



Washington State  
Health Care Authority  
Health Technology Assessment

## **Health Technology Assessment Clinical Committee Meeting**

### **Program Overview**

*Josh Morse, MPH  
Health Technology Assessment  
May 18, 2012*

## **Presentation Overview**

### **Today's Topics**

- Upper Endoscopy for Gastroesophageal Reflux Disease (GERD) & Upper Gastrointestinal (GI) Symptoms
- Robotic Assisted Surgery
- HTA Program Overview
- HTA Program Process Improvement

## **Background**

- 2006 Legislation created the HTA program to use an evidence report and a clinician panel to make coverage decisions about whether agencies should pay for certain medical procedures and tests based on:
  - Safety
  - Efficacy/effectiveness, and
  - Cost-effectiveness
- The HTA Program is within the Health Care Authority (HCA)
- Multiple agencies participate to identify topics and implement policy decisions:
  - HCA (Uniform Medical Plan, Medicaid)
  - Dept of Labor and Industries
  - Dept of Corrections
- Implementation:
  - Agencies implement determinations of the HTA program within their existing statutory framework.

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## **WA HTA Program Purpose**

### **Primary purpose:**

To ensure medical treatments, devices and services paid for with state health care dollars are safe and proven to work.

- Provide resources for state agencies purchasing health care.
- Develop scientific, evidence-based reports on medical devices, procedures, and tests.
- Facilitate an independent clinical committee of health care practitioners to determine which medical devices, procedures, or tests meet safety, efficacy, and cost tests.

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## Why Health Technology Assessment?

### Medical Technology is a primary driver of cost:

- The development and diffusion of **medical technology** are **primary factors** in explaining the persistent difference between health spending and overall economic growth.
- New medical technology may account for about **one-half or more of real long-term spending growth**.

Kaiser Family Foundation, March 2007: *How Changes in Medical Technology Affect Health Care Costs*

- Since **technological change is the biggest contributor**, an effective long-term strategy for controlling health care spending will probably **have to address the health care system's way of incorporating new technologies into practice**.

U.S. Congressional Budget Office, *Technological Change and the Growth in Health Care Spending, 2008*. Report available at [www.cbo.gov](http://www.cbo.gov).

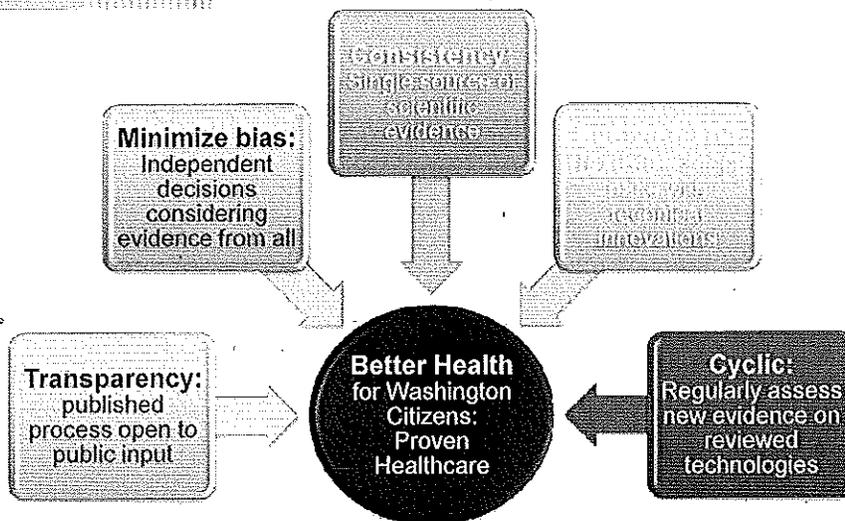
### Medical Technology has quality gaps:

- Medical technology diffusing without evidence of improving quality. Highly correlated with misuses, over- and under-utilization.

Cathy Schoen, Karen Davis, Sabrina K.H. How, and Stephen C. Schoenbaum, "U.S. Health System Performance: A National Scorecard," *Health Affairs*, Web Exclusive (September 20, 2006): w459

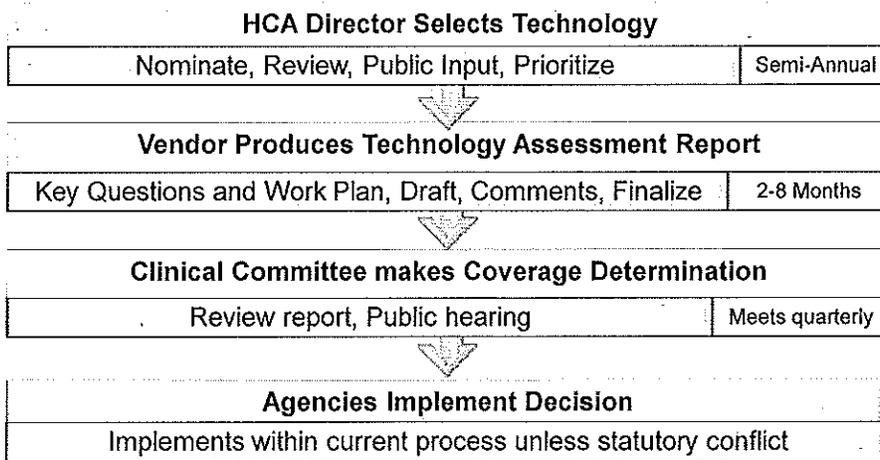
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## Program Objective



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## **WA HTA Process Overview**



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## **HTCC Decision Basis**

**Clinical Committee Decision must give greatest weight to most valid and reliable evidence.**

- Objective Factors for evidence consideration
  - > Nature and Source of evidence
  - > Empirical characteristics of the studies or trials upon which evidence is based
  - > Consistency of outcomes with comparable studies
- Additional evaluation factors
  - > Recency (date of information)
  - > Relevance (applicability of the information to the key questions presented or participating agency programs and clients)
  - > Bias (presence of conflict of interest or political considerations)

WAC 182-55-030: Committee coverage determination process

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## ***Selected Technologies***

- Sleep Apnea Diagnosis and Treatment
- Bone Morphogenetic Proteins
- Upper Endoscopy for GERD and GI Symptoms
- Robotic Assisted Surgery
- Stereotactic Radiosurgery (SRS) and Stereotactic Body Radiation Therapy (SBRT)
- Intensity Modulated Radiation Therapy (IMRT)
- Vitamin D Screening and Testing
- Hyperbaric Oxygen Therapy for Wound Care and Brain Injury
- Prostate-Specific Antigen Testing
- Ablation Procedures for Supraventricular Tachycardia
- Carotid Artery Stenting
- Cervical Level Fusion for Degenerative Disk Disease
- Cochlear Implants (Bi- or Uni-lateral)
- Cardiac Nuclear Imaging

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## ***HTA Program Process Improvement***

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## ***Stakeholder Engagement Project***

Two part qualitative review conducted in 2011

### **1. Review of HTA Programs**

- Reported on components of HTA programs

### **2. Stakeholder Engagement**

- September through December 2011
- Engaged all stakeholders through an Online Survey, Key informant interviews and facilitated discussions

Report completed in January 2012

Report is available here:

<http://www.hta.hca.wa.gov/stakeholder.html>

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## ***Stakeholder Engagement Project***

### **Recommendations**

- Improve access and usability of information about the program
- Improve outreach to individuals and organizations, particularly patients, patient groups and providers
- Publish timelines for each report
- Extend the comment period for draft reports
- Publish the disposition of public comments
- Explain the purpose and role for each opportunity of stakeholder involvement
- Include contextual information by:
  - Providing clinical background for the topic; and
  - Providing cost data, when available, for a topic

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# Stakeholder Engagement Project

## Key changes to date:

- ✓ Expanded comment period on Draft Report
  - ✓ From 2 weeks to 4 weeks
  
- ✓ Publishing all comments received on Key Questions and response to comments.

# Workplan

PHASE 1: Timely and transparent transparency (DSM Complete)			5/3/2012	
✓ External draft opt public comment for Mar & May topics in 3 sites	✓ External availability of meeting content in 2 sites	✓ External draft opt public comment for Sep & Oct topics in 4 sites	✓ Adjust presentation due date for meeting with obj	Develop timeline tool for web display
PHASE 2: Transparent disposition of public comments (DSM Complete)				
✓ Create summaries of KO comments for web	✓ Publish KO comment summaries for Sep topics	Adjust KO handling to allow time for public response publication		
PHASE 3: Website usability (Phase 3 W&A Update) (DSM Complete)				
Usability assessment	Purpose and role clarification (stakeholder involvement)	Simplify and clarification of page information about progress		
PHASE 4: Outreach materials and timing (DSM Complete)				
Add cost data to key questions and topic selection steps	Identify global healthcare organizations for outreach	Add 'outreach identification' to key questions dev. Phase		

More information:

<http://www.hta.hca.wa.gov/stakeholder.html>

## **HTA Contact Information**

Email Distribution List: [shtap@hca.wa.gov](mailto:shtap@hca.wa.gov)

HTA Web Pages: <http://www.hta.hca.wa.gov/>

Josh Morse, MPH  
Program Director  
360-725-0839  
[Josh.Morse@HCA.WA.GOV](mailto:Josh.Morse@HCA.WA.GOV)

Thank you!

**Health Technology Clinical Committee**

**Date: March 16, 2012**

**Time: 8:00 am – 4:30 pm**

**Location: SeaTac Airport Conference Center**

**Adopted:**

Meeting materials and transcript are available on the HTA website at:

[http://www.hta.hca.wa.gov/past\\_materials.html](http://www.hta.hca.wa.gov/past_materials.html)

### HTCC MINUTES

**Members Present:** C. Craig Blackmore MD, MPH; Marie-Annette Brown PhD, RN; Carson E. Odegard DC, MPH; Richard C. Phillips MD, MS, MPH; Seth Schwartz MD, MPH; Christopher Standaert, MD; Kevin Walsh MD

**Late Arrival:** Michelle Simon PhD, ND (present for afternoon topic)

**Members Absent:** Joann Elmore MD, MPH; David K. McCulloch MD; Michael Souter MB, Ch-B, DA

### HTCC FORMAL ACTION

- 1. Call to Order:** Dr. Blackmore, Chair, called the meeting to order. Sufficient members were present to constitute a quorum.  
Josh Morse, HTA Program Director, introduced the technology topics scheduled for discussion:
  - Staff provided an overview of the HTA program and the topics for the meeting.
- 2. March 16<sup>th</sup>, 2012 Meeting Minutes:** Chair referred members to the previous meeting business-three parts, beginning with draft minutes; motion to approve and second, and adopted by the committee.
  - *Action: Seven committee members approved the November 12th, 2011 meeting minutes.*
- 3. Microprocessor Controlled Lower Limb Prosthesis (MCLLP) Draft Findings & Decision:** Chair referred members to the draft findings and decision and called for a motion for approval or further discussion; motion to approve and second. The MCLLP draft findings & decision was approved and adopted by the committee.
  - *Action: Seven committee members approved the MCLLP draft findings & decision document.*
- 4. Osteochondral Allograft and Autograft Transplantation (OAT) Draft Findings & Decision:** Chair referred members to the draft findings and decision and called for a motion to approve; motion to approve and second. The OAT draft finding and decision was approved and adopted by the committee.
  - *Action: Seven committee members approved the OAT findings & decision document.*

**5. Sleep Apnea Diagnosis and Treatment: Scheduled and Open Public Comment:**

➤ **Scheduled and Open Public Comment:**

The Chair called for public comments.

Scheduled Public Comments: No stakeholders scheduled time for public comments.

Open Public Comments: Two individual stakeholders requested scheduled time for public comments. The stakeholders submitted their conflict of interest declarations for the committee’s consideration prior to providing public comment.

- Ed Weaver MD, MPH, sleep medicine and sleep surgeon provided comment.
- Robert Michaelson MD, PhD, Vice President of the Washington State Chapter of the American Society for Metabolic and Bariatric Surgery provided comment.

➤ **Agency Utilization and Outcomes:**

Steve Hammond MD, PhD, Chief Medical Officer, Department of Corrections, presented the agency utilization and outcomes for Sleep Apnea, full presentation published with meeting materials.

**Vendor Report and HTCC Q & A**

Chair introduced the clinical expert, Amir Khan MD.

The Center for Evidence-based Policy, Oregon Health Sciences University presented an overview of their evidence report on Sleep Apnea Diagnosis and Treatment in Adults, full presentation published with meeting materials.

➤ **Committee Discussion and Decision**

The Chair led a discussion of the evidence related to the safety, efficacy, and cost-effectiveness of sleep apnea treatments followed by discussion of sleep apnea diagnosis.

HTCC reviewed and considered the Sleep Apnea technology assessment report; information provided by the Administrator; state agencies; and public members. The also heard comments from the evidence reviewer, HTA program, the clinical expert, the public and agency medical directors. The committee considered all the evidence and gave greatest weight to the evidence it determined, based on objective factors, to be the most valid and reliable.

<b>HTCC COMMITTEE COVERAGE DETERMINATION VOTE</b>			
	<b>Not covered</b>	<b>Covered Unconditionally</b>	<b>Covered Under Certain Conditions</b>
Sleep apnea diagnosis	0	0	<b>7</b>
Sleep apnea treatment- non-surgical	0	0	<b>7</b>
Sleep apnea treatment- surgical	0	0	<b>7</b>

*Discussion:* The Chair called for discussion of conditions of coverage for sleep apnea diagnosis and treatment following the majority voting for coverage. The determination is limited to adults age 18 years and older for diagnosis and treatment of obstructive sleep apnea (OSA). The following conditions were discussed and approved by a majority of the clinical committee:

*Limitations of Coverage:* Sleep apnea diagnosis and treatment is a covered benefit when the following conditions are met:

- Adults age 18 years and older;
  - State agency approved providers;
  - Consistent with the Medicare national coverage determination *Continuous positive airway Pressure CPAP Therapy for Obstructive Sleep Apnea (OSA) and Sleep Testing for Obstructive Sleep Apnea* excluding Coverage with Evidence Development (CED); and
  - Consistent with the Medicare Local coverage determination (L30731) for *Surgical Treatment of Obstructive Sleep Apnea*.
- *Action:* The committee chair directed HTA staff to prepare a *Findings and Coverage document on Sleep Apnea Diagnosis and Treatment* reflective of the determination.

## **6. Bone Morphogenetic Proteins (BMP):**

### ➤ **Scheduled and Open Public Comment:**

The Chair called for public comments.

Scheduled Public Comments: Five stakeholders scheduled time for public comments; three addressed the committee.

- John Ratliff MD on behalf of the American Association of Neurological Surgeons and the Congress of Neurological Surgeons,
- John Schuster MD a surgeon from Eastern Washington
- Julie Bearcroft PhD representing Medtronic Spine & Biologics

### ➤ **Agency Utilization and Outcomes:**

Robert Mootz DC, Associate Medical Director, Department of Labor and Industries, presented the agency utilization and outcomes for BMP to the committee, full presentation published with meeting materials.

### ➤ **Vendor Report and HTCC Q & A**

Chair introduced the clinical expert Michael Jihoon Lee MD.

Spectrum Research, Inc. presented an overview of their evidence report on Bone Morphogenetic Proteins for Use in Spinal Fusion, full presentation published with meeting materials.

### ➤ **Committee Discussion and Decision**

Dr. Blackmore, Committee Chair, led a discussion of the evidence related to the safety, efficacy, and cost-effectiveness of BMP for spinal fusion. The HTCC reviewed and considered the BMP technology assessment report; information provided by the Administrator; state agencies; public members; and heard comments from the evidence

reviewer, HTA program, an invited clinical expert, the public and agency medical directors. The committee considered all the evidence and gave greatest weight to the evidence it determined, based on objective factors, to be the most valid and reliable.

<b>HTCC COMMITTEE COVERAGE DETERMINATION VOTE</b>			
	<b>Not covered</b>	<b>Covered Unconditionally</b>	<b>Covered Under Certain Conditions</b>
Bone morphogenetic protein-2	0	0	<b>8</b>
Bone morphogenetic protein-7	<b>8</b>	0	0

- ✓ *Discussion:* The Chair called for discussion on conditions for use of BMP-2 due to the majority voting for coverage. The following conditions were discussed and approved by a majority:

*Limitations of Coverage:* rhBMP-2 for use in lumbar fusion is a covered benefit when the following conditions are met:

- Adults age 18 years and over;
- Lumbar spine only;
- Primary anterior open or laparoscopic fusion at one level between L4 and S1; or
- Revision lumbar fusion on a compromised patient for whom autologous bone and bone marrow harvest are not feasible or not expected to result in fusion.

- *Action:* The Chair directed HTA staff to prepare a Findings and Decision document on Bone Morphogenetic Proteins for use in lumbar fusion reflective of the majority vote for final approval at the next public meeting.

The committee reviewed the clinical guidelines and checked for the availability of a Medicare decision. The Centers for Medicare and Medicaid Services have no published national coverage determinations (NCD) for Bone Morphogenetic Proteins for use in lumbar fusion.

7. The Chair called for further comments. Meeting adjourned.

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**Health Technology Clinical Committee  
DRAFT Findings and Decision**

**Topic:** Sleep Apnea Diagnosis and Treatment  
**Meeting Date:** March 16, 2012  
**Final Adoption:**

**Number and Coverage Topic**

20120316A – Sleep Apnea Diagnosis and Treatment

**HTCC Coverage Determination**

Sleep apnea diagnosis and treatment is **covered benefit with conditions** consistent with the criteria identified in the reimbursement determination.

**HTCC Reimbursement Determination****❖ Limitations of Coverage**

Sleep apnea diagnosis and treatment coverage criteria:

- Adults, age 18 years and older;
- State approved providers;
- Consistent with the Medicare national coverage determination *Continuous Positive Airway Pressure (CPAP) Therapy for Obstructive Sleep Apnea (OSA) and Sleep Testing for Obstructive Sleep Apnea* excluding Coverage with Evidence Development (CED); and
- Consistent with the Medicare Local coverage determination (L30731) for *Surgical Treatment of Obstructive Sleep Apnea*.

**❖ Non-Covered Indicators**

As indicated in referenced Medicare national and local coverage determinations

**Agency Contact Information**

<b>Agency</b>	<b>Phone Number</b>
Labor and Industries	1-800-547-8367
Public Employees Health Plan	1-800-762-6004
Health and Recovery Services Administration	1-800-562-3022

**HTCC COVERAGE VOTE AND FORMAL ACTION**

March 16, 2012 meeting transcript can be found at: [http://www.hta.hca.wa.gov/past\\_materials.html](http://www.hta.hca.wa.gov/past_materials.html)

**Committee Decision**

Based on the deliberations of key health outcomes, the committee decided that it had the most complete information: a comprehensive and current evidence report, public comments, and agency and state utilization information. The committee concluded that the current evidence on sleep apnea diagnosis and treatment (surgical and non-surgical) is sufficient to cover with conditions. The committee considered all the evidence and gave greatest weight to the evidence it determined, based on objective factors, to be the most valid and reliable. Based on these findings, the committee voted to cover diagnostic and treatment services (devices and procedures) for sleep apnea consistent with the coverage determinations outlined in the Medicare national coverage determination, with the exception of coverage with evidence development, and to cover surgical treatments consistent with the Medicare local coverage determination (L30731) for *Surgical Treatment of Obstructive Sleep Apnea*.

**Sleep Apnea Diagnosis and Treatment Coverage Vote**

<b>HTCC Committee Coverage Determination Vote</b>			
	<b>Not covered</b>	<b>Covered Unconditionally</b>	<b>Covered Under Certain Conditions</b>
Sleep apnea diagnosis	0	0	7
Sleep apnea treatment- non-surgical	0	0	7
Sleep apnea treatment- surgical	0	0	7

- ✓ *Discussion:* The Chair called for discussion on conditions of coverage for sleep apnea diagnosis and treatment following the majority voting for coverage. The determination is limited to adults age 18 years and older for diagnosis and treatment of obstructive sleep apnea (OSA). The following conditions were discussed and approved by a majority of the clinical committee:
- ✓ *Limitations of Coverage:* Sleep apnea diagnosis and treatment is a covered benefit when the following conditions are met:
  - Adults age 18 years and older;
  - State agency approved providers;
  - Consistent with the Medicare national coverage determination *Continuous positive airway Pressure CPAP Therapy for Obstructive Sleep Apnea (OSA) and Sleep Testing for Obstructive Sleep Apnea* excluding Coverage with Evidence Development (CED); and
  - Consistent with the Medicare Local coverage determination (L30731) for *Surgical Treatment of Obstructive Sleep Apnea*.
- ✓ *Action:* The committee chair directed HTA staff to prepare a Findings and Coverage document on Sleep Apnea diagnosis and treatment reflective of the determination.

Complete text of the Medicare national coverage decision and local coverage determination is available in Appendix 2 of the Sleep Apnea report on pages 391 through 399 on the HTA website at [http://www.hta.hca.wa.gov/documents/sleep\\_apnea\\_final\\_report.pdf](http://www.hta.hca.wa.gov/documents/sleep_apnea_final_report.pdf). Excerpts of the text directly applicable to this coverage decision are included below.

**Medicare National Coverage Determinations Manual Chapter 1, Part 4**

**240.4 – Continuous positive Airway Pressure CPAP Therapy for Obstructive Sleep Apnea (OSA) (Various Effective Dates)**

(Rev. 96, Issued: 10-15-08, Effective: 03-13-08, Implementation: 08-04-08)

[https://www.cms.gov/medicare-coverage-database/details/ncddetails.aspx?NCDId=226&ncdver=3&NCAId=204&NcaName=Continuous+Positive+Airway+Pressure+\(CPAP\)+Therapy+for+Obstructive+Sleep+Apnea+\(OSA\)&IsPopup=y&bc=AAAAAAAAAIAAA&](https://www.cms.gov/medicare-coverage-database/details/ncddetails.aspx?NCDId=226&ncdver=3&NCAId=204&NcaName=Continuous+Positive+Airway+Pressure+(CPAP)+Therapy+for+Obstructive+Sleep+Apnea+(OSA)&IsPopup=y&bc=AAAAAAAAAIAAA&)

**Nationally Covered Indications**

**B. Nationally Covered Indications**

Effective for claims with dates of service on and after March 13, 2008, the Centers for Medicare & Medicaid Services (CMS) determines that **CPAP therapy when used in adult patients with OSA is considered reasonable and necessary under the following situations:**

1. The use of CPAP is covered under Medicare when used in adult patients with OSA. Coverage of CPAP is initially limited to a 12- week period to identify beneficiaries diagnosed with OSA as subsequently described who benefit from CPAP. CPAP is subsequently covered only for those beneficiaries diagnosed with OSA who benefit from CPAP during this 12- week period.
2. The provider of CPAP must conduct education of the beneficiary prior to the use of the CPAP device to ensure that the beneficiary has been educated in the proper use of the device. A caregiver, for example a family member, may be compensatory, if consistently available in the beneficiary's home and willing and able to safely operate the CPAP device.
3. A positive diagnosis of OSA for the coverage of CPAP must include a clinical evaluation and a positive:
  - a. attended PSG performed in a sleep laboratory; or
  - b. unattended HST with a Type II home sleep monitoring device; or
  - c. unattended HST with a Type III home sleep monitoring device; or
  - d. unattended HST with a Type IV home sleep monitoring device that measures at least 3 channels.
4. The sleep test must have been previously ordered by the beneficiary's treating physician and furnished under appropriate physician supervision.
5. An initial 12- week period of CPAP is covered in adult patients with OSA if either of the following criterion using the AHI or RDI are met:
  - a. AHI or RDI greater than or equal to 15 events per hour, or
  - b. AHI or RDI greater than or equal to 5 events and less than or equal to 14 events per hour with documented symptoms of excessive daytime sleepiness, impaired cognition, mood disorders or insomnia, or documented hypertension, ischemic heartdisease, or history of stroke.
6. The AHI or RDI is calculated on the average number of events of per hour. If the AHI or RDI is calculated based on less than 2 hours of continuous recorded sleep, the total number of recorded events to calculate the AHI or RDI during sleep testing must be at a minimum the number of events that would have been required in a 2- hour period.
7. Apnea is defined as a cessation of airflow for at least 10 seconds. Hypopnea is defined as an abnormal respiratory event lasting at least 10 seconds with at least a 30% reduction in thoracoabdominal movement or airflow as compared to baseline, and with at least a 4% oxygen desaturation.

**C. Nationally Non- covered Indications**

Effective for claims with dates of services on and after March 13, 2008, other diagnostic tests for the diagnosis of OSA, other than those noted above for prescribing CPAP, are not sufficient for the coverage of CPAP.

**240.4.1 – Sleep Testing for Obstructive Sleep Apnea (OSA) (Effective March 3, 2009)**

(Rev. 103, Issued: 07-10-09, Effective: 03-03-09, Implementation: 08-10-09)

[http://www.cmms.hhs.gov/medicare-coverage-database/details/ncddetails.aspx?NCDId=330&ncdver=1&NCAId=227&NcaName=Sleep+Testing+for+Obstructive+Sleep+Apnea+\(OSA\)&IsPopup=y&bc=AAAAAAIAAAA&](http://www.cmms.hhs.gov/medicare-coverage-database/details/ncddetails.aspx?NCDId=330&ncdver=1&NCAId=227&NcaName=Sleep+Testing+for+Obstructive+Sleep+Apnea+(OSA)&IsPopup=y&bc=AAAAAAIAAAA&)

**B. Nationally Covered Indications**

Effective for claims with dates of service on and after March 3, 2009, the Centers for Medicare & Medicaid Services finds that the evidence is sufficient to determine that the results of the sleep tests identified below can be used by a beneficiary's treating physician to diagnose OSA, that the use of such sleep testing technologies demonstrates improved health outcomes in Medicare beneficiaries who have OSA and receive the appropriate treatment, and that these tests are thus reasonable and necessary under section 1862(a)(1)(A) of the Social Security Act.

1. Type I PSG is covered when used to aid the diagnosis of OSA in beneficiaries who have clinical signs and symptoms indicative of OSA if performed attended in a sleep lab facility. Type II or Type III sleep testing devices are covered when used to aid the diagnosis of OSA in beneficiaries who have clinical signs and symptoms indicative of OSA if performed unattended in or out of a sleep lab facility or attended in a sleep lab facility.
2. Type IV sleep testing devices measuring three or more channels, one of which is airflow, are covered when used to aid the diagnosis of OSA in beneficiaries who have signs and symptoms indicative of OSA if performed unattended in or out of a sleep lab facility or attended in a sleep lab facility.
3. Sleep testing devices measuring three or more channels that include actigraphy, oximetry, and peripheral arterial tone, are covered when used to aid the diagnosis of OSA in beneficiaries who have signs and symptoms indicative of OSA if performed unattended in or out of a sleep lab facility or attended in a sleep lab facility.

**C. Nationally Non- Covered Indications**

Effective for claims with dates of services on and after March 3, 2009, other diagnostic sleep tests for the diagnosis of OSA, other than those noted above for prescribing CPAP, are not sufficient for the coverage of CPAP and are not covered.

**Medicare Local coverage determination L30731 (updated 3/24/11) (40 states – includes Washington)**

A. Uvulopalatopharyngoplasty (UPPP) is covered for those patients who have all of the following:

1. Obstructive sleep apnea diagnosed (prior to any proposed surgery) in a certified sleep disorders laboratory (certification body recognized by the American Academy of Sleep Medicine);
2. A Respiratory Disturbance Index of 15 or higher
3. Failed to respond to Continuous Positive Airway Pressure therapy or cannot tolerate CPAP or other appropriate non- invasive treatment;
4. Documented counseling by a physician, with recognized training in sleep disorders, about the potential benefits and risks of the surgery; and
5. Evidence of retropalatal or combination retropalatal/retrolingual obstruction as the cause of the obstructive sleep apnea.

B. Mandibular Maxillary Osteotomy and Advancement and /or genioglossus advancement with or without hyoid suspension is covered for those patients who have all of the following:

1. Obstructive sleep apnea diagnosed (prior to any proposed surgery) in a certified sleep disorders laboratory (certification body recognized by the American Academy of Sleep Medicine);
2. A Respiratory Disturbance Index of 15 or higher;
3. Failed to respond to Continuous Positive Airway Pressure therapy or cannot tolerate CPAP or other appropriate non- invasive treatment;
4. Documented counseling by a physician, with recognized training in sleep disorders, about the potential benefits and risks of the surgery; and
5. Evidence of retrolingual obstruction as the cause of the obstructive sleep apnea, or previous failure of UPPP to correct the obstructive sleep apnea.

Regarding the Mandibular Maxillary Osteotomy and Advancement operation:

- a. Separate repositioning of teeth would not be necessary except under unusual circumstances; but if necessary the dental work would be covered.
- b. Application of an interdental fixation device is occasionally necessary, and is a covered service (see Documentation Requirements).

C. Tracheostomy is covered for obstructive sleep apnea that is in the judgment of the attending physician, unresponsive to other means of treatment or in cases where other means of treatment would be ineffective or not indicated.

D. When obstructive sleep apnea is caused by discrete anatomic abnormalities of the upper airway (such as, but not limited to, enlarged tonsils or an enlarged tongue), surgery to correct these abnormalities is covered if medically necessary based on adequate documentation in the medical records supporting the significant contribution of these abnormalities to OSA. Submucous radiofrequency reduction of hypertrophied turbinates is covered as an appropriate treatment for nasal obstruction due to turbinate hypertrophy that significantly contributes to OSA or significantly compromises CPAP therapy.

E. The following procedures are not covered at this time.

1. Laser- assisted uvulopalatoplasty (LAUP) is not covered at this time since it is not considered effective for OSA. LAUP must not be billed as 42145, Palatopharyngoplasty (e.g., uvulopalatopharyngoplasty, uvulopharyngoplasty). This code is not appropriate for this procedure. If LAUP is billed for denial purposes, it should be coded as 42299, (unlisted procedure, palate, uvula) with "LAUP" listed in Item 19 on the CMS- 1500 claim form or equivalent field for electronic claims. The claim will then be appropriately denied as not proven effective.
2. Somnoplasty™ is a trade name for palate reduction with the Somnoplasty™ System of Somnus Medical Systems. This is not a term recognized by this Contractor as a covered procedure under Medicare Part B. Therefore Somnoplasty™ must not be billed as 42145. This code is not appropriate for this procedure. If Somnoplasty™ is billed for denial purposes, it should be coded as 42299, (unlisted procedure, palate, uvula) with "Somnoplasty™" listed in Item 19 on the CMS- 1500 claim form or equivalent field for electronic claims. This claim will then be appropriately denied as not proven effective.
3. The Pillar Procedure™ is a trade name for palatal implants. Palatal implants have not been shown effective for the treatment of obstructive sleep apnea and are not covered. This procedure should be billed by the physician as 42299 (unlisted procedure, palate, uvula) with "Pillar Procedure™" or "palatal implant" listed in Item 19 on the CMS- 1500 claim form or equivalent field for electronic claims. This claim will then be denied as not proven effective. Hospital outpatient would use code C9727.
4. Submucosal ablation of the tongue base, radiofrequency, one or more sites, per session (41530) is not covered

**Health Technology Clinical Committee Authority**

Washington State's legislature believes it is important to use a scientific based, clinician centered approach for difficult and important health care benefit decisions. Pursuant to chapter 70.14 RCW, the legislature has directed the Washington State Health Care Authority, through its Health Technology Assessment program to engage in a process for evaluation process that gathers and assesses the quality of the latest medical evidence using a scientific research company and takes public input at all stages. Pursuant to RCW 70.14.110 a Health Technology Clinical Committee (HTCC) composed of eleven independent health care professionals reviews all the information and renders a decision at an open public meeting. The Washington State Health Technology Clinical Committee (HTCC) determines how selected health technologies are covered by several state agencies (RCW 70.14.080-140). These technologies may include medical or surgical devices and procedures, medical equipment, and diagnostic tests. HTCC bases their decisions on evidence of the technology's safety, efficacy, and cost effectiveness. Participating state agencies are required to comply with the decisions of the HTCC. HTCC decisions may be re-reviewed at the determination of the HCA Administrator.



# Sleep Apnea

## *Draft Findings & Decision Timeline and Overview of Comments*

The Health Technology Assessment (HTA) program received comments in response to the posted Health Technology Clinical Committee (HTCC) draft findings and decision on Sleep Apnea.

Category	Comment Period	
	April 20 – May 2, 2012	Cited Evidence
Patient, relative, and citizen	0	0
Legislator and public official	0	0
Physician and health care professional	2	1
Industry & manufacturer	0	0
Professional society & advocacy organization	0	0
<b>Total</b>		<b>2</b>

### **Comments with Evidence:**

#### Physician and health care professional comments

*Edward M Weaver, MD, Seattle WA*

Supports adoption of the Medicare national coverage determination for CPAP and for Sleep Testing, and adoption of the Medicare local coverage determination (L307731) for Surgical Treatment of Obstructive Sleep Apnea. Requests three changes to the policy on the Surgical Treatment of Obstructive Sleep Apnea, to make the surgery policy consistent with the larger policy on Sleep Apnea Diagnosis and Treatment and with the latest and highest level evidence. Provided two attachments: a retired policy for Local Coverage Determination (LCD) for Treatment of Obstructive Sleep Apnea (L19078) and findings of a randomized trial of temperature-controlled radiofrequency, continuous positive airway pressure, and placebo for obstructive sleep apnea syndrome.

### **Comments without Evidence:**

#### Physician and health care professional comments

*Jan Zempenyi, MD, Bellevue, WA*

Applauds the Committee's approach in basing their proposed policy to reflect the nationally-accepted criteria. Requests consideration of three refinements to the proposed draft.

### Actual Timeline

<b>Study Stage</b>	<b>Date</b>	<b>Public Comment</b>
Preliminary recommendations published	October 15, 2008	
Public comments due	October 29, 2008	<b>14 days</b>
Selected set of topics published	December 12, 2008	
Public comments due	January 11, 2009,	<b>30 days</b>
Draft Key Questions published (AHRQ)	February 14, 2011	
Public comments due	November 17, 2011	
Key Questions finalized	December 5, 2011	
Draft report due	January 10, 2012	
Draft report published	January 12, 2012	
Public comments due	January 30, 2012	<b>20 days</b>
Final report due	February 10, 2012	
Final report published	February 15, 2012	
Public meeting date	March 16, 2012	
Findings & decision published	April 20, 2012	
Public comments due	May 2, 2012	<b>12 days</b>

**JAN ZEMPLENYI, MD, FACS**

*Certified by American Board of Facial Plastic & Reconstructive Surgery*

*Diplomate of American Board of Cosmetic Surgery*

*Certified by American Board of Otolaryngology*

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May 2, 2012

Mr. Josh Morse  
Executive Director  
Health Technology Clinical Assessment Committee

**RE: TACC Sleep Apnea Diagnosis and Treatment**

Dear Mr. Morse:

While I serve as a representative of Otolaryngology (ENT) to the WSMA Inter-specialty Council, a member of the WSMA Board of Trustees and a former President of the Northwest Academy of Otolaryngology, I am making these comments as a practicing specialist in Otolaryngology & Facial Plastic Surgery with clinical experience in private practice since 1987. A significant percentage of my practice is devoted to medical and surgical treatment of nasal airway problems, snoring and obstructive sleep apnea. My recommendations are made following a discussion with several of my otolaryngology colleagues.

In general, I applaud the Committee's approach in basing their proposed policy to reflect the nationally-accepted criteria. However, as our knowledge is progressing I would request your consideration of the following refinements to the proposed draft:

1. The Medicare Nationally Coverage diagnostic criteria listed in section #5 based on AHI and RDI used to justify a twelve-week trial of CPAP should be **the same** as those listed in section A. 2. with respect to justification of uvulopalatopharyngoplasty (UVPP). The current draft lists only a RDI > 15.
2. The Medicare Nationally Coverage diagnostic criteria for obstructive sleep apnea listed in section #3 that include both a full diagnostic polysomnogram (PSG) in a sleep laboratory & the type II through type IV home sleep studies should be **the same** as those listed in A. section 1 that currently specifies the full diagnostic polysomnogram (PSG) in a sleep laboratory only as a for justification of UVPP. From our perspective, home sleep studies are a cost-effective way to screen, diagnose and assess post-operative results of treatment, and these studies need to be more widely utilized.
3. Otolaryngology literature supports evidence of efficacy of submucosal channeling treatment (CPT 41530) for reduction of volume and induction of scarring within the base of the tongue. Therefore, exclusion of this modality as stated in section E.5 is not justified based on the latest literature.

Thank you in advance for your attention to this matter.  
Jan Zempenyi, MD.



May 2, 2012

Washington State Health Care Authority  
Health Technology Clinical Committee  
shtap@hca.wa.gov

RE: Public Comments on the Draft Findings and Decision for 20120316A –  
Sleep Apnea Diagnosis and Treatment

Dear WA State HCA & Health Technology Clinical Committee:

Thank you for your health technology assessment of Sleep Apnea Diagnosis and Treatment.

I strongly support your adoption of the Medicare national coverage determination for CPAP and for Sleep Testing, and your adoption of the Medicare local coverage determination (L307731) for Surgical Treatment of Obstructive Sleep Apnea. These policies are supported by the current evidence and by thoughtful processes of development, except where noted below.

I wish to request three minor, but important, changes to the policy on the Surgical Treatment of Obstructive Sleep Apnea, to make the surgery policy consistent with the larger policy on Sleep Apnea Diagnosis and Treatment and with the latest and highest level evidence.

**1) DIAGNOSIS OF OBSTRUCTIVE SLEEP APNEA REQUIRED FOR SURGERY SHOULD BE THE SAME AS THE POLICY OF THE DIAGNOSIS OF OBSTRUCTIVE SLEEP APNEA IN GENERAL.**

Where surgery requires sleep apnea diagnosed “in a certified sleep disorders laboratory,” it should be updated to be consistent with the general policy for the diagnosis of sleep apnea. The policy for the diagnosis of sleep apnea recommended by the Health Technology Clinical Committee reflects the Medicare national coverage determination and recommends diagnosis by attended polysomnography performed in a sleep laboratory; or unattended home sleep tests with a Type II, III, or IV monitoring device of at least 3 channels including airflow, in patients with clinical signs and symptoms of obstructive sleep apnea (Item B in the draft policy). This request to allow home sleep testing for surgery applies to each type of surgery: uvulopalatopharyngoplasty, mandibular maxillary osteotomy & advancement, genioglossus advancement, hyoid suspension, and other medically necessary procedures to treat sites of anatomic obstruction contributing to obstructive sleep apnea.

**2) SEVERITY OF OBSTRUCTIVE SLEEP APNEA REQUIRED FOR SURGERY SHOULD BE THE SAME AS THE SEVERITY OF OBSTRUCTIVE SLEEP APNEA REQUIRED FOR OTHER TREATMENT.**

Where surgery requires a “Respiratory Disturbance Index of 15 or higher,” it

should be updated to be consistent with the criteria to treat obstructive sleep apnea by other means. The policy for the treatment of sleep apnea by CPAP recommended by the Health Technology Clinical Committee reflects the Medicare national coverage determination and recommends treatment for “A) Apnea-Hypopnea Index or Respiratory Disturbance Index greater than or equal to 15 events per hour, or B) Apnea-Hypopnea Index or Respiratory Disturbance Index greater than or equal to 5 events per hour and less than or equal to 14 events per hour with documented symptoms of excessive daytime sleepiness, impaired cognition, mood disorders or insomnia, or documented hypertension, ischemic heart disease, or history of stroke.” This request to cover surgical treatment of mild sleep apnea (5-14 events per hour) when symptomatic or associated with adverse health morbidity, if CPAP has not been successful, applies to each type of surgery: uvulopalatopharyngoplasty, mandibular maxillary osteotomy & advancement, genioglossus advancement, hyoid suspension, and other medically necessary procedures to treat sites of anatomic obstruction contributing to obstructive sleep apnea.

**3) SUBMUCOSAL ABLATION OF THE TONGUE BASE, RADIOFREQUENCY, ONE OR MORE SITES, PER SESSION (41530) SHOULD BE A COVERED PROCEDURE.**

This procedure was covered in the Medicare Local Coverage Determination (L19078, retired in 2011, Attachment A), based on strong evidence supporting its safety and efficacy in improving obstructive sleep apnea. There is even a randomized sham-placebo-controlled trial (Attachment B) showing tongue/palate ablation improved the important outcomes of sleep apnea related quality of life, objective reaction times, and objective apnea index, relative to sham-placebo. It improved sleep apnea related quality of life and reaction times as well as or better than CPAP. Adverse outcomes were minor and rare. Long-term follow up showed maintenance of these improvements by this procedure for at least two years (Attachment C). Other studies also support its safety and benefit.

When our Medicare region merged with other states, including Wisconsin, the Local Coverage Determination was revised in late 2011 to include elements of the past (outdated) Wisconsin policy, specifically including the policy not to cover this procedure and specifying the sleep apnea severity criterion as only a Respiratory Disturbance Index >15 as described in (2) above (Attachment D with outdated parts crossed out in red). These changes were reversions to a past, outdated policy. I request that the Health Technology Clinical Committee revise this policy back to the more up-to-date policy that was part of the Local Coverage Determination 2005-2011 (L19078, Attachment A, underlined in green).

Thus, these requested changes reflect more up-to-date evidence and practice of surgery for obstructive sleep apnea.

My qualification for making these requests and recommendations are listed here:

- Official representative of the American Academy of Otolaryngology—Head

and Neck Surgery (AAO-HNS) to comment on this policy.

- Former chair of the AAO-HNS Sleep Disorders Committee
- Former chair of the AAO-HNS Outcome Research Steering Committee
- Former chair of the AAO-HNS Outcomes Research & Evidence-Based Medicine Subcommittee.
- Board certified in Sleep Medicine & Otolaryngology
- Fellowship-trained in outcomes research (RWJ Clinical Scholars Program)
- Masters in Public Health in Health Services Research
- Continuously funded for sleep apnea outcomes research and clinical epidemiology by NIH for almost 10 years
- Co-Director of the UW Sleep Institute and Chief of Sleep Surgery at UW.
- Co-author on 5 surgery studies and 2 guidelines cited in the review used by the Health Technology Clinical Committee
- Co-author of the Medicare LCD for surgical treatment of sleep apnea (L19078) in effect 2005-2011 (and modified partly by others in late 2011).

My potential conflicts of interest:

- No commercial conflicts of interest
- I practice sleep medicine and sleep surgery (surgical treatment of sleep apnea) at UW Medicine and the Seattle VA Medical Center.
- While this experience might pose a potential conflict of interest, I believe it also provides critical insight.

Thank you for the opportunity to comment.

Sincerely,

Edward M. Weaver, MD, MPH

# RETIRED Local Coverage Determination (LCD) for Treatment of Obstructive Sleep Apnea (L19078)

**RETIRED**

**Please note:** This is a Retired LCD.

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## Contractor Information

<b>Contractor Name</b> Noridian Administrative Services, LLC	<b>Contractor Number</b> 00821	<b>Contractor Type</b> Carrier
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## LCD Information

### Document Information

**RETIRED**

**LCD ID Number**  
L19078

**LCD Title**  
Treatment of Obstructive Sleep Apnea

**Contractor's Determination Number**  
B2002.13 R3

**AMA CPT/ADA CDT Copyright Statement**  
CPT codes, descriptions and other data only are copyright 2011 American Medical Association (or such other date of publication of CPT). All Rights Reserved. Applicable FARS/DFARS Clauses Apply. Current Dental Terminology, (CDT) (including procedure codes, nomenclature, descriptors and other data contained therein) is copyright by the American Dental Association. © 2002, 2004 American Dental Association. All rights reserved. Applicable FARS/DFARS apply.

### Primary Geographic Jurisdiction

Alaska  
Oregon  
Washington

**Oversight Region**  
Region X

**Original Determination Effective Date**  
For services performed on or after 12/31/2005

**Original Determination Ending Date**  
04/15/2011

**Revision Effective Date**  
For services performed on or after 01/01/2009

**Revision Ending Date**  
04/15/2011

## CMS National Coverage Policy

Title XVIII of the Social Security Act, Section 1862(a)(1)(A). This section allows coverage and payment for only those services that are considered to be medically reasonable and necessary.

Title XVIII of the Social Security Act, Section 1833(e). This section prohibits Medicare payment for any claim which lacks the necessary information to process the claim.

Medicare National Coverage Determination Manual, Part 4, Section 240.4 [formerly Coverage Issues Manual (CIM) Section 60-17]: Refer to "Indications and Limitations of Coverage and/or Medical Necessity" section below.

Medicare Benefit Policy Manual, Pub. 100-02, Chapter 16, [formerly Medicare Carriers Manual (MCM) Section 2136]:

#### "Section 140 - DENTAL SERVICES EXCLUSION

Items and services in connection with the care, treatment, filling, removal, or replacement of teeth or structures directly supporting the teeth are not covered. Structures directly supporting the teeth mean the periodontium, which includes the gingivae, dentogingival junction, periodontal membrane, cementum, and alveolar process. " End of Quote

In addition, see:

(a) Medicare General Information, Eligibility and Entitlement Manual, Chapter 5, Section 70 and 70.1,

(b) Medicare Benefit Policy Manual, Pub. 100-02, Chapter 15, Section 30.3, [formerly Medicare Carriers Manual (MCM)],

(c) Medicare National Determination Manual, Section 260.6 (formerly Medicare Carrier's Manual Section 2020.3 and Coverage Issues Manual, Section 50-26) for specific services that may be covered when furnished by a dentist. If an otherwise noncovered procedure or service is performed by a dentist as incident to and as an integral part of a covered procedure or service performed by him/her, the total service performed by the dentist on such an occasion is covered.

### **Indications and Limitations of Coverage and/or Medical Necessity**

Sleep Disordered Breathing, often referred to as Obstructive Sleep Apnea (OSA), is characterized by frequent episodes of hypopnea or apnea during sleep. Multiple detrimental physiologic changes may result from these hypopneic and apneic episodes. A monitored polysomnogram is generally necessary for correct diagnosis. However, an unattended exam performed according to the provisions of the NCD for Continuous Positive Airway Pressure (CPAP) Therapy For Obstructive Sleep Apnea (OSA) (240.4), is sufficient to support payment for CPAP. Non-surgical and surgical approaches to obstructive apnea and hypopnea have been developed.

Intraoral orthotics, designed to keep the tongue and jaw forward, are effective in up to 80% of patients.

## Continuous Positive Airway Pressure (CPAP):

Nasal CPAP prevents upper airway occlusion by splinting the pharyngeal airway with a positive pressure delivered through a nose mask. Used full time during sleep, it may be the most successful long-term approach to treatment, though this clearly creates practical problems for the patient.

With attention and compassionate follow-up, a large proportion of OSA patient will respond to CPAP and this more conservative approach must be aggressively pursued to the extent possible and feasible. Comprehensive surgical treatment may be effective in a portion of OSA patients, including those who fail nonsurgical treatment. Published data support site-directed treatment. To meet Medicare medical necessity guidelines, the record must clearly establish the inability to adequately address the patient's sleep apnea with a more conservative approach and the necessary, expected improvement attainable by each component of any proposed surgery with specific, objective evidence of the site(s) of obstruction.

Uvulopalatopharyngoplasty (UPPP) is an accepted means of surgical treatment for palate (retropalatal) obstruction, resulting in substantially fewer episodes of apnea, a reduction in mortality hazard and, in some patients, apparent cure. UPPP by itself is less successful in patients with multiple sites of obstruction, and in a portion of these patients there may therefore be a demonstrable need for multi-site surgery.

Various other anatomic abnormalities (such as, but not limited to, enlarged tonsils, enlarged tongue, intraoral abnormalities, or nasal obstruction) sometimes cause or exacerbate OSA. Surgical approaches to these abnormalities will vary according to the anatomic defect demonstrated to be causing the obstruction and the procedure(s) needed to correct the defined problem. For example, reduction of obstructing hypertrophied turbinates has been shown to significantly improve nasal airflow and improve both CPAP usage and OSA symptoms.

For those patients where it is documented in the medical record that the above approaches are inadequate or inappropriate, and when documented that retrolingual obstruction is a significant component, genioglossus advancement and/or hyoid suspension may be indicated to reduce the obstruction.

Mandibular maxillary osteotomy and advancement is a procedure developed for those patients with retrolingual obstruction, with or without retropalatal obstruction, who have not responded to CPAP, usually following other site-specific surgical treatments noted above.

Tracheostomy remains the most effective of all surgical and nonsurgical treatments for OSA since it bypasses all areas of obstruction in the nasal, palatal, lingual and pharyngeal areas. However, tracheostomy is associated with significant morbidity, and is usually reserved for patients who have failed other medical or surgical methods of treatment, or who are unsuited for other methods of treatment for various reasons.

## Oral Appliances for OSA

The Durable Medical Equipment Regional Carrier (DMERC) considers oral appliances for OSA to be Durable Medical Equipment and lists the following items of information that must accompany a claim.

1. The name of the manufacturer of the specific device provided.
2. A statement of the estimated appliance useful lifetime before replacement is necessary.
3. Documentation from the treating physician stating the diagnosis, what other therapy had been tried or considered and why the oral appliance is being ordered.
4. A copy of the polysomnogram report which documents the patient's sleep disorder and a copy of a sleep study report which documents improvement with the use of the oral appliance.

The following is taken from CMS Change Request 1949, Transmittal 150, dated December 26, 2001 and Medicare National Coverage Determination Manual, Section 240.4:

### **240.4 – "Continuous Positive Airway Pressure (CPAP) Therapy For Obstructive Sleep Apnea (OSA) (Effective April 4, 2005)**

#### "A. General

"CPAP is a non-invasive technique for providing single levels of air pressure from a flow generator, via a nose mask, through the nares. The purpose is to prevent the collapse of the oropharyngeal walls and the obstruction of airflow during sleep, which occurs in OSA.

#### "B. Nationally Covered Indications

"The use of CPAP is covered under Medicare when used in adult patients with moderate or severe OSA for whom surgery is a likely alternative to CPAP. The use of CPAP devices must be ordered and prescribed by the licensed treating physician to be used in adult patients with moderate to severe OSA if either of the following criterion using the Apnea-Hypopnea Index (AHI) are met:

- AHI *greater than or equal to 15 events per hour, or*
- AHI *greater than or equal to 5 and less than or equal to 14 events per hour with documented symptoms of excessive daytime sleepiness, impaired cognition, mood disorders or insomnia, or documented hypertension, ischemic heart disease, or history of stroke.*

"The AHI is equal to the average number of episodes of apnea and hypopnea per hour and must be based on a minimum of 2 hours of sleep recorded by polysomnography using actual recorded hours of sleep (i.e., the AHI may not be extrapolated or projected).

"Apnea is defined as a cessation of airflow for at least 10 seconds. Hypopnea is defined as an abnormal respiratory event lasting at least 10 seconds with at least a 30 percent reduction in thoracoabdominal movement or airflow as compared to baseline, and with at least a 4 percent oxygen desaturation.

"The polysomnography must be performed in a facility - based sleep study laboratory, and not in the home or in a mobile facility, except when performed as an unattended home study, consistent with the terms of the CPAP NCD.

"Initial claims must be supported by medical documentation (separate documentation where electronic billing is used), such as a prescription written by the patient's attending physician that specifies:

- A diagnosis of moderate or severe obstructive sleep apnea, and
- Surgery is a likely alternative.

"The claim must also certify that the documentation supporting a diagnosis of OSA (described above) is available.

### "C. Nationally Non-covered Indications

"A supplier with a significant financial interest in facilities providing testing for diagnosing OSA for purposes of supporting use of CPAP would not be considered a qualified provider or supplier of these tests for purposes of Medicare coverage for CPAP devices. This prohibition does not apply to studies conducted by hospitals certified to do such tests.

UPPP is covered **only** for those patients who have **all** of the following:

- 1) Obstructive sleep apnea diagnosed (prior to any proposed surgery) in a sleep disorders laboratory;
- 2) An apnea-hypopnea index as noted above.
- 3) Failure to respond to CPAP therapy or demonstrated inability to tolerate CPAP or other appropriate non-invasive treatment;
- 4) Counseling by a physician with recognized experience in sleep disorders, about the potential benefits and risks of the surgery; and
- 5) Evidence of retropalatal or combination retropalatal/retrolingual obstruction as the cause of the obstructive sleep apnea. The medical record must document the specific nature and extent of the obstruction, such as elongated soft palate, redundant lateral pharyngeal wall and/or excess tonsillar tissue.

Genioglossus advancement and/or hyoid suspension, and/or mandibular maxillary osteotomy and advancement are covered **only** for patients who have **all** of the following:

- 1) Obstructive sleep apnea diagnosed (prior to any proposed surgery) in a sleep disorders laboratory;
- 2) An apnea-hypopnea index as noted above.
- 3) Failure to respond to Continuous Positive Airway Pressure therapy or demonstrated inability to tolerate CPAP and other appropriate non-invasive treatment;

- 4) Evidence of retrolingual obstruction (alone or as a significant contributor in combination with other site(s) of obstruction) as the cause of the obstructive sleep apnea, or previous failure of UPPP to correct the obstructive sleep apnea with evidence that retrolingual obstruction remains a significant, and potentially correctable cause, and
- 5) Counseling by a physician, with recognized experience in both sleep disorders, and potential, alternative surgical approaches, about the potential risks and benefits of the surgery.

Regarding mandibular maxillary osteotomy and advancement:

- 1) Separate repositioning of teeth would not be necessary except under unusual circumstances, but if necessary, the dental work would be covered.
- 2) Application of an interdental fixation device is occasionally necessary and is then a covered service (see documentation requirements).

Tracheostomy is covered for OSA that is unresponsive to other means of treatment or in cases where other means of treatment would be ineffective or not indicated.

When OSA is caused by discrete anatomic abnormalities of the upper airway (such as, but not limited to, enlarged tonsils, enlarged tongue, intraoral abnormalities, or nasal obstruction), surgery to correct these abnormalities is covered if medically necessary based on adequate documentation in the medical records supporting the significant contribution of these abnormalities to OSA. Submucous radiofrequency reduction of hypertrophied turbinates is covered as an appropriate treatment for nasal obstruction due to turbinate hypertrophy that significantly contributes to OSA or significantly compromises CPAP therapy.

Radiofrequency tongue base reduction is covered in treating obstructive sleep apnea only in selected patients meeting the above criteria who do not or can not achieve or sustain adequate improvement from CPAP, when performed in sites and by providers experienced in the procedure, and where all of the following are met and documented in the record:

- 1) Obstructive sleep apnea diagnosed (prior to any proposed surgery) in a sleep disorders laboratory;
- 2) An apnea-hypopnea index as noted above.
- 3) Failure to respond to Continuous Positive Airway Pressure therapy or demonstrated inability to tolerate CPAP and other appropriate non-invasive treatment;
- 4) Evidence of lingual obstruction specifically documented to be due to tongue hypertrophy as the cause of the obstructive sleep apnea (alone or as a significant contributor in combination with other site(s) of obstruction), and
- 5) Counseling by a physician, with recognized experience in both sleep disorders, and potential, alternative surgical approaches, about the potential risks and benefits of the surgery.

Radiofrequency tongue base reduction is billed using 41530 Submucosal ablation of the tongue base, radiofrequency, one or more sites, per session.

Laser-assisted uvulo-palatoplasty (LAUP) is not covered at this time since it is not considered effective for OSA. LAUP must not be billed as 42145, Palatopharyngoplasty (e.g., uvulopalatopharyngoplasty, uvulopharyngoplasty). This code is not appropriate for this procedure.

Somnoplasty™ is a trade name for palate reduction with the Somnoplasty™ System of Somnus Medical Systems. This is not a term recognized by NAS as a covered procedure under Medicare Part B. Therefore Somnoplasty™ must not be billed as 42145. This code is not appropriate for this procedure.

The Pillar Procedure™ is a trade name for palatal implants. Palatal implants have not been shown effective for the treatment of obstructive sleep apnea and are not covered.

Compliance with the provisions in this policy is subject to monitoring by post payment data analysis and subsequent medical review.

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## Coding Information

**[RETIRED]**

### Bill Type Codes:

Contractors may specify Bill Types to help providers identify those Bill Types typically used to report this service. Absence of a Bill Type does not guarantee that the policy does not apply to that Bill Type. Complete absence of all Bill Types indicates that coverage is not influenced by Bill Type and the policy should be assumed to apply equally to all claims.

999x	Not Applicable
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### Revenue Codes:

Contractors may specify Revenue Codes to help providers identify those Revenue Codes typically used to report this service. In most instances Revenue Codes are purely advisory; unless specified in the policy services reported under other Revenue Codes are equally subject to this coverage determination. Complete absence of all Revenue Codes indicates that coverage is not influenced by Revenue Code and the policy should be assumed to apply equally to all Revenue Codes.

99999	Not Applicable
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### CPT/HCPCS Codes

#### GroupName

21110	APPLICATION OF INTERDENTAL FIXATION DEVICE FOR CONDITIONS OTHER THAN FRACTURE OR DISLOCATION, INCLUDES REMOVAL
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21141	RECONSTRUCTION MIDFACE, LEFORT I; SINGLE PIECE, SEGMENT MOVEMENT IN ANY DIRECTION (EG, FOR LONG FACE SYNDROME), WITHOUT BONE GRAFT
21145	RECONSTRUCTION MIDFACE, LEFORT I; SINGLE PIECE, SEGMENT MOVEMENT IN ANY DIRECTION, REQUIRING BONE GRAFTS (INCLUDES OBTAINING AUTOGRAFTS)
21196	RECONSTRUCTION OF MANDIBULAR RAMI AND/OR BODY, SAGITTAL SPLIT; WITH INTERNAL RIGID FIXATION
21199	OSTEOTOMY, MANDIBLE, SEGMENTAL; WITH GENIOGLOSSUS ADVANCEMENT
21685	HYOID MYOTOMY AND SUSPENSION
30140	SUBMUCOUS RESECTION INFERIOR TURBINATE, PARTIAL OR COMPLETE, ANY METHOD
30802	ABLATION, SOFT TISSUE OF INFERIOR TURBINATES, UNILATERAL OR BILATERAL, ANY METHOD (EG, ELECTROCAUTERY, RADIOFREQUENCY ABLATION, OR TISSUE VOLUME REDUCTION); INTRAMURAL (IE, SUBMUCOSAL)
31600	TRACHEOSTOMY, PLANNED (SEPARATE PROCEDURE);
31610	TRACHEOSTOMY, FENESTRATION PROCEDURE WITH SKIN FLAPS
41530	SUBMUCOSAL ABLATION OF THE TONGUE BASE, RADIOFREQUENCY, 1 OR MORE SITES, PER SESSION
42145	PALATOPHARYNGOPLASTY (EG, UVULOPALATOPHARYNGOPLASTY, UVULOPHARYNGOPLASTY)
E0601	CONTINUOUS AIRWAY PRESSURE (CPAP) DEVICE
E1399	DURABLE MEDICAL EQUIPMENT, MISCELLANEOUS

### ICD-9 Codes that Support Medical Necessity

**Note:** Diagnosis codes are based on the current ICD-9-CM codes that are effective at the time of LCD publication. Any updates to ICD-9-CM codes will be reviewed by NAS; and coverage should not be presumed until the results of such review have been published/posted.

These are the **only** covered diagnoses for CPT codes **21685, and 42145**. This list will not address the other listed HCPCS services/procedures.

327.23	OBSTRUCTIVE SLEEP APNEA (ADULT) (PEDIATRIC)
780.51	INSOMNIA WITH SLEEP APNEA, UNSPECIFIED
780.53	HYPERSOMNIA WITH SLEEP APNEA, UNSPECIFIED
780.57	UNSPECIFIED SLEEP APNEA

These are the **only** covered diagnoses for CPT code **41530**:

**Both** ICD-9-CM code 327.23 (Obstructive sleep apnea) and at least one of the following two codes (529.8 or 750.15) must be present on the claim.

**Primary diagnosis code for CPT code 41530:**

327.23*	OBSTRUCTIVE SLEEP APNEA (ADULT) (PEDIATRIC)
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\*Both ICD-9-CM code 327.23 (Obstructive sleep apnea) and at least one of the following two codes (529.8 or 750.15) must be present on the claim

These are the **only** covered diagnoses for CPT code **41530**:

**Both** ICD-9-CM code 327.23 (Obstructive sleep apnea) and at least one of the following two codes (529.8 or 750.15) must be present on the claim.

**Secondary diagnosis code for CPT code 41530:**

529.8*	OTHER SPECIFIED CONDITIONS OF THE TONGUE
750.15*	MACROGLOSSIA

\* Both ICD-9-CM code 327.23 (Obstructive sleep apnea) and at least one of the following two codes (529.8 or 750.15) must be present on the claim. Note that ICD-9-CM code 529.8 may be used only for tongue hypertrophy. Each of the conditions must be documented in the medical record which must be made available to Medicare on request.

### Diagnoses that Support Medical Necessity

**All** ICD-9-CM codes listed in this policy under “ICD-9-CM Codes that Support Medical Necessity” above.

### ICD-9 Codes that DO NOT Support Medical Necessity

**All** ICD-9-CM codes **not** listed in this policy under “ICD-9-CM Codes that Support Medical Necessity” above.

### ICD-9 Codes that DO NOT Support Medical Necessity Asterisk Explanation

### Diagnoses that DO NOT Support Medical Necessity

**All** ICD-9-CM codes **not** listed in this policy under “ICD-9-CM Codes that Support Medical Necessity” above.

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## General Information

**RETIRED**

### Documentations Requirements

Claims for co-surgery will require an accompanying written report of the procedure and justifications for co-surgery.

**Laser-assisted uvulo-palatoplasty (LAUP) is not covered at this time since it is not considered effective for OSA. LAUP must not be billed as 42145. (See information in attached Coding Guidelines.)**

**Somnoplasty™ is a trade name for palate reduction with the Somnoplasty™ System of Somnus Medical Systems. This is not a term recognized by Noridian as a covered procedure under Medicare Part B. Therefore Somnoplasty™ must not be billed as 42145. (See information in attached Coding Guidelines.)**

**The Pillar Procedure™ is a trade name for palatal implants. Palatal implants are not a term recognized by Noridian as a covered procedure under Medicare Part B. Therefore the Pillar Procedure™ or palatal implants must not be billed as 42145. (See information in attached Coding Guidelines.)**

Documentation supporting the medical necessity for any dental work done with the procedure must be submitted with the claim. Claims submitted without that documentation will have the dental work automatically denied.

Documentation supporting the medical necessity for the procedure, including all documentation listed under the Indications and Limitations of Coverage section, must be made available to Medicare upon request.

Documentation of the counseling of the risks and benefits of the procedure must be available, if necessary, for review.

Documentation that CPAP or other modes of continuous positive airway pressure therapy for OSA has had adequate trial under the care of a physician especially trained in sleep disordered breathing must be available, if necessary, for review. Absence of this information could result in denial of payment.

Any claim which includes application of an interdental fixation device will require submission of a written report attesting to the medical necessity of the device.

The HCPCS/CPT code(s) may be subject to Correct Coding Initiative (CCI) edits. This policy does not take precedence over CCI edits. Please refer to the CCI for correct coding guidelines and specific applicable code combinations prior to billing Medicare.

When the documentation does not meet the criteria for the service rendered or the documentation does not establish the medical necessity for the services, such services will be denied as not reasonable and necessary under Section 1862(a)(1) of the Social Security Act.

When requesting a written redetermination (formerly appeal), providers must include all relevant documentation with the request.

## **Appendices**

### **Utilization Guidelines**

#### **Sources of Information and Basis for Decision**

1. Davila, D. G., 1995, " Medical Considerations in Surgery for Sleep Apnea", *Oral and Maxillofacial Surgery Clinics of North America*, 7: 205-221.
2. Riley, R.W., et al, 1993, "Obstructive Sleep Apnea Syndrome: a Review of 306 Consecutively Treated Surgical Patients", *Otolaryngol Head Neck Surg*, 108: 117-125.
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**Advisory Committee Meeting Notes** This medical policy was presented at the Medicare Part B Open Public Meeting held on 01/04/2005, and discussed at the following Carrier Advisory Committee meetings on the following dates:

Alaska - 03/03/2005  
Oregon - 02/05/2005  
Washington - 02/15/2005

This policy does not reflect the sole opinion of the contractor or contractor medical directors. Although the final decision rests with the contractor, this policy was developed in cooperation with the Carrier Advisory Committees, which include representatives from various medical specialties.

The Section titled "Does the 'CPT 30% Rule' apply" needs clarification. This rule comes from the AMA (American Medical Association), the organization that holds the copyrights for all CPT codes. The rule states that if, in a given section (e.g., **surgery**) or subsection (e.g., surgery, **integumentary**) of the CPT Manual, more than 30% of the codes are listed in the LCD, then the short descriptors must be used rather than the long descriptors found in the CPT Manual.

This policy is subject to the reasonable and necessary guidelines and the limitation of liability provision.

**This medical policy consolidates and replaces all previous policies and publications on this subject by Noridian Administrative Services (NAS) and its predecessors for Medicare Part B.**

#### **NAS' Responses to Provider Recommendations:**

1) Several physicians requested reconsideration of NAS' earlier noncoverage decision on the use of RFA for obstruction related to tongue hypertrophy, and multiple articles and series reviews were submitted to support this position. In addition, iterative comments and replies were received as NAS further evaluated this issue, leading to a conclusion that this has been established as effective and appropriate in selected patients where the source of obstruction has been documented to be a result of tongue hypertrophy.

2) One commenter pointed out that palatal implants have not been shown effective for the treatment of obstructive sleep apnea and should not be covered. NAS agrees.

**Start Date of Comment Period** 12/20/2004

**End Date of Comment Period** 04/15/2005

**Start Date of Notice Period** 11/11/2005

## Revision History Number R3

### Revision History Explanation B2002.13

This medical policy was revised and renumbered to create consistency among the eleven Part B Noridian states and to incorporate recent CMS changes.

For Alaska, Arizona, Hawaii, Nevada, Oregon and Washington, there was no previous medical policy, so this is Not Applicable.

For Colorado, North Dakota, South Dakota and Wyoming, the original medical policy (Policy Number 96.10) was effective for dates of service on/after October 01, 1996 through September 30, 1997, as published in "Medicare B News," Issue 148, and a revised medical policy (Policy Number 97.01) effective for dates of service on/after October 01, 1997, as published in Issue 159, with an update in Issue 188.

For Iowa, the original medical policy (Policy Number S97 002) was effective for dates of service on/after July 15, 1997, as published in "Medicare Info," dated June 1997.

#### **B2002.13 R1**

This is the first revision to LCD B2002.13.

11/26/2005 - The description for CPT/HCPCS code 30140 was changed in group 1

11/26/2005 - The description for CPT/HCPCS code 30802 was changed in group 1

#### **B2002.13 R2**

Inappropriate wording removed (fraud) per CMS Instructions, PIM Ch. 13 §13.1.3.

11/30/2006 - In accordance with Section 911 of the Medicare Modernization Act of 2003, Arizona was transitioned from Carrier Noridian Administrative Services, LLC (00821) to MAC - Part B Noridian Administrative Services (03102).

#### **B2002.13 R3**

11/09/2008 - CPT/HCPCS code 0088T was deleted from group 1 and replaced with CPT 41530, effective 01/01/2009.

Verbiage was also updated to be consistent with the following NCD revision, "The AHI and/or RDI may be measured by polysomnography (PSG) in a facility-based sleep study laboratory, or by a Type II home sleep test (HST) monitor, a Type III HST monitor, or a Type IV HST monitor measuring at least 3 channels." effective 3/13/08 for implementation on 8/04/08.

Coding guidelines were removed from the body of the LCD and incorporated into a coding guidelines attachment.

11/15/2009 - The description for CPT/HCPCS code 30802 was changed in group 1

11/15/2009 - The description for CPT/HCPCS code 41530 was changed in group 1

11/21/2010 - For the following CPT/HCPCS codes either the short description and/or the long description was changed. Depending on which description is used in this LCD, there may not be any change in how the code displays in the document:

21141 descriptor was changed in Group 1

21145 descriptor was changed in Group 1

42145 descriptor was changed in Group 1

Note that analyses of claim billings and medical records indicate providers understand the medical necessity criteria for the services covered in these LCDs. The LCD is primarily an educational document, intended to provide information about the medical necessity of services or drugs. Retirement does not mean that medical necessity has changed or that the LCD no longer reflects appropriate criteria. Rather, retirement is a reflection of the provider community's understanding of the medical necessity criteria for the services covered by and compliance with Medicare guidelines on these LCDs.

## Reason for Change

## Related Documents

This LCD has no Related Documents.

## LCD Attachments

[Coding Guidelines - Treatment of Obstructive Sleep Apnea - B2002.13 R3 \(PDF - 9 KB \)](#)

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# A randomized trial of temperature-controlled radiofrequency, continuous positive airway pressure, and placebo for obstructive sleep apnea syndrome

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**OBJECTIVE:** The study goal was to determine the effectiveness of (1) multilevel temperature-controlled radiofrequency tissue ablation (TCRFTA) or (2) continuous positive airway pressure (CPAP) for the treatment of mild to moderate obstructive sleep apnea syndrome (OSAS).

**STUDY DESIGN AND METHODS:** We conducted a randomized, placebo-controlled, 2-site trial, comparing TCRFTA (n = 30) and CPAP (n = 30) with sham-placebo (n = 30) using intention-to-treat analysis.

**RESULTS:** Compared with pretreatment baseline, TCRFTA improved reaction time, OSAS-specific quality of life (QOL), and subjective sleepiness (all  $P < 0.05$ ). Compared with sham-placebo, TCRFTA improved QOL, airway volume, apnea index, and respiratory arousal index (all  $P < 0.05$ ). TCRFTA side effects and complications were mild, temporary, and similar to sham-placebo. CPAP improved QOL and sleepiness compared with baseline and QOL when compared with sham-placebo (all  $P < 0.05$ ).

Significant differences were not seen between TCRFTA and CPAP outcomes.

**CONCLUSION:** TCRFTA and CPAP each improve QOL for mild-moderate OSAS patients. TCRFTA improvements may result from changes in airway volume, apnea index, and respiratory arousal index. (Otolaryngol Head Neck Surg 2003;128:848-61.)

**S**leep disordered breathing defined by an Apnea-Hypopnea Index (AHI) of 5 or more events per hour is estimated to affect 9% to 24% of middle-aged adults.<sup>1</sup> Obstructive sleep apnea syndrome (OSAS) includes both sleep disordered breathing and excessive daytime somnolence<sup>2</sup> and affects 2% to 4% of adults.<sup>1</sup> It is associated with cardiovascular disease, quality of life and performance deficits, and motor vehicle accidents.<sup>3-6</sup> Within the OSAS population, a large proportion of the patients manifest mild or moderate disease (AHI < 30 events per hour).<sup>1</sup>

First-line treatment for many OSAS patients is nasal continuous positive airway pressure (CPAP). When used adequately, CPAP improves sleepiness, performance, quality of life, and cardiovascular risk.<sup>4,7,8</sup> However, the effectiveness of CPAP in patients with milder OSAS remains unclear.<sup>9-11</sup>

Temperature-controlled radiofrequency tissue ablation (TCRFTA) applied to the tongue base and palate have been described to treat OSAS. Several case series and one large multicenter clinical trial have demonstrated improvement in polysomnographic parameters and in clinically important outcomes, with low morbidity and complication rates.<sup>12-14</sup> Studies have also demonstrated TCRFTA successfully reduces soft tissue volume of the tongue.<sup>12</sup> However, none of these studies included control subjects. Thus, this study was undertaken to evaluate the effects of multilevel (tongue and palate) TCRFTA on clinically important outcomes in patients with mild to moderate

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OSAS. Sham-placebo and nasal CPAP arms were included for controlled comparison.

## METHODS

### Study Design and Objectives

A 2-institution randomized placebo-controlled trial was performed to test the hypothesis that multilevel (tongue base and palate) TCRFTA is more effective than sham-placebo for improvement of clinically important outcomes in patients with mild to moderate OSAS. This trial was also performed to test the hypothesis that nasal CPAP is more effective than sham-placebo.

### Participants

Eligibility criteria included (1) age 18 to 65 years, (2) self-reports of daytime somnolence, (3) body mass index (BMI)  $\leq 34$  kg/m<sup>2</sup>, (4) no prior surgical or CPAP treatment for OSAS, and (5) mild to moderate OSAS defined by an AHI of 10 to 30 on screening sleep study. Exclusion criteria included (1) another significant sleep disorder (eg, insomnia, periodic limb movement), (2) tonsillar hypertrophy, (3) nasal or supraglottic obstruction on examination, (4) ASA class IV/V, (5) claustrophobia, (6) Latex allergy, (7) pregnancy or plans to become pregnant, (8) major depression or non-stabilized psychiatric disorder, (9) drug or alcohol abuse, (10) history of an accident secondary to sleepiness, or (11) participation in another study. Eligible subjects passing all exclusion criteria then had a baseline full polysomnography (PSG) and were included if AHI was 5 to 40 (Fig 1).

Subjects were recruited directly from the academic otolaryngology practices and from poster and newspaper advertisements. This study was designed, performed, and reported according to the Revised CONSORT Statement<sup>15</sup> and with approval from local institutional review boards. All patients gave informed consent. Subject flow is summarized in Figure 1.

### Polysomnography/Sleep Studies

Screening sleep studies included home Autoset PDS (ResMed Inc, Poway, CA) or full in-laboratory PSG (if performed within 1 year of enrollment). All subjects underwent a subsequent baseline full PSG (unless full in-laboratory PSG performed within 6 months of enrollment), which

included an electroencephalogram ( $\geq 2$  channels), electrooculogram, chin and leg muscle electromyograms, electrocardiogram, measures of oronasal airflow, thoracic and abdominal efforts, body position, and pulse oximetry. *Apnea* was defined as cessation of inspiratory airflow of at least 10 seconds. *Hypopnea* was defined as a reduction of inspiratory airflow of at least 10 seconds, with an associated 4% decrease in oxyhemoglobin saturation or an electroencephalographic arousal. Respiratory arousals were quantified on PSGs at University of Cincinnati and were defined as arousals associated with an apnea or hypopnea. AHI, apnea index (AI), total arousal index, and respiratory arousal index were calculated as the number of events, respectively, per hour of sleep. For CPAP subjects, treatment AHI and AI were downloaded from Autoset T (ResMed Inc).

### Interventions

Nasal CPAP therapy was titrated unattended over 3 or more nights with the AutoSet T device.<sup>16</sup> Final constant CPAP pressure was set as the 95 percentile pressure and was continued for 8 weeks. Subjects were seen at 1, 2, and 4 weeks to troubleshoot and optimize compliance. Side effects were identified by questionnaire at each visit and were treated appropriately (eg, nasal medication, heated humidifier, etc). Side effects recorded on the final (8-week) questionnaire is reported (see Table 3). Objective pressure-on time was acquired from usage software within the CPAP device, and self-reported use was recorded at each visit.

Active temperature-controlled radiofrequency tissue ablation (TCRFTA) was performed with the Somnoplasty radiofrequency generator (Gyrus-ENT, Memphis, TN). Five tongue and 2 palate sessions were planned for each active subject. Subjects were treated perioperatively with oral antibiotics, prednisone, antiseptic oral rinse, analgesic (as needed), and nonsteroidal anti-inflammatory medication (as needed). A local anesthetic mixture (2.5 mL of 2% lidocaine with 1:100,000 epinephrine, 2.0 mL of normal saline, and 0.5 mL of 8.4% sodium bicarbonate) was injected into each tongue treatment site, and 1% lidocaine with 1:100,000 epinephrine (1 to 2 mL) was injected into each palate site. Radiofrequency energy was delivered to create nonoverlapping lesions in 2 or

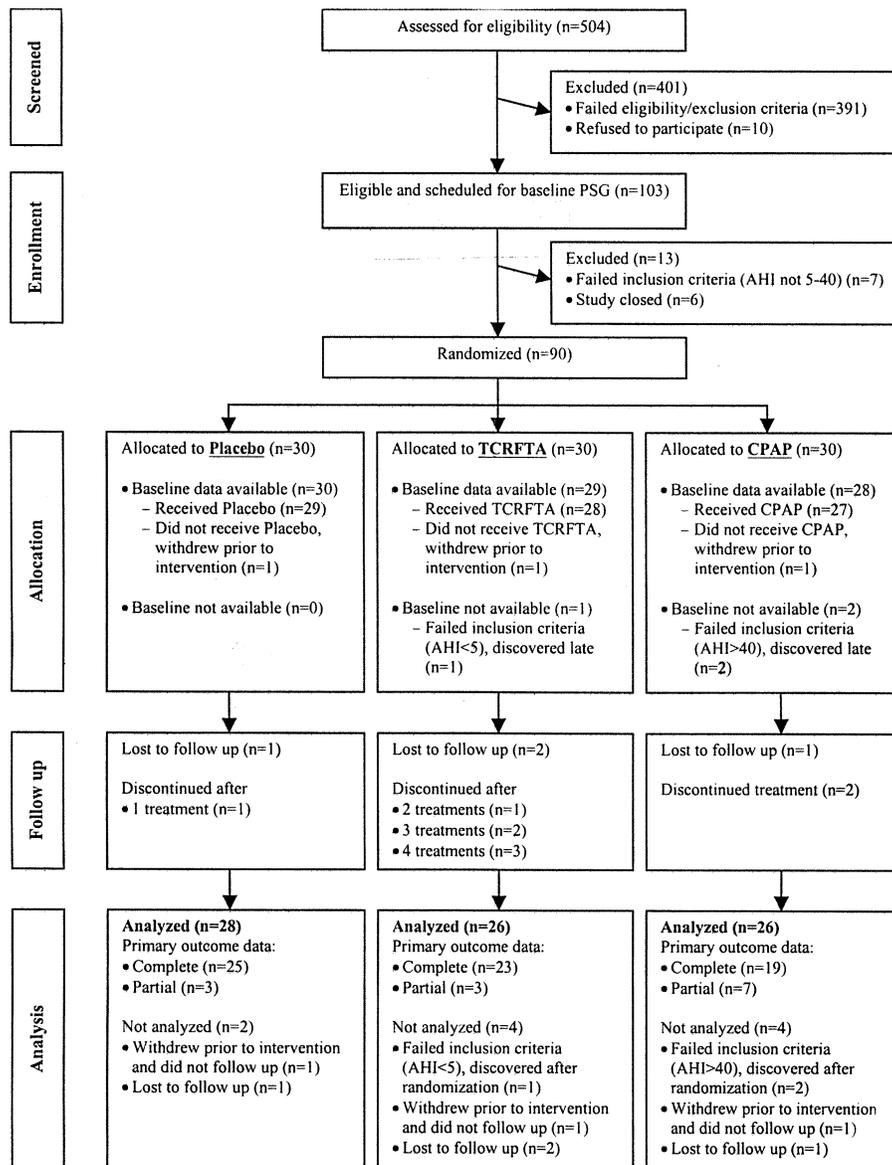


Fig 1. Flow diagram of subject progress through trial. Flow diagram of subjects' progress through the screening, enrollment, allocation, follow-up, and analysis.

3 tongue sites (1000 or 750 J, respectively, per site; target temperature 85° C; maximum power 10 W) per tongue treatment session, which occurred at 4-week intervals. Radiofrequency energy was delivered to create 1 midline and 2 lateral lesions (nonoverlapping) to the soft palate (650 J and 325 J, respectively) in each palate treatment session. Investigators were instructed to adjust lesion numbers per treatment session based on clinical judgment and patient tolerance. When tongue and palate sessions were combined, the subject was offered overnight hospital admission. Investiga-

tors were instructed to perform sequential and not simultaneous tongue and palate treatments if there were concerns about airway edema or patient tolerance. Attempts were made to apply similar levels of energy in all patients irrespective of the timing of sessions.

Sham-placebo TCRFTA was performed as described above for tongue TCRFTA except that a blocking control box on the radiofrequency generator was set to "off" to prevent delivery of energy. Three tongue sessions were planned for each sham-placebo subject at 4-week intervals,

with 3 tongue lesions created per session. Subjects were anesthetized and medicated as described for active tongue TCRFTA. The sham treatment sessions were limited to 3 to balance the risk of hematoma, edema, or abscess formation at the site of anesthetic injection or TCRFTA probe insertion versus the goal of providing a realistic placebo.

## Outcomes

The primary outcome measures were chosen a priori to represent meaningful measurements of patient function and quality of life. The primary outcome measures are changes in slowest reaction time (SRT) and OSAS-specific quality of life. Slowest reaction time was measured as the mean of the slowest 10% of reaction times on the Psychomotor Vigilance Task (PVT-192; Ambulatory Monitoring Inc, Ardsley, NY) with a total test time of 10 minutes and stimulus interval of 2 to 10 seconds. SRT was analyzed as the reciprocal ( $1/\text{SRT}$ ) to minimize the contribution of very long lapses.<sup>17</sup> OSAS-specific quality of life was measured with 2 validated questionnaires: (1) Functional Outcomes of Sleep Questionnaire (FOSQ)<sup>18</sup> and (2) Symptoms of Nocturnal Obstruction and Related Events (SNORE25), formerly the OSA Patient Oriented Severity Index.<sup>19</sup>

The secondary outcome measures include changes in (1) median reaction time (RT) and fastest reaction time (mean of fastest 10% reaction times, FRT) measurements, using the Psychomotor Vigilance Task as described above<sup>17</sup>; (2) daytime sleepiness using the Epworth Sleepiness Scale (ESS); (3) general health status measured with the SF36 (version 1) Mental Component Summary (MCS) and Physical Component Summary (PCS) scales; (4) total upper airway volume (incisors to epiglottis) using acoustic pharyngometry (SensorMedics, Yorba Linda, CA); and (5) in sham-placebo and TCRFTA subjects, PSG parameters (AHI, AI, lowest oxyhemoglobin saturation [LSAT], total arousal index, and respiratory arousal index). Pain and swallowing side effects were assessed 1 and 3 weeks after each TCRFTA and sham-placebo treatment session, using 10-cm visual analog scales (pain: 0 = "no pain" and 10 = "severe pain"; swallowing: 0 = "normal swallow" and 10 = "unable to swallow without pain, even with medication"). Adverse events were re-

corded with a description, course of action, and sequelae and were reported to local institutional review boards. Adverse event rates are reported as events per treatment session.

## Randomization and Blinding

Random treatment assignment was made with block randomization by site, using a computer-generated random number table. Randomization was concealed before assignment using sealed envelopes. Those responsible for randomization were not involved in enrollment or treatment assignment.

Patients were blinded to active versus placebo TCRFTA treatment. Subjects were blinded to the difference in treatment schedule between placebo and active TCRFTA groups. CPAP patients were not blinded. Treating investigators and study coordinators were not blinded to intervention group; however, medical assistants delivering self-administered subjective questionnaires were blinded. Furthermore, sleep laboratory staff including those scoring the PSGs were blinded to active or placebo TCRFTA treatment as well as to baseline or posttreatment status. Last, as treatment assignment was performed after baseline evaluations, all involved were blinded to treatment group for baseline assessments.

## Data Management and Statistical Methods

Data were collected on case report forms at each site. Copies were mailed to the sponsor's data coordinators, who entered the data and visually checked for accuracy. The principal investigator at each treatment site verified data accuracy. Data were also checked statistically and inconsistencies were resolved with the raw data at each site.

The sample size was calculated as 30 patients per treatment group, based on the primary outcome  $1/\text{SRT}$ , using the 2-sample  $t$  test with  $\alpha = 0.05$ , power = 90%, standard deviation  $1/\text{SRT} = 0.3$ ,<sup>17</sup> the minimal clinically important treatment effect (difference) =  $0.27$ ,<sup>17</sup> and accounting for a 10% dropout rate.

Subjects were analyzed according to their original group assignment (intention-to-treat analysis). For all analyses of continuous variables, normality was tested with the Shapiro-Wilk  $W$  test, Shapiro-

**Table 1.** Baseline Characteristics

Variable	Norm	Placebo* (n = 30)	TCRFTA* (n = 29)	CPAP* (n = 28)	P value†
Demographics					
Age (yr)		46.0 ± 8.1	49.4 ± 9.2	51.7 ± 8.6	0.04‡
Male gender (%)		70.0	89.7	75.0	0.17
Anatomy					
Body mass index (kg/m <sup>2</sup> )	<25	28.5 ± 4.2	27.7 ± 3.6	29.1 ± 3.7	0.36
Neck circumference (cm)	<43	40.6 ± 3.6 (29)	40.9 ± 3.3 (28)	41.4 ± 3.3 (27)	0.69
Upper airway volume (cm <sup>3</sup> )		77.1 ± 18.0 (28)	73.6 ± 19.8 (27)	69.3 ± 15.4 (22)	0.31
Polysomnography parameters					
Apnea-Hypopnea Index (events/hr)	<5 <sup>2</sup>	15.4 ± 7.8	21.3 ± 11.1	19.8 ± 9.9 (27)	0.06
Apnea Index (events/hr)	<5	3.9 ± 4.1	7.5 ± 10.9	6.2 ± 7.5 (27)	0.21
Lowest saturation (%)	>90	88.3 ± 3.9	86.3 ± 7.6	86.0 ± 6.4 (27)	0.32
Symptoms and quality of life					
Epworth Sleepiness Scale	<10	11.6 ± 3.5	11.9 ± 4.6	12.6 ± 5.0 (27)	0.68
Functional Outcomes of Sleep questionnaire	>17.8 <sup>18</sup>	16.8 ± 2.1	16.5 ± 2.0	16.0 ± 2.6 (27)	0.38
Symptoms of Nocturnal Obstruction and Related Events Questionnaire		1.6 ± 0.7	1.6 ± 0.7 (28)	1.5 ± 0.6 (27)	0.51
SF36 Mental Component Summary	50	46.7 ± 9.8	46.4 ± 9.4 (28)	47.2 ± 10.5 (27)	0.95
SF36 Physical Component Summary	50	49.9 ± 8.0	50.1 ± 8.3 (28)	50.7 ± 6.7 (27)	0.92
Psychomotor vigilance					
1/Slowest reaction time (1/msec)	≥2.88 <sup>17</sup>	2.88 ± 0.55 (29)	2.71 ± 0.69	2.77 ± 0.66	0.60
Median reaction time (msec)	≤231 <sup>17</sup>	227 ± 35 (29)	236 ± 41 (28)	226 ± 34	0.55
Fastest reaction time (msec)	≤191 <sup>17</sup>	184 ± 18 (29)	192 ± 26	183 ± 24	0.31

TCRFTA, temperature-controlled radiofrequency tissue ablation group; CPAP, continuous positive airway pressure group.

\*Values given in mean ± SD. n indicated in parentheses if less than the whole group.

†ANOVA ( $\chi^2$  for gender variable). For nonnormal distributions, normal transformations (Box-Cox, logarithmic, or square root) revealed similar results (not shown).

‡P-value <0.05 is significant.

Francia W' test, and combined skewness and kurtosis tests. For non-normality by any one of these tests, non-parametric tests or normal transformations (Box-Cox, logarithmic, or square root) were used to confirm parametric test results.

Baseline characteristics between groups were compared using ANOVA for continuous variables and the  $\chi^2$  test for the categorical variable (sex) (Table 1). Objective versus self-reported CPAP treatment data were compared with the paired *t* test (normal continuous variable), Wilcoxon sign-rank test (non-normal continuous variable), and Fisher's exact test (proportions) (see Table 3). The paired *t* test for continuous normal variables and the sign test for continuous nonnormal variables were used to test the null hypothesis that changes within groups were equal to zero (see Table 5). One-tailed tests were used for TCRFTA and

CPAP groups because an effect was expected a priori. Two-tailed tests were used for the placebo group because an effect was not expected a priori. The unpaired 2-sample *t* test (1-tailed) was used to test the null hypothesis that TCRFTA and CPAP were no different from-placebo (see Table 6). Statistical results were confirmed adjusting for study site (ANCOVA) (not shown). Normal transformations and/or the Mann-Whitney *U* test were used to confirm the statistical testing for non-normal variables (not shown). The unpaired 2-sample *t* test (2-tailed) was used to test the null hypothesis that TCRFTA was no different from CPAP (see Table 7), confirming with study site-adjusted ANCOVA (not shown) and with normal transformations or Mann-Whitney *U* test for nonnormal variables (not shown). Fisher's exact test (2-sided) was used to test the null hypothesis that TCRFTA

**Table 2.** Placebo and TCRFTA treatment data

Variable	Placebo (n = 28)	TCRFTA (n = 26)
Tongue		
No. of sessions	2.9 ± 0.4	4.5 ± 0.8
No. of lesions/session	2.7 ± 0.5	2.8 ± 0.5
Time/lesion (sec)	96 ± 12	219 ± 62
Energy/lesion (J)	0	770 ± 118
Energy/session (J)	0	2144 ± 375
Total energy (J)	0	9700 ± 2000
Palate		
No. of sessions	0	1.5 ± 0.7
No. of lesions/session		2.7 ± 0.8
Time/midline lesion (sec)		129 ± 43
Time/lateral lesion (sec)		59 ± 10
Energy/midline lesion (J)		624 ± 74
Energy/lateral lesion (J)		309 ± 29
Energy/session (J)		1129 ± 330
Total energy (J)		1785 ± 904

TCRFTA, temperature-controlled radiofrequency tissue ablation group.

success was no different from CPAP success, and logistic regression (Wald test) was used to test the null hypothesis adjusting for study site (not shown). Success was defined as achieving an effect size  $\geq 0.50$  over placebo.

All results of continuous variables are expressed as mean  $\pm$  SD. Within-group effect size was calculated as (posttreatment mean – baseline mean)/(baseline SD) as per Kazis et al.<sup>20</sup> Positive sign denotes improvement; negative sign denotes worsening. Between group effect size was calculated as (active treatment mean change – placebo mean change)/(placebo change SD). Positive sign denotes improvement in active treatment group over placebo; negative sign denotes worsening. The data were analyzed with Intercooled Stata 7.0 software (Stata Corp, College Station, TX).  $P < 0.05$  was considered statistically significant. Corrections for multiple comparisons were not made because the primary outcomes were limited to 3.

## RESULTS

Details of subject recruitment and the final sample of study participants are outlined in Figure 1. The dropout rate was 12% (Fig 1). Data were not complete on all follow-up subjects, but all available data were analyzed.

The 3 treatment groups were not significantly different with respect to all baseline variables except age, which was not considered a clinically

relevant difference (Table 1). On average, subjects had moderate OSA by AHI criteria,<sup>2</sup> and evidence of OSAS with excessive daytime sleepiness and deficits in OSAS-specific quality of life. BMI did not change significantly within groups (overall mean increase  $0.2 \pm 0.7$  kg/m<sup>2</sup>,  $P > 0.10$  for each group) or between groups ( $P = 0.64$ ).

Sham-placebo and TCRFTA treatment data are shown in Table 2, and CPAP treatment data are shown in Table 3. Subjects overestimated their actual CPAP use. Built-in CPAP apnea/hypopnea monitors demonstrate efficacy of prescribed pressures (Table 3). Between CPAP users ( $\geq 4$  hr/night and  $\geq 5$  nights/wk<sup>21</sup>) and nonusers, there were no significant differences in prescribed pressure ( $8.4 \pm 1.2$  versus  $7.6 \pm 1.8$  cm water,  $p = 0.24$ ) or residual AHI ( $5.1 \pm 2.1$  versus  $4.6 \pm 2.9$  events/hr,  $P = 0.59$ ).

Adverse events were mild and temporary in all cases, and the frequency was comparable between sham-placebo and TCRFTA groups (Table 4). No adverse events were seen with palate TCRFTA. Three subjects received additional medication (prednisone and/or prophylactic amoxicillin/clavulanate). Pain and swallowing difficulty increased mildly 1 week after treatment for both the placebo and TCRFTA groups but returned to baseline by 3 weeks with no significant differences noted between groups. After simultaneous tongue

**Table 3.** CPAP treatment data

Variable	Objective measure*	Self-report*†	P value‡ objective versus self-report
Use (hrs/night used)	4.2 ± 2.5 (24)	4.9 ± 2.5 (22)	0.09 (19)
Use (nights/wk)	4.0 ± 2.5 (25)	5.7 ± 2.1 (22)	0.002 (20)
No. of nights recorded	63.0 ± 29.7 (27)		
Adequate use§	9/24, 37.5%	17/22, 77.3%	0.007
CPAP (cm H <sub>2</sub> O)	7.9 ± 1.6 (24)		
Apnea-Hypopnea Index on CPAP   (events/hr)	4.6 ± 2.7 (24)		
Apnea Index on CPAP   (events/hr)	0.5 ± 1.0 (24)		

CPAP, continuous positive airway pressure.

\*\*Values given in mean ± SD. n indicated in parentheses if less than the whole group.

†Self-report based on report at final follow up (8 weeks after CPAP started).

‡P value based on paired *t* test (use hr/night, normal distribution), Wilcoxon sign-rank test (use nights/wk, nonnormal distribution), and Fisher's exact test (adequate use, proportions). *P*, < 0.05 is significant.

§Adequate use: ≥4 hr/night used and ≥5 nights/wk.<sup>21</sup>

||Apnea-Hypopnea Index and Apnea Index readings from built-in CPAP monitor (not polysomnography).

**Table 4.** Adverse events and side effects

Event	Placebo (n = 28)	TCRFTA (n = 26)	Event	CPAP (n = 21)
Adverse events				
No. of hematomas (% of sessions)	3 (3.5%)	3 (2.3%)		
No. of ulcerations (% of sessions)	0 (0%)	1 (0.8%)		
No. of infections (% of sessions)	0 (0%)	0 (0%)		
Side effects*				
Pain pretreatment	0.37 ± 0.78 (17)	0.64 ± 1.46 (19)	Nasal	8 (38%)
Pain 1 wk†	1.84 ± 2.35 (81)	1.64 ± 2.19 (75)	Sleep	9 (43%)
Pain 3 wk†	0.33 ± 0.65 (58)	0.71 ± 1.13 (68)	Inconvenience	7 (33%)
Swallow pretreatment	1.32 ± 2.08 (17)	0.85 ± 1.63 (19)	Air mechanics	7 (33%)
Swallow 1 wk††	1.73 ± 2.44 (81)	2.14 ± 2.52 (76)	Skin or eyes	8 (38%)
Swallow 3 wk†	0.57 ± 0.99 (59)	0.85 ± 1.36 (68)	Subjects affected	20 (95%)

TCRFTA, temperature-controlled radiofrequency tissue ablation group; CPAP, continuous positive airway pressure group.

\*Pain and swallow side effects measured in placebo and TCRFTA patients at baseline and after tongue treatments, presented as mean ± SD of 10-cm visual analog scale (pain: 0 = "no pain" and 10 = "severe pain"; swallowing: 0 = "normal swallow" and 10 = "unable to swallow without pain, even with medication"). n indicated in parentheses if less than the whole group. CPAP side effects measured in CPAP patients only, presented as number (percentage) of patients. Nasal = dryness, congestion, bleeding, and/or sinusitis; sleep = delayed sleep and/or subjective sleep fragmentation; inconvenience = noise and/or spouse objection; air mechanics = aerophagia, chest wall discomfort, and/or mouth breathing.

†1 wk = mean at 1 wk for all 3 tongue-only treatments; 3 wk = mean at 3 wk for all 3 tongue-only treatments.

and palate TCRFTA, mean pain scores were 2.8 ± 2.5 at 1 week and 0.7 ± 1.2 at 3 weeks, and mean swallowing scores were 2.6 ± 2.6 at 1 week and 1.0 ± 1.4 at 3 weeks. Most CPAP subjects experienced at least one side effect but none were serious (Table 4).

Table 5 and Figure 2 display the absolute changes and effect sizes for most outcome variables in each group compared with their pretreatment baseline. The placebo effects were small and not statistically significant. TCRFTA subjects improved on all primary outcome measures. CPAP

subjects improved on all primary outcome measures, but without statistical significance on the objective primary outcome (1/SRT). Among secondary outcomes, CPAP subjects had a large improvement on AHI measured by AutoSet (effect size 1.5, *P* < 0.001). Compared with the entire CPAP group, CPAP users (*n* = 9, use ≥4 hr/night on ≥5 nights/wk) had larger improvements on FOSQ, SNORE25, and ESS, but similar improvements on all 3 reaction time outcomes, SF36 MCS, SF36 PCS, and total airway volume (data not shown).

**Table 5.** Treatment effects for each group

Outcome	Placebo				TCRFTA				CPAP			
	n	Change*	P value†	Effect size‡	n	Change*	P value†	Effect size‡	n	Change*	P value†	Effect size‡
Primary												
1/SRT (1/msec)	25	0.05 ± 0.66	0.68	0.09	23	0.32 ± 0.57	<b>0.006</b>	0.42	19	0.18 ± 0.60	0.11	0.30
FOSQ	28	0.4 ± 2.0	0.18	0.18	26	1.2 ± 1.6	<b>0.005</b>	<b>0.66</b>	25	1.5 ± 2.1	<b>0.02</b>	<b>0.61</b>
SNORE25	28	-0.21 ± 0.56	0.06	0.31	25	-0.43 ± 0.56	<b>&lt;0.001</b>	<b>0.65</b>	24	-0.30 ± 0.52	<b>0.005</b>	0.46
Secondary												
RT (msec)	27	-4.4 ± 22.6	0.32	0.12	23	-10.0 ± 19.5	<b>0.03</b>	0.23	22	-3.1 ± 27.6	0.26	0.09
FRT (msec)	25	-3.1 ± 16.7	0.37	0.14	23	-10.2 ± 21.9	<b>0.02</b>	0.37	19	-0.8 ± 13.0	0.82	0.03
ESS	28	-1.0 ± 3.1	0.11	0.27	26	-2.1 ± 3.9	<b>0.005</b>	<b>0.50</b>	25	-2.3 ± 5.2	<b>0.02</b>	0.44
MCS	27	0.4 ± 6.4	0.70	0.04	24	2.9 ± 7.3	0.08	0.32	24	2.0 ± 6.1	0.73	0.22
PCS	27	1.5 ± 7.8	0.44	0.18	24	0.5 ± 6.8	0.42	0.06	24	0.1 ± 7.7	0.08	0.02
AHI (events/hr)	28	-1.8 ± 11.5	0.34	0.24	24	-4.5 ± 13.8	0.34	0.38				
AI (events/hr)	28	1.7 ± 5.4	1.00	-0.54	24	-3.1 ± 9.5	0.25	0.27				
LSAT (%)	28	0.6 ± 4.7	0.54	0.15	24	-0.6 ± 4.6	0.81	-0.08				
Total Vol (cm <sup>3</sup> )	26	-3.7 ± 15.7	0.17	-0.20	22	6.6 ± 19.5	0.14	0.27				

TCRFTA, temperature-controlled radiofrequency tissue ablation group; CPAP, continuous positive airway pressure group; 1/SRT, slowest reaction time (reciprocal); FOSQ, functional Outcomes of sleep questionnaire; SNORE25, symptoms of Nocturnal Obstruction and Related Events questionnaire; RT, reaction time; FRT, fastest reaction time; ESS, Epworth Sleepiness Scale; MCS, SF36 Mental Component Summary; PCS, SF36 Physical Component Summary; AHI, Apnea-Hypopnea Index; AI, Apnea Index; LSAT, lowest oxyhemoglobin saturation; Total Vol, volume of upper airway.

\*Change = posttreatment mean - baseline mean. Values given in mean ± SD.

†P value based on paired *t* test for comparison of means for normally distributed variables or sign test for comparison of medians for nonnormally distributed variables. Two-sided tests used for placebo (no effect expected a priori), one-sided tests used for TCRFTA and CPAP groups (effect expected a priori). *P* < 0.05 is significant (**bold**).

‡Effect size = (posttreatment mean - baseline mean)/(baseline standard deviation). Positive indicates improvement, negative indicates worsening. Subject not included in effect size calculation if baseline or posttreatment data missing. Effect size ≥0.50 is at least moderate (**bold**).

Table 6 and Figure 3 display the absolute differences and effect sizes for most outcome variables in the treatment groups compared with sham-placebo. TCRFTA subjects had clinically important improvement on all primary outcomes, with statistical significance or a statistical trend. TCRFTA subjects also improved on most secondary outcomes compared with sham-placebo, but only AI and total airway volume were statistically significant. TCRFTA also improved the respiratory arousal index over sham-placebo (effect size 0.95, *P* < 0.04), but data were available from only one site (n = 11). Other standard PSG parameters (HI, percent sleep time with oxyhemoglobin saturation <90%, and total arousal index) were not significantly different between TCRFTA and sham-placebo groups (data not shown). CPAP subjects had a statistically significant moderate improvement in FOSQ but no statistically significant improvement over sham-placebo on the other outcomes measured (Table 6 and Fig 3).

Statistical significance did not change with adjustment for study site (not shown).

The primary and many of the secondary outcomes were comparable between TCRFTA and CPAP groups with no significant differences noted between treatments (Table 7). However, a significantly greater proportion of TCRFTA subjects achieved a moderate improvement over placebo on the SNORE25 questionnaire compared with CPAP subjects (52% versus 21%, *P* = 0.04) (Table 8). As expected, TCRFTA subjects experienced a statistically significantly greater enlargement of the upper airway volume than CPAP subjects, consistent with this mode of therapy (*P* = 0.02). The CPAP group experienced a statistically significantly greater reduction in AHI during CPAP use (measured by AutoSet) than the TCRFTA group experienced after treatment (measured on PSG) (*P* = 0.004). However, average CPAP use was only 16.8 hr/wk (4.2 hr/CPAP-night × 4.0 nights/wk, Table 3), which translates

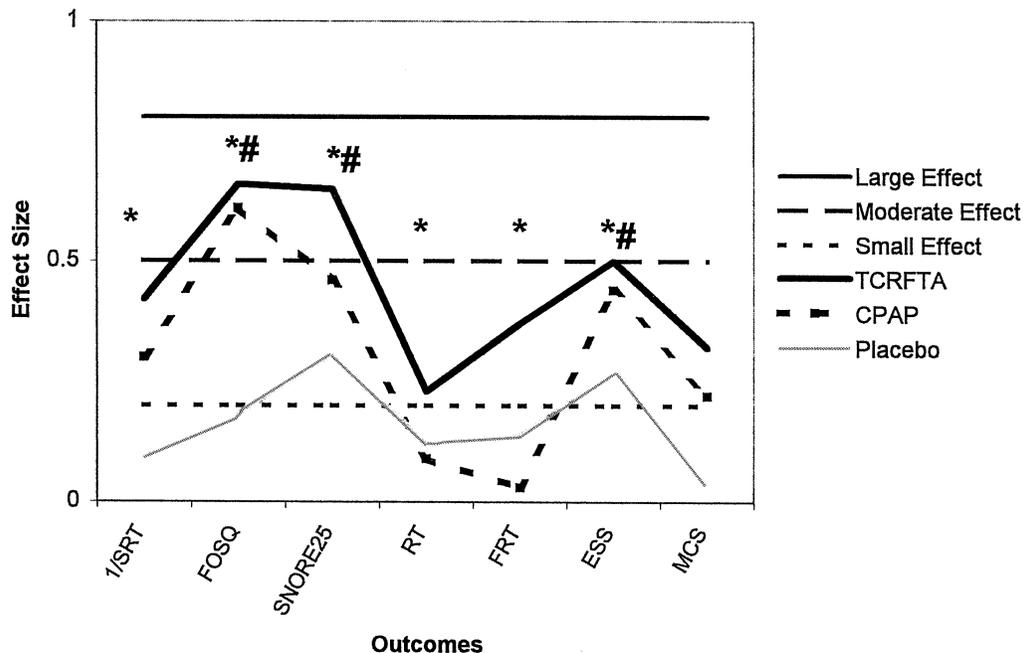


Fig 2. Effect sizes (before–after). Posttreatment effect sizes over baseline measures for all primary and several secondary outcome measures in each treatment group. TCRFTA, temperature-controlled radiofrequency tissue ablation group; CPAP, nasal continuous positive airway pressure group; 1/SRT, slowest reaction time (reciprocal); FOSQ, Functional Outcomes of Sleep Questionnaire; SNORE25, Symptoms of Nocturnal Obstruction and Related Events questionnaire; RT, median reaction time; FRT, fastest reaction time; ESS, Epworth Sleepiness Scale; MCS, SF36 Mental Component Summary. Statistically significant ( $P < 0.05$ ) effects are indicated by \* (TCRFTA) and # (CPAP).

into 30% of the 56 hr/wk (8 hours nightly) of recommended sleep time.

## DISCUSSION

### Treatment Effects and Outcome Measures

These results suggest that either multilevel (tongue and palate) TCRFTA or nasal CPAP significantly improves sleep apnea quality of life for patients with mild to moderate OSAS compared with pretreatment baseline (Table 5) or a sham-placebo treatment (Table 6). Compared with pretreatment baseline, TCRFTA but not nasal CPAP significantly improves reaction time testing, an objective measurement of patient function. TCRFTA appears to enlarge the airway and improve some PSG parameters (AI and respiratory arousal index), which may represent the mechanism by which this treatment improves function and OSAS quality of life.

The clinical importance of therapeutic effect may be inferred from analyses of effect sizes (small = 0.2, moderate = 0.5, and large = 0.8).<sup>20</sup> These data suggest a very consistent small to moderate therapeutic effect of TCRFTA across both

subjective and objective outcome measures compared with baseline or sham-placebo (Figs 2 and 3). Analysis of CPAP effect sizes suggests a small to moderate therapeutic effect for subjective measures compared with pretreatment baseline or sham-placebo (Figs 2 and 3).

CPAP is efficacious in improving respiratory parameters while it is actually used; however, its effectiveness in improving clinically important outcomes is limited by inadequate usage. Despite all efforts to optimize CPAP use in our patients and despite normalization of AHI with CPAP use, only 38% demonstrated adequate use by objective measurement. Similar patterns of use are reported in other randomized trials.<sup>9,11</sup> Thus, it is important to distinguish CPAP efficacy (ie, effect when actually used) from effectiveness (ie, effect in everyday life).<sup>22</sup> Respiratory parameters measured while using the CPAP device inherently represent efficacy measures. Because compliance is moot after surgical treatment, use of respiratory parameters as outcome measures unfairly compare CPAP efficacy to

**Table 6.** Outcomes comparison: Active treatments versus placebo

Outcome	Placebo (n)	TCRFTA					CPAP				
		n	Diff*	95% CL†	P value‡	Effect size§	n	Diff*	95% CL†	P value‡	Effect size§
Primary											
1/SRT (1/msec)	25	23	0.27	-0.09, 0.62	0.07	0.41	19	0.12	-0.26, 0.51	0.26	0.18
FOSQ	28	26	0.9	-0.1, 1.9	<b>0.04</b>	0.45	25	1.2	0.1, 2.3	<b>0.02</b>	<b>0.60</b>
SNORE25	28	25	-0.22	-0.53, 0.09	0.08	0.39	24	-0.09	-0.39, 0.21	0.28	0.16
Secondary											
RT (msec)	27	23	-5.6	-17.5, 6.4	0.18	0.25	22	1.4	-13.4, 16.2	0.57	-0.06
FRT (msec)	25	23	-7.1	-18.5, 4.3	0.11	0.43	19	2.3	-6.8, 11.3	0.69	-0.14
ESS	28	26	-1.2	-3.1, 0.8	0.12	0.39	25	-1.4	-3.8, 1.1	0.13	0.45
MCS	27	24	2.5	-1.4, 6.4	0.10	0.39	24	1.7	-1.8, 5.2	0.17	0.27
PCS	27	24	-1.0	-5.1, 3.1	0.69	-0.13	24	-1.4	-5.8, 3.0	0.74	-0.18
AHI (events/hr)	28	24	-2.7	-9.9, 4.5	0.23	0.23					
AI (events/hr)	28	24	-4.8	-9.3, 0.4	<b>0.02</b>	<b>0.89</b>					
LSAT (%)	28	24	-1.2	-3.8, 1.4	0.83	-0.26					
Total Vol (cm <sup>3</sup> )	26	22	9.3	-1.1, 19.8	<b>0.04</b>	<b>0.59</b>					

TCRFTA, temperature-controlled radiofrequency tissue ablation group; CPAP, continuous positive airway pressure group; CL, confidence limits; 1/SRT, slowest reaction time (reciprocal); FOSQ, Functional Outcomes of Sleep Questionnaire; SNORE25, Symptoms of Nocturnal Obstruction and Related Events questionnaire; RT, reaction time; FRT, fastest reaction time; ESS, Epworth Sleepiness Scale; MCS, SF36 Mental Component Summary; PCS, SF36 Physical Component Summary; AHI, Apnea-Hypopnea Index; AI, Apnea Index; LSAT, lowest oxyhemoglobin saturation; Total Vol, volume of upper airway.

\*\*Diff = active treatment change - placebo change.

†95% CL may include 0 with a one-sided  $P < 0.05$ .

‡P value based on two-sample Student's  $t$  test (one-sided) for comparison of mean diffs displayed. For nonnormal variables,  $P$  values were confirmed with normal transformations (not shown) or when adequate transformation not available by nonparametric (Mann-Whitney  $U$ ) test.  $P$  values not changed significantly after adjusting for study site (ANCOVA) (not shown). One-sided tests used because a net effect was expected a priori for each group over placebo.  $P$  value  $< 0.05$  is significant (**bold**). One-sided  $t$  test shown, but two-sided non-parametric test was not statistically significant.

§Effect size = (active treatment mean change - placebo mean change)/(placebo change standard deviation). Positive indicates improvement in active group over placebo, negative indicates worsening. Effect size  $\geq 0.50$  is at least moderate (**bold**).

surgical effectiveness. In contrast, reaction time tests and quality of life questionnaires measure CPAP effectiveness.

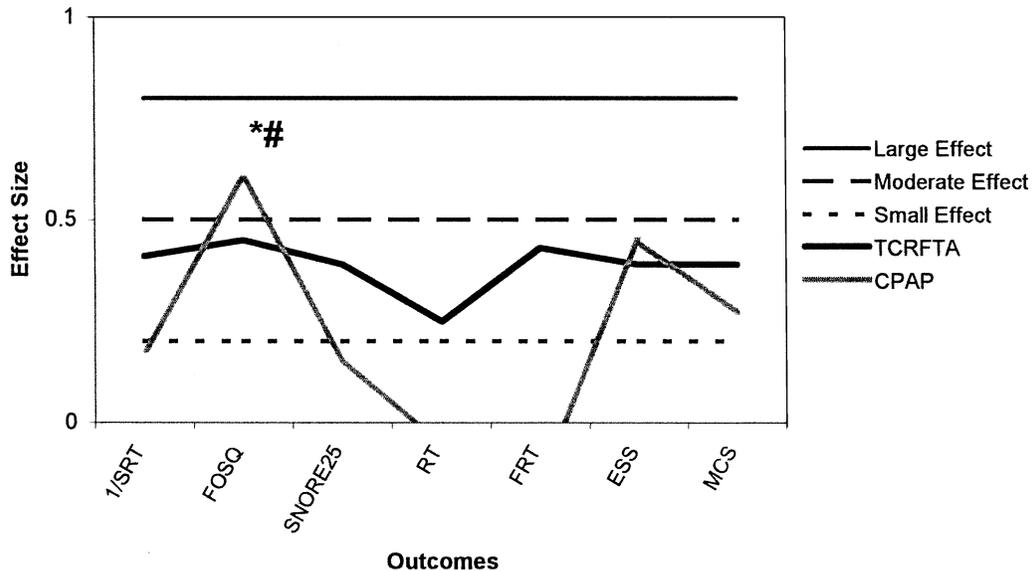
Reaction time and quality of life represent clinically important outcomes. The day-to-day effects of untreated OSAS manifest as compromised function and poor quality of life. Patients seek treatment to improve these problems. PSG parameters, on the other hand, are surrogate measures of clinically important outcomes. They appear to predict cardiovascular risk, which is clinically important; however, they are not clinically important per se. Thus we chose to study reaction time and OSAS quality of life as our primary outcomes.

### Role for TCRFTA in the Treatment of OSAS

These findings suggest an important role for TCRFTA in the treatment of OSAS. Because

CPAP therapy poses no risks and CPAP users achieve good outcomes, CPAP continues to represent a primary therapeutic option for patients with mild to moderate OSAS. TCRFTA may represent an alternative treatment in mild to moderate OSAS patients that refuse CPAP, demonstrate inadequate use, or experience insufficient improvement. TCRFTA may represent an alternative treatment in mild to moderate OSAS patients that refuse CPAP, demonstrate inadequate use, or experience insufficient improvement. Surgical treatment offers the major advantage of not depending on nightly compliance to achieve an adequate treatment effect. TCRFTA may also represent an adjunctive therapy to other surgical or non-surgical treatments of OSAS.

The low morbidity with TCRFTA is a major benefit over traditional OSAS surgery. Our find-



**Fig 3.** Effect sizes: active treatments versus placebo. Active treatment effect sizes over placebo for all primary and several secondary outcome measures. TCRFTA, temperature-controlled radiofrequency tissue ablation group; CPAP, nasal continuous positive airway pressure group; 1/SRT, slowest reaction time (reciprocal); FOSQ, Functional Outcomes of Sleep Questionnaire; SNORE25, Symptoms of Nocturnal Obstruction and Related Events questionnaire; RT, median reaction time; FRT, fastest reaction time; ESS, Epworth Sleepiness Scale; MCS, SF36 Mental Component Summary. Statistically significant ( $P < 0.05$ ) effects are indicated by \* (TCRFTA) and # (CPAP).

**Table 7.** Outcomes comparison: TCRFTA versus CPAP

Outcome	n (TCRFTA)	n (CPAP)	Difference*	95% CL	P value†	Effect size‡
Primary						
1/SRT (1/msec)	23	19	-0.15	-0.22, 0.52	0.43	-0.26
FOSQ	26	25	-0.29	-1.35, 0.77	0.58	-0.16
SNORE25	25	24	-0.13	-0.44, 0.18	0.41	0.24
Secondary						
RT (msec)	23	22	-6.9	-21.4, 7.6	0.34	0.29
FRT (msec)	23	19	-9.4	-20.4, 1.6	0.09	0.50
ESS	26	25	0.20	-2.39, 2.80	0.87	-0.04
MCS	24	24	0.83	-3.07, 4.74	0.67	0.12
PCS	24	24	0.38	-3.86, 4.62	0.86	0.05

TCRFTA, temperature-controlled radiofrequency tissue ablation group; CPAP, continuous positive airway pressure group; CL, confidence limits; 1/SRT, slowest reaction time (reciprocal); FOSQ, Functional Outcomes of Sleep Questionnaire; SNORE25, Symptoms of Nocturnal Obstruction and Related Events questionnaire; RT, reaction time; FRT, fastest reaction time; ESS, Epworth Sleepiness Scale; MCS, SF36 Mental component Summary; PCS, SF36 Physical Component Summary.

\*Difference = TCRFTA change - CPAP change.

†P value based on two-sample Student's *t* test (two-sided) for comparison of mean differences displayed. For nonnormal variables, p-values were confirmed with normal transformations (not shown) or when adequate transformation not available by nonparametric (Mann-Whitney *U*) test. P values not changed significantly after adjusting for study site (ANCOVA) (not shown). Two-sided tests used because a difference between TCRFTA and CPAP was not expected a priori. P value < 0.05 is significant.

‡Effect size = (TCRFTA mean change - CPAP mean change)/(combined standard deviation). Positive indicates TCRFTA better than CPAP; negative indicates TCRFTA worse than CPAP. Effect size  $\geq 0.50$  is at least moderate.

ings demonstrate mild, transient side effects (pain and swallowing difficulty) and low complication rates. The most common complication (hematoma) appears not to result from the radiofrequency

energy, because sham-placebo subjects had a similar rate of hematoma. Nonsteroidal anti-inflammatory medication can inhibit platelet activity and may have contributed to the occurrence of hema-

**Table 8.** Outcomes success (effect size  $\geq 0.50$ ) comparison: TCRFTA versus CPAP

Outcome	Success criteria*	TCRFTA success†	CPAP success†
Primary			
1/Slowest reaction time (1/msec)	0.383	10/23,43%	6/19,32%
Functional Outcomes of Sleep Questionnaire	1.34	12/26,46%	10/25,40%
Symptoms of Nocturnal Obstruction and Related Events Questionnaire	-0.486	13/25,52%	5/24,21%
Secondary			
Reaction time (msec)	-15.73	6/23,26%	5/22,23%
Fastest reaction time (msec)	-11.39	7/23,30%	5/19,26%
Epworth Sleepiness Scale	-2.50	11/26,42%	8/25,32%
SF36 Mental Component Summary	3.55	7/24,29%	7/24,29%
SF36 Physical Component Summary	5.40	3/21,13%	3/21,13%
Upper airway volume (cm <sup>3</sup> )	4.11	12/22,55%	
Apnea-Hypopnea Index (events/hr)	-7.50	9/15,38%	
Apnea Index (events/hr)	-0.96	11/24,46%	
Lowest saturation (%)	2.95	5/24,21%	

TCRFTA, temperature-controlled radiofrequency tissue ablation group; CPAP, continuous positive airway pressure group; 1/SRT, slowest reaction time (reciprocal).

\*Success criteria = change in each outcome measure required for active treatment to have an effects size  $\geq 0.50$  over placebo. Effect size = (active treatment mean change - placebo mean change)/(placebo change standard deviation); positive indicates improvement over placebo, negative indicates worsening.

†Proportion of subjects in each treatment group achieving treatment success criteria (effect size  $\geq 0.50$  over placebo).

tomas. Other investigators have found similar low morbidity associated with TCRFTA, with significantly less pain than other surgical therapies for OSAS.<sup>12,23</sup> Major complications from TCRFTA include tongue base abscess or airway obstruction, seen in approximately 1% to 8% of treatment sessions in previous case series.<sup>14,24,25</sup> We observed no major complications, possibly related to perioperative antiseptic rinse, antibiotics, and steroids. All complications were mild, without airway compromise, and resolved completely.

### Study Limitations and Strengths

Limitations to these results include limited statistical power, a sham-placebo schedule that was not identical to active treatment, a nonstandard CPAP titration method, incomplete follow-up data, risk of type I error due to multiple testing, and the lack of long-term outcomes assessment. The study had adequate power to achieve statistical significance for moderate effect sizes but insufficient power to achieve statistical significance for small clinically important effect sizes (possible type II errors). Ideally, the sham-placebo schedule would have been identical to the active TCRFTA schedule; however, ethical concerns regarding unnecessary potential complications from repeated

placebo treatment superseded this study design concern. Multilevel treatment was used in the active group because it was an a priori opinion that we could not rely consistently on pretreatment examination to eliminate the need for multilevel treatment. Preliminary analysis of pretreatment examination data has confirmed this assumption (data not shown). Furthermore, both active and sham-placebo TCRFTA groups remained blind to treatment group. Ideally, CPAP would have been titrated with overnight, in-laboratory polysomnography. Expense precluded this titration method, and autotitrating CPAP has been shown to reduce PSG parameters to levels comparable to in-laboratory titrations.<sup>16</sup> Titration was performed over several nights to optimize CPAP pressures, which were documented to dramatically improve AHI and AI (Table 3).

Twelve percent of randomized subjects were lost to follow-up, and only partial follow-up data were available on others. The follow-up rates were similar between treatment groups. All baseline variables except FOSQ and SNORE25 were similar between those with complete follow-up data and those with incomplete follow-up data. Baseline OSAS quality of life (FOSQ and SNORE25)

was worse in subjects with incomplete follow-up data compared with those with complete follow-up data (both  $P < 0.05$ ); however, this discrepancy was no different between treatment groups (all  $P > 0.3$ ). This study includes multiple outcome measures. We defined 3 primary outcomes a priori to reduce the risk of type I error caused by multiple testing. The consistency of improvement across all primary and most secondary outcomes in the TCRFTA group suggests that statistically significant improvements were not by chance alone.

Ideally, long-term outcomes would be assessed; however, long-term outcomes were not studied for several reasons. First, short-term improvements in quality of life and sleepiness appear to persist greater than 2 years after TCRFTA,<sup>13</sup> and short-term CPAP use reflects long-term use.<sup>26</sup> Second, long-term outcomes are particularly difficult to justify in a randomized, placebo-controlled trial where placebo patients' treatment is deferred. Third, we will follow TCRFTA patients (and sham-placebo or CPAP subjects who subsequently underwent active TCRFTA) to assess long-term outcomes.

The methodologic rigor (randomized, placebo-controlled, blinded, analyzed by intention-to-treat) is a major strength for these results. Some of the other strengths include the measurement of clinically important outcomes (both subjective and objective) rather than just surrogate outcomes, consistency of treatment effect observed, separate screening and baseline measurements, and a low dropout rate. This study is the first conclusive, placebo-controlled OSAS surgery trial to achieve level I evidence according to Sackett's criteria.<sup>27</sup>

## CONCLUSION

The results of this study suggest that both TCRFTA and nasal CPAP improve quality of life for mild to moderate OSAS patients compared with sham-placebo TCRFTA. The treatment effect sizes of both therapies over sham-placebo are small to moderate, but clinically important, for most outcomes. TCRFTA improvements may result from an increase in upper airway volume and a reduction in apnea and respiratory arousal indices; however, these hypotheses require independent testing in a separate sample of patients.

TCRFTA is a low morbidity procedure. Side effects of CPAP were mild but common.

The authors thank Dr Mona Patil, Laura Brusky, MD, Lynn Prost, and Colleen Eigel for research study coordination; Jim Snider at Sleepcare Diagnostics; and Ahmad Nasef MD for polysomnographic assistance.

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**Health Technology Clinical Committee****DRAFT Findings and Decision****Topic: Bone Morphogenetic Proteins for use in Lumbar Fusion****Meeting Date: March 16, 2012****Final Adoption:****Number and Coverage Topic**20120316B – **Bone Morphogenetic Proteins for Use in Lumbar Fusion****HTCC Coverage Determination**Bone morphogenetic protein-2 (rhBMP-2) is a **covered benefit with conditions**.Bone morphogenetic protein-7 (rhBMP-7) is **not a covered benefit**.**HTCC Reimbursement Determination****❖ Limitations of Coverage**

BMP-2 coverage criteria:

- For use in the Lumbar spine only;
- Adults 18 years of age and over; and,
- For primary anterior open or laparoscopic fusion at one level between L4 and S1, OR
- Revision lumbar fusion on a compromised patient for whom autologous bone and bone marrow harvest are not feasible or not expected to result in fusion

**❖ Non-Covered Indicators**Bone morphogenetic protein-7 is **not a covered benefit**.**Agency Contact Information**

<b>Agency</b>	<b>Phone Number</b>
Labor and Industries	1-800-547-8367
Public Employees Health Plan	1-800-762-6004
Health and Recovery Services Administration	1-800-562-3022

**HTCC COVERAGE VOTE AND FORMAL ACTION**

March 16, 2012 Meeting Transcript can be found here: [http://www.hta.hca.wa.gov/past\\_materials.html](http://www.hta.hca.wa.gov/past_materials.html)

**Committee Decision**

Based on the deliberations of key health outcomes, the committee decided that it had the most complete information: a comprehensive and current evidence report, public comments, and agency and state utilization information. The committee concluded that the current evidence on Bone Morphogenetic Protein-2 (BMP-2) demonstrates that there is sufficient evidence to cover with conditions. The committee concluded that the current evidence on Bone Morphogenetic Protein-7 (BMP-7) is insufficient evidence to cover. The committee considered all the evidence and gave greatest weight to the evidence it determined, based on objective factors, to be the most valid and reliable. Based on these findings, the committee voted to cover with conditions BMP-2 for use in lumbar fusion. Based on these findings, the committee voted to not cover BMP-7.

**Bone Morphogenetic Proteins Coverage Vote**

<b>HTCC Committee Coverage Determination Vote</b>			
	<b>Not covered</b>	<b>Covered Unconditionally</b>	<b>Covered Under Certain Conditions</b>
Bone morphogenetic protein-2	0	0	<b>8</b>
Bone morphogenetic protein-7	<b>8</b>	0	0

- *Discussion:* The Chair called for discussion on conditions for use of BMP-2 due to the majority voting for coverage. The following conditions were discussed and approved by a majority:
  - *Limitations of Coverage:* rhBMP-2 for use in lumbar fusion is a covered benefit when the following conditions are met:
    - Adults age 18 years and over
    - Lumbar spine only
    - Primary anterior open or laparoscopic fusion at one level between L4 and S1, OR
    - Revision lumbar fusion on a compromised patient for whom autologous bone and bone marrow harvest are not feasible or not expected to result in fusion
  
- *Action:* The committee Chair directed HTA staff to prepare a Findings and Decision document on Bone Morphogenetic Proteins for use in lumbar fusion reflective of the majority vote for final approval at the next public meeting.

The committee reviewed the Clinical guidelines and Medicare decision. The Centers for Medicare and Medicaid Services have no published national coverage determinations (NCD) for Bone Morphogenetic Proteins for use in lumbar fusion.

**Health Technology Clinical Committee Authority**

Washington State’s legislature believes it is important to use a scientific based, clinician centered approach for difficult and important health care benefit decisions. Pursuant to chapter 70.14 RCW, the legislature has directed the Washington State Health Care Authority, (HCA) through its Health Technology Assessment (HTA) program to engage in an evaluation process that gathers and assesses the quality of the latest medical evidence using a scientific research company and takes public input at all stages.

Pursuant to RCW 70.14.110 a Health Technology Clinical Committee (HTCC) composed of eleven independent health care professionals reviews all the information and renders a decision at an open public meeting. The Washington State Health Technology Clinical Committee (HTCC) determines how selected health technologies are covered by several state agencies (RCW 70.14.080-140). These technologies may include medical or surgical devices and procedures, medical equipment, and diagnostic tests. HTCC bases its decisions on evidence of the technology’s safety, efficacy, and cost effectiveness. Participating state agencies are required to comply with the decisions of the HTCC. HTCC decisions may be re-reviewed at the determination of the HCA Administrator.



# Bone Morphogenetic Protein

## *Draft Findings & Decision Timeline and Overview of Comments*

The Health Technology Assessment (HTA) program received comments in response to the posted Health Technology Clinical Committee (HTCC) draft findings and decision on Bone Morphogenetic Protein (BMP).

Category	Comment Period	
	April 20 – May 2, 2012	Cited Evidence
Patient, relative, and citizen	0	0
Legislator and public official	0	0
Physician and health care professional	1	1
Industry & manufacturer	1	0
Professional society & advocacy organization	1	0
<b>Total</b>		<b>3</b>

### **Comments with Evidence:**

#### Physician and health care professional comments

*David A. Yam, Neurosurgeon, Walla Walla, WA*

Disagrees with the coverage determination. Additional clinical evidence for bone morphogenetic protein is expected to be published soon.

### **Comments without Evidence:**

#### Professional society & advocacy organization comments

*Mitchel S. Berger MD, President American Association of Neurological Surgeons*  
*Christopher E Wolfla, MD, President Congress of Neurological Surgeons*

Both Associations endorse the use of rhBMP as a viable alternative to autograft and allograft for clinically appropriate cases.

*Doug King, President, Medtronic Spine Restorative Therapies Group, Medtronic Inc.*

Appreciates the value of the HTCC's appraisal of evidence and public comments on rhBMT. Submits three clarifications related to the appraisal of the technology for committee consideration. Attached information regarding the association between the clinical use of INFUSE® Bone Graft and the incidence of cancer.

### Actual Timeline

<b>Study Stage</b>	<b>Date</b>	<b>Public Comment</b>
Preliminary recommendations published	November 2, 2010	
Public comments due	November 16, 2010	<b>14 days</b>
Selected set of topics published	December 17, 2010	
Public comments due	January 16, 2011	<b>30 days</b>
Draft Key Questions published	October 26, 2011	
Public comments due	November 9, 2011	<b>14 days</b>
Key Questions finalized	November 14, 2011	
Draft report due	January 10, 2012	
Draft report published	January 12, 2012	
Public comments due	January 30, 2012	<b>18 days</b>
Final report due	February 10, 2012	
Final report published	February 14, 2012	
Public meeting date	March 16, 2012	
Findings & decision published	April 20, 2012	
Public comments due	May 2, 2012	<b>12 days</b>

April 24, 2012

Health Technology Clinical Committee,

I spent hours reading your latest clinical evidence summary, meeting minutes, and draft decision on the use of BMP in Washington State. I found most of the meeting minutes to be a confused discussion about BMP and lumbar fusion. I am a neurological surgeon practicing in Southeast Washington and use BMP-2 (Infuse) in nearly 90% of my lumbar spinal fusions. I do not use the product in patients with a personal history of cancer which would account for the other 10% of patients. I do not use the product in the anterior cervical spine due to swelling complications that can occur. I currently use the product off-label in nearly 100% of cases that it is used in and consider using BMP-2 the standard of care for the state and the nation. A final decision to exclude the product from coverage will mean one of two things for my practice:

1. I will no longer care for patients covered by this decision, or
2. I will leave the state and practice in a state that is not regressive towards medical care for spine patients.

I spent a great deal of time reading about how little the committee understands about the use of BMP-2 in modern spine surgery. Questions about plastic, sponges, on-label, off-label, etc. show how little the technique and use is understood. The whole process of fusion is clearly also heavily misunderstood. At one critical point, in the discussion Seth Schwartz states that the non-union rate from a lumbar fusion is 3-5%. I would ask where does that number come from? The most common consensus based on literature is that in the low-risk, non-smoking, healthy patient that the fusion rate without BMP is between 65-95% (Boden 1995, Kim 2006). Even the paid consultant quoted a rate of 88% with autograft bone in the powerpoint slides provided. Most people understand the fusion rate in the real world to be around 70-80% with autograft for lumbar spinal fusions. I see this every week in my practice because I get referrals for non-unions from other surgeons throughout the state all the time. In my practice, with BMP-2 use, I have a non-union rate of 0.6% in nearly 2 years of practice. That's one patient out of the last 165 or so. I use BMP-2 soaked on its approved collagen carrier for > 15 minutes in anterior lumbar fusions in a plastic interbody spacer or in a plastic interbody spacer placed through a posterior TLIF approach. I will rarely use it posterolaterally in patients with a history of non-union from a prior surgery in the cervical or lumbar spine. I use a BMP-2 dose of 0.7 mg per level and no more. The 4-40 mg references quoted in your discussion are at much higher levels, and I have no experience with using that amount. The cost of 0.7 mg of BMP is less than \$800 and is much less morbid and less costly in my hands than carving bone off a patient's hip which can have a long term complication rate as high as 99% causing life long donor site pain. I gathered that last statistic from the committee's review of lumbar fusion in 2007 which in my opinion should be prospectively reviewed. I have put together a powerpoint slide showing my particular use of BMP-2. It should be used to educate the committee, and my recommendation is that you table any decision on BMP-2 until more data is gathered on the subject in this state and in the nation. There are a number of ongoing trials on BMP-2 use in the cervical and lumbar spine with results that will follow in the scientific literature in the near future. These will help address questions that the committee considers

valuable including efficacy and safety matters. I do believe in some aspects of evidenced based medicine and would yield my use of the product to solid evidence that suggested I was my harming patients. In my opinion, your discussion and evidence review does not contain information that is pertinent to the majority of patients receiving BMP-2 in this state or this nation. If the committee would also like first hand knowledge of what a spinal revision surgery is and also of what the procedures they are discussing are, I would be happy to provide my clinical expertise and demonstrate my art on the subject in person. Neither the art of medicine is perfect, nor will the science of it ever be. Please do not restrict the art while we obtain the scientific answers that you seek. You will be directly harming my patients if a rushed decision is made on this particular subject.

Sincerely,

David A. Yam, M.D.

[Spine \(Phila Pa 1976\)](#). 1995 Dec 15;20(24 Suppl):113S-123S.

# Biologic enhancement of spinal fusion.

[Boden SD](#), [Schimandle JH](#).

## Source

Department of Orthopaedic Surgery, Emory University School of Medicine, Atlanta, Georgia, USA.

## Abstract

### STUDY DESIGN:

Literature review.

### OBJECTIVES:

To review the available animal and clinical data on biologic enhancements of spinal fusion.

### SUMMARY OF BACKGROUND DATA:

Lumbar spinal arthrodesis may result in pseudarthrosis in 5% to 35% of patients. Although much research has focused on the mechanical factors affecting spinal fusion, the use of internal fixation has not eliminated the problem of spinal nonunions. Accordingly, biologic enhancement of spinal fusion has become an important focus of spinal research.

### METHODS:

Medline and hand searches.

### RESULTS:

Electric stimulation, bone graft substitutes, and bone growth factors have been researched most extensively. Electric stimulation and early attempts at bone graft substitutes (allograft, xenograft) have yielded variable results. The feasibility of biologic enhancement of spinal fusion with osteoinductive growth factors has been shown in animals.

### CONCLUSION:

The efficacy of bone growth factors for lumbar fusion remains to be definitively established in humans.

# Pseudarthrosis in long adult spinal deformity instrumentation and fusion to the sacrum: prevalence and risk factor analysis of 144 cases.

[Kim YJ](#), [Bridwell KH](#), [Lenke LG](#), [Rhim S](#), [Cheh G](#).

## Source

Washington University Medical Center, St. Louis, MO, USA.

## Abstract

### STUDY DESIGN:

Retrospective study.

### OBJECTIVE:

To analyze the incidence of and risk factors for pseudarthrosis in long adult spinal instrumentation and fusion to S1.

### SUMMARY OF BACKGROUND DATA:

Few studies on pseudarthrosis in long adult spinal instrumentation and fusion to S1 exist.

### METHODS:

A clinical and radiographic assessment of 144 adult patients with spinal deformity (average age 52.0 years; range 21.1-77.6) who underwent long (5-17 vertebrae, average 11.9) spinal instrumentation and fusion to the sacrum at a single institution between 1985 and 2002, with a minimum 2-year follow-up (average 3.9; range 2-14) was performed.

### RESULTS:

Of 144 patients, 34 (24%) had pseudarthroses. There were 17 patients who had pseudarthroses at T10-L2 and 15 at L5-S1. A total of 24 patients (71%) presented with multiple levels involved (2-6). Pseudarthrosis was most commonly detected within 4 years postoperatively (31 patients; 94%). Factors that statistically increased the risk of pseudarthrosis were: thoracolumbar kyphosis (T10-L2  $\geq$  or  $\leq$  20 degrees vs.  $<$  20 degrees,  $P < 0.0001$ ); osteoarthritis of the hip joint ( $P = 0.002$ ); thoracoabdominal approach (vs. paramedian approach,  $P = 0.009$ ); positive sagittal balance  $\geq$  or  $\leq$  5 cm at 8 weeks postoperatively (vs.  $<$  or  $\leq$  5 cm,  $P = 0.012$ ); age at surgery older than 55 years (vs. 55 years or younger,  $P = 0.019$ ); and incomplete sacropelvic fixation (vs. complete sacropelvic fixation,  $P = 0.020$ ). Fusion from upper thoracic spine (T2-T5) did not statistically increase the pseudarthrosis rate compared to lower thoracic spine (T9-T12) ( $P = 0.20$ ). Patients with pseudarthrosis had significantly lower Scoliosis Research Society 24 outcome scores (average score 71/120) than those without (average score 90/120;  $P < 0.0001$ ) at ultimate follow-up.

**CONCLUSION:**

The overall prevalence of pseudarthrosis following long adult spinal deformity instrumentation and fusion to S1 was 24%. Thoracolumbar kyphosis, osteoarthritis of the hip joint, thoracoabdominal approach (vs. paramedian approach), positive sagittal balance  $\geq$  5 cm at 8 weeks postoperatively, older age at surgery (older than 55 years), and incomplete sacropelvic fixation significantly increased the risks of pseudarthrosis to an extent that was statistically significant. Scoliosis Research Society 24 outcomes scores at ultimate follow-up were adversely affected when pseudarthrosis developed.



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Subject: Coverage of Bone Morphogenetic Proteins for use in Lumbar Fusion

To whom it may concern:

The American Association of Neurological Surgeons (AANS) and the Congress of Neurological Surgeons (CNS) applaud the efforts of the Washington State Health Care Authority's Health Technology Clinical Committee (HTCC) in their review and analysis of the use of recombinant Bone Morphogenic Protein (rhBMP) in lumbar fusion surgeries. We strongly believe, however, that the published draft findings should be reexamined and modified.

The HTCC has voted to not cover rhBMP-7 and to cover rhBMP-2 with conditions. The conditions for coverage of rhBMP-2 include: use in the lumbar spine only, use in adults 18 years or older for primary anterior open or laparoscopic fusion at one level between L4 and S1 or for revision lumbar fusion on a compromised patient for whom autologous bone and bone marrow harvest are not feasible or not expected to result in fusion.

**As noted in our original comments, we believe rhBMPs are a comparably safe and effective bone graft alternative appropriate in patients with medical indications as determined by their treating surgeon.** FDA approval of the on-label indications of rhBMP noted equivalent or superior fusion rates, shorter operative times, and decreased bone graft donor site complications. Our assessment of the literature would indicate that rhBMPs are appropriate bone graft options for single level anterior and posterior lumbar interbody fusion, and can also be considered an appropriate bone graft substitute in single-level posterolateral lumbar fusion.

It is our position that the HTCC concentrated on the "on-label" use of rhBMP-2 that was originally studied in patients undergoing an interbody fusion via an anterior approach. Some of the committee's concerns regarding the safety of rhBMP-2 may actually be secondary to the choice of surgical approach; these complications, primarily retrograde ejaculation in males, are well-known and reported in the literature.

We believe that possibly safer approaches, including posterior lumbar interbody fusion, transforaminal lumbar interbody fusion, extreme lateral interbody fusion, and direct lateral interbody fusion, should be considered as appropriate surgical approaches for placement of rhBMP-2 to achieve fusion in the interbody space. Therefore, we strongly urge the HTCC to consider covering any single level lumbar fusion regardless of the surgical approach utilized to gain access to the interbody space. By restricting rhBMP use to only anterior approaches, the HTCC is denying patients a more efficacious fusion with potentially lower morbidity, since many patients are unable to safely undergo an anterior lumbar approach.

Any potential adverse effect of BMP use should be weighed against those of autograft and allograft. Iliac crest bone grafting and harvest has well-known morbidity that may be permanent. With the exception of anterior cervical spine fusion, the present literature does not support that complication rates in patients undergoing spine fusion with BMP (on label or off label) are significantly higher than those patients undergoing autograft harvest.

We support the HTCC decision regarding the use of rhBMP-2 in patients undergoing revision surgery where autologous bone and bone marrow harvest are not feasible or not expected to result in fusion. This off-label use of rhBMP-2 will allow the surgeon to determine the best treatment for these often difficult and compromised patients. We would proffer, however, that similar indications for rhBMP use may be present in non-revision cases.

### **Conclusion**

We appreciate the opportunity to review the draft Washington State Health Care Authority's draft coverage policy for BMP for use in Lumbar Fusion. **The AANS and CNS believe rhBMP remains a viable alternative to autograft and allograft for clinically appropriate cases, as chosen by treating surgeons.** The full potential of rhBMP as an adjunct to spinal fusion cannot be determined by the current literature. It is almost certain that there are a number of patients for whom rhBMP will maximize the potential for a successful clinical outcome and restoration of an acceptable quality of life.

While we recognize that rhBMP is a costly technology and is not appropriate for the majority of spinal fusion procedures, we respectfully request that the Washington State Health Care Authority consider the following changes to the draft recommendations:

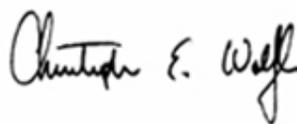
- Provide coverage for off-label use of rhBMP when clinically appropriate, as chosen by treating surgeon
- Allow for use of rhBMP in surgical approaches other than anterior lumbar interbody procedures

Thank you for considering our comments. If you have any questions, please feel free to contact John Ratliff (jratliff@stanford.edu) or Joseph Cheng, MD (joseph.cheng@vanderbilt.edu).

Sincerely,



Mitchel S. Berger, MD, President  
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May 1, 2012

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**RE: Comments on Draft Coverage Decision for Bone Morphogenic Proteins for use in Spinal Fusion**

Dear Mr. Morse,

Thank you for the opportunity to provide public testimony at the March 15, 2012 meeting on Bone Morphogenetic Proteins (BMPs) for use in Spinal Fusion. Medtronic recognizes the value of the Health Technology Clinical Committee's (HTCC) appraisal of the evidence and public comments on rhBMP and appreciates the thoughtfulness of the discussion. As we detailed in our public comments, Medtronic Spinal and Biologics Division manufactures and distributes products that treat a variety of disorders of the spine. In 2002, Medtronic's INFUSE<sup>®</sup> Bone Graft/ LT-CAGE<sup>®</sup> received pre-market approval (PMA) for use in anterior lumbar interbody fusion (ALIF) to treat patients with degenerative disc disease (DDD).<sup>1</sup> Outside of the spine, INFUSE has received pre-market approval for use in orthopedic trauma (i.e. open tibial fractures) and certain oral maxillofacial reconstructions.

We believe that rhBMP-2 is an important orthopedic innovation and alternative to iliac crest and support the Committee's decision to cover it in specific patient populations. However, based on our evaluation of the HTCC's discussion on rhBMP-2 for use in spinal fusion, we would like to clarify a few areas that are critical to an accurate appraisal of the technology. To that end, we respectfully submit the following comments for the Committee's consideration at this time:

1. The coverage language regarding the levels of use of rhBMP-2 in the spine should be revised to reflect the Food and Drug Administration's (FDA) current approved indication for INFUSE<sup>®</sup> Bone Graft/ LT-CAGE<sup>®</sup>.
2. The distinction between clinical data on INFUSE<sup>®</sup> Bone Graft/ LT-CAGE<sup>®</sup> and the clinical data on unapproved rhBMP-2 products used to evaluate rhBMP-2 should be clarified as these products differ in composition.

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<sup>1</sup> FDA. INFUSE<sup>®</sup> Bone Graft/ LT-CAGE<sup>®</sup> Lumbar Tapered Fusion Device (P000058). Approval Date: July 2, 2002. Available at: [http://www.accessdata.fda.gov/cdrh\\_docs/pdf/P000058a.pdf](http://www.accessdata.fda.gov/cdrh_docs/pdf/P000058a.pdf).

3. The public record should reflect the fact that the clinical evidence for the use of rhBMP-2 in approved spine applications does not suggest an increased incidence of cancer.

**1. The coverage language regarding the levels of use of rhBMP-2 in the spine should be changed to reflect the FDA’s current approved indication for INFUSE® Bone Graft/ LT-CAGE®.**

The draft coverage decision specifies that one of the coverage criteria for rhBMP-2 is that it is used “for primary anterior open or laparoscopic fusion at one level between **L4 and S1**.”<sup>2</sup> Based on our observations at the public meeting, the committee closely followed the labeling provided in the original FDA approval order for INFUSE® Bone Graft/ LT-CAGE® to inform this criterion. As such, Medtronic believes it is important to note that the most up-to-date labeling for INFUSE defines appropriate use as between **L2 and S1**.<sup>3</sup> The vertebral span changed from L4-S1 to L2-S1 to reflect supplemental FDA approval in 2004. Medtronic recommends the Committee to update its language to be consistent with the FDA label when finalizing the coverage decision.

**2. The distinction between the clinical data on INFUSE® Bone Graft/ LT-CAGE® and the clinical data on unapproved rhBMP-2 products used to evaluate rhBMP-2 should be clarified as these products differ in composition.**

The Washington State Department of Labor & Industries Medical Director’s presentation to the HTCC and subsequent discussion among the Committee members appeared to conflate the data on AMPLIFY™ rhBMP-2 Matrix with the off-label use of INFUSE. As we mentioned in our public comments and comment letter in response to the draft Health Technology Assessment (HTA) report, it is important for the Committee to clearly differentiate the clinical data between FDA-approved and unapproved rhBMP-2 products. Currently, INFUSE is the only FDA-approved rhBMP-2 product for use in the spine. Although AMPLIFY was classified as “off-label use for rhBMP-2” by Spectrum in their report, AMPLIFY is not commercially available for any indication in the U.S. or elsewhere at this time.

Although both use the same active ingredient, rhBMP-2, AMPLIFY and INFUSE are substantially different with respect to their concentration, carrier composition, and clinical indications, as further detailed in Figure 1 below. These formulation differences have an impact on the delivery of rhBMP-2 as demonstrated by the change in local residence time of the rhBMP-2 molecule supplied in the last row.

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<sup>3</sup> FDA. PMA Supplement for INFUSE BONE GRAFT/LT-CAGE LUMBAR TAPERED FUSION DEVICE (P000058). Decision date: 7/29/2004. Available at: <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=9462>

**Figure 1. Differences between AMPLIFY and INFUSE**

	<b>AMPLIFY™ rhBMP-2 Matrix</b>	<b>INFUSE® Bone Graft</b>
FDA Approval	Not FDA-approved	Received PMA from the FDA in 2002
Spine fusion indications	Posterolateral fusion (bridges placed between the vertebrae transverse processes in the posterior part of the spine)	Anterior lumbar spine fusion (fusion of the vertebrae interbody)
Concentration after reconstitution	2.0 mg/mL	1.5 mg/mL
Maximum dose applied during clinical studies in spine surgery	Up to 40 mg	Up to 12 mg in spine indication
Carrier	Compression resistant collagen matrix (CRM) made of Type I bovine collagen imbedded with Calcium Phosphate granules (15% hydroxyapatite / 85% $\beta$ -tricalcium phosphate)	Absorbable collagen sponge made of Type I bovine collagen
Graft Volume	20cc	XXS Kit – 0.7cc XS Kit – 1.4 cc Small Kit – 2.8cc Medium Kit – 5.6cc Large Kit – 8.0cc
Local Mean Residence Time and Half-Life	Mean: 17.4 days +/- 4.9 days Half-Life: 12.5 days +/- 3.7 days	Mean: 12.3 days +/- 2.9 days Half-Life: 8.7 days +/- 2.7 days

INFUSE has been evaluated in multiple clinical studies and has more Level 1 clinical evidence than any other bone growth protein.<sup>4</sup> Outside of the spine, INFUSE has received separate FDA approvals in 2004 for use in orthopedic trauma (i.e. open tibial fractures) and in 2007, for certain oral maxillofacial reconstructions. INFUSE and the complete data from its pivotal trials have undergone multiple independent reviews as part of the approval process in the U.S. and abroad and each time, the agencies have found INFUSE to be safe and effective for the approved indications. In their presentation to the HTCC, the American Association of Neurological Surgeons and Congress of Neurological Surgeons

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<sup>4</sup> Resnick DK, Choudhri TF, Dailey AT, Groff MW, Khoo L, Matz PG, Mummaneni P, Watters WC, Wang J, Walters BC, Hadley MN, “Guidelines for the performance of fusion procedures for degenerative disease of the lumbar spine. Part 16: bone graft extenders and substitutes.” *Journal of Neurosurgery: Spine* 2 (2005): 733-736.

jointly stated that the literature supports use of rhBMP-2 for single level ALIF and posterior lumbar interbody fusions and referenced the Spectrum HTA as supporting this conclusion. Medtronic places high confidence in these assessments and their subsequent determinations that rhBMP-2 is safe and effective for its approved indication in the spine. We ask the Committee to clarify this distinction between INFUSE and AMPLIFY in the public record and focus solely on evaluating the evidence on INFUSE when finalizing its coverage determination. As we detail below, this distinction is particularly important when evaluating the incidence of cancer associated with rhBMP-2.

**3. The public record should reflect the fact that the clinical evidence for the use of rhBMP-2 in approved spine applications does not suggest an increased incidence of cancer.**

Medtronic recognizes that the rate of cancer in rhBMP-2 patients is a key area of concern for the Committee. Medtronic takes safety concerns very seriously. However, in order to appropriately evaluate patient safety, it is important that only the evidence on FDA-approved products be evaluated. To that end, the clinical evidence on INFUSE should be the only evidence evaluated since other rhBMP-2 products have not been FDA-approved and are not commercially available at this time. As noted above, AMPLIFY and INFUSE are substantially different with respect to their concentration, carrier composition, and clinical indications. These formulation differences have an impact on the delivery of rhBMP-2 and patient outcomes.

As concluded by Spectrum, the clinical evidence for the use of INFUSE in approved spine applications does not suggest an increased incidence of cancer.<sup>5</sup> No statistically significant difference was observed in the incidence of malignancy between INFUSE and non-INFUSE Bone Graft groups in clinical studies for the approved indications. The actual cancer cases observed in both the INFUSE group and the non-INFUSE group were consistent with the rates expected to be seen in the studied patient populations. Further, clinical evidence using the SEER (Surveillance, Epidemiology and End Result) categorization of cancer events, developed by the National Cancer Institute, demonstrates that there is no statistically significant difference in the incidence of the rate of total malignancies nor specific cancer types between INFUSE and non-INFUSE groups. The distribution of cancer types was broad in both groups, as would be expected in the general population and demonstrated by the SEER analysis. We have attached a document titled “Just the Facts” that further details findings on the safety of INFUSE. It contains more extensive data drawn from additional FDA-regulated clinical studies using INFUSE in the approved spine indication to address concerns raised by the HTCC regarding the challenges in determining relative risk for rare events. We ask the Committee to update the public record to reflect the fact that use of INFUSE according to its FDA-approved spine indication does not suggest an increased incidence of cancer.

## **Conclusion**

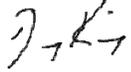
Medtronic appreciates this opportunity to provide comments to the Committee on the draft coverage determination. Moving forward, we encourage the Washington Health Care Authority to create an opportunity for guest speakers to engage in dialogue with the Committee members during the meeting. Such conversations would be beneficial; allowing guest speakers to immediately address areas of potential misinterpretation and questions raised by the Committee at the time of discussion would ensure there is no misunderstanding or remaining questions regarding the evidence.

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<sup>5</sup> Spectrum. “On- and off-label uses of rhBMP-2 or rhBMP-7 for spinal fusion.” Prepared for Washington State Health Care Authority. [http://www.hta.hca.wa.gov/documents/bmp\\_final\\_report.pdf](http://www.hta.hca.wa.gov/documents/bmp_final_report.pdf) (p.33)

We appreciate your consideration and are happy to provide further information or assist with any additional questions. Please feel free to contact me should you have any questions or wish to discuss our comments in further detail.

Sincerely,

A handwritten signature in black ink, appearing to read 'DK', with a stylized flourish extending from the end.

Doug King  
President, Medtronic Spine  
Restorative Therapies Group  
Medtronic, Inc.  
2600 Sofamor Danek Drive  
Memphis, TN 38132



# Just the Facts

Addressing Safety Concerns with INFUSE® Bone Graft

*"To strive without reserve for the greatest possible reliability and quality in our products; to be the unsurpassed standard of comparison and to be recognized as a company of dedication, honesty, integrity, and service."*

## Opening Statement

- » Medtronic's Mission Statement, a portion of which is quoted above, is the foundation upon which our company is built. Patient safety and data integrity are at the center of all that we do in our business.
- » Questions have been raised regarding the association between the clinical use of INFUSE® Bone Graft and the incidence of cancer.
- » INFUSE® Bone Graft contains recombinant human bone morphogenetic protein-2 (rhBMP-2), a manufactured version of a naturally occurring protein, BMP-2, that is important for bone formation and healing.
  - It delivers rhBMP-2 at a concentration of 1.5 mg/cc when combined with an absorbable collagen sponge (ACS) carrier.
- » It is reasonable to ask about the potential for rhBMP-2 to promote cancer growth and development due to a broad range of expected cellular responses.
  - BMP-2 is an important protein involved in a myriad of biological processes, such as cell recruitment, cell differentiation, and new blood vessel formation.
  - BMP-2 is a critical molecule as illustrated by the fact that it is essential to embryological development (i.e., a fetus will not survive if an animal cannot produce it).<sup>1</sup>
- » Medtronic wishes to provide accurate and relevant information specifically pertaining to these concerns and to summarize the available scientific evidence derived from nonclinical and clinical studies conducted by Medtronic and its partners since 1991.
- » INFUSE® Bone Graft has been approved by the FDA for three indications:
  1. Anterior lumbar interbody fusion (ALIF) with the LT-CAGE® Lumbar Tapered Fusion Device, INTER FIX™ Threaded Fusion Device, or INTER FIX™ RP Threaded Fusion Device
  2. Acute open tibial fracture with intramedullary (IM) nail
  3. Sinus lift or alveolar ridge augmentation

## Scientific Evidence Summary

- » Considering all the currently available evidence derived from an extensive set of nonclinical and clinical studies, the following conclusions can be drawn:
  - There is no evidence that rhBMP-2 is carcinogenic or mutagenic (i.e., no indication that rhBMP-2 can transform healthy cells into cancer cells).
  - The clinical evidence for the use of INFUSE® Bone Graft in approved spine applications does not suggest an increased incidence of cancer.
  - It is not known whether direct implantation of rhBMP-2 on the ACS carrier into a tumor site could affect tumor growth rate.
  - In an *in vivo* study performed after the approval of INFUSE® Bone Graft, implantation of rhBMP-2 had no impact on the aggressiveness of distant malignant tumors.
- » Therefore, Medtronic remains confident in the safety of INFUSE® Bone Graft.
  - It is important to note, however, that our approved labeling contains the following important contraindication to the use of INFUSE® Bone Graft:

"INFUSE® Bone Graft should not be used in the vicinity of a resected or extant (existing) tumor, in patients with any active malignancy or patients undergoing treatment for malignancy."



### Observation #1: There is no evidence that rhBMP-2 is carcinogenic or mutagenic.

- » Extensive literature reviews conducted in 2011 did not reveal any evidence indicating that transformation of normal cells into cancer cells by rhBMP-2 can occur.<sup>2</sup>
- » Lack of mutagenicity was verified in a series of standard AMES tests, which are *in vitro* biological assays used to assess the mutagenic potential of compounds.<sup>3</sup>

### Observation #2: The clinical evidence for the use of INFUSE® Bone Graft in approved spine applications does not suggest an increased incidence of cancer.

- » Five IDE studies comprise the total body of evidence for the use of INFUSE® Bone Graft in approved spine applications. These studies include:
  - INFUSE® Bone Graft with the LT-CAGE® Device<sup>4</sup>
    - » Pilot IDE clinical study
    - » Randomized IDE clinical study, using an open surgical approach
    - » Single-arm IDE clinical study, using a laparoscopic surgical approach
  - INFUSE® Bone Graft with the INTER FIX™ Device<sup>5</sup>
    - » Randomized pilot IDE clinical study
  - INFUSE® Bone Graft with the LT-CAGE® Device<sup>6</sup>
    - » Control group in a randomized IDE clinical study of a lumbar artificial disc
- » This pooled dataset contains more patients than those included in the package insert due to the addition of the last two studies listed above.
- » In total, 1047 patients were enrolled and treated, of which 485 received INFUSE® Bone Graft.
- » The follow-up endpoints for the INFUSE® Bone Graft patients ranged from 24-72 months, while follow-up for the non-INFUSE® Bone Graft patients ranged from 24-60 months.

No statistically significant difference was observed in the incidence of malignancy between the INFUSE® Bone Graft and non-INFUSE® Bone Graft groups in clinical studies for the approved indications.

Simple Comparison of Malignancy Cases  
(INFUSE® Bone Graft vs. non-INFUSE® Bone Graft Patients)

Malignancy Type	INFUSE® Bone Graft Group		Non-INFUSE® Bone Graft Group		p-value (Fisher's exact test)	
	Number of Cases	Number (%) of Patients (n=485)	Number of Cases	Number (%) of Patients (n=562)		
SEER malignancies	9	9 (1.9%)	7	7 (1.2%)	0.46	Not Statistically Significant
Non-SEER malignancies	2	2 (0.4%)	1	1 (0.2%)	0.60	Not Statistically Significant
<b>Total malignancies</b>	<b>11</b>	<b>10* (2.1%)</b>	<b>8</b>	<b>8 (1.4%)</b>	<b>0.48</b>	<b>Not Statistically Significant</b>

n=number of patients who had any follow-up visit after treatment

\*In the INFUSE® Bone Graft group, one patient reported both a SEER and a non-SEER cancer. This explains the discrepancy in the number of cases vs. the number of patients.

- » The SEER (Surveillance, Epidemiology and End Result) Program was developed by the US National Cancer Institute to categorize cancer events and is recognized as the gold standard for cancer statistics and cancer surveillance.<sup>7</sup>
  - The SEER program captures all invasive cancers (e.g., breast cancer).
    - » An invasive cancer is defined as one that has spread beyond the layer of tissue in which it developed and is growing into the surrounding healthy tissue.<sup>8</sup>
  - Non-SEER events are not captured in the SEER Program since these are non-invasive cancer types.
    - » Examples of such events include basal cell carcinoma and squamous cell carcinoma, which are two common types of skin cancers.<sup>9</sup>
- » The simple comparison above does not adjust for differences in duration of follow-up and patient demographics.
  - A more sensitive approach is to utilize a time-to-event analysis, which takes into account differences in follow-up time, as well as patient age, gender, and race, for comparing the two treatment groups.
- » When all of these factors are taken into account, no difference is shown between the INFUSE® Bone Graft and non-INFUSE® Bone Graft groups, both for the rate of SEER malignancies (p=0.63, Cox PHREG) and the rate of total malignancies (p=0.68, Cox PHREG).<sup>10</sup>

The distribution of cancer types was broad in both groups, as expected in the general population.

Number of Cases and Types of Malignancies Observed

SEER Cancer Classification	INFUSE® Bone Graft Group (n=485)	Non-INFUSE® Bone Graft Group (n=562)
Breast	2	1
Colon and Rectum	1	0
Corpus Uteri	0	1
Hodgkin Lymphoma	0	1
Leukemia	0	1
Liver and Bile Duct	1	0
Melanoma of the skin	2	0
Pancreas	1	0
Prostate	0	1
Testis	1	0
Thyroid	1	2
<b>Total SEER Cancer</b>	<b>9</b>	<b>7</b>
<b>Non-SEER Cancer</b>	<b>2</b>	<b>1</b>

\* SEER=Surveillance, Epidemiology and End Result

- » The table above provides a complete listing of reported SEER and non-SEER cancers for this population.
- » Each case shown in this chart was diagnosed after the patient underwent surgery.
  - Patients were not actively pre-screened for malignancy; however, each patient was asked whether they had an active malignancy prior to enrollment and treatment.

The actual cancer cases observed in both the INFUSE® Bone Graft group and the non-INFUSE® Bone Graft group were consistent with the rates expected to be seen in the studied patient populations.

Standardized Incidence Ratio (SIR) Analysis

Malignancy SEER Category	Number of Expected	Number of Observed	SIR		
			Observed SIR*	95% CI	p-value**
<b>INFUSE® Bone Graft Group</b>					
All Cancer Sites	8.30	9	1.08	(0.49, 1.86)	0.77
<b>Non-INFUSE® Bone Graft Group</b>					
All Cancer Sites	7.71	7	0.91	(0.36, 1.67)	0.84

\*SIR = the number of the observed cases divided by number of the expected cases.

\*\*Mid-P exact test.

- » The Standardized Incidence Ratio (SIR) analysis is a standard method utilized by epidemiologists to compare the observed incidence with that among the normal population.<sup>11</sup>
- » The “expected” number of events calculated from the SIR analysis includes adjustments for such patient factors as age, gender, and race.
  - In the INFUSE® Bone Graft group, the expected number of malignancy cases was 8.30, as compared to 9 actual cases observed.
  - In the non-INFUSE® Bone Graft group, the expected number of malignancies was 7.71, as compared to 7 actual cases observed.

**Observation #3: It is not known whether direct implantation of rhBMP-2 on the ACS carrier into a tumor site could affect tumor growth rate.**

- » Many cell types have BMP receptors. This indicates their ability to respond to BMP, although the exact response in each cell type at each stage of development is not yet known.
- » Review of the current literature investigating the effects of direct exposure of rhBMP-2 on cancer cell lines has suggested both positive and negative effects. Whether the effects are positive or negative is highly dependent on the cell culture medium used, the exposure regimen, and the type and stage of progression of cell line used.<sup>12</sup>
- » Beginning in the early 1990s, several cell culture studies performed by Medtronic’s partner showed no growth stimulation and, in some cases, growth inhibition of cancer cell lines in response to rhBMP-2 exposure.<sup>13</sup>
  - It was not verified, however, whether these primary tumor cell lines or tumor isolates could respond to BMP since the presence of BMP receptors was not determined as part of these studies.

Summary of Non-Clinical *In Vitro* Studies

Type of Study	Samples Tested	Results	Year Completed
Tumor cell line study (rhBMP-2 0-1000 ng/mL)	14 cell lines, including osteosarcoma, breast, prostate, and lung cancer	All cell lines either unaffected or growth inhibited	1991
Tumor isolates study (rhBMP-2 10,100, and 1000 ng/ml)	65 evaluable samples from patients (17 breast, 15 ovarian, 14 lung)	None showed growth stimulation – 16 of 65 inhibited at 1000 ng/ml	1998

- » rhBMP-2 is at least indirectly angiogenic.
  - While no tumors have been observed at the site of INFUSE® Bone Graft implantation in the IDE clinical trials, a local increase in blood vessel formation could theoretically enhance existing tumor growth in the vicinity or re-growth of a resected tumor.<sup>14</sup>
  - Since the product was released in 2002, a contraindication has been in place advising against the implantation of INFUSE® Bone Graft in the vicinity of a resected or extant (existing) tumor.

**Observation #4: In an *in vivo* study performed after the approval of INFUSE® Bone Graft, implantation of rhBMP-2 had no impact on the aggressiveness of distant malignant tumors.**

- » In order for rhBMP-2 to have an effect on cells, the protein must reach the cell and bind to its BMP receptors at a sufficient concentration for a sufficient duration to stimulate a response.
- » rhBMP-2 acts locally at the site of implantation because systemic exposure is minimized. It is retained at the site by the ACS carrier, slowly released over several weeks, and rapidly cleared from circulation. In addition, the protein is rapidly catabolized in the body.
- » Although growth was not detected in the cell culture studies above, animal studies were conducted following the approval of INFUSE® Bone Graft to examine the potential for tumor growth remote from the implantation site to occur.
  - Tumor cells, confirmed to have BMP receptors, were implanted subcutaneously on one flank in nude mice.
  - On the opposite flank, rhBMP-2/ACS was simultaneously implanted.
    - » To model a worst case scenario, the concentrations of rhBMP-2 were four to 40 times greater than that commonly used to form bone in this animal model.<sup>15</sup>
- » It is unknown how these data translate to the clinical setting in humans.

Post-Approval\* Nonclinical Study Summary

Type of Study	Samples Tested	Results	Year Completed
Assessment of tumor cell lines for rhBMP-2 receptors	Screened 21 cancer cell lines for BMP receptor mRNA	10 of 21 cell lines had functionally relevant levels of receptor mRNA	2002
<i>In vitro</i> tumor cell line study (rhBMP-2 0-100 ng/mL)	10 receptor positive cell lines and 1 osteosarcoma	No effect on 10 cell lines - 1 prostate tumor cell line was inhibited	2002
<i>In vivo</i> implantation of tumor cells and rhBMP-2/ACS (0.4 & 4 mg/mL) at remote location in mice	5 cell lines that express BMP receptors and 2 that do not	No increase in tumor growth or metastasis	2004

\* Performed as part of post-approval conditions for INFUSE® Bone Graft, PMA P000058.

### Next Steps

The body of evidence outlined above supports Medtronic's belief that INFUSE® Bone Graft is safe and effective for its approved indications. Furthermore, Medtronic is committed to transparency and open access to scientific research and has provided a grant to Yale University to independently analyze clinical data.

Further questions should be directed to the Office of Medical Affairs at 1-800-876-3133, extension 6044.

## Brief Summaries

### BRIEF SUMMARY OF INDICATIONS, CONTRAINDICATIONS, AND WARNINGS FOR:

#### INFUSE® BONE GRAFT/LT-CAGE® LUMBAR TAPERED FUSION DEVICE INFUSE® BONE GRAFT/INTER FIX™ THREADED FUSION DEVICE INFUSE® BONE GRAFT/INTER FIX™ RP THREADED FUSION DEVICE

The INFUSE® Bone Graft/Medtronic Titanium Threaded Interbody Fusion Device is indicated for spinal fusion procedures in skeletally mature patients with degenerative disc disease (DDD) at one level from L2-S1, who may also have up to Grade I spondylolisthesis or Grade 1 retrolisthesis at the involved level. The INFUSE® Bone Graft/ LT-CAGE® Lumbar Tapered Fusion Device is to be implanted via an anterior open or an anterior laparoscopic approach. INFUSE® Bone Graft with either the INTER FIX™ or INTER FIX™ RP Threaded Fusion Device is to be implanted via an anterior open approach.

The INFUSE® Bone Graft/Medtronic Titanium Threaded Interbody Fusion Device consists of two components containing three parts– a metallic spinal fusion cage, a recombinant human bone morphogenetic protein and a carrier/scaffold for the bone morphogenetic protein and resulting bone. **These components must be used as a system for the prescribed indication described above. The bone morphogenetic protein solution component must not be used without the carrier/scaffold component or with a carrier/scaffold component different from the one described in this document. The INFUSE® Bone Graft component must not be used without the Medtronic Titanium Threaded Interbody Fusion Device component.**

NOTE: The INTER FIX™ Threaded Fusion Device and the INTER FIX™ RP Threaded Fusion Device may be used together to treat a spinal level. LT-CAGE® Lumbar Tapered Fusion Device implants are not to be used in conjunction with either the INTER FIX™ or INTER FIX™ RP implants to treat a spinal level.

The INFUSE® Bone Graft/Medtronic Titanium Threaded Interbody Fusion Device is contraindicated for patients with a known hypersensitivity to recombinant human Bone Morphogenetic Protein-2, bovine Type I collagen or to other components of the formulation and should not be used in the vicinity of a resected or extant tumor; in patients with any active malignancy or patients undergoing treatment for a malignancy; in patients who are skeletally immature; in pregnant women; or in patients with an active infection at the operative site or with an allergy to titanium or titanium alloy.

There are no adequate and well-controlled studies in human pregnant women. In an experimental rabbit study, rhBMP-2 has been shown to elicit antibodies that are capable of

crossing the placenta. Women of child bearing potential should be warned by their surgeon of potential risk to a fetus and informed of other possible orthopedic treatments. The safety and effectiveness of this device has not been established in nursing mothers. Women of child-bearing potential should be advised to not become pregnant for one year following treatment with this device.

**Please see the package insert for the complete list of indications, warnings, precautions, adverse events, clinical results, definition of DDD, and other important medical information. The package insert also matches the sizes of those sized devices that are indicated for use with the appropriate INFUSE® Bone Graft kit.**

**CAUTION:** Federal (USA) law restricts this device to sale by or on the order of a physician with appropriate training or experience.

### BRIEF SUMMARY OF INDICATIONS, CONTRAINDICATIONS, AND WARNINGS FOR: INFUSE® BONE GRAFT

INFUSE® Bone Graft is indicated for treating acute, open tibial shaft fractures that have been stabilized with IM nail fixation after appropriate wound management. INFUSE® Bone Graft must be applied within 14 days after the initial fracture. Prospective patients should be skeletally mature.

INFUSE® Bone Graft consists of two components – recombinant human Bone Morphogenetic Protein-2 solution and a carrier/scaffold for the bone morphogenetic protein solution and resulting bone. **These components must be used as a system. The bone morphogenetic protein solution component must not be used without the carrier/scaffold component or with a carrier/scaffold component different from the one described in this document.**

INFUSE® Bone Graft is contraindicated for patients with a known hypersensitivity to recombinant human Bone Morphogenetic Protein-2, bovine Type I collagen or to other components of the formulation and should not be used in the vicinity of a resected or extant tumor, in patients with an active malignancy or patients undergoing treatment for a malignancy. INFUSE® Bone Graft should also not be used in patients who are skeletally immature, in patients with an inadequate neurovascular status, in patients with compartment syndrome of the affected limb, in pregnant women, or in patients with an active infection at the operative site.

There are no adequate and well controlled studies in human pregnant women. In an experimental rabbit study, rhBMP-2 has been shown to elicit antibodies that are capable of crossing the placenta. Women of child bearing potential

should be warned by their surgeon of potential risk to a fetus and informed of other possible orthopedic treatments. The safety and effectiveness of this device has not been established in nursing mothers. Women of child-bearing potential should be advised to not become pregnant for one year following treatment with this device.

**Please see the package insert for the complete list of indications, warnings, precautions, adverse events, clinical results, and other important medical information.**

**CAUTION:** Federal (USA) law restricts this device to sale by or on the order of a physician with appropriate training or experience.

**BRIEF SUMMARY OF INDICATIONS, CONTRAINDICATIONS, WARNINGS, AND PRECAUTION FOR INFUSE® BONE GRAFT FOR CERTAIN ORAL MAXILLOFACIAL AND DENTAL REGENERATIVE USES**

INFUSE® Bone Graft is indicated as an alternative to autogenous bone graft for sinus augmentations, and for localized alveolar ridge augmentations for defects associated with extraction sockets.

The INFUSE® Bone Graft consists of two components – recombinant human Bone Morphogenetic Protein-2 (rhBMP-2) placed on an absorbable collagen sponge (ACS). **These components must be used as a system for the prescribed indication. The bone morphogenetic protein solution component must not be used without the carrier/scaffold component or with a carrier/scaffold component different from the one described in the package insert.**

INFUSE® Bone Graft is contraindicated for patients with a known hypersensitivity to recombinant human Bone Morphogenetic Protein-2, bovine Type I collagen or to other components of the formulation and should not be used in the vicinity of a resected or extant tumor, in patients with any active malignancy or patients undergoing treatment for a malignancy, in pregnant women, or patients with an active infection at the operative site.

There are no adequate and well-controlled studies in human pregnant women. In an experimental rabbit study, rhBMP-2 has been shown to elicit antibodies that are capable of crossing the placenta. Women of child bearing potential should be warned by their surgeon of potential risk to a fetus and informed of other possible dental treatments. The safety and effectiveness of this device has not been established in nursing mothers. Women of child-bearing potential should be advised to not become pregnant for one year following treatment with this device.

INFUSE® Bone Graft has not been studied in patients who are skeletally immature (<18 years of age or no radiographic evidence of epiphyseal closure).

**Please see the package insert for the complete list of indications, warnings, precautions, adverse events, clinical results, and other important medical information.**

## References

- <sup>1</sup> Zhang, Hongbing and Bradley, Allan, *Mice deficient for BMP2 are nonviable and have defects in amnion/chorion and cardiac development.* Development 122, 2977-2986 (1996).
- <sup>2</sup> Data on file.
- <sup>3</sup> INFUSE® Bone Graft Summary of Safety & Effectiveness Data. P000058 (2002).
- <sup>4</sup> Data on file.
- <sup>5</sup> Data on file.
- <sup>6</sup> Data on file.
- <sup>7</sup> National Cancer Institute, *Surveillance Epidemiology and End Results.* seer.cancer.gov (last accessed November 14, 2011).
- <sup>8</sup> National Cancer Institute, *Dictionary of Cancer Terms.* www.cancer.gov/dictionary (last accessed November 14, 2011).
- <sup>9</sup> National Cancer Institute, *Dictionary of Cancer Terms.* www.cancer.gov/dictionary (last accessed November 14, 2011).
- <sup>10</sup> Data analysis on file.
- <sup>11</sup> National Cancer Institute, *Surveillance Epidemiology and End Results.* http://seer.cancer.gov/seerstat/WebHelp/Standardized\_Incidence\_Ratio\_and\_Confidence\_Limits.htm (last accessed November 14, 2011).
- <sup>12</sup> Data on file.
- <sup>13</sup> Data on file. See also INFUSE® Bone Graft Summary of Safety & Effectiveness Data, P000058 (2002).
- <sup>14</sup> Oklu et al., *Angiogenesis and Current Antiangiogenic Strategies for the Treatment of Cancer,* J Vasc Interv Radiol, 21, 1791-1805 (2010).
- <sup>15</sup> Data on file.

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