diabetes Care* 1992; 15: 1598–604.
- Steed DL, Ricotta JJ, Prendergast JJ, et al. Promotion and acceleration of diabetic ulcer healing by arginine-glycine-aspartic acid (RGD) peptide matrix. RGD Study Group. *Diabetes Care* 1995; 18: 39–46.
- Richard JL, Parer-Richard C, Daures JP, et al. Effect of topical basic fibroblast growth factor on the healing of chronic diabetic neuropathic ulcer of the foot. A pilot, randomized, double-blind, placebo-controlled study. *Diabetes Care* 1995; 18: 64–9.
- Gentzkow GD, Iwasaki SD, Hershon KS, et al. Use of dermagraft, a cultured human dermis, to treat diabetic foot ulcers. *Diabetes Care* 1996; 19: 350–4.

27. Wieman TJ, Smiell JM, Su Y. Efficacy and safety of a topical gel formulation of recombinant human platelet-derived growth factor-BB (becaplermin) in patients with chronic neuropathic diabetic ulcers. A phase III randomized placebo-controlled double-blind study. *Diabetes Care* 1998; 21: 822–7.
28. Edmonds M. Apligraf in the treatment of neuropathic diabetic foot ulcers. *Int J Low Extrem Wounds* 2009; 8: 11–8.
29. International consensus. Acellular matrices for the treatment of wounds. An expert working group review. London: Wounds International, 2010.
30. Gibson D, Cullen B, Legerstee R, Harding K, Schultz G. MMPs made easy. *Wound Int* 2009; 1: 1–6. Available at <http://www.woundsinternational.com>. (accessed May 29, 2014).
31. Ulrich D, Smeets R, Unglaub F, Woltje M, Pallua N. Effect of oxidized regenerated cellulose/collagen matrix on proteases in wound exudate of patients with diabetic foot ulcers. *J Wound Ostomy Continence Nurs* 2011; 38: 522–8.
32. Rizzi SC, Upton Z, Bott K, Dargaville TR. Recent advances in dermal wound healing: biomedical device approaches. *Expert Rev Med Devices* 2010; 7: 143–54.
33. Gethin G, Cowman S. Wound measurement: the contribution to practice. *EWMA J*. 2007; 7: 26–8.
34. Brem H, Sheehan P, Rosenberg HJ, Schneider JS, Boulton AJ. Evidence-based protocol for diabetic foot ulcers. *Plast Reconstr Surg* 2006; 117 (7 Suppl.): 193S–209S; discussion 210S–211S.
35. Plassmann P. Measuring wounds. A guide to the use of wound measurement techniques. *J Wound Care* 1995; 4: 269–72.
36. Moiemens NS, Staiano JJ, Ojeh NO, Thway Y, Frame JD. Reconstructive surgery with a dermal regeneration template: clinical and histologic study. *Plast Reconstr Surg* 2001; 108: 93–103.
37. Stern R, McPherson M, Longaker MT. Histologic study of artificial skin used in the treatment of full-thickness thermal injury. *J Burn Care Rehabil* 1990; 11: 7–13.

# EXECUTIVE SUMMARY

## Indications for Use

Integra LifeSciences Corporation submitted this premarket approval (PMA) supplement for Integra® Dermal Regeneration Template (Integra®) PMA P900033 to obtain an additional indication for use in the treatment of partial and full-thickness diabetic foot ulcers, in conjunction with standard diabetic ulcer care regimens including sharp debridement, non-adherent dressings, and offloading.

Integra® Dermal Regeneration Template was originally indicated for the post-excisional treatment of life-threatening full-thickness or deep partial-thickness thermal injuries where sufficient autograft is not available at the time of excision or not desirable due to the physiological condition of the patient.

Integra® Dermal Regeneration Template is also indicated for the repair of scar contractures when other therapies have failed or when donor sites for repair are not sufficient or desirable due to the physiological condition of the patient.

After approval of the PMA supplement on January 7, 2016, the new indications for use are as follows:

- Integra® Dermal Regeneration Template is indicated for: the postexcisional treatment of life-threatening full-thickness or deep partial-thickness thermal injuries where sufficient autograft is not available at the time of excision or not desirable due to the physiological condition of the patient; repair of scar contractures when other therapies have failed or when donor sites for repair are not sufficient or desirable due to the physiological condition of the patient; **and treatment of partial and full-thickness neuropathic diabetic foot ulcers that are greater than six weeks in duration with no capsule, tendon or bone exposed, when used in conjunction with standard diabetic ulcer care.**

Because Integra will also provide IDRT under a new product label, Omnigraft™, FDA approved this product with the following indication:

- Integra® Omnigraft™ Dermal Regeneration Matrix is indicated for use in the **treatment of partial and full-thickness neuropathic diabetic foot ulcers that are greater than six weeks in duration, with no capsule, tendon or bone exposed, when used in conjunction with standard diabetic ulcer care.**

## **Device Description**

Integra<sup>®</sup> Dermal Regeneration Template (Integra template), available in Meshed and Non-Meshed configurations, is a bilayer matrix for dermal regeneration. The dermal replacement layer consists of a porous, three-dimensional matrix, comprised of collagen and chondroitin-6-sulfate (C6S) that is designed with a controlled porosity and defined degradation rate to promote wound healing. The temporary epidermal layer is made of a thin polysiloxane (silicone) layer to provide immediate wound coverage and control moisture loss from the wound.

Integra<sup>®</sup> is provided sterile and non-pyrogenic. The inner foil pouch and product should be handled using sterile technique. Integra<sup>®</sup> should not be re-sterilized.

Integra<sup>®</sup> will also be marketed as Omnigraft<sup>™</sup> Dermal Regeneration Matrix, specifically for the indication in the treatment of diabetic foot ulcers.

## **Alternative Practices and Procedures**

Currently, the standard of care for diabetic foot ulcers is sharp debridement, moist wound therapy with daily wound care dressings, off-loading, and infection control<sup>1</sup>. However, the majority of diabetic foot ulcers that undergo this treatment do not heal completely and are considered to be non-responsive to conventional therapy if the diabetic foot ulcer has not shown significant improvement in four weeks<sup>2</sup>. For these non-healing, chronic diabetic foot ulcers, there have been a number of other commercially available devices that are cellular and/or tissue based products, previously known as skin substitutes. Some have been evaluated in multicenter, randomized, controlled clinical trials which have demonstrated varying degrees of success<sup>3-6</sup>. The products evaluated in these randomized, controlled trials consist of cell-based products and minimally processed human tissue allografts.

## **Marketing History**

Integra<sup>®</sup> Dermal Regeneration Template (Integra<sup>®</sup>) was first granted FDA Premarket Approval for use in life-threatening thermal injuries under PMA P900033 on 01 March 1996. On 19 April

2002, PMA Supplement P900033/S008 was approved, expanding the indication for use to include repair of scar contractures. On 23 April 2004, FDA approved an electron beam (e-beam) sterilized version of the Integra<sup>®</sup> under PMA Supplement P900033/S011. Terminally-sterilized Integra<sup>®</sup> was the device evaluated under IDE G090146 and therefore the subject device of this PMA panel-track supplement.

Integra<sup>®</sup> was granted CE Mark approval in the European Union on 20 March 1998. The Integra<sup>®</sup> product line is currently approved for marketing in the United States, European Union, Canada, Mexico, Argentina, Brazil, Colombia, Costa Rica, Peru, South Africa, Turkey, United Arab Emirates, Saudi Arabia, Israel, Egypt, Serbia, Jordan, Japan, New Zealand, Australia, and Singapore for use in burns and reconstructive surgery. It is estimated that over 90,000 units of Integra<sup>®</sup> have been sold worldwide since market release and the device has not been recalled or withdrawn for any reason related to the safety or effectiveness of the device.

The Integra<sup>®</sup> collagen and chondroitin-6-sulfate (C6S) and silicone bilayer matrix is also marketed as Integra<sup>®</sup> Bilayer Matrix Wound Dressing under Premarket Notification 510(k) K021792, indicated for the management of wounds. Integra<sup>®</sup> Meshed Bilayer Wound Matrix is also FDA cleared under Premarket Notification 510(k) K081635 and has similar indications as Integra<sup>®</sup> Bilayer Matrix Wound Dressing.

In total since launch in 1996, approximately 199,000 units of product from the Integra<sup>®</sup> product family have been sold. In searching Integra's internal complaint system, it was found that a total of 169 Medical Device Reports (MDRs) have been submitted in that time frame. Of these MDRs, 58 were non-clinical complaints (unacceptable/damaged packaging or product, shipping errors, expired product) and 111 were clinical performance related (infection, poor take/graft loss, allergic reaction, events related to non-healing or poor quality healing). This results in an MDR frequency of 0.085%.

## **Summary of Clinical Study for Diabetic Foot Ulcers**

The following is a summary of the clinical study design and data used to support the approval of the Integra<sup>®</sup> Dermal Regeneration Template for an additional indication for use in the treatment of diabetic foot ulcers. The study, '*A Multi-center, Randomized, Controlled Clinical Trial to Evaluate the Safety and Effectiveness of Integra<sup>®</sup> Dermal Regeneration Template for the Treatment of Neuropathic Diabetic Foot Ulcers*' was approved under IDE G090146.

## Objective

The objective of this study was to evaluate the safety and effectiveness of the Integra<sup>®</sup> Dermal Regeneration Template for the treatment of diabetic foot ulcers located distal to the malleolus in subjects with diabetes mellitus, neuropathy, and without significantly compromised arterial circulation.

## Pivotal Diabetic Foot Ulcer Study Design

### *Study Design and Methods*

This study was a pivotal, multi-center, controlled, stratified, randomized, parallel-group clinical trial, designed to establish the superior effectiveness of the Integra<sup>®</sup> Dermal Regeneration Template (Integra<sup>®</sup>), over that of Standard of Care, for healing diabetic foot ulcers in subjects with diabetes. The Standard of Care therapy in this study was moist wound therapy consisting of 0.9% Sodium Chloride gel. Both treatment groups received debridement prior to application of treatment, appropriate secondary dressings (consisting of a non-adherent foam dressing and an outer gauze wrap which was selected to maintain a moist wound environment) and off-loading/protective devices appropriate to the location of the ulcer, as well as nutritional support. The region of interest on the foot included only those areas distal to the malleolus.

The design of this study was based on FDA's *Guidance for Industry: Chronic Cutaneous Ulcer and Burn Wounds – Developing Products for Treatment* (FDA 2006). The study was designed in three phases: a two week Screening/Run-in Phase, a sixteen week Randomization/Treatment Phase and a twelve week Follow-up Phase.

### *Run-in Phase:*

After providing written informed consent, and prior to randomization, subjects entered a Screening/Run-in Phase. During this phase a series of screening assessments were performed to determine subject eligibility. During the two-week Run-in period, patients were treated with debridement and the Standard of Care treatment of moist wound therapy, plus secondary dressings and off-loading. The inclusion and exclusion criteria for the study that were reviewed during this phase are listed in **Table 1.1** and **Table 1.2**.



**Table 1.1 - Inclusion Criteria for the Diabetic Foot Ulcer (DFU) Clinical Trial**

Inclusion Criteria
1. A signed and dated ICF has been obtained
2. The subject was able and willing to comply with study procedures
3. The subject, of either sex, is $\geq 18$ years of age
4. The subject, if female and of child-bearing potential, has a negative serum pregnancy test at Screening
5. The subject had Type I or Type II diabetes mellitus
6. The subject had a glycosylated hemoglobin (HbA1c) level $\leq 12\%$
<p>7. Presence of at least one DFU that met all of the following criteria:</p> <ul style="list-style-type: none"> <li>a) Ulcer had been diagnosed as a full-thickness neuropathic DFU and was located distal to the malleolus (ulcer between the toes were excluded but those of the heel were allowed)</li> <li>b) There was a minimum 2 cm margin between the qualifying study ulcer and any other ulcers on the affected foot after debridement</li> <li>c) Ulcer size (area) was <math>\geq 1 \text{ cm}^2</math> and <math>\leq 12 \text{ cm}^2</math> (post debridement at time of randomization)</li> <li>d) Wagner grade 1 or 2</li> <li>e) Depth <math>\leq 5\text{mm}</math> with no exposed capsule, tendon or bone and no tunneling, undermining or sinus tracts</li> <li>f) Duration of the study ulcer was at least 30 days at the time of the Screening visit</li> </ul> <p>Note: If the subject had more than one qualifying DFU, the ulcer designated as the study ulcer was at the discretion of the Investigator. Non-study ulcers being treated during the course of the study could only be treated with moist wound therapy (the Standard of Care identified under this study).</p>
<p>8. Subject had adequate vascular perfusion of the affected limb, as defined by at least one of the following:</p> <ul style="list-style-type: none"> <li>a) Ankle-Brachial Index (ABI): <math>\geq 0.65</math> and <math>\leq 1.2</math></li> <li>b) Toe Pressure (plethysmography) <math>&gt; 50\text{mm Hg}</math></li> <li>c) TcPO<sub>2</sub> <math>&gt; 40 \text{ mm Hg}</math></li> <li>d) Doppler ultrasound (biphasic or triphasic waveforms) consistent with adequate blood flow to the affected extremity, as determined by the Standard of Care practices of the Investigator and the investigational study site</li> </ul>
9. Subject or responsible caregiver was willing and able to maintain the required off-loading (as applicable for the location of the ulcer) and applicable dressing changes

**Table 1.2 - Exclusion Criteria for the Diabetic Foot Ulcer (DFU) Clinical Trial**

Exclusion Criteria
1. Subject had suspected or confirmed signs/symptoms of gangrene or wound infection on any part of the affected limb (subjects with wound infection at the Screening visit could be treated and subsequently re-screened for participation in the study after eradication of the infection)
2. Subject had a history of hypersensitivity to bovine collagen and/or chondroitin
3. Subject was pregnant at the time of treatment
4. Subject was previously treated under this clinical study protocol
5. Subject had participated in another clinical study involving a device or a systematically administered investigational study drug or treatment within 30 days of the randomization visit
6. Subject was currently receiving (within 30 days of the randomization visit) or was scheduled to receive a medication or treatment which, in the opinion of the Investigator, was known to interfere with, or affect the rate and quality of, wound healing (e.g., systemic steroids, immunosuppressive therapy, autoimmune disease therapy, cytostatic therapy within 12 months prior to randomization, dialysis, radiation therapy to the foot, vascular surgery, angioplasty or thrombolysis)
7. Subject had any of the following unstable conditions or circumstances that could interfere with treatment regimen compliance, such as the following: <ul style="list-style-type: none"> <li>a) Ability to perform required dressing changes</li> <li>b) Ability to comply with treatment visit schedule</li> <li>c) Mental incapacity</li> <li>d) Current substance abuse</li> </ul>
8. Subject had excessive lymphedema, which, in the opinion of the Investigator, could interfere with wound healing
9. Subject had unstable Charcot foot or Charcot with boney prominence that, in the opinion of the Investigator, could inhibit the wound healing
10. Subject had ulcers secondary to diseases other than diabetes, e.g., vasculitis, neoplasms, or hematological disorders
11. Subject had osteomyelitis with necrotic soft bone. (If the Investigator suspected the presence of osteomyelitis, the diagnosis required confirmation by plain film X-ray)
12. Subject had Chopart amputation
13. Subject had a history of bone cancer or metastatic disease of the affected limb, radiation therapy to the foot, or had had chemotherapy within the 12 months prior to randomization
14. Subject had been treated with wound dressings that included growth factors, engineered tissues, or skin substitutes (e.g., Regranex <sup>®</sup> , Dermagraft <sup>®</sup> , Apligraf <sup>®</sup> , GraftJacket <sup>®</sup> , OASIS <sup>®</sup> , Primatrix <sup>®</sup> , Matristem <sup>®</sup> ) within 30 days of randomization or was scheduled to receive these during the study
15. Subject had been treated with hyperbaric oxygen within 5 days of Screening or was scheduled to receive this therapy during the study
16. Subject had a non-study ulcer that required a treatment other than moist wound therapy (i.e., the Standard of Care identified under this study)

### Exclusion Criteria

17. Subject had a history of or any of the following intercurrent illnesses or conditions that could compromise the safety of the subject or the normal wound healing process:

- a) End stage renal disease
- b) Immunosuppression
- c) Severe malnutrition
- d) Liver disease
- e) Aplastic anemia
- f) Scleroderma
- g) Acquired immune deficiency disease (AIDS) or Human Immunodeficiency Virus (HIV) positive
- h) Connective tissue disorder
- i) Exacerbation of sickle cell anemia

18. Subject was an employee or relative or any member of the Investigational site or the Sponsor.

19. At the end of the Run-in period, and prior to Randomization, the subject was excluded if either of the following conditions were met:

- a) Subject did not continue to meet the entrance criteria (inclusion and exclusion) above, or
- b) The size of the study ulcer, following debridement, had decreased by more than 30% from the baseline assessment measured at Screening.

After the two-week Run-in period, subjects whose ulcers exhibited less than 30% re-epithelialization and who continued to meet the eligibility criteria were randomized to either Active Treatment [Integra<sup>®</sup> Dermal Regeneration Template (IDRT)] or Control Treatment (Standard of Care) for the Treatment Phase of the study.

#### ***Treatment Phase:***

During the Treatment Phase, subjects were treated according to the study-specified therapies (IDRT or Control Treatment, plus sponsor-provided secondary dressings and an off-loading/protective device) for up to 16 weeks or until the study ulcer completely healed, and were evaluated weekly. Efficacy evaluations during this phase included weekly Investigator assessments of wound closure in addition to planimetric evaluations of ulcer size, as well as a Quality of Life questionnaire which subjects completed at the start and at the end of the Treatment Phase. Safety evaluations included assessment for adverse events and use of medications and new therapies.

At the completion of the Treatment Phase:

- Subjects with 100% healed ulcers were considered treatment successes and entered the Follow-up Phase.
- Subjects with unhealed ulcers at the end of the Treatment Phase were considered treatment failures, but continued in the study (entered the Follow-up Phase).

### ***Follow-up Phase:***

Four weeks after either the study ulcer was confirmed as completely healed or the final Treatment Visit was completed, subjects entered the 12-week Follow-up phase. During the Follow-up Phase, visits occurred monthly (i.e., every four weeks). Subjects with complete wound closure were monitored for efficacy and safety. Efficacy evaluations included clinical evaluation of the study ulcer site for breakdown and recurrence and administration of the Quality of Life Questionnaire.

Safety evaluations during the Follow-up Phase for both treatment successes and treatment failures consisted of adverse event assessments at each visit and measurement of clinical laboratory parameters at the last Follow-up visit.

At the end of the Follow-up Phase, study status was assessed as follows:

- Subjects who entered the Follow-up Phase as treatment successes were considered:
  - Follow-up successes if their ulcer did not recur
  - Follow-up failures if their ulcer recurred
- All subjects entering and completing the Follow-up Phase (both healed and unhealed ulcers) were considered Follow-up Phase completers

### ***Diabetic Foot Ulcer Study Endpoints***

#### ***Primary Efficacy Endpoint***

The primary efficacy endpoint for the study was the percentage of subjects with complete closure of the study ulcer, as assessed by the Investigator, during the Treatment Phase.

#### ***Secondary Efficacy Endpoints***

Secondary endpoints which were also evaluated included:

1. Percentage of subjects with complete wound closure of the study ulcer, as assessed by computerized planimetry, during the Treatment Phase.
2. Time to complete wound closure, as assessed by the Investigator.
3. Time to complete wound closure, as assessed by computerized planimetry.
4. Rate of wound closure, as assessed by computerized planimetry.
5. Incidence of ulcer recurrence at the site of the study ulcer during the Follow-up Phase.
6. Change in Quality of Life metrics.

#### ***Safety Endpoints***

Safety endpoints included:

- Adverse events (type and frequency)
- Changes in laboratory values for serum creatinine, blood urea nitrogen (BUN), serum glucose, HbA1c, pre-albumin and CBC with differential

### *Study Hypothesis*

This clinical trial was designed to test the hypothesis that the Integra<sup>®</sup> will result in superior healing of neuropathic foot ulcers compared to a Standard of Care treatment in subjects with diabetes mellitus, neuropathy, and without significantly compromised arterial circulation.

### **Patient Accountability**

During the Diabetic Foot Ulcer Clinical Trial, a total of 545 subjects were screened, and 307 subjects were randomized. One hundred and fifty four (154) subjects were randomized into the IDRT Treatment group and 153 subjects were randomized into the Control Treatment group. In the IDRT Treatment group, 128 subjects completed the Treatment phase and 106 subjects completed the Follow-up phase. In the Control Treatment group, 117 subjects completed the Treatment phase and 82 subjects completed the Follow-up phase.

For this study, there were three analysis populations (Intent-to-Treat (ITT), Per Protocol, and Safety Population) which are described below.

Intent-to-Treat Population: all randomized subjects. This population was used as the primary population for the analyses of primary and secondary efficacy endpoints.

Per Protocol Population: all randomized subjects who were not associated with a major protocol violation. This population was identified before database lock. Analyses of efficacy endpoints using this population were considered as supportive.

Safety Population: any subject receiving Study Treatment after randomization. This population was used for the analysis of safety parameters.

### **Study Population Demographics and Baseline Parameters**

The baseline demographics in the Integra and Control arms were comparable for all parameters evaluated, including, but not limited to, severity and type of diabetes, gender, race, age, and ulcer size area. The population demographics are shown in **Table 1.3**.

The demographic groups represented in this study correlate to the population that is affected by diabetic foot ulcers.

**Table 1.3 - Demographic Characteristics, ITT Population**

Characteristic	Statistic	IDRT	Control	Total
		N = 154	N = 153	N = 307
Age (years)[1]	Mean (SD)	55.8 (10.6)	57.3 (9.7)	56.5 (10.1)
	Median	56.0	57.0	57.0
	Min, Max	31.0, 82.0	28.0, 82.0	28.0, 82.0
Gender	Male, n (n/N%)	118 (76.6)	114 (74.5)	232 (75.6)
	Female, n (n/N%)	36 (23.4)	39 (25.5)	75 (24.4)
Race	American Indian/Alaskan Native, n (n/N%)	0 (0.0)	2 (1.3)	2 (0.6)
	Asian, n (n/N%)	1 (0.6)	2 (1.3)	3 (1.0)
	Black Or African American, n (n/N%)	28 (18.2)	34 (22.1)	62 (20.1)
	Native Hawaiian Or Pacific Islander, n (n/N %)	1 (0.6)	0 (0.0)	1 (0.3)
	Caucasian, n (n/N %)	118 (76.6)	111 (72.1)	229 (74.4)
	Other, n (n/N %)	6 (3.9)	5 (3.2)	11 (3.6)
Ethnicity	Not Hispanic/Latino, n (n/N%)	108 (70.1)	116 (75.8)	224 (73.0)
	Hispanic or Latino, n (n/N%)	46 (29.9)	37 (24.2)	83 (27.0)
N = number of subjects within the population and treatment group and the denominator for percentages				
n = number of subjects within the population and treatment group and the numerator for percentages				
SD = standard deviation				
Min = minimum value				
Max = maximum value				
[1] Age (years) = integer of [(date of informed consent - date of birth)/ 365.25+ 0.5]				
Source location in CSR, <b>Attachment 9.1: Section 11.2.1, Table 11-2</b>				

Due to the target patient population, there were many comorbidities that the subjects of this study faced. The summary of medical histories of the patients is presented in **Table 1.4** by the medical body system that was affected by the medical condition. Almost all of the conditions were ongoing throughout the study. The findings were comparable between the two treatment groups.

**Table 1.4 - Summary of Comorbidities of all Patients in the Study**

Medical Body System [1]	IDRT	Control	Total
	N = 154	N = 153	N = 307
	n (n/N%)	n (n/N%)	n (n/N%)
Cardiovascular	137 (89.0)	137 (89.5)	274 (89.3)
Dermatologic	44 (28.6)	51 (33.3)	95 (30.9)
Endocrine	154 (100)	153 (100)	307 (100)
Gastrointestinal	49 (31.8)	57 (37.3)	106 (34.5)
Genitourinary	24 (15.6)	25 (16.3)	49 (16.0)
Hematologic	18 (11.7)	35 (22.9)	53 (17.3)
Hepatic	4 (2.6)	7 (4.6)	11 (3.6)
Immunologic	15 (9.7)	18 (11.8)	33 (10.7)
Lymphatic	11 (7.1)	6 (3.9)	17 (5.5)
Neurological	108 (70.1)	111 (72.5)	219 (71.3)
Other	97 (63.0)	98 (64.1)	195 (63.5)
Psychiatric	30 (19.5)	37 (24.2)	67 (21.8)
Renal	15 (9.7)	33 (21.6)	48 (15.6)
Respiratory	21 (13.6)	30 (19.6)	51 (16.6)
[1] A subject is counted only once within each category.			
N = number of subjects within the population and treatment group and the denominator for percentages			
n = number of subjects within the population and treatment group and the numerator for percentages			
<i>Source location in CSR, Attachment 9.1: Section 11.2.3, Table 11-7</i>			

## Safety and Effectiveness Results

### *Safety Results*

The analysis of the safety was based on the treated Safety Population of 307 total patients, 154 IDRT Treatment and 153 Control Treatment. The key safety outcomes for this study are presented below in **Table 1.6**, **Table 1.7**, and **Table 1.8** which show that the IDRT Treatment group had less adverse events, serious adverse events, and potentially related adverse events than the Control group. **Table 1.5** contains a summary of the most frequently occurring adverse events reported during the study.

## Adverse Events

All adverse events that were reported in the study evaluating Integra<sup>®</sup> for the treatment of diabetic foot ulcers at a frequency of  $\geq 5\%$  in either cohort are presented in **Table 1.5**. This table includes adverse events that were both attributed to and not attributed to treatment. The adverse events are listed in descending order according to their frequency in the Integra<sup>®</sup> cohort. There were no unanticipated adverse effects in the clinical trial.

**Table 1.5 - Adverse Events Reported in Greater than 5% of Patients in the Diabetic Foot Ulcer Study**

Adverse event	IDRT N=154 Subjects n (n/N%)	Control N= 153 subjects n (n/N%)
Diabetic foot infection	23 (14.9)	23 (15.0)
Diabetic foot <sup>1</sup>	22 (14.3)	31 (20.3)
Pain in extremity	14 (9.1)	20 (13.1)
Cellulitis	13 (8.4)	13 (8.5)
Osteomyelitis	9 (5.8)	19 (12.4)
Condition aggravated	6 (3.9)	14 (9.2)
N = number of subjects within the population and treatment group and the denominator for percentages		
n = number of subjects within the population and treatment group and the numerator for percentages		
<i>Source location in CSR, Attachment 9.1: Section 14.3.1, Table 14.3.1.1, Section 16, Appendix 16.2, Listing 16.2.7.1</i>		
<sup>1</sup> The preferred term Diabetic Foot includes new, worsening or recurring ulcer.		

A total of 798 adverse events occurred in 216 of the 307 randomized subjects as presented in **Table 1.6**. Of the 798 adverse events, 444 occurred in the Control arm, treated with the standard of care established within this trial. The remaining 354 AEs occurred in the IDRT arm, treated with the Integra<sup>®</sup>.



**Table 1.6 - Summary of Adverse Events, Safety Population**

Number of subjects	IDRT (N = 154)		Control (N = 153)		Total (N = 307)	
	n (n/N %)	All incidences	n (n/N %)	All incidences	n (n/N %)	All incidences
With any reported AE	101 (65.6)	354	115 (75.2)	444	216 (70.4)	798
N = number of subjects within the population and treatment group and the denominator for percentages						
n = number of subjects within the population and treatment group and the numerator for percentages						
<i>Source location in CSR, Attachment 9.1: Section 12.2.1, Table 12-2</i>						

Twenty-eight (28) adverse events were reported by investigators as being related to the study treatment, as summarized in **Table 1.7**. Eleven (11) potentially related adverse events occurred within the IDRT arm and were therefore considered related to the Integra<sup>®</sup>, and 17 adverse events were considered potentially related to the control treatment. Of the 11 device-related AEs in the IDRT group, four (4) were considered Serious Device-Related Adverse Events (sepsis, diabetic foot infection, cellulitis, and infected skin ulcer). None of the Serious Device-Related Adverse Events were unanticipated.

**Table 1.7 - Summary of Adverse Events by Relationship to Treatment, Safety Population**

Relationship	IDRT (N=154)		Control (N=153)		Total (N=307)	
	n (n/N %)	All incidences	n (n/N %)	All incidences	n (n/N %)	All instances
Potentially related	7 (4.5)	11	8 (5.2)	17	15 (4.9)	28
Unlikely or not related	97 (63.0)	343	115 (75.2)	427	212 (69.1)	770
Note: Subjects are counted only once within each category						
N = number of subjects within the population and treatment group and the denominator for percentages						
n = number of subjects within the population and treatment group and the numerator for percentages						
<i>Source location in CSR, Attachment 9.1: Section 12.2.3.2, Table 12-7</i>						

Adverse events were recorded as mild, moderate, severe or life-threatening. There were three (3) life-threatening adverse events reported in the IDRT group and 10 in the Control group; none of the life-threatening adverse events in either group were considered related to treatment.

Overall, adverse events occurred in 66% of Integra<sup>®</sup> subjects and 75% of Control subjects (**Table 1.6**). Those adverse events determined to be serious occurred in 25% of IDRT subjects and 36% of Control subjects. A summary of Serious Adverse Events is provided in **Table 1.8**.

**Table 1.8 - Summary of Serious Adverse Events, Safety Population**

Parameter	IDRT	Control	Total
	N = 154	N = 153	N = 307
	n (n/N %)	n (n/N %)	n (n/N %)
Number of subjects with any SAE	38 (24.7)	55 (35.9)	93 (30.3)
Number of all incidences	54	89	143
Note: Note: Subjects are counted only once within each category			
N = number of subjects within the population and treatment group and the denominator for percentages			
n = number of subjects (or observations) within the population and treatment group and the numerator for percentages			
<i>Source location in CSR, Attachment 9.1: Section 12.3.1.2, Table 12-10</i>			

#### *Laboratory Results*

None of the subjects in this trial had the Study Treatment discontinued or trial terminated due to laboratory abnormalities.

Changes in the serum chemistry that were deemed clinically significant by the Investigators were reported as adverse events. There were two (2) subjects with SAEs reported as hypoglycemia: one (1) subject (Subject 029002) from the IDRT group and one (1) subject (Subject 029015) from the Control group. However, neither of the SAE incidences were considered related to the Study Treatment based on the Investigator's assessment.

#### *Diabetic Foot Ulcer Study Withdrawals due to Adverse Events and Investigator Decision*

During the Treatment Phase, of the 62 subjects that discontinued, 29 subjects (9.4%) withdrew due to AEs (13 subjects from the IDRT group and 16 subjects from the Control group). A total of 16 subjects (5.2%) were withdrawn at the Investigator's decision (eight (8) subjects in the IDRT group and eight (8) subjects in the Control group).

During the Follow-up Phase, of the 57 subjects that discontinued, nine (9) subjects (2.9%) withdrew due to AEs (zero (0) subjects from the IDRT group and nine (9) subjects from the Control group). A total of 14 subjects (4.6 %) were withdrawn at the Investigator's decision (six (6) in the IDRT group and eight (8) in the Control group).

In total, of the 119 subjects that discontinued from the study, 38 subjects withdrew due to AEs and 30 were withdrawn due to Investigator's decision.

*Diabetic Foot Ulcer Study Drop-outs*

In total, 38.8% of the total randomized subjects (119/307) discontinued from the study; forty eight (48) and 71 subjects in the IDRT and Control groups, respectively, discontinued prior to Treatment Phase completion.

***Effectiveness Results***

*Diabetic Foot Ulcer Study Primary Endpoint*

***Complete Wound Closure – Investigator Assessment:*** A higher percentage of subjects treated with Integra<sup>®</sup> had 100% complete wound closure of the study ulcer (51.3%) in comparison to subjects from the Control group (32.0%), resulting in a treatment difference [delta ( $\Delta$ )] of 19.3%. The difference between the two treatment groups was statistically significant (p-value = 0.0007). The results were based on the Investigator assessment and Intent-to-Treat (ITT) population and are summarized in **Table 1.9**.

**Table 1.9 - Summary of Complete Wound Closure based on the Investigators Assessment of the ITT Population**

Parameter	IDRT	Control	p-value
	N = 154	N = 153	
	n (n/N %)	n (n/N %)	
Subjects with Complete Wound Closure	79 (51.3)	49 (32.0)	0.0007
Subjects without Complete Wound Closure	75 (48.7)	104 (68.0)	
N = number of subjects within the population and treatment group and the denominator for percentages			
n = number of subjects within the population and treatment group and the numerator for percentages			
<i>Source location in CSR, Attachment 9.1: Section 11.4.3, Table 11-11</i>			

*Diabetic Foot Ulcer Study Secondary Endpoints*

- Complete Wound Closure – Computerized Planimetry:*** Statistically significant results were obtained by planimetric measurement of complete wound closure. A significantly higher percentage of subjects showed complete wound closure in the IDRT group (50.0%) in comparison to the Control group (31.4%). The difference ( $\Delta = 18.6\%$ ) between the two treatment groups was statistically significant (p-value = 0.0010). The agreement between the planimetric and Investigator assessments was found to be very strong with a Kappa coefficient of 0.9798.

2. ***Time to Complete Wound Closure – Investigator Assessment:*** Time to complete wound closure of the study ulcer was faster in subjects from the IDRT group than in the Control group when assessed by the investigator. Kaplan-Meier results showed that 50% of the subjects in the IDRT group were estimated to achieve complete wound closure by Day 85 while less than 50% subjects (32%) in the Control group achieved complete wound closure at the end of the Treatment Phase. Similarly, 25% of the subjects in the IDRT group achieved complete wound closure at 43 days, while 92 days were needed for 25% of the subjects in the Control group to achieve complete wound closure. In addition, from the population of subjects with complete wound closure, the median time to complete closure of the wound, when assessed by the Investigator, was 5 weeks shorter for the IDRT group: 43 days for the IDRT group, versus 78 days for the Control group.
3. ***Time to Complete Wound Closure – Computerized Planimetry:*** The finding that subjects in the IDRT group, compared to subjects from the Control group, required a shorter duration of time to achieve complete wound closure was consistent between the Investigator and Planimetric assessments of time to healing. The planimetry assessment of the time to healing correlated significantly with the Investigator assessment (p-value < 0.0001, correlation coefficient = 0.7227). Based on the planimetry assessment, by Day 43, 25% of the subjects in the IDRT group achieved complete wound closure whereas the same statistic for the Control group was 78 days.
4. ***Rate of Wound Size Reduction:*** Subjects treated with Integra<sup>®</sup> demonstrated a significantly higher rate of wound size reduction compared to subjects treated with control. Rate of wound healing (wound size reduction) determined by week, using planimetric measurements, was significantly higher (p-value = 0.0115) in the IDRT group (7.15% healed/week) in comparison to Control group (4.81% healed/week). The cumulative rates of wound size reduction were consistently higher in the IDRT group than in the Control group starting from Treatment Visit 4 to Treatment Visit 17. On average, the wound size reduction per week in the IDRT group was 50% faster than in the Control group.
5. ***Incidence of Ulcer Recurrence:*** The percentage of subjects with ulcer recurrence in the IDRT group was lower than in Control group (19.0% vs. 26.5%, respectively). However, this difference between the treatment groups ( $\Delta = 8\%$ ) was not statistically significant (p-value = 0.3192).
6. ***Change in Quality of Life Metrics:*** The improvement in the Quality of Life metrics were measured and evaluated using the Quality of Life Questionnaire SF-36v2<sup>™</sup> Health Survey by QualityMetric Incorporated and Medical Outcomes Trust (SF-36). Changes in Quality of Life derived upon the normed based scores, showed a significant improvement in Physical Functioning for IDRT treated subjects compared to Control group (p-value =

0.0466). Additionally, subjects treated with the Integra<sup>®</sup> indicated significant reduction in Bodily Pain compared to subjects from the Control group (p-value = 0.0333). A difference trending toward significance was noted for Role Physical category (p-value = 0.0751) where subjects from the IDRT group showed reduced limitations to physical health in comparison to subjects from the Control group. No significant differences were observed between the two treatment groups for other Quality of Life metrics including General Health, Social Functioning, Role Emotional, Mental Health or Vitality.

## **Conclusions Drawn from the Studies**

The data presented in this PMA supplement, coupled with the extensive safety and effectiveness data and reports of clinical experience available on Integra<sup>®</sup> Dermal Regeneration for a similar indication, provides assurance of the safety and effectiveness of this device. Integra<sup>®</sup> provides an alternative method for treatment of diabetic full-thickness foot ulcers which have not adequately responded to conventional ulcer therapy.

## **References**

Copies of the following references, cited in the above section, are provided in full or abstract in **Attachment 1.1**. Where abstracts are provided, copies of the articles will be provided upon request.

1. Ribu L, Hanestad B, Moum T, Birkeland K, Rustoen T. A comparison of the health-related quality of life in patients with diabetic foot ulcers, with a diabetes group and a nondiabetes group from the general population. *Qual Life Res* 2007;16:179-89.
2. Snyder RJ, Kirsner RS, Warriner RA, 3rd, Lavery LA, Hanft JR, Sheehan P. Consensus recommendations on advancing the standard of care for treating neuropathic foot ulcers in patients with diabetes. *Ostomy Wound Manage* 2010;56:S1-24.
3. Reyzelman A, Crews RT, Moore JC, et al. Clinical effectiveness of an acellular dermal regenerative tissue matrix compared to standard wound management in healing diabetic foot ulcers: a prospective, randomised, multicentre study. *Int Wound J* 2009;6:196-208.
4. Veves A, Falanga V, Armstrong DG, Sabolinski ML. Graftskin, a human skin equivalent, is effective in the management of noninfected neuropathic diabetic foot ulcers: a prospective randomized multicenter clinical trial. *Diabetes Care* 2001;24:290-5.
5. Marston WA, Hanft J, Norwood P, Pollak R. The efficacy and safety of Dermagraft in improving the healing of chronic diabetic foot ulcers: results of a prospective randomized trial. *Diabetes Care* 2003;26:1701-5.
6. Lavery LA, Fulmer J, Shebetka KA, et al. The efficacy and safety of Graftix for the treatment of chronic diabetic foot ulcers: results of a multi-centre, controlled, randomised, blinded, clinical trial. *Int Wound J* 2014.

**Bibliography**  
**INTEGRA® Dermal Regeneration Template**

1. Abai B, Elahi MM, Glat PM. Scalp Reconstruction After Resection of Malignant Fibrous Histiocytoma Utilizing a Dermal Regeneration Template: A Case Report. *Wounds* 16(2):71-75, 2004.
2. Abai B, Thayer D, Glat PM. The use of a dermal regeneration template (Integra) for acute resurfacing and reconstruction of defects created by excision of giant hairy nevi. *Plast Reconstr Surg* Jul 2004, 114(1):162-8.
3. Agaoglu G, Erol OO.; A prefabricated, tissue-engineered integra free flap.; *Plast Reconstr Surg*. 2008 Aug;122(2):682.
4. Ahmed S, Hussein SS, Philp B, Healy C; Use of biologic dressing as a temporary wound dressing in reconstruction of a significant forehead Mohs defect; *Dermatol Surg*. 2006 May;32(5):765-7.
5. Aikawa N; Aoki; Yamazaki M. Recent Advances in the Management of Severely Burned Patients. *Nippon Geka Gakkai Zasshi* 1999 Jul; 100(7):424-9.
6. Akhtar S, Hasham S, Abela C, Phipps AR; The use of Integra in necrotizing fasciitis; *Burns*. 2006 Mar;32(2):251-4. Epub 2006 Jan 30.
7. Almond SL, Goyal A, Jesudason EC, Graham KE, Richard B, Selby A, Losty PD. Novel use of skin substitute as rescue therapy in complicated giant exomphalos. *J Pediatr Surg*. 2006 Mar;41(3):e1-2.
8. Anderson, A., and J. Steinberg. . "Can a New Biologic Matrix Facilitate Improved Wound Healing?" *Podiatry Today*, Feb. 2005: 16-18.
9. Baldwin C, Potter M, Clayton E, Irvine L, Dye J.; Topical negative pressure stimulates endothelial migration and proliferation: a suggested mechanism for improved integration of Integra.; *Ann Plast Surg*. 2009 Jan;62(1):92-6.
10. Bansky R. The use of dermal template INTEGRA in a scalpatation injury of hand. *Bratisl Lek Listy*. 2005;106(6-7):221-5.
11. Bargues L, Boyer S, Leclerc T, Duhamel P, Bey E.; [Incidence and microbiology of infectious complications with the use of artificial skin Integra® in burns.]; *Ann Chir Plast Esthet*. 2009 Feb 13. [Epub ahead of print] French.
12. Bar-Meir E, Mendes D, Winkler E; Skin substitutes; *Isr Med Assoc J*. 2006 Mar;8(3):188-91.
13. Bello YM, Falabella AF, Eaglstein Wh. Tissue-Engineered Skin. Current Status in Wound Healing. *Am J Clin Dermatol* 2001;2(5):305-13.
14. Berger A, Tanzella H, Machens G, Liebu J. The Use of Integra in primary burns and unstable secondary repairs. *Chirug* 2000; 71:558-563.
15. Besner GE; Klamar JE. Integra Artificial Skin as a Useful Adjunct in the Treatment of Purpura Fulminans. *J Burn Care Rehabil* 1998; 19:324-329.
16. Bhavsar D, Tenenhaus M.; The use of acellular dermal matrix for coverage of exposed joint and extensor mechanism in thermally injured patients with few options.; *Eplasty*. 2008 Jun 24;8:e33.

**Bibliography**  
**INTEGRA® Dermal Regeneration Template**

17. Blanco NM, Edwards J, Zamboni WA. Dermal substitute (Integra) for open nasal wounds. *Plast Reconstr Surg Jun* 2004, 113(7):2224-5.
18. Boyce ST; Kagan RJ; Meyer NA; Yakuboff KP; Warden GD. The 1999 Clinical Research Award. Cultured Skin Substitutes Combined with INTEGRA® Artificial Skin to Replace Native Skin Autograft and Allograft for the Closure of Excised Full-Thickness Burns. *J Burn Care Rehabil* 1999 Nov-Dec; 20(6):453-61.
19. Bozinko GM, Lowe KE, Reigart CL. A new option for burn victims. *Registered Nurse*. November 1998;2-4.
20. Branski LK, Herndon DN, Pereira C, Mlcak RP, Celis MM, Lee JO, Sanford AP, Norbury WB, Zhang XJ, Jeschke MG; Longitudinal assessment of Integra in primary burn management: a randomized pediatric clinical trial; *Crit Care Med*; 2007 Nov;35(11):2615-23.
21. Burd A, Wong PS.; One-Stage Integra reconstruction in head and neck defects.; *J Plast Reconstr Aesthet Surg*. 2009 Feb 28. [Epub ahead of print]
22. Burd A. The role of serendipity in the evolving indications for Integra dermal regeneration template. *Plast Reconstr Surg* 2002 Apr 15;109(5):1764-6.
23. Burke JF, Yannas IV, Quinby WC, et al. Successful use of a physiologically acceptable artificial skin in the treatment of extensive burn injury. *Ann Surg*. October 1981; 194 (4):413-428.
24. Burke JF. Observations on the development and clinical use of artificial skin: An attempt to employ regeneration rather than scar formation in wound healing. *Jpn J. Surg* 1987; 17(6)431-438.
25. Butler CE; Orgill DP; Yannas IV; Compton CC. Effect of Keratinocyte Seeding of Collagen-Glycosaminoglycan Membranes on the Regeneration of Skin in a Porcine Model. *Plastic & Reconstructive Surgery*; May 1998; 101(6):1572-1579.
26. Butler CE; Yannas IV; Compton CC; Correia CA; Orgill DP. Comparison of Cultured and Uncultured Keratinocytes Seeded into a Collagen-GAG Matrix for Skin Replacements. *BR J Plast Surg* 1999 Mar; 52(2):127-32.
27. Campitiello E, Della Corte A, Fattopace A, D'Acunzi D, Canonico S. The use of artificial dermis in the treatment of chronic and acute wounds: regeneration of dermis and wound healing. *Acta Biomed Ateneo Parmense*. 2005;76 Suppl 1:69-71.
28. Carothers JT, Brigman BE, Lawson RD, Rizzo M. Stacking of a dermal regeneration template for reconstruction of a soft-tissue defect after tumor excision from the palm of the hand: a case report. *J Hand Surg [Am]*. 2005 Nov;30(6):1322-6.
29. Carstens M. Clinical Utility of Integra® Artificial Skin in Pediatric Reconstructive Surgery. Department of Plastic and Reconstructive Surgery, Children's Hospital Oakland. Abstract; 2-28.
30. Cedidi C; Hartmann B; Schepler H; Raff T. Grafting of deeply burned problem zones in the lower extremity with a dermal substitute. Unpublished article. *Eur J Plast Surg* 1998; 438:1-6.



**Bibliography**  
**INTEGRA® Dermal Regeneration Template**

31. Chan ES, Lam PK, Liew CT, Lau HC, Yen RS, King WW. A new technique to resurface wounds with composite biocompatible epidermal graft and artificial skin. *J Trauma* 2001. Feb;50(2):358-62.
32. Chong AK, Chang J; Tissue engineering for the hand surgeon: a clinical perspective; *J Hand Surg [Am]*. 2006 Mar;31(3):349-58.
33. Chou TD, Chen SL, Lee TW, et al. Reconstruction of Burn Scar of the Upper Extremities with Artificial Skin. *Reconstruction of Burn Scar*. October 2000;Vol 108(2):378-385.
34. Chu CS, McManus AT, Matylevich NP, Goodwin CW, Pruitt BA Jr. Integra as a dermal replacement in a meshed composite skin graft in a rat model: a one-step operative procedure. *J Trauma* 2002. Jan;52(1):122-9.
35. Clayman MA, Clayman SM, Mozingo DW; The use of collagen-glycosaminoglycan copolymer (Integra) for the repair of hypertrophic scars and keloids; *J Burn Care Res*. 2006 May-Jun;27(3):404-9.
36. Clayton MC, Bishop JF. Perioperative and Postoperative Dressing Techniques for INTEGRA® Artificial Skin: Views from Two Medical Centers. *Journal of Burn Care & Rehabilitation*. 1998; 19(4):358-363.
37. Collier M; The use of advanced biological and tissue-engineered wound products; *Nurs Stand*. 2006 Oct 25-31;21(7):68, 70, 72 passim.
38. Compton CC, Butler CE, Yannas IV, Warland G, Orgill DP. Organized Skin Structure is Regenerated In-vivo from Collagen-GAG Matrices Seeded with Autologous Keratinocytes. *J Invest Dermatol* June 1998; 110(6)908-916.
39. Dadban A, Luong MS, Teot L, Dereure O, Guillot B; An unexpected side-effect of a dermal regeneration dressing; *J Wound Care*. 2006 Oct;15(9):405.
40. Dagalakakis N, Flink J, Stasikelis P, et al. Design of an artificial skin: Part III. Control of pore structure. *J Biomed Mater Res* 1980; 14:511-528.
41. Dagregorio G, Guillet G. Artificial skin as a valuable adjunct to surgical treatment of a large squamous cell carcinoma in a patient with epidermolysis bullosa. *Dermatol Surg*. 2005 Apr;31(4):474-6.
42. Dantzer E, Braye FM. Reconstructive surgery using an artificial dermis (Integra): results with 39 grafts. *Br J Plast Surg* 2001; Dec;54(8):659-64.
43. Dantzer E, Queruel P, Salinier L, Palmier B, Quinot JF. Dermal regeneration template for deep hand burns: clinical utility for both early grafting and reconstructive surgery. *Br J Plast Surg*. 2003 Dec;56(8):764-74.
44. Dantzer E, Queruel P, Salinier L, Palmier B, Quinot JF. Integra®, a new surgical alternative for the treatment of massive burns. Clinical assessment of acute surgery and reconstructive surgery: on 39 cases. *Annales de Chirurgie et esthetique*, 2001, Vol 46(3):173-189.

**Bibliography**  
**INTEGRA® Dermal Regeneration Template**

45. Demarest GB, Resurrecion R, Lu S, Schermer CA. Experience with Bilaminate Bioartificial Skin Substitute and Ultrathin Skin Grafting in Non-Burn Soft-Tissue Wound Defects. *Wounds* 15(8):250-256, 2003.
46. Descamps H, et al. Reeducation de L'enfant Grand Brule Traite Par Peau Artificielle Integra®. *Brulures* 2000, 1(2):84-88.
47. Dhennin C. Methods of covering severe burns. *Soins* 2002 Oct;(669):45-7.
48. Driver VR, et al, A Clinical Trial of Integra® Template for Diabetic Foot Ulcer Treatment, Wound Regeneration (2015)
49. Druecke D, Lamme EN, Hermann S, Pieper J, May PS, Steinau HU, Steinstrasser L. Modulation of scar tissue formation using different dermal regeneration templates in the treatment of experimental full-thickness wounds. *Wound Repair Regen* Sep-Oct 2004, 12(5):518-27.
50. Duteille F, Perrot P, Pannier M, Hubert L. Evaluation of the advantages of Integra for covering Chinese flap donor sites: a series of 10 cases. *Plast Reconstr Surg* Jul 2004, 114(1):264-6.
51. Edlich RF, Winters KL, Woodard CR, Britt LD, Long WB 3<sup>rd</sup>. Massive soft tissue infections: necrotizing fasciitis and purpura fulminans. *J Long Term Eff Med Implants* 2005, 15(1):57-65.
52. Estrada SI, Gottlieb ME, Trepeta RW. Role of Embryonic Histogenesis in the Healing of Chronic Wounds Using Integra Dermal Regenerative Template. *AM J Dermatopathology* Jun 2006, 28(3):230.
53. FangP, Engrav LH, Gibran NS, Honari S, Kiriluk DB, Cole JK, Fleckman P, Heimbach DM, Bauer GJ, Matsumura H, Warner P. Dermatome setting for autografts to cover INTEGRA. *J Burn Care Rehabil* 2002 Sep-Oct;23(5):327-32.
54. Ferdman AG, Yannas IV. Scattering of Light from Histologic Sections: A New Method for the Analysis of Connective Tissue. *The Society for Investigative Dermatology, Inc.* 1993; 100(5):710-716.
55. Figus A, Leon-Villapalos J, Philp B, Dziewulski P; Severe multiple extensive postburn contractures: a simultaneous approach with total scar tissue excision and resurfacing with dermal regeneration template; *J Burn Care Res*; 2007 Nov-Dec;28(6):913-7.
56. Fitton AR, Drew P, and Dickson WA. The Use of a Bilaminate Artificial Skin Substitute (Integra™) in Acute Resurfacing of Burns: An Early Experience. *Br J Plast Surg.* 2001; 54:208-212.
57. Frame JD, Still J, Lakhel-LeCoadou A, Carstens MH, Lorenz C, Orlet H, Spence R, Berger AC, Dantzer E, Burd A. Use of dermal regeneration template in contracture release procedures: a Multicenter evaluation. *Plast Reconstr Surg* 2004 Apr 15, 113(5):1330-8.

**Bibliography**  
**INTEGRA® Dermal Regeneration Template**

58. Frame, J.D., and J.E. Frame. Modifying Integra as a Regeneration Template in Deep Tissue Planes. *Journal of Plastic, Reconstructive and Aesthetic Surgery*, 2006; 59, 460-464.
59. Fridman R, Bar-David, T. Integra® Bioengineered skin substitute for salvage of complex lower extremity wounds. Poster Presentation at the *Symposium for Advanced Wound Care*, San Diego, California April 24 -27, 2008.
60. Frye KE; Luterman A. Burns and Fractures. *Orthopaedic Nursing*. January/February 1999; 30-35.
61. Gavenis K, Schmidt-Rohlfing B, Mueller-Rath R, Andereya S, Schneider U; In vitro comparison of six different matrix systems for the cultivation of human chondrocytes; *In Vitro Cell Dev Biol Anim*. 2006 May-Jun;42(5-6):159-67.
62. Giovannini UM, Teot L. Aesthetic complex reconstruction of the lower leg: application of a dermal substitute (Integra) to an adipofascial flap. *Br J Plast Surg*. 2002, Mar; 55(2):171-2.
63. Gladstone HB Md, Stewart D Md Phd; An Algorithm for the Reconstruction of Complex Facial Defects; *Skin Therapy Lett*. 2007 Mar;12(2):6-9.
64. Gonyon D, Zenn M. Simple Approach to the Radiated Scalp Wound Using INTEGRA Skin Substitute. *Annals of Plastic Surgery* 2003, Mar;50(3):315-319
65. Goodenough RD, Molnar JA, Burke JF. Closure of burn wounds using an artificial skin. *Surg Rounds*. November 1982; 5(11):16-22.
66. Gottlieb ME, Furman J. Successful Management and Surgical Closure of Chronic and Pathological Wounds using Integra®. *J Burns & Surg Wound Care* [serial online] 2004;3(1):4. Available from: URL: <http://www.journalofburns.com>.
67. Gottlieb, Marc E. Management of Complex and Pathological Wounds with Integra. The Wound Management Manual, 2005; 226-289.
68. Grant I, Green C, Martin R. Strategies to improve the take of commercially available collagen/glycosaminoglycan wound repair material investigated in an animal model. *Burns* 2001; Nov;27(7):699-707.
69. Grant I, Warwick K, Marshall J, Green C, Martin R. The co-application of sprayed cultured autologous keratinocytes and autologous fibrin sealant in a porcine wound model. *Br J Plast Surg* 2002 Apr;55(3):219-27.
70. Gravvanis A, Kakagia D, Papadopoulos S, Tsoutsos D.; Dermal skin template for the management of multiple cutaneous leiomyomas.; *J Cutan Med Surg*. 2009 Mar-Apr;13(2):102-5.
71. Greenhalgh DG, Gaboury R, Warden GD. The Early Release of Axillary Contractures in Pediatric Patients with Burns. *J of Burn Care & Rehab*, January/February 1993.
72. Griffin JE, Johnson DL. Management of the maxillofacial burn patient: current therapy. *J Oral Maxillofac Surg* 2005 Feb; 63(2):247-52.

**Bibliography**  
**INTEGRA® Dermal Regeneration Template**

73. Groos N, Guillot M, Zilliox R, Braye FM. Use of an artificial dermis (Integra) for the reconstruction of extensive burn scars in children. About 22 grafts. *Eur J Pediatr Surg*. 2005 Jun;15(3):187-92.
74. Haertsch P. Reconstructive surgery using an artificial dermis (Integra). *Br J Plast Surg* 2002 Jun;55(4):362-3.
75. Halmy C, Hábel T, Pesthy P, Nádai Z, Juhász Z, Deé J, Tóth M.; [The use of Integra "artificial skin, dermal regeneration template" and the reverse radial forearm fasciocutaneous flap in the primary reconstruction of a septic hand injury]; *Orv Hetil*. 2008 Aug 31;149(35):1653-6. Hungarian.
76. Hansen SL, Voight DW, Wiebelhaus P, Paul SN. Using Skin Replacement Products to Treat Burns and Wounds. *Advances in Skin & Wound Care*. January/February 2001. Vol 14(1):37-44.
77. Heimbach D, Luterman A, Burke J, et al. Artificial dermis for major burns: A multi-center randomized clinical trial. *Ann Surg*. September 1988; 208(3):313-320.
78. Heimbach D, Warden G, Luterman A. Multicenter Postapproval Clinical Trial of Integra® Dermal Regeneration Template for Burn Treatment. *J Burn Care Rehabil* 2003;24:42-48.
79. Heimbach DM, Luterman A, Warden GD et al. Safety and Efficacy of Integra ® Dermal Regeneration Template in Burn Wound Coverage. Presented at the J Boswick Burn & Wound Care Symposium 2001 February 19-23.
80. Heitland A, Piatkowski A, Noah EM, Paullau N. Update on the use of collagen/glycosaminoglycate skin in 15 German burn centers. *Burns* 2004 Aug;30(5):471-5.
81. Helgeson MD, Potter BK, Evans KN, Shawen SB; Bioartificial dermal substitute: a preliminary report on its use for the management of complex combat-related soft tissue wounds; *J Orthop Trauma*; 2007 Jul;21(6):394-9.
82. Herlin C, Louhaem D, Bigorre M, Dimeglio A, Captier G; Use of Integra in a Paediatric Upper Extremity Degloving Injury; *J Hand Surg [Br]*. 2007 Apr;32(2):179-184.
83. Honari S; Gibran NS; Engrav LH; Clayney C; Heimbach DM. Three Years' Experience with 55 INTEGRA® (Artificial Skin) Patients since FDA Approval. *J Burn Care Rehabil*. 2000 Jan-Feb; 21(1)(2):190.
84. Houle JM, Neumeister MW; A prefabricated, tissue-engineered Integra free flap; *Plast Reconstr Surg*; 2007 Oct;120(5):1322-5.
85. Hrabchak C, Flynn L, Woodhouse KA; Biological skin substitutes for wound cover and closure; *Expert Rev Med Devices*. 2006 May;3(3):373-85.
86. Huang C, Yannas IV. Mechanochemical studies of enzymatic degradation of insoluble collagen fibers. *J Biomed Mater Res*. November 8, 1977; 137-154.

**Bibliography**  
**INTEGRA® Dermal Regeneration Template**

87. Hunt JA, Moisisidis E, Haertsch P. Initial experience of Integra in the treatment of post-burn anterior cervical neck contracture. *Br J of Plast Surg* 2000; 53:652-658.
88. Ismail A, Jarvi K, Canal AC; Successful resurfacing of scars from previous deliberate self-harm using Integra dermal matrix substitute; *J Plast Reconstr Aesthet Surg*; 2007 Apr 2 [Epub ahead of print]
89. Iwuagwu FC, Wilson D, Bailie F. The Use of Skin Grafts in Postburn Contracture Release: A 10-Year Review. Presented in part at the 29<sup>th</sup> Annual Meeting of the British Burns Association, April 11, 1996.
90. Jaksic T, Burke JF. The use of artificial skin for burns. *Ann Rev Med.* 1987; 38:107-117.
91. Jeng JC, Fidler PE, Sokolich JC, Jaskille AD, Khan S, White PM, Street JH 3rd, Light TD, Jordan MH; Seven years' experience with Integra as a reconstructive tool; *J Burn Care Res.* 2007 Jan-Feb;28(1):120-6.
92. Jeschke MG, Rose C, Angele P, Fuchtmeyer B, Nerlich MN, Bolder U. Development of new reconstructive techniques: use of Integra in combination with fibrin glue and negative-pressure therapy for reconstruction of acute and chronic wounds. *Plast Reconstr Surg.* 2004 Feb;113(2):525-30.
93. Jones I, Currie L, Martin R. A guide to biological skin substitutes. *Br J Plast Surg* 2002 Apr;55(3): 185-93.
94. Jones I, James SE, Rubin P, Martin R. Upward migration of cultured autologous keratinocytes in Integra artificial skin: a preliminary report. *Wound Repair Regen.* 2003 Mar-Apr;11(2):132-8.
95. Kagan RJ. Invited editorial. *J Burn Rehabil* 2002 Sep-Oct;23(5):326.
96. Katrana F, Kostopoulos E, Delia G, Lunel GG, Casoli V.; Reanimation of thumb extension after upper extremity degloving injury treated with Integra.; *J Hand Surg Eur Vol.* 2008 Dec;33(6):800-2. Epub 2008 Oct 20.
97. Kealey GP, Aguiar J, Lewis II RW, et al. Cadaver Skin allografts and Transmission of Human Cytomegalovirus to Burn Patients. *The American College of Surgeons.* 1996; 182:201-205.
98. Kearney JN. Clinical evaluation of skin substitutes. Elsevier Science Ltd. and ISBI 2001; *Burns* 27:545-551.
99. King P. Artificial skin reduces nutritional requirements in a severely burned child. Elsevier Science Ltd and ISBI 2000; *Burns* 26:501-503.
100. Klein MB, Engrav LH, Holmes JH, Friedrich JB, Costa BA, Honari S, Gibran NS. Management of facial burns with a collagen/glycosaminoglycan skin substitute-prospective experience with 12 consecutive patients with large, deep facial burns. *Burns* 2005 May;31(3):257-61.

**Bibliography**  
**INTEGRA® Dermal Regeneration Template**

101. Koenen W, Goerdts S, Faulhaber J; Removal of the outer table of the skull for reconstruction of full-thickness scalp defects with a dermal regeneration template; *Dermatol Surg*; 2008 Mar;34(3):357-63.
102. Komorowska-Timek E, Gabriel A, Bennett DC, Miles D, Garberoglio C, Chen C, Gupta S. Artificial Dermis as an Alternative for Coverage of Complex Scalp Defects following Excision of Malignant Tumors. *Plast Reconstr Surg* 2005 Apr;115(4):1010-7.
103. Kopp J, Magnus Noah E, Rubben A, Merk HF, Pallua N. Radical resection of giant congenital melanocytic nevus and reconstruction with meek-graft covered integra dermal template. *Dermatol Surg*. 2003 Jun;29(6):653-7.
104. Kremer M, Lang E, Berger A. Organotypical engineering of differentiated composite-skin equivalents of human keratinocytes in a collagen-GAG matrix (INTEGRA Artificial Skin) in a perfusion culture system. *Langenbecks Arch Surg* 2001; Aug;386(5):357-63.
105. Kremer M, Lang E, Berger AC. Evaluation of dermal-epidermal skin equivalents ('composite-skin') of human keratinocytes in a collagen-glycosaminoglycan matrix (INTEGRA® Artificial Skin, Dermal Regeneration Template. *Br J Plast Surg*. 2000;53:459-465.
106. Lam PK, Chan ES, Liew CT, Lau C, Yen SC, King WW. Combination of a new composite biocompatible skin graft on the neodermis of artificial skin in an animal model. *ANZ J Surg* 2002 May;72(5):360-3.
107. Lam PK, Chan ES. Integra and cultured epithelium. *J Burn Care Rehabil* 2001; Mar-Apr;22(2):197-8.
108. Lee LF, Porch JV, Spenler W, Garner WL.; Integra in lower extremity reconstruction after burn injury.; *Plast Reconstr Surg*. 2008 Apr;121(4):1256-62.
109. Li WP, Zhu ZX, Yang WQ, Xu XG, Zhang LY, Wang DX, Xu X; Application of intergra for reconstruction of burn scar contracture; *Zhonghua Zheng Xing Wai Ke Za Zhi*. 2006 May;22(3):210-2.
110. Lorenz CH, Petracic A, Hohl H-P, Wessel L., Waag, K-L Early wound closure and early reconstruction. Experience with a dermal substitute in a child with 60 percent surface area burn. *Burns*. 1997; 23(6):505-508.
111. Loss M, Wedler V, Kuzi W, Meuli-Simmen C, Meyer, E. Artificial skin, split-thickness autograft and cultured autologous keratinocytes combined to treat a severe burn injury of 93% TBSA. Elsevier Science Ltd and ISBI 2000; *Burns* 26:644-652.
112. Lozano DD. The Use of a Dermal Regeneration Template for the Repair of Degloving Injuries: A Case Report. *Wounds* 15(12):395-398, 2003.
113. Luterman A. Burns and Metabolism. The American College of Surgeons. February 2000; 190(2):104-114.

**Bibliography**  
**INTEGRA® Dermal Regeneration Template**

114. Martinet L, Pannier M, Duteille F; Effectiveness of Integra in the management of complete forearm degloving injury: A case report; *Chir Main*; 2007 Apr; 26(2):124-6.
115. McAllister RMR, Moiemmen N, Thway Y, Frame JD. Integra™ skin template used for secondary resurfacing following burn scar excision; a dilemma for the NHS. Unpublished article. St. Andrews Centre for Plastic Surgery, Broomfield Hospital, Chelmsford CM1 7ET.
116. McEwan W, Brown TL, Mills SM, Muller MJ. Suction dressings to secure a dermal substitute. *Burns* 2004 May;30(3):259-61.
117. McGuigan FX; Skin Substitutes as Alternatives to Autografting in a Wartime Trauma Setting; *J Am Acad Orthop Surg*, Vol 14, No 10, September 2006, S87-S89.
118. Messineo A, Innocenti M, Gelli R, Pancani S, Lo Piccolo R, Martin A; Multidisciplinary surgical approach to a surviving infant with sirenomelia; *Pediatrics*. 2006 Jul;118(1):e220-3.
119. Michaeli D, McPherson M. Immunologic study of artificial skin used in the treatment of thermal injuries. *J Burn Care Rehabil*. 1990; 11:21-26.
120. Mis B, Rolland E, Ronfard V. Combined use of collagen-based dermal substitute and a fibrin-based cultured epithelium: a step toward a total skin replacement for acute wounds. *Burns* 2004 Nov;30(7):713-9.
121. Moiemmen NS, Staiano JJ, Ojeh NO, et al. Reconstructive Surgery with a Dermal Regeneration Template: Clinical and Histologic Study. *Plastic and Reconstructive Surgery*. July 2001;pp93-103.
122. Moiemmen NS, Vlachou E, Staiano JJ, Thawy Y, Frame JD ; Reconstructive surgery with Integra dermal regeneration template: histologic study, clinical evaluation, and current practice; *Plast Reconstr Surg*. 2006 Jun;117(7 Suppl):160S-174S.
123. Molnar JA, DeFranzo AJ, Hadaegh A, Morykwas MJ, Shen P, Argenta LC. Acceleration of Integra incorporation in complex tissue defects with subatmospheric pressure. *Plast Reconstr Surg* 2004 Apr 15;113(5):1339-46.
124. Moore C, Lee S, Hart A, Watson S. Use of Integra to resurface a latissimus dorsi free flap. *Br J Plast Surg*. 2003 Jan;56(1):66-9.
125. Muangman P, Deubner H, Honari S, Heimbach DM, Engrav LH, Klein MB, Gibran NS; Correlation of clinical outcome of Integra application with microbiologic and pathological biopsies; *J Trauma*. 2006 Nov;61(5):1212-7.
126. Muangman P, Engrav LH, Heimbach DM, Harunari N, Honari S, Gibran NS, Klein MB; Complex wound management utilizing an artificial dermal matrix; *Ann Plast Surg*. 2006 Aug;57(2):199-202.
127. Murphy GF, Orgill DP, Yannas IV. Partial dermal regeneration is induced by biodegradable collagen-glycosaminoglycan grafts. *Lab Invest*. March 1990; 62(3):305-13.

**Bibliography**  
**INTEGRA® Dermal Regeneration Template**

128. Navsaria HA, Ojeh NO, Moiemmen N, Griffiths MA, Frame JD. Reepithelialization of a full-thickness burn from stem cells of hair follicles micrografted into a tissue-engineered dermal template (Integra). *Plast Reconstr Surg* 2004 Mar;113(3):978-81.
129. Neumeister MW.; A prefabricated, tissue-engineered integra free flap: reply.; *Plast Reconstr Surg*. 2008 Aug;122(2):682-3. No abstract available.
130. Newman C, DeFranzo, Jr AJ, Marks MW, Molnar JA; One Stage Integra® and Skin Grafting of Full-Thickness Human Wounds; American Society of Plastic Surgeons, San Francisco, CA, 8 October 2006, poster # 10490
131. Nguyen DQ, Dickson WA; A review of the use of a dermal skin substitute in burns care; *J Wound Care*. 2006 Sep;15(8):373-6.
132. Noah EM, Unglaub F, Ulrich D, Hartmann T, Pallua N. A case of successful delayed reconstruction using a collagen based dermal substitute of a chemical burn injury to the face caused by sulphuric acid. *Burns* 2004 May;30(3):280-2.
133. Ojeh NO, Frame JD, Navsaria HA. In vitro characterization of an artificial dermal scaffold. *Tissue Eng* 2001; Aug;7(4):457-72.
134. Orgill DP, Butler CE, Regan JF. Behavior of Collagen-GAG Matrices as Dermal Replacement in Rodent and Porcine Models. *Wounds*. September/October 1996; 8(5):150-157.
135. Orgill DP; Butler C; Regan JF; Barlow MS; Yannas IV; Compton CC. Vascularized Collagen-Glycosaminoglycan Matrix provides a Dermal Substrate and Improves Take of cultured Epithelial Autografts. *Plast Reconstr Surg*. August 1998; 102(2):423-429.
136. Orgill DP; Yannas IV. Design of an artificial skin. IV. Use of island graft to isolate organ regeneration from scar synthesis and other processes leading to skin wound closure. *J Biomed Mater Res*, 1998; 39:531-535.
137. Ozerderm OR, Wolfe SA, Marshall D. Use of skin substitutes in pediatric patients. *J Craniofac Surg*. 2003 Jul; 14(4):517-20.
138. Palao R, Gomez P, Huguet P. Burned breast reconstructive surgery with Integra dermal regeneration template. *Br J Plast Surg*. 2003 Apr;56(3):252-9.
139. Pandya AN; Woodward B; Parkhouse N. The Use of Cultured Autologous Keratinocytes with Integra in the Resurfacing of Acute Burns. *Plast Reconstr Surg*; September 1998; 102(3):825-828.
140. Papp A, Harma M. A collagen based dermal substitute and the modified Meek technique in extensive burns. Report of three cases. *Burns*. 2003 Mar;29(2):167-71.
141. Park CA, Defranzo AJ, Marks MW, Molnar JA .; Outpatient reconstruction using Integra\* and subatmospheric pressure.; *Ann Plast Surg*. 2009 Feb;62(2):164-9.
142. Payne CE, Williams AM, Hart NB; Lotus petal flaps for scrotal reconstruction combined with Integra trade mark resurfacing of the penis and anterior abdominal



**Bibliography**  
**INTEGRA® Dermal Regeneration Template**

- wall following necrotizing Fasciitis; *J Plast Reconstr Aesthet Surg*; 2007 Oct 30 [Epub ahead of print]
143. Pham C, Greenwood J, Cleland H, Woodruff P, Maddern G; Bioengineered skin substitutes for the management of burns: a systematic review; *Burns*; 2007 Dec; 33(8):946-57.
144. Pham TN, Hanley C, Palmieri T, Greenhalgh DG. Results of early excision and full-thickness grafting of deep palm burns in children. *J Burn Care Rehabil*. 2001 Jan-Feb;22(1):54-57.
145. Phillips TJ. New Skin for Old – Developments in Biological Skin Substitutes. *Arch Derm*. March 1998; 134:344-349.
146. Pollard RL, Kennedy PJ, Maitz PK; The use of artificial dermis (Integra) and topical negative pressure to achieve limb salvage following soft-tissue loss caused by meningococcal septicaemia; *J Plast Reconstr Aesthet Surg*; 2008; 61(3):319-22.
147. Popescu S, Ghetu N, Grosu O, Nastasa M, Pieptu D; Integra--a therapeutic alternative in reconstructive surgery. Our first experience; *Chirurgia (Bucur)*; 2007 Mar-Apr;102(2):197-204.
148. Priya SG, Jungvid H, Kumar A. Skin tissue engineering for tissue repair and regeneration. *Tissue Eng Part B Rev*. 2008 Mar;14(1):105-18.
149. Prystowsky J, Nowygrod R, Marboe C, et al. Artificial Skin (Integra™ Dermal Regeneration Template) for Closure of Lower Extremity Wounds. *Vasc Surg* November/December 2001; 34(6)557-567.
150. Ramasamy A, Jeffery SL; The use of a dermal regeneration template following excision of a giant melanocytic nevus in a potential Army recruit; *Mil Med*; 2008 Jan;173(1):105-6.
151. Ryan CM, Schoenfeld DA, Malloy M, Schulz JT 3<sup>rd</sup>, Sheridan RL, Tompkins RG. Use of Integra artificial skin is associated with decreased length of stay for severely injured adult burn survivors. *J Burn Care Rehabil* 2002 Sep-Oct;23(5):311-7.
152. Saffle JR; Covering massive burn injuries: integra-ting and interpreting the data; *Crit Care Med*; 2007 Nov;35(11):2661-2.
153. Sakaki S; Tanaka H; Wada; Takami Y; Yukioka T; Matsuda H; Shimazaki S. A Clinical Comparison Between Cryopreserved Allograft Skin and Artificial Skin Graft. *J Burn Care Rehabil*.2000 Jan-Feb; 21(1)(2): 191.
154. Sasidaran R, Dorai AA, Sulaiman WA, Halim AS.; Use of dermal regeneration template (INTEGRA) in reconstructive burn surgery.; *Med J Malaysia*. 2008 Jul;63 Suppl A:29.
155. Schiestl C, Stiefel D, Meuli M.; Giant naevus, giant excision, eleg(i)ant closure? Reconstructive surgery with Integra Artificial Skin® to treat giant congenital melanocytic naevi in children.; *J Plast Reconstr Aesthet Surg*. 2009 Mar 13. [Epub ahead of print]

**Bibliography**  
**INTEGRA® Dermal Regeneration Template**

156. Schneider J, Biedermann T, Widmer D et al. Matriderm® versus Integra®: A comparative experimental study. *Burns*. 2008 Oct 23. [Epub ahead of print]
157. Schultz JT 3<sup>rd</sup>, Tompkins RG, Burke JF. Artificial Skin. *Annu Rev Med* 2000; 51:231-44.
158. Sheridan RL, Hegarty M, Tompkins RG, Burke JF. Artificial skin in massive burns - results to ten years. *Eur J Plast Surg*. 1994; 17:91-93.
159. Shermak MA, Wong L, Inoue N, Nicol T. Reconstruction of complex cranial wounds with demineralized bone matrix and bilayer artificial skin. *J Craniofac Surg* 2000; May;11(3):224-31.
160. Silverstein G. Dermal regeneration template in the surgical management of diabetic foot ulcers: a series of five cases. *J Foot Ankle Surg*. 2006 Jan-Feb;45(1):28-33.
161. Spector JA, Glat PM; Hair-bearing scalp reconstruction using a dermal regeneration template and micrograft hair transplantation; *Ann Plast Surg*; 2007 Jul;59(1):63-6.
162. Stern R, McPherson M, Longaker MT. Histologic study of artificial skin used in the treatment of full-thickness thermal injury. *J Burn Care Rehabil*. 1990;11:7-13.
163. Stiefel D, Schiestl CM, Meuli M.; The positive effect of negative pressure: vacuum-assisted fixation of Integra artificial skin for reconstructive surgery.; *J Pediatr Surg*. 2009 Mar;44(3):575-80.
164. Suzuki S. Artificial Dermis. *Nippon Geka Gakkai Zasshi* 1999 Sep; 100(9):534-8.
165. Suzuki S; Shin-ya K; Kawai K; Nishimura Y. Application of Artificial Dermis Prior to Full-Thickness Skin Grafting for Resurfacing the Nose. *Ann Plast Surg* 1999 Oct; 43(4):439-42.
166. Sylvester MF, Yannas IV, Salzman EW, Forbes MJ. Collagen banded fibril structure and the collagen-platelet reaction. *Thrombosis Res* SS. 1989; 135-148.
167. Tompkins RG, Hilton JF, Burke JF, et al. Increased survival after massive thermal injuries in adults: preliminary report using artificial skin. *Critical Care Medicine*. 1989; 17(8):734-740.
168. Trumble, MD, Thomas E. A Comparison of Polyglycolic Acid Versus Type 1 Collagen Bioabsorbable Nerve Conduits in a Rat Model: An Alternative to Autografting. *The Journal of Hand Surgery*. 2007, 32(10), 1521-1529.
169. Tsoutsos D, Stratigos A, Gravvanis A, Zapandioti P, Kakagia D; Burned breast reconstruction by expanded artificial dermal substitute; *J Burn Care Res*; 2007 May-Jun ;28(3):530-2.
170. Tufaro AP, Buck DW 2nd, Fischer AC; The use of artificial dermis in the reconstruction of oncologic surgical defects; *Plast Reconstr Surg*; 2007 Sep;120(3):638-46.
171. Unglaub F, Ulrich D, Pallua N. Reconstructive surgery using an artificial dermis (Integra): results with 19 grafts. *Zentralbl Chir*. 2005 Apr;130(2):157-61.

**Bibliography**  
**INTEGRA® Dermal Regeneration Template**

172. Upadhyaya M, Orford JE, Smith N, Barker A, Gollow I; Incorporation of Integra in tissue defects: a pilot study in the rat model; *Pediatr Surg Int*; 2007 Jul; 23(7):669-73.
173. Van Holder C, Ortiz Carillo S, Malevez C, Jacobs F, Lasudry J; Reconstruction of a fulminant necrotizing fasciitis of the face and neck with a dermal regeneration template; *Eur J Plast Surg* (2006) 29:147–150.
174. Vazquez Rueda F, Ayala Montoro J, Blanco Loopez F, Ocana Losa JM. First results with Integra artificial skin in the management of severe tissue defects in children. *Cir Pediatr* 2001; Jul;14(3):91-4.
175. Verolino P, Casoli V, Masia D, Delia G, Isacu C, Castede JC; A skin substitute (Integra®) in a successful delayed reconstruction of a severe injured hand; *Burns*; 2008 Mar; 34(2):284-7.
176. Violas P, Abid A, Darodes P, Galinier P, de Gauzy JS, Cahuzac JP. Integra artificial skin in the management of severe tissue defects, including bone exposure, in injured children. *J Pediatr Orthop B*. 2005 Sep;14(5):381-4.
177. Voigt, MD, David W., et al. Economic Study of Collagen-Glycosaminoglycan Biodegradable Matrix for Chronic Wounds. *Wounds*. 2006; 18(1), 1-7.
178. Wang JCY, To EWH. Application of dermal substitute (Integra) to donor site defect of forehead flap. *Br J Plast Surg* 1999; 70-72.
179. Wilcke I, Lohmeyer JA, Liu S, Condurache A, Krüger S, Mailänder P, Machens HG; VEGF(165) and bFGF protein-based therapy in a slow release system to improve angiogenesis in a bioartificial dermal substitute in vitro and in vivo; *Langenbecks Arch Surg*; 2007 May; 392(3):305-14.
180. Winfrey ME, Cochran M, Hegarty M. A New Technology in Burn Therapy: INTEGRA® Artificial Skin. *Dimensions of Critical Care Nursing*. 1999; 18(1):14-20.
181. Wisser D, Rennekampff HO, Schaller HE. Skin assessment of burn wounds covered with a collagen based dermal substitute in a 2 year-follow-up. *Burns* 2004 Jun;30(4):399-401.
182. Wisser D, Steffes J. Skin replacement with a collagen based dermal substitute, autologous keratinocytes and fibroblasts in burn trauma. *Burns*. 2003 Jun;29(4):375-80.
183. Wolter TP, Noah EM, Pallua N. The use of Integra (®) in an upper extremity avulsion injury. *Br J Plast Surg* 2005 Apr;58(3):416-8.
184. Wood FM, Stoner ML, Fowler BV, Fear MW; The use of a non-cultured autologous cell suspension and Integra dermal regeneration template to repair full-thickness skin wounds in a porcine model: a one-step process; *Burns*; 2007 Sep; 33(6):693-700.

**Bibliography**  
**INTEGRA® Dermal Regeneration Template**

185. Xie WG, Lindenmaier W, Gryzybowski S, Machens HG. Influence of vascular endothelial growth factor gene modification on skin substitute grafted on nude mice. *Zhonghua Shao Shang Za Zhi*. 2005 Jun;21(3);2003-6.
186. Yannas IV, Burke JF, Gordon PL, et al. Design of an artificial skin: II. Control of chemical composition. *J Biomed Mater Res*. 1980; 14:107-132.
187. Yannas IV, Burke JF, Huang C, et al. Correlation of in vivo collagen degradation rate with in vitro measurements. *J. Biomed Mater Res*. 1975; 9:623-628.
188. Yannas IV, Burke JF, Huang C. et al. Control of Biodegradation rate in design of collagenous skin substitutes. *Int Biomater Symp*. April 1977; 3:114(Abstract 107).
189. Yannas IV, Burke JF, Orgill DP, et al. Skin regeneration by use of a bioreplaceable polymeric template. *Abstr Pap Am Chem Soc*. March 1983; 185:30 (Abstract).
190. Yannas IV, Burke JF, Orgill DP, Skrabut EM. Wound tissue can utilize a polymeric template to synthesize a functional extension of skin. *American Association for the Advancement of Science*. January 8, 1992;215:174-176.
191. Yannas IV, Burke JF, Skrabut EM. Artificial skin: Early, single-application closure of full-thickness skin wounds without use of autograft. *Fed Proc*. 1981; 40(3 pt 1):S20. (Abstract 1655).
192. Yannas IV, Burke JF, Umbreit M, et al. Progress in design of an artificial skin. *Fed Proc* 1979; 38:988.(Abstract 4000).
193. Yannas IV, Burke JF, Warpehoski M, et al. Prompt, long-term functional replacement of skin. *Trans Am Soc Artif Intern Organs*. 1981; 27:19-23.
194. Yannas IV, Burke JF. Artificial skin design: Performance of stage 1. *Abstr World Biomater Congress*. 1980; 1:1.4.1(Abstract).
195. Yannas IV, Burke JF. Design of an artificial skin: I. Basic design principles. *J Biomed Mater Res*. 1980; 14:65-81,339.
196. Yannas IV, Hansbrough JF, Boyce ST, et al. What criteria should be used for designing artificial skin replacements and how well do the current grafting materials meet these criteria. *J Trauma*. 1984; 24 (Suppl 9):S29-S39.
197. Yannas IV, Lee E, Bentz DM. Control of skin wound contraction rate by critically insoluble collagen matrices. *Applied Bioactive Polymeric Materials*. 1988.
198. Yannas IV, Lee E, Orgill DP, et al: De novo synthesis of skin. *Polym Mater Sci Eng*. 1987; 57:28-32.
199. Yannas IV, Lee E, Orgill DP, et al. Synthesis and characterization of a model extracellular matrix that induces partial regeneration of adult mammalian skin. *Proc Natl Acad Sci USA*. February 1989; 86(3):933-937.
200. Yannas IV, Orgill DP. Artificial Skin: A Fifth Route to Organ Repair and Replacement. ATNEC 85, *The Society of Plastic Engineers, Inc., 43rd Annual Technical Conference*. 1985; 119-133.

**Bibliography**  
**INTEGRA® Dermal Regeneration Template**

201. Yannas IV, Tobolsky AV. Cross linking of gelatine by dehydration. *Nature*. 1967; 215(5100):509-510.
202. Yannas IV. Certain biological implications of mammalian skin regeneration by a model extracellular matrix. Cutaneous Development Aging and Repair. *Fidia Research Series*. 1989; 18.
203. Yannas IV. Control of Kinetics and Mechanism of Skin Wound Healing by Use of a Bilayer Polymeric Membrane. Engineering Applications of New Composites, S.A. Paipetis and G.C. Papanicolaus, Editors, Omega Scientific, Wallingford. 1988.
204. Yannas IV. Regeneration of Skin and Nerve by Use of Collagen Templates, Collagen. Volume m, Biotechnology, Nmni, M.E., Ed., Copyright, CRC Press, Inc., Boca Raton, FL. 1988; Chap. 4:87-115.
205. Yannas IV. Tissue Regeneration by Use of Collagen-Glycosaminoglycan Copolymers. *Clin Mat*. 1992; 9:179-187.
206. Yannas IV. Use of artificial skin in wound management. The Surgical Wound, Peter Dineen, editor, Lea & Febiger, Philadelphia. 1981.
207. Yannas, IV, Burke JF, Warpehoski M, Stasikelis P, Skrabut EM, Orgill DP, Giard D. Design Principles and Preliminary Clinical Performance of an Artificial Skin. Biomaterials: Interfacial Phenomena and Applications. 1981; 475-481.
208. Yeong EK, Huang HF, Chen YB, Chen MT; The use of artificial dermis for reconstruction of full thickness scalp burn involving the calvaria; *Burns*. 2006 May;32(3):375-9.
209. Yeong EK, Yang CC. Chronic leg ulcers in Werner's syndrome. *Br J Plast Surg*. 2004 Jan;57(1):86-8.
210. Young RC, Burd A. Paediatric upper limb contracture release following burn injury. *Burns* 2004 Nov;30(7):723-8.