



Health Technology Assessment Program

Health Technology Clinical Committee
October 2009 Meeting

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Washington's Health Technology Assessment Program Background

- **Part of Governor's 2006 Five point health strategy for state to lead by example**
 - **Emphasize evidence-based health care**
<http://www.hca.wa.gov/conf/contf/doc/GovGregoireHealthBrief.pdf>

- **Program Purpose: Achieve better health by paying for technologies that work**
 - Better health with better information: investigate what works and maintain a centralized website.
 - Open and transparent process: publish process, criteria, reports, and committee decisions in public meeting.
 - Eliminate Bias: contract for independent evidence report and independent clinical committee.
 - Promote consistency: state agencies rely on a single, scientifically based source.
 - Flexible: review evidence regularly to ensure update information is included.

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- ❑ Overall Issue: WA citizens pay high cost for health care and receive poorer outcomes
- ❑ Government Issue: Public Programs have limited and/or shrinking resources and rising costs and needs.
- ❑ Common reaction: Reduce Eligibility, Rates or Benefits
 - “Thin the soup or cut the line”

Vision: Transform WA state from a passive payer to an active purchaser of higher quality, more efficient health care

- ❑ Action: Ensure WA pays for technologies that are proven safe, effective and cost-effective
 - “Better ingredients in the soup make it go farther”

Outcome: Pay for What Works

- Coverage decisions:
 - ❑ scientifically based
 - ❑ use transparent process, and
 - ❑ consistent across state health care purchasing agencies
- Formal, systematic process to identify, review, and cover appropriate health care technologies.
 - ❑ Is it safe?
 - ❑ Is it effective?
 - ❑ Does it provide value (improve health outcome)?

HTA Program – Ongoing Operations

Pay for What Works: Better Information is Better health

- Coverage Decisions
 - Cardiac Stents Finalization
 - Bone Growth Stimulator Finalization
 - Vagal Nerve Stimulator Finalization
- Evidence Reports
 - Calcium Scoring (CACS) - Complete
 - Hip Resurfacing - Complete
 - Electrical Neural Stimulation (ENS) - Complete
 - Sleep Apnea Diagnosis and Treatment – AHRQ underway
 - Glucose Monitoring – AHRQ underway
- Staffing Changes
 - Program Manager Hire – Margaret Dennis
 - Clinical Consultant – contract refresh

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HTA Program – Ongoing Operations

Pay for What Works: Better Information is Better health

- Topic Selection – 2010 Potential Topics Posted
 1. Kyphoplasty / Sacroplasty / Vertebroplasty
 2. Hyaluronic Acid Injections
 3. Spinal Injections
 4. MRI for Breast Cancer
 5. CT/MRI for abdomen/pelvis
 6. Spinal Cord Stimulation
 7. ABA Therapy for Autism
 8. Routine Ultrasound for Pregnancy
 9. Knee Replacement
 10. Prostate Specific Antigen Testing

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1. HCA Administrator Selects Technology
Nominate, Review, Public Input, Prioritize
↓ *Semi-annual*
2. Vendor Produce Technology Assessment Report
Key Questions and Work Plan, Draft, Comments, Finalize
2-8 Months ↓
3. Clinical Committee Makes Coverage Determination
Review Report, Public Hearing
↓ *Meet Quarterly*
4. Agencies Implement Decision
Implements within current process unless statutory conflict

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Hierarchy of Evidence

- Best:** Meta-analysis of large randomized head-to-head trials.
- Large, well-designed head-to head randomized controlled clinical trials (RCT):
- Long-term studies, real clinical endpoints
 - Well accepted intermediates
 - Poorly accepted intermediates
- Smaller RCTs, or separate, placebo-controlled trials
- Well-designed observational studies, e.g., cohort studies, case-control studies
- Safety data without efficacy studies
- Case series, anecdotes
- Least:** Expert opinion, non-evidence-based expert panel reports, and other documents with no direct clinical evidence

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Evidence in Health Care Decision Making



- **Level 3:** “What would I recommend to the state or nation?”
 - **Must be based on rigorous assessment of the scientific evidence.**
 - **Affects hundreds of thousands, even millions of people.**
- **Level 2:** “What would I recommend to my patient/client?”
 - Influenced by prior experience, but the scientific evidence may play a greater role.
 - Affects possibly hundreds of people.
- **Level 1:** “Would you have this done for yourself or for someone else in your immediate family?”
 - Influenced by one’s personal experience with the disease and capacity to deal with risk.
 - Affects few people.

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Evidence for use in Policy Decisions

Different Data Sources

- **Efficacy**
 - How technology functions in “best environments”
 - Randomized trials-distinguish technology from other variables
 - Meta-analysis
- **Effectiveness**
 - How technology functions in “real world”
 - Population level analyses
 - Large, multicenter, rigorous observational cohorts (consecutive pts/objective observers)
- **Safety**
 - Variant of effectiveness
 - Population level analyses
 - Case reports/series, FDA reports
- **Cost**
 - Direct and modeled analysis
 - Administrative/billing data (charge vs cost)
- **Context**
 - Mix of historic trend, utilization data, beneficiary status, expert opinion

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Health Technology Clinical Committee

Date: August 28, 2009

Time: 8:00 am – 5:00 pm

Location: Marriott Hotel – 3201 South 176th Street, Seattle, WA 98188

Teleconference Bridge: 1-309-946-5000 Access Code: 9461464

Adopted:

HTCC MINUTES

Members Present: Brian Budenholzer; Michael Myint; Carson Odegard; Michael Souter; C. Craige Blackmore; Louise Kaplan; Megan Morris and Christopher Standaert; Richard Phillips* (*after 9:00 a.m.).

Members Absent: Jay Klarnett and Michelle Simon

HTCC FORMAL ACTION

1. **Call to Order:** Dr. Budenholzer, Chair, called the meeting to order. Sufficient members were present to constitute a quorum.
2. **May 8th, 2009 Meeting Minutes:** Chair referred members to the draft minutes; motion to approve and second, discussion ensued.
 - *Action: Eight committee members unanimously approved the May 8th, 2009 meeting minutes.*
3. **Cardiac Stent Findings & Decision:** Chair referred members to the draft findings and decision; motion to approve and second, discussion ensued. Motion to table vote, and direct chair to convene an ad hoc advisory group to provide expert input on potential additional groups at high risk of restenosis and any evidence supporting.
 - *Action: Seven committee members approved convening an ad hoc advisory committee. Two voted against.*
4. **Vagal Nerve Stimulation for Epilepsy and Depression:** The HTCC reviewed and considered Vagal Nerve Stimulation for the treatment of Epilepsy and Depression technology assessment report; information provided by the Administrator; state agencies; public members; and heard comments from the evidence reviewer, HTA program, agency medical directors, a clinical expert, and several public members. 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.
 - **Conditions for coverage for Epilepsy:** The committee decided to cover Vagal Nerve Stimulation for management of seizures for epilepsy in patients twelve years of age or older that have a medically refractory seizure disorder.

Draft Version Not Officially adopted – 08/28/2009



HTCC COMMITTEE COVERAGE DETERMINATION VOTE			
	Not covered	Covered Unconditionally	Covered Under Certain Conditions
Epilepsy	0	0	9
Depression	9	0	0

- *Action:* The committee chair directed HTA staff to prepare a Findings and Decision document on Vagal Nerve Stimulators reflective of the majority vote for final approval at the next public meeting.

5. **Bone Growth Stimulators:** The HTCC reviewed and considered the Bone Growth Stimulators technology assessment report; information provided by the Administrator; state agencies; public members; and heard comments from the evidence reviewer, HTA program, agency medical directors, a clinical expert, and several public members. 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.

HTCC COMMITTEE COVERAGE DETERMINATION VOTE			
	Not covered	Covered Unconditionally	Covered Under Certain Conditions
Bone Growth Stimulators	0	0	9

- Conditions for coverage: The committee decided to cover with conditions Bone Growth Stimulators, conditions for coverage are consistent with Medicare’s national coverage decision plus ultrasonic stimulation for treatment of fresh fractures that are at high risk of non-union.
- Medicare Covered conditions include:
 - *Electrical Noninvasive and Invasive Stimulator device is covered only for the following indications:* (a) Nonunion of long bone fractures (3 or more months ceased healing, 2 radiographs minimum 90 days apart); (b) Failed fusion, where a minimum of 9 months has elapsed since the last surgery; or adjunct to fusion for patients with a previously failed fusion and high risk of psuedarthrosis; and (c) Congenital psuedarthrosis (noninvasive only).
 - *Ultrasonic stimulator:* (a) Nonunion confirmed by 2 radiographs minimum 90 days apart and physician statement of no clinical evidence of fracture healing.
 - Non Covered Indications: (a) Nonunion of skull, vertebrae or tumor related; and (b) Ultrasonic stimulator – delayed fractures and concurrent use with other noninvasive stimulator.
- *Action:* The committee chair directed HTA staff to prepare a Findings and Decision document on Bone Growth Stimulators reflective of the majority vote for final approval at the next public meeting.



SUMMARY OF HTCC MEETING TOPICS, PRESENTATION, AND DISCUSSION

Agenda Item: Welcome & Introductions

- ✓ The Health Technology Clinical Committee (HTCC) met on August 28th, 2009.

Agenda Item: Meeting Open and HTA Program Update

Dr. Brian Budenholzer, HTCC Chair, opened the public meeting. Leah Hole-Curry, HTA Program Director, provided an overview of the agenda, meeting guide and purpose, room logistics, and introductions.

Leah Hole-Curry, HTA Program Director, provided an update on HTA program activities and outcomes.

- ✓ Evidence Reports Underway: Calcium Scoring, Hip Resurfacing and Electrical Neural Stimulation (ENS) are currently underway with the vendor and the HTA program. Evidence Reports not yet started are Glucose Monitoring and Sleep Apnea Diagnosis and Treatment.

Agenda Item: Previous Meeting Business

May 8th, 2009 Meeting Minutes: Chair referred members to the draft minutes and called for a motion and discussion. Minutes were circulated prior to the meeting and posted. No committee requests for changes were received.

- *Action: Eight committee members unanimously approved the May 8th, 2009 meeting minutes.*

Cardiac Stents Findings and Decision: Chair referred members to the draft findings and decision and called for further discussion. (Postponed discussion to later in meeting to ensure attendance and input of late member).

- ✓ The committee met on May 8, 2009 to review the topic of bare metal versus drug eluting cardiac stents. The committee made a draft decision to cover bare metal stents, and cover drug eluting stents under certain conditions. The conditions are: cover for patients at high risk of restenosis, including patients with – diabetes, vessels smaller than 3 mm, or lesions longer than 15 mm.
- ✓ Subsequent to the meeting, staff drafted a Cardiac Stent Findings and Decision document based on committee discussion and direction and posted for comment. Comments were received from a committee member, 3 providers (Dr. Larry Dean, Dr. Steve Goldberg, and Providence Health & Services), and 3 professional groups (SCAI, Washington State Hospital Association and Swedish Heart & Vascular Institute). Commenter's expressed concerns or disagreement with the draft decision. Comments were collated and sent to committee members in advance. One commenter believed a technical error in the document was present and requested staff confirm through the hearing record accuracy. Staff confirmed accuracy and reported to committee.
- ✓ Based on public input and committee discussion, the committee would like additional expert input prior to finalizing the conditional coverage criteria, specifically around high risk groups. The committee agreed that the Chair would work with staff in convening an ad hoc advisory committee.
 - *Action: Seven committee members approved convening an ad hoc advisory committee. One committee member voted against the formation of an ad hoc advisory committee.*

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Agenda Item: Vagal Nerve Stimulation for Epilepsy and Depression Topic Review

Leah Hole-Curry, HTA Program Director, introduced the first technology topic up for discussion:

- ✓ Vagal Nerve Stimulation for the treatment of Epilepsy and Depression: review of the evidence of the safety, efficacy and cost-effectiveness of Vagal Nerve Stimulation.

Vagal Nerve Stimulation – Epilepsy and Depression

- ✓ Epilepsy is a neurological condition impacting 2.3 million people in the US, with an estimated 600,000 experiencing complex partial seizures.
 - Epilepsy causes seizures that can involve loss of consciousness and may not be controlled by medication.
- ✓ Depression (major depressive disorder) is a mood disorder that affects approximately 18.8 million adults in the US annually.
 - Depression has a high recurrence rate and associated burden, interfering with ability to work, sleep, eat and function, and with symptoms from persistent sadness or anxiety to suicide.
 - The etiology of depression is unclear, and it appears that a variety of genetic, environmental and psychological factors may be involved in the onset of a depressive period.
- ✓ VNS first was clinically applied as an anti-convulsant in 1980s and is now being explored for disease beyond epilepsy, including depression.
- ✓ VNS stimulates the left vagus nerve using electrical signals generated by an implanted pulse generator. The vagus nerve carries sensory information to the brain from the head, neck, thorax and abdomen.
- ✓ Evolving understanding continues on the neurobiological effects of VNS therapy as a function of the different use parameters (frequency, intensity, pulse width, duration and dose).
- ✓ Exact mechanism of action by which VNS reduces clinical symptoms is not known, but imaging and clinical studies demonstrate brain function changes.
- ✓ One of several forms of therapeutic physical brain stimulation (both invasive and non-invasive) includes: electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS) and deep brain stimulation (DBS). Alternative treatments include: pharmacotherapy and brain surgery.
- ✓ VNS has been used as an adjunct treatment for epilepsy (most continue with medication) in patients 12 years of age or older, who continue to suffer from partial-onset seizures, generally with: a seizure frequency of at least six per month while on antiepileptic medication, and who have either failed surgical treatment or are not suitable surgical candidates.
 - VNS was recently approved as an adjunct to treat major treatment resistant depression in persons over 18 years of age.
- ✓ Treatment expectation with VNS is a reduction in frequency and severity and length of seizures or depressive episodes.



- ✓ VNS Complications: Changing the stimulation parameters reverses many minor complications such as voice changes while others are permanent or may require device explantation. VNS may increase depression and suicide ideation and suicide attempts.
- ✓ FDA Approval:
 - 1997 – FDA approval to treat medically refractory, complex partial seizures in patients over age 12.
 - 2005 – FDA approval as adjunct to treat chronic or recurrent depression in patients over 18 years of age experiencing major depressant episode without sufficient response to four or more adequate antidepressant treatments.
- ✓ Medicare Coverage and Clinical Guidelines:
 - There is a National Medicare policy on VNS for both epilepsy and depression (VNS policy for Epilepsy did not cite evidence, but depression policy does) --
 - VNS is a reasonable and necessary for patients with medically refractory partial onset seizures for whom surgery is not recommended or for whom surgery has failed (1999).
 - VNS is not reasonable and necessary for resistant depression (2007).
 - VNS Clinical Guidelines for Epilepsy –
 - Three cited in report – two supports FDA indicated use, one does not (MSAC, Australia, 2008; British Medical Journal Review, 2009; and NICE, England, 2004).
 - VNS Clinical Guidelines for Depression –
 - Three cited in report – all concluding insufficient evidence to recommend (California Technology Assessment Forum, CTAF, 2006; Institute for Clinical Systems Improvement, ICSI, 2009; and Kaiser Permanente Care Management Institute, 2006).

Agenda Item: Public Comments

- ✓ Scheduled Public Comments: No scheduled public comments.
- ✓ Open Public Comments: Three individuals provided comments during the open portion (limited to three minute comments):
 - Stan Jackson, Cyberonics, manufacturer, provided a statement on coverage for VNS, including a New York Blue Cross Blue Shield plan that covered VNS after reviewing evidence.
 - Brent Herrmann, Epilepsy Foundation NW, provided a statement regarding the positive impacts on quality of life that VNS has for epileptic individuals.
 - Ryder Guinn, neurosurgeon at Swedish Medical Center, representing himself, provided a statement that evidence shows measurable benefit even though patients and level of difference is unknown.



Agenda Item: Vagal Nerve Stimulation Topic – Agency Data

Dr. Nancy Fisher, Health Care Authority (HCA) Medical Director, presented to the committee the agency utilization and outcomes for Vagal Nerve Stimulation.

- ✓ Key agency concerns for prioritization:
 - Efficacy concerns – High: adjunct treatment; patient selection and stimulation parameters are still under study. Low evidence, but pressure to diffuse to uses other than anti-convulsant.
 - Safety concerns – High: VNS implantation and surgical risk; long term use unknowns and may increase suicide ideation. The etiology of depression is unclear, and it appears that a variety of genetic, environmental, and psychological factors may be involved in the onset of a depressive period.
 - Cost concerns – High: about over or mis-utilization and expansion to other treatment areas, and cost of additional (not replacement) treatment if no or little advantage.

✓ Implantation Procedure by Conditions for Vagal Nerve Stimulation --
 UMP & Medicaid Only (2003 – 2008) - 138 procedures

✓ Total * Payments for Vagus Nerve Stimulators --
 UMP & Medicaid Only (2003 – 2008)

	2003	2004	2005	2006	2007	2008	Total
Epilepsy	\$74,053	\$312,322	\$276,473	\$371,855	\$510,892	\$407,164	\$1,952,758
Depression	\$12,514	\$0	\$0	\$7,426	\$1,020	\$1,240	\$22,200
Total	\$86,567	\$312,322	\$276,473	\$379,281	\$511,912	\$408,404	\$1,974,958

* Total includes inpatient, outpatient, implantations, revisions, removals, analysis, and medical devices
 ** Average expense of NCP \$1,974,958/138 = \$14,310

- ✓ VNS Challenges: plethora of clinical complications; close monitoring; difficulty in titrating stimulation dose; and treatment of effect delayed in epilepsy, unknown for depression.
- ✓ Agency Recommendations:
 - Epilepsy: complex partial seizures – cover with conditions. Other seizure disorders – no coverage.
 - Depression: major depressive disorder (MDD) – no coverage. Bipolar disorder – no coverage.
 - Consistent with CMS and other health plans and evidence-based coverage policies.

Agenda Item: Evidence Review Presentation

Hayes, Inc. presented an overview of their evidence report on Vagus Nerve Stimulation for Epilepsy and Depression.

- ✓ Epilepsy Scope: PICO approach --

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- Population: Adults and children with medically intractable epilepsy
 - Intervention: VNS as an adjunct to medical treatment
 - Comparators: Sham-VNS, antiepileptic medication, surgical resection
 - Outcomes: Seizure severity; duration; frequency; quality of life; complications
 - ✓ Vagus Nerve Stimulation is a programmable pulse generator implanted into the patient's chest that delivers current via electrodes attached to the vagus nerve. VNS has adjustable stimulation parameters, and a magnet can be used to control stimulation.
 - ✓ Clinical Overview: VNS was introduced as a treatment for intractable partial epilepsy in 1997. Approximately 2.3 million people in the US have epilepsy. 600,000 experience partial complex seizures. 33% of patients have inadequate seizure control.
 - Resective brain surgery can be effective in some patients but carries significant risk to the patient.
 - ✓ Literature Search: Previous Hayes reports (2007); MEDLINE/EMBASE (2007 to July 2009) and websites of MED Project core sources. Selection: meta-analysis / systematic reviews; primary studies (not in systematic reviews) that included – prospective controlled and uncontrolled studies > 10 patients; and retrospective studies > 50 patients (other types of seizures, young children, long-term follow-up).
 - ✓ Selected Reviews and Studies: 1 Cochrane meta-analysis was included; and 30 primary studies were included – 2 randomized controlled trials (RCTs); 4 nonrandomized controlled trials; and 33 uncontrolled studies.
 - ✓ Effect of VNS on Seizure Control in Partial Epilepsy –
 - VNS reduced seizure frequency by 24.5% to 27.9% from baseline compared with 6.1% to 15.2% in sham VNS.
 - Overall, 21% to 75% of patients experienced at least a 50% mean reduction.
 - Treatment benefit was maintained for up to 10 years.
 - Adults and children older than 12 years of age seem to benefit equally from the treatment.
 - ✓ Generalized Seizures and Lennox-Gastaut Syndrome – limited evidence was available for generalized seizures and Lennox-Gastaut syndrome. VNS therapy may be effective for these types of seizures, but the quality of the evidence was poor. Controlled studies are needed to confirm results.
 - ✓ Effect of VNS on Quality of Life in Epilepsy – the effect of VNS on quality of life is unclear. While VNS improved elements of quality of life in some patients, the specific number and type of improvements were inconsistent among studies. However, insufficient power to detect a significant effect makes interpretation of these results difficult.
 - ✓ Safety of VNS for Epilepsy – safety data for VNS are available for a time frame of up to ten years.
 - Most common complications: voice alterations, hoarseness, cough, pain, dyspnea, infection, paresthesia, headache and pharyngitis.

- These problems were generally mild, decreased over time, or could be resolved by changing device parameters.
 - There is no indication that VNS increases the incidence of Sudden Unexpected Death in Epilepsy (SUDEP).
- ✓ Differential Effectiveness – there is currently insufficient evidence to suggest that effectiveness may vary by patient characteristics and predictors of a treatment response have not been established. However, the current evidence from small pilot studies suggests that VNS may also be effective in patients 12 years of age or younger and those older than 50 years of age. VNS may be more effective for patients who had no previous surgical treatment for epilepsy.
- ✓ Economic Evaluations – six economic evaluations were identified and summarized. All indicated cost savings from significant decrease in healthcare utilization, e.g., avoidance of ER visits (\$3,000 per year in 1 study; 99% decline in another).
- ✓ Conclusions and Discussion – Synopsis of Evidence: there is high quality evidence from RCTs and long-term studies regarding the benefit and safety of VNS to conclude that VNS reduces seizure rates in some patients older than 12 years of age with medically refractory partial seizures who are not suitable candidates for surgery or in whom surgical treatment has failed.
 - Low Quality Evidence: (1) that VNS may also benefit some patients with generalized seizures or Lennox-Gastaut syndrome and (2) that VNS may also benefit patients younger than 12 years of age.
- ✓ Conclusions and Discussion – Translation to Policy / Practice: patients with chronic, severe, medication-resistant epilepsy have few treatment options. Not all patients respond to VNS treatment and response may vary considerably among patients. Patients who had previously undergone antiepileptic surgery may benefit less from VNS. Risks and benefits of VNS versus epilepsy surgery have to be taken into consideration.
- ✓ Depression Scope: PICO Approach –
 - Population: Patients with chronic, severe, treatment-resistant MDD or bipolar disorder
 - Intervention: VNS as an adjunct to medical treatment
 - Comparators: Pharmacotherapy, psychotherapy, electroconvulsive therapy, sham treatment
 - Outcomes: Changes in depression severity, complications, quality of life, function, length of depression-related hospitalization, number of required psychiatric treatments.
- ✓ Clinical Overview: Depression is a mood disorder that affects approximately 5% to 10% of adults. Major depressive episodes are treated pharmacologically or with electroconvulsive therapy (ECT). VNS is being investigated for the treatment of chronic, severe, treatment-resistant major depressive disorder and bipolar disorders.
- ✓ Policy Overview: One estimate is that 200,000 patients have treatment-resistant major depression. In July 2005, the FDA approved the VNS Therapy™ System (Cyberonics, Inc.) for treatment-resistant depression (FDA, 2005).
 - CMS does not cover VNS as a treatment for depression at this time (CMS, 2009).
- ✓ Literature Search: Previous Hayes reports (2005); MEDLINE/EMBASE (2005 to June 2009) and websites of MED Project core sources. Selection: meta-analysis; primary studies (not in

systematic reviews) that included – prospective controlled and uncontrolled studies > 10 patients; and retrospective studies > 50 patients.

- ✓ Selected Reviews and Studies: 1 double-blind, randomized, parallel-group, sham-controlled study of VNS for treatment-resistant depression (D02 trial); 1 small, prospective, open-label study using sex-matched and age-matched controls (MDD); and 5 uncontrolled studies.
- ✓ Effect of VNS on the Severity of Depression – RCT showed no significant difference between active (n=112) and sham VNS (n=110) in treatment response rates (15.2% versus 10.0, respectively; P=0.251). There were no significant differences between active and sham VNS groups for 4 of 5 scales used as secondary measures of efficacy.
 - Data analysis without adjustment for confounding factors suggests that VNS plus standard treatment was superior treatment alone.
 - Medium-Term Effectiveness – patients who respond to the treatment at 3 or 13 months are likely to maintain the response for up to 24 months.
 - A concern for these studies is that they used a lower threshold for the definition of responders; therefore, if the response rates had been based on the original threshold, actual long-term response rates might be lower. Lastly, the study was uncontrolled, thus the potential for bias.
- ✓ Safety of VNS for Depression – worsening of depression and attempted suicides occurred but was not correlated with VNS use. Medium-term safety data were only available from uncontrolled trials for up to 2 years.
 - In the RCT (D02 trial, n=235): device explantation due to infection in 1 patient and 1 suicide in the active VNS group. Other complication rates were similar between active and sham treatment.
- ✓ Differential Effectiveness – the evidence is insufficient to establish patient selection criteria for VNS in patients with treatment-resistant depression, and significant predictors of response have not yet been identified.
- ✓ Economic Evaluations – 2 economic evaluations identified and summarized. Both projected substantial cost savings. However, since efficacy has not been proven, economic evaluations cannot substantiate cost-effectiveness.
- ✓ Conclusions and Discussion – Synopsis of Evidence: the currently available evidence is of low overall quality and does not support the use of VNS as an adjunct therapy in adult patients with treatment-resistant MDD and bipolar disorders. While a moderate treatment effect was observed in the uncontrolled studies, the only randomized controlled study failed to demonstrate a statistically significant difference in primary outcomes after 10 weeks of active or sham VNS.

Agenda Item: HTCC Vagal Nerve Stimulation for Epilepsy and Depression
Discussion and Findings

Brian Budenholzer, Committee Chair, led a discussion of the evidence related to the safety, efficacy, and cost effectiveness of Vagal Nerve Stimulators beginning with identification of key factors and health outcomes, and then a discussion of what evidence existed on those factors.

1. Evidence availability and technology features

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- 1.2 Vagal Nerve Stimulation – Epilepsy. The evidence based technology assessment report identified a relatively large amount of literature. The reviews and studies selected for this detailed review included one meta-analysis (Privitera, 2002), and 39 primary studies. The primary studies consisted of data from two randomized trials, four nonrandomized controlled trials, and 33 uncontrolled studies. The body of evidence reviewed involved studies with 13 to 454 patients, as well as registry data for 4,743 patients with medically refractory epilepsy syndromes and one retrospective analysis involving 1,819 patients of the incidence of sudden death in epilepsy (SUDEP).
- 1.3 Vagal Nerve Stimulation – Depression. The evidence based technology assessment report did not identify a meta-analysis that met the criteria for review. The majority of the available evidence regarding the safety and efficacy of VNS for treatment-resistant depression comes from studies funded by or performed in collaboration with Cyberonics (2009) in patient groups ranging from 9 to 235. Overall, the manufacturer planned and/or executed six studies, although, to date, complete data sets have not been published for all of the studies. The search of the peer-reviewed literature identified the following controlled studies: one double-blind, randomized, parallel-group, sham-controlled study; one post hoc comparative analysis; one nonrandomized comparison study; and one small, prospective, open-label study. The remaining evidence was from five uncontrolled studies. There were two articles reporting on the prospective, uncontrolled extensions of the RCT. There were six articles reporting data from one open-label, nonrandomized, uncontrolled clinical study. One study reported on the results of a prospective, open-label, single-arm study. Finally, the evidence also included one small, prospective, open-label, single-arm pilot study of VNS for chronic treatment-resistant depression; and one prospective, open-label, single-arm study investigating VNS in patients with rapid cycling bipolar disorder.
- 1.4 The committee also reviewed information provided by the Administrator, state agencies, and public members; and heard comments from the evidence reviewer, HTA program, agency medical director, subject matter experts; and several public members.

2. Evidence about the technology's safety

The committee discussed multiple key factors and health outcomes that were important for consideration in their overall decision on whether the technology is safe. Summary of committee considerations follows.

- 1.5 Mortality – the evidence based technology assessment report indicated little evidence of increased mortality.
 - Specific to epilepsy, no evidence that VNS increases incidence of Sudden Unexpected Death in Epilepsy, rates from one cohort study of overall death were 4.1 per 1000 for VNS patients and 4.5 per 1000 in cohort.
 - Specific to depression, evidence is more limited, and the one RCT reported one death due to suicide in VNS group. Worsening of depression and attempted suicides occurred, but evidence does not yet correlate to VNS use; data more short term (2 year).
- 1.6 Morbidity - the evidence based technology assessment report indicated data on complications related to epilepsy were available up to ten years and depression up to two years. Most common complications were mild including: voice alterations, hoarseness, cough, pain, dyspnea, infection, paresthesia, headache, and pharyngitis. Additional complications reported related to treatment for depression included: attempted suicide, suicide ideation, worsening of depression, manic episodes, agitation, hypomania, and cardiovascular events.
 - Committee identified dyspnea as potentially more significant concern, with the evidence based technology assessment reporting one RCT rate of dyspnea at 25% in VNS group.

- 1.7 The evidence based technology assessment report indicated that evidence for pediatric patients demonstrated similar adverse effects, though the evidence base is small, pilot studies and follow up length is not as long.

3. Evidence about the technology's efficacy and effectiveness

The committee discussed multiple key factors and health outcomes that were important for consideration in their overall decision on whether the technology is effective. Summary of committee considerations follows.

- 1.8 Epilepsy – Reduction in severity or frequency of seizure is the primary outcome measured. The treatment does not cure or eliminate seizures, though one comparator -surgical treatment's goal is to eliminate seizures.
- Effect of VNS on Seizure Control in Partial Epilepsy – two randomized placebo controlled trials (n=312) reduced seizure frequency by 25% from baseline compared with 6.1% to 15.2% in sham VNS. Sample size and use of sham treatment (low pulse) strengthened results as VNS can be felt. Overall, 21% to 75% of patients experienced at least a 50% mean reduction. Treatment benefit was maintained for up to 10 years.
 - One prospective study is available for generalized Seizures and Lennox-Gastaut Syndrome (n=78) – the limited evidence suggests VNS therapy may be effective for these types of seizures, but the quality of the evidence was poor. Controlled studies are needed to confirm results.
 - Insufficient evidence related to population characteristics, but small pilot studies of patients under 12 and older than 50 with no previous surgical treatment may be responsive to VNS; those with higher baseline seizure and who were older with onset of seizures may benefit more.
- 1.9 Depression – Reduction in severity or frequency of depressive episodes is the primary outcome measured. The evidence based technology assessment report indicates one randomized control trial with 235 patients and a placebo lasting 12 weeks did not demonstrate a statistically significant difference.
- Treatment is potentially investigated for chronic, severe, treatment resistant major depression disorder or bipolar disorder. Definition is not uniformly defined in literature.
 - The evidence based technology assessment report also provided information on the different instruments to measure changes in depression, and indicating a threshold of more than 50% change over baseline generally considered clinically meaningful; however the final scores must also be taken into account as changes can be misleading if the final scores still fall below the threshold for severe depression. Additionally, comparators varied in studies and may confound results, especially if comparator treatments changed during study.
 - Limited uncontrolled trials produced conflicting results compared to standard treatment and had substantial limitations beyond study design in that significant heterogeneity among comparison groups was not adjusted for in one study, and a lower than originally defined threshold for “responders” was adopted in a second study.
 - All studies were industry sponsored or supported.
- 1.10 Quality of Life: The evidence based technology report included quality of life as a key outcome.
- Epilepsy related quality of life data is of moderate level with inconsistent results which may be due to insufficient power to detect difference.



- Depression related quality of life data was not separately reported from the depression rating scales.

4. Evidence about the technology's value and cost-effectiveness

The committee discussed multiple key factors that were important for consideration in their overall decision on whether the technology has value and is cost-effective. Summary of committee considerations follows.

- 1.11 Epilepsy – the technology assessment report indicated that several small European studies conclude VNS could be cost-effective by reduction in unplanned hospital and other treatment costs by average of \$3000 per patient (N= 20 and 19 patients).
- 1.12 Depression – the technology assessment report included two economic evaluations; however, when efficacy has not been proven, economic evaluations cannot substantiate cost-effectiveness.

Medicare Decision and Expert guidelines

Committee reviewed and discussed the Medicare coverage decision and expert guidelines as identified and reported in the technology assessment report.

Epilepsy –

- Centers for Medicare and Medicaid Services (1999) – there is a national coverage decision (NCD) relating to Vagal Nerve Stimulators for Epilepsy. The NCD states that VNS is reasonable and necessary for patients with medically refractory partial onset seizures for whom surgery is not recommended or for whom surgery has failed.
- Guidelines – three guidelines were stated in the technology assessment evidence report, those included: (1) MSAC, Australia, 2008, VNS is reasonably safe in context of the condition being treated but insufficient evidence of effectiveness and net benefit of VNS for patients with medically refractory epilepsy; (2) Clinical Evidence: British Medical Journal Review, 2009, reported high level VNS may reduce seizure frequency in people with partial seizures that are refractory to medication, complications and long term effect unknown; and (3) NICE, 2004, VNS indicated for use as an adjunctive therapy in reducing the frequency of seizures in children and adults who are refractory to antiepileptic medication and who are not suitable candidates for resective surgery. VNS is indicated for patients with epileptic disorder with predominantly partial seizures, with or without secondary generalized epilepsy, and generalized epilepsy.

Depression –

- Centers for Medicare and Medicaid Services (2007) – there is a national coverage decision (NCD) relating to Vagal Nerve Stimulators for Depression. The NCD states that VNS is not reasonable and necessary for resistant depression (not covered).
- Guidelines – three guidelines were included in the technology assessment evidence report, those included: (1) CTAF, 2006, concluded that VNS for depression does not meet criteria four and five for effectiveness and improvement of health outcomes in treatment resistant depression; (2) ISCI, 2009, concluded that quality of evidence currently does not meet ICSI's threshold for recommendation; and (3) Kaiser Permanente Care Management, 2006, concluded insufficient evidence to recommend VNS.

Committee Conclusions

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

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1. Evidence availability and technology features

The committee concludes that the best available evidence on vagus nerve stimulators has been collected and summarized. The evidence is comprehensive and robust:

- 1.1. Evidence from meta-analysis and several well designed randomized, controlled trials, with adequate participants, appropriate controls or alternative(s), and patient centered outcomes were available for epilepsy treatment.
- 1.2. Patients with medically refractory epilepsy who are unsuccessful or non-surgical candidates have few treatment alternatives and face difficult and sometimes severe complications from the disease.
- 1.3. Evidence from one controlled trial and several other trials is available on VNS for medically refractory depression; a condition that has serious impacts and few additional treatment options.

2. Is it safe?

The committee concludes that the comprehensive evidence reviewed shows that the VNS technology is safe compared with alternative management for epilepsy and unproven compared to alternative management for depression. Key factors to the committee's conclusion included:

- 2.1. Mortality – the committee agreed with the evidence report conclusions that indicated little evidence of increased mortality generally, but remain concerned with the suicide death reported in the VNS treatment group related to depression and overall more limited evidence and follow up length in studies for depression treatment.
- 2.2. Morbidity - the committee generally agreed with the evidence report conclusions that most adverse effects were mild, especially in comparison with epilepsy condition specifically, and based on explantation or voluntary termination could be addressed.
- 2.3. Committee identified dyspnea as potentially more significant concern, with the evidence based technology assessment reporting one RCT rate of dyspnea at 25% in VNS group.
- 2.4. Committee discussed rate of explantation or voluntary termination (not well reported) in relation to harms because the device can be removed or turned off to alleviate some complications thus limiting the magnitude of adverse effect, and as factor or proxy for how severe complications might be (group voluntarily discontinued).
- 2.5. The committee found evidence insufficient on safety for use in pediatric (under 12) given the very small and limited evidence base identified in the evidence report and discussed this as a larger concern given the limited ability to generalize to children, and the potential for serious complications.

3. Is it effective?

The committee concludes that the comprehensive evidence reviewed shows that VNS is proven more effective for treatment of medically refractory epilepsy and unproven from treatment of depression:

- 3.1. For Epilepsy – the measure of reduction in severity or frequency of seizure is an important, patient centered, and appropriate measure of effectiveness. The committee agreed that evidence indicated VNS was effective in reducing severity or frequency of seizures in patients with medically refractory epilepsy.
- 3.2. For Depression – the committee agreed that an appropriate measure would be the reduction in frequency or duration of major depressive episodes in patients with medically refractory depression, and concluded that the current best evidence (one

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RCT) does not currently demonstrate an improvement in this measure. Additional high quality evidence is needed.

5. Evidence about the technology's special populations, patient characteristics and adjunct treatment

The committee discussed multiple other factors that were important for consideration in their overall decision. Summary of committee considerations follows.

- 3.3. Epilepsy special populations - age: Committee agreed that the data presented in both the technology evidence report and what the FDA as approved, that VNS treatment is effective for those 12 years of age or older for epilepsy treatment. Committee discussed VNS treatment for those patients under the age of 12; however, the committee agreed that not enough data exists on safety and efficacy for children less than 12 years of age and current IRB approved trials should be utilized to access treatment while assessing benefit.

4. Is it cost-effective?

The Committee concludes that the comprehensive evidence review shows that VNS is equally or more cost effective for epilepsy and unproven for depression.

- 4.1. Epilepsy – Committee agreed that limited data existed; however, several studies did show that VNS treatment to be cost-effective due to the reduction in seizures that necessitated medical treatment. Committee agreed that long term, good quality evidence would be desirable, but is not available. Committee agreed that no evidence in the report displayed any evidence to say otherwise.
- 4.2. Depression – Committee agreed that primarily where evidence of effectiveness has not yet been shown, cost-effectiveness cannot be shown, and the cost studies available for VNS treatment of depression are low quality.

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, input from a clinical expert, and agency and state utilization information. The committee concluded that the current evidence on Vagal Nerve Stimulators demonstrates that there is sufficient evidence to cover the use of Vagal Nerve Stimulators for Epilepsy, but not cover the use of Vagal Nerve Stimulators for Depression. 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. The committee found that Vagal Nerve Stimulators for Epilepsy didn't have a significant mortality rate; serious morbidity from VNS was unusual; and VNS was effective in reducing severity or frequency of seizures. The committee found that Vagal Nerve Stimulators were proven to be more effective for patients 12 years and older.

Epilepsy – Based on these findings, the committee unanimously voted 9 to 0 to cover Vagal Nerve Stimulation, with conditions: limited Vagal Nerve Stimulation for management of seizures for epilepsy for patients with 12 years of age or older that have a refractory disorder.

Depression – Based on these findings, the committee unanimously voted 9 to 0 no coverage on Vagal Nerve Stimulation for the treatment of depression.

Vagal Nerve Stimulators Vote

The clinical committee utilized their decision tool to first gauge committee judgment on the status of the evidence in the three primary areas of safety, efficacy, and cost.

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Vagal Nerve Stimulation Evidentiary Votes:

Is there sufficient evidence under some or all situations that Vagal Nerve Stimulation for Epilepsy is:

	Unproven (no)	Equivalent (yes)	Less (yes)	More (yes)
Effective	1	0	0	8
Safe	0	8	0	1
Cost-effective Overall	4	1	0	4

Is there sufficient evidence under some or all situations that Vagal Nerve Stimulation for Depression is:

	Unproven (no)	Equivalent (yes)	Less (yes)	More (yes)
Effective	9	0	0	0
Safe	5	2	2	0
Cost-effective Overall	9	0	0	0

Vagal Nerve Stimulators vote: Based on the evidence provided and the information and comments presented, the committee moved to a vote on coverage.

HTCC COMMITTEE COVERAGE DETERMINATION			
	Not covered	Covered Unconditionally	Covered Under Certain Conditions
Epilepsy	0	0	9
Depression	9	0	0

- Outcome: The committee chair directed HTA staff to prepare a Findings and Decision document on Vagal Nerve Stimulators reflective of the majority vote for final approval at the next public meeting.
 - Vagal Nerve Stimulation is conditionally covered. VNS treatment is covered for management of seizures in epilepsy patients 12 years of age or older that have a medically refractory seizure disorder. Vagal Nerve Stimulation for Depression is not covered.

Agenda Item: Bone Growth Stimulators Topic Review

Dr. Dave Flum, HTA Clinical Consultant, introduced the second technology topic up for discussion:

- ✓ Bone Growth Stimulators: review of the evidence of the safety, efficacy and cost-effectiveness of Bone Growth Stimulators.

Bone Growth Stimulators

- ✓ Bone fractures are a common musculoskeletal injury with 7.9 million occurring in the US annually.
- ✓ Majority of fractures heal without complications following standard nonsurgical or surgical therapy, healing is delayed or impaired in 5% to 10% of cases.
 - Delayed healing is associated with longer recovery, reduction in quality of life and function, and pain.
 - There is no standard definition of nonunion; FDA considers a nonunion to be established “when a minimum of 9 months has elapsed since injury and the fracture site shows no visibly progressive signs of healing for minimum of 3 months.”
 - There are variations in the clinical and radiographic findings used to diagnose nonunion.
- ✓ Bone union is also a potential concern in patients who undergo joint fusion surgery and in patients with fresh fractures who are at risk of delayed or nonunion.
 - Lifestyle modification (smoking, obesity, alcoholism) and infection control are important.
- ✓ Clinical Theory: bone healing requires stability and blood supply. Clinical studies demonstrate that bone healing is associated with electrical potentials (appropriate blood flow) at the site.
- ✓ BGS attempts to harness the electrical-biological link through the use of applied electrical fields to promote healing but link between biophysical stimulation and the cellular responses is not fully understood.
- ✓ BGS uses either electrical stimulation or low intensity pulsed ultrasound to induce bone growth and promote fracture healing. Invasive BGS are surgically implanted; non-invasive or worn externally.
- ✓ BGS are used as an adjunctive treatment with other fracture healing treatments including immobilization; surgical techniques; bone grafts; treatment of infection or other causes of non-union; and orthobiologics.
- ✓ FDA Approval:
 - 2009 – FDA approves bone growth stimulators as Class III devices, meaning that they are deemed to pose the highest level of risk and thus require premarket approval. No information regarding approved indications is currently available from the FDA database.
 - A search of the Premarket Approval (PMA) database indicates that the agency began approving electrical bone growth stimulators in 1980 and ultrasonographic osteogenic stimulators in 1994.
- ✓ Medicare Coverage and Clinical Guidelines – there is a National Medical policy on BGS:
 - Electrical noninvasive and invasive stimulator device is covered only for the following indications:

- Nonunion of long bone fractures (3 or more months ceased healing, 2 radiographs min. 90 days apart);
 - Failed fusion, where a minimum of 9 months has elapsed since the last surgery; or adjunct to fusion for patients with a previously failed fusion and high risk of psuedarthrosis; and
 - Congenital pseudarthroses (noninvasive only)
- Ultrasonic stimulator:
 - Nonunion confirmed by 2 radiographs min. 90 days apart and physician statement of no clinical evidence of fracture healing.
- Non covered indications:
 - Nonunion of the skull, vertebrae or tumor related.
 - Ultrasonic stimulator – fresh, delayed fractures and concurrent use with other noninvasive stimulator.
- ✓ BGS Clinical Guidelines –
 - Two cited in report:
 - American Association of Neurological Surgeons / Congress of Neurological Surgeons (AANS / CNS), 2009, guideline regarding BGS and lumbar fusion – Treatment standard: Insufficient evidence. Treatment guideline: electrical stimulation recommended as an adjunct to spinal fusion for patients at high risk for arthrodesis; PMEF stimulation recommended as adjunct to increase fusion rates in similar patients treated with lumbar interbody fusion procedures.
 - Agency for Healthcare Research and Quality (AHRQ), 2005, evidence review for CMS – Overall evidence quality low; treatment effect of device could not be distinguished from possible therapeutic effects of concurrent treatments.

Agenda Item: Public Comments

- ✓ Scheduled Public Comments: Four scheduled public comments (limited to five minute comments):
 - Dr. Naresh Patel, Orthofix, provided a statement advocating the benefits of external pulsed electromagnetic filed (PEMF) stimulation.
 - Dr. Mark Olson, Orthofix, provided a statement advocating the benefits of external pulsed electromagnetic filed (PEMF) stimulation against non-union and bone grafting procedures.
 - James Ryaby, Ph.D., DJO, provided a statement advocating that bone growth stimulation has been rigorously evaluated in prospective clinical trials.
 - Barbara Rohan; Dr. Mohit Bhandari and Dr. Neil Pounder; Smith & Nephew, provided a statement advocating Exogen, a low intensity pulsed ultrasound, which has shown compelling evidence on healing for certain fresh fractures.
- ✓ Open Public Comments: No individuals provided comments during the open portion (limited to three minute comments):



Agenda Item: Bone Growth Stimulators – Agency Data

Dr. Nancy Fisher, Health Care Authority (HCA) Medical Director, presented to the committee the agency utilization and outcomes for Bone Growth Stimulators.

- ✓ Key agency concerns for prioritization:
 - Efficacy concerns – High: low quality evidence currently available for most uses; adjunct treatment confounds results; patient selection and stimulation parameters (high dose; low dose; length of treatment and duration) unclear; patient compliance problematic.
 - Safety concerns – Low: non-invasive little risk concern; implantable BGS – concern regarding device implantation risk.
 - Cost concerns – Medium: about over or mis-utilization; expansion to other treatment areas; and cost of additional (not replacement) treatment.

✓ BGS Procedure Codes By Year:

PROC CODE (ICD-9, CPT, HCPCS)	2005	2006	2007	2008	Total
Total	255	258	275	312	1100

ICD-9, CPT, HCPCS codes are unduplicated counts. HCPCS codes not available for cases listed by ICD-9 or CPT code. Counts for E0749 not available due to bundled billing.

✓ Distribution of Procedures by Bone Type

UMP, Medicaid, L&I 2005-2008				
	Bone Type			
HCPCS CODE	Long	Spine	Other*	Total
E0747 (Noninvasive electrical, other than spine)	109	7	443	559
E0748 (Noninvasive electrical, spine)	0	203	61	264
E0760 (Noninvasive ultrasound)	72	0	121	193
Total	181	210	625	1016

* Other bones typically include bones of the hand and foot.

✓ Average Payments by Procedure:

UMP, Medicaid, L&I 2005-2008	
HCPCS CODE	Average Payments
E0747 (Noninvasive electrical, other than spine)	\$3,688
E0748 (Noninvasive electrical, spine)	\$3,537
E0760 (Noninvasive ultrasound)	\$2,820

* Weighted average

✓ Total Payments by Procedure by Year:

UMP, Medicaid, L&I 2005-2008					
HCPCS CODE	2005	2006	2007	2008	Total



E0747	\$503,083	\$573,974	\$488,099	\$489,267	\$2,054,424
E0748	\$186,835	\$89,177	\$265,033	\$311,419	\$852,464
E0760	\$101,781	\$124,291	\$130,185	\$179,616	\$535,873
Total	\$791,700	\$787,442	\$883,317	\$980,302	\$3,442,761

✓ Diagnosis by Procedure Code:

UMP, Medicaid, L&I 2005-2008	HCPCS CODE			
	E0747	E0748	E0760	Total
Nonunion of fracture	170	1	5	176
Arthrodesis status	27	87	0	114
Fracture metatarsal-closed	26	0	44	70
Back disorder NOS	4	17	0	21
Fracture ankle NOS-closed	0	0	13	13
Total	227	105	62	394

✓ Safety and Effectiveness:

- Ultrasound and non-invasive BGS – no serious concerns.
- Increased complications with invasive devices in high risk patients.
- No studies looking at patients by age groups.
- No clearly identified factors for treatment success.

✓ Scientific Evidence:

- Conflicting, moderate to low quality -- systematic reviews reveals variation across studies; no recent studies for effect or different treatment parameters; no elucidated specific factors for use in fresh fractures; and no clearly identified factors for treatment success.
- The validity of patient compliance in unknown; no controlled studies compared the use of BGS with and without concomitant treatment; there is no high quality studies for direct comparison between types of BGS; and no blinded assessment of X-rays following invasive procedure.

✓ Economic Studies:

- Evidence does not demonstrate consistent outcomes across populations; therefore, economic studies are not appropriate until large randomized control and observational studies are done.

✓ Agency Recommendations:

- Larger randomized trails and observational studies are needed to – (1) confirm positive benefits; (2) identify any rare adverse events; (3) demonstrate effectiveness / safety; and (4) identify patient selection criteria.

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- Non-coverage or very limited coverage (i.e., for patients at high risk for pseudo-arthritis following fusion).

Agenda Item: Evidence Review Presentation

Hayes, Inc. presented an overview of their evidence report on Bone Growth Stimulators.

- ✓ Report Scope: PICO approach --
 - Population(s): Adults and children being treated for traumatic fracture or diseases requiring fusion of the spine or joints.
 - Intervention(s): LIPUS, invasive electrical stimulation, noninvasive electrical stimulation.
 - Comparator(s): No stimulation or sham stimulation.
 - Outcome(s): (1) Healing; (2) Reduction in pain, return to function, impact on quality of life.
- ✓ Bone Growth Stimulators deliver energy to induce osteogenesis: (1) ultrasound (pressure waves) and (2) electrical – invasive or semi-invasive (direct current) or noninvasive (electromagnetic field or capacitively coupled current).
- ✓ Clinical Overview: 7.9 million bone fractures each year in the United States. Cost of treating hospitalized musculoskeletal injuries is about \$26.6 billion (88% attributable to fractures). Healing delayed or impaired in 5% - 10% of fractures. Arthrodesis can also be delayed after spinal or joint fusion (up to 28% multilevel anterior cervical fusion with bone graft and instrumentation; up to 50% lumbar fusion; up to 16% subtalar joint; and up to 41% ankle).
- ✓ Policy Context: In clinical use for over 30 years, but uncertainty remains: (1) efficacy relative to stand or usual treatment; (2) ability to reduce pain, accelerate return to function, restore quality of life; (3) long-term safety; and (4) differential effectiveness according to patient characteristics.
- ✓ Literature Search: Previous Hayes reports (2003, 2004); MEDLINE/EMBASE (2003 to 2009) and websites of MED Project core sources. Selection included: (1) Published systematic reviews – systematic literature search, critical appraisal, synthesis, and explicit conclusions; and (2) Primary Studies – not in systematic reviews, unique information (population, indication, analysis), or > 50 (LIPUS, noninvasive electrical) or > 20 (invasive).
- ✓ Selected Reviews and Studies:
 - LIPUS – Hayes (2003); Busse et al. (2009): 13 RCTs, 2 non-RCTs; primary studies: 1 RCT, 4 non-RCTs.
 - Invasive electrical stimulation – Hayes (2004a): 2 RCTs, 13 non-RCTs; primary studies: 3 non-RCTs.
 - Noninvasive electrical stimulation – Hayes (2004b); Mollon et al. (2008): 14 RCTs, 5 non-RCTs; primary studies: 2 RCTs, 3 non-RCTs.
- ✓ Definition of Terms:
 - Radiographic healing / union / fusion: no clinical assessment
 - Clinical healing: discontinuation of immobilization, motion at fracture site, strength, tenderness, avoidance of surgery.

-
- Fresh fracture: recent (e.g., < 7 days), no treatment prior to fixation.
 - Delayed union: lack of complete healing at 3 to 9 months, depending on fracture type.
 - Non-union: lack of complete healing by 9 months and no signs of healing within past 3 months.
 - ✓ Effectiveness of Bone Growth Stimulators:
 - Fresh fractures –
 - LIPUS, non-operative management: positive, moderate-quality evidence for healing (sig. pooled relative reduction in RH time of 36.9%), more evidence for long bones; conflicting, low-quality evidence for functional outcomes.
 - LIPUS, operative management: mixed, low-quality evidence for both RH and functional recovery.
 - Semi-invasive electrical stimulation: sparse, low-quality evidence for RH. Pain, function, quality of life: no evidence.
 - Delayed Union or Nonunion fractures –
 - LIPUS: positive, low-quality evidence for RH.
 - Invasive / semi-invasive electrical stimulation: positive, low-quality evidence for RH; most evidence for long bone fractures.
 - Noninvasive electrical stimulation: generally positive, moderate-quality evidence for RH (sig. 21% - 60% absolute improvement, 3 RCTs; no improvement, 1 RCT); most evidence for PEMF stimulation and long bones. Pain, function, quality of life: no positive evidence for any form of stimulation.
 - Adjunct treatment, spinal fusion –
 - Invasive electrical stimulation: generally positive, low-quality evidence of RH, most evidence for lumbar / lumbosacral fusion. Pain, function, quality of life: positive, low-quality evidence of impact.
 - Noninvasive electrical stimulation: generally positive, low-quality evidence for RH. Pain, function, quality of life: generally negative, low-quality evidence.
 - Adjunct treatment, foot / ankle arthrodesis –
 - Invasive electrical stimulation: positive, sparse, low-quality evidence of impact on CH and quality of life.
 - Noninvasive electrical stimulation (PEMF): positive, sparse, low-quality evidence for healing, primarily RH.
 - Salvage treatment, spinal fusion or joint arthrodesis –
 - Invasive / noninvasive electrical stimulation: conflicting, largely negative, low-quality evidence for RH. Pain, function, quality of life: No evidence.
 - ✓ Safety of Bone Growth Stimulators –
 - LIPUS and noninvasive electrical stimulation: To date, no important safety issues. No data on but also no suspicion of long-term adverse effects.

- Invasive electrical stimulation: Serious complications in several high-risk patients. Some instances of device-related, mechanical problems.
- ✓ Differential Effectiveness – LIPUS for delayed / nonunion fractures: Low quality evidence that treatment effect is greater (1) in patients with younger, more recent, fractures; and (2) in patients who have risk factors for prolonged fracture healing. Otherwise, at best, only very sparse evidence of relationship between any one patient characteristic (including type of bone) and treatment success. Study populations: adult patients without serious comorbidities who are not dependent on drugs or alcohol and who do not take medications that would interfere with treatment.
- ✓ Economic Evaluations – No economic evaluations of electrical stimulation; 3 for ultrasound (US), fresh fractures:
 - 1997 models predicted health cost savings, US combined with standard treatment (operative or non-operative); however, potential bias due to (1) author affiliation with earlier trial supported by manufacturer; (2) no indirect cost included; and (3) no cost-effectiveness analysis.
 - 2001 Australian healthcare system cost analysis: higher total costs (direct and indirect) with adjunctive use of US than with standard treatment alone; and no distinction between operative / non-operative standard treatment.
 - 2005 cost analysis from perspectives: (a) public payer, Ontario Ministry of health and long-term care; and (b) societal.
- ✓ Conclusion and Discussion – Synopsis of Evidence: In adults, generally safe; variable efficacy by indication; no single indication with high-quality evidence; one indication, moderate-quality evidence for radiographic healing (fresh fractures treated with LIPUS as part of a non-operative management strategy); further study merited in other application; and effect on pain, function, or quality of life are very sparse and conflicting.

Agenda Item: HTCC Bone Growth Stimulators Discussion and Findings

Brian Budenholzer, Committee Chair, led a discussion of the evidence related to the safety, efficacy, and cost effectiveness of Bone Growth Stimulators beginning with identification of key factors and health outcomes, and then a discussion of what evidence existed on those factors. Having made findings as to the most significant and relevant evidence regarding health outcomes, key factors and identified evidence related to those factors, primarily based on the evidence based technology assessment report, the committee concludes:

1. Evidence availability and technology features

- 1.1 Bone Growth Stimulators. The evidence based technology assessment report identified previously completed Hayes Medical Technology Directory Reports published in 2003 and 2004 and primary studies published more recently if they were not included in the selected systematic reviews and if they met sample size thresholds and/or provided information not available from the systematic reviews.
- 1.2 Key data limitations included the overall available body of evidence was limited to small sample sizes, few studies per indication, no RCT's for some indications, substantial loss to follow up, difficulty separating treatment effect of stimulation from placebo effect or other effects where multiple interventions used, and no assessment of pain or functional outcomes in most studies. Studies of application to fresh fractures were further weakened by the use of

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radiographic fusion as the only measure of healing. The appropriate clinical and patient oriented endpoints are not clearly identified or agreed upon; the number of surgical interventions avoided is a central concern but not adequately reported.

- 1.3 Ultrasonic stimulators: had two systematic reviews, a Hayes Medical Technology Directory Report (2003), and a systematic review and meta-analysis from the peer-reviewed literature. The Hayes report included three RCTs and two retrospective case series studies published in October 2003 or earlier. Five primary studies -- these five studies consisted of three prospective, uncontrolled studies; one randomized, placebo-controlled study that provided long-term (18 month) follow-up data; and one retrospective study with multiple regression analysis to evaluate prognostic factors.
- 1.4 Electrical Stimulation, Invasive and semi-invasive -- A Hayes Medical Technology Directory Report (2004a) was the only systematic review. This report included two RCTs, eight nonrandomized comparative studies, and five case series studies published in February 2004 or earlier and three primary studies. A total of 3,683 patients were involved across all studies, with sample sizes ranging from 28 to 1,686.
- 1.5 Electrical Stimulation, Noninvasive -- A Hayes Medical Technology Directory Report (2004b) and a systematic review from the peer-reviewed literature. The report reviewed 15 studies, including 10 RCTs and five primary studies. A total of 2,130 patients were involved across all studies, with sample sizes ranging from 16 to 201 in most studies, with one study having a sample size of 1,098. Eight of the 15 studies investigated pulsed electromagnetic field (PEMF) stimulation, 5 investigated capacitive coupling, and 2 investigated combined magnetic field (CMF) stimulation. The review by Mollon and colleagues included 11 RCTs. Four selected trials, which were published in 1996 or earlier, were not reviewed in the Hayes report. The Hayes report included some observational studies that were excluded by Mollon, as well as three RCTs that were not included by Mollon.

2. Evidence about the technology's safety

The committee discussed multiple key factors and health outcomes that were important for consideration in their overall decision on whether the technology is safe. Summary of committee considerations follows.

- 1.6 Mortality: Device related complications from DCES (implanted) were not found, though general and surgical complications do occur, the relationship to the device is unknown, as well as an long term implications for elderly or adolescents. Serious device related complications were not reported by any of the large number of studies in non-invasive technology and though quantity of long term date is modest, the literature does not suggest suspicion of long term adverse effects.
- 1.7 Morbidity: For external devices, evidence does not demonstrate serious complications; implanted devices addressed above.
- 1.8 Overall: the committee agreed that no evidence of mortality or serious adverse effects risk for external BGS exist; however, for implanted BGS devices an increased risk of infection, by virtue of additional devices is likely, though additional harm risk is limited. No data separately reported on stimulator related infection.
 - a. Special populations: no children or safety data was presented and committee was concerned that the generalizability of safety data would not extend to patients that are not yet skeletally mature.

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3. Evidence about the technology's efficacy and effectiveness

The committee discussed multiple key factors and health outcomes that were important for consideration in their overall decision on whether the technology is effective. Summary of committee considerations follows.

Lumbar Spinal Fusion –

- 1.1 The committee concluded that of the four studies on lumbar fusion, none of them selected high risk patients. All four reported high results. Sample sizes ranged from 179 to 201 patients; fusion success in the controlled group; 13% to 30% absolute difference in healing; follow-up ranging from 9 months to 1 year; and included all initial fusion, including smokers and non-smokers. In controlled group, healing rates occurred in the range of 43% to 86% (successfully fused). In the stimulated group, healing rates occurred in the range of 64% to 91%. Below is a breakdown of all the systematic studies from the technology evidence report the committee reviewed and discussed:
 - a. Mooney, 1990 – in a moderate size, multicenter, randomized trial, consistent users of pulsed electromagnetic field (≥ 8 hrs / day, later set to 2 hrs / day) had significantly higher success rate of interbody spinal fusion than patients in placebo group (92% and 67%, respectively). Inconsistent pulsed electromagnetic field users achieved success rate similar to patients in placebo group.
 - b. Jenis, 2000 – a small, randomized trial compared the effect of adjunctive noninvasive pulsed electromagnetic field and invasive direct current stimulation on augmentation of instrumented lumbar spinal fusion. Neither form of electrical stimulation resulted in improved fusion rates or clinical outcome (pain, function) in instrumented lumbar arthrodesis. However, there was an insignificant trend toward increased fusion mass bone mineral density in both electrical stimulation groups relative to surgery-only group.
 - c. Goodwin, 1999 – in 1 moderate-size RCT, capacitive coupling was used adjunctively to primary lumbar spine fusion. The overall success rate (both clinical and radiographic) was 85% for the active group compared with 65% for the placebo group, a statistically significant difference. When clinical outcomes were assessed separately, between group difference favored stimulation.
 - d. Linovitz, 2002 – in 1 RCT with 201 patients with noninstrumented posterolateral fusions, adjunctive use of combined electromagnetic field electrical stimulation significantly increased the 9-month radiographic fusion success rates in the overall (64% vs 43%). In addition, there was an acceleration of the healing process.
- 1.2 Invasive stimulation (referenced as Table 3 & 4 in the report) – 2 RCTs reported conflicting results. Other studies had historical or conflicting controls. High risk patients. 81% in the stimulated and 54% in the un-stimulated – 63 patients total in this trial. The committee concluded that mostly positive large evidence exists for non-invasive stimulation; however, conflicting data and lack of evidence exists for invasive stimulation. Below is the study the committee reviewed and discussed from the technology evidence report:
 - a. Kane, 1988 – 1 RCT reported successful spinal fusion in 81% of high-risk patients who had direct current electrical stimulation as adjunct to noninstrumented spinal fusion, compared with only 54% of high-risk patients who underwent surgery alone (63 patients met inclusion criteria, 59 available for follow-up [9.4%]).
- 1.3 The committee discussed and read the 2005 CMS coverage decision. The committee concluded that the CMS coverage decision included spinal fusion and revision surgery (external or adjunct); although, in sufficient data was presented on revision surgery.

- 1.4 The committee concluded that some RCT data exists for lumbar fusion; however no data exists on revision surgery (or failed surgery). Effectiveness level of evidence is moderate, at best.

Fractures –

- 1.5 Non-union fractures versus delayed union – committee agreed that overall low quality evidence was presented (referenced as Table 5 and 6 in the report) – consistent results from RCTs in benefits. Below the studies the committee reviewed and discussed from the technology evidence report are expressed below:
- a. Sharrard study, 1990 – 1 small RCT; nonunion or delayed union fractures (tibial fractures); 45 strictly selected patients total; actively stimulated group; radiographic assessment found significant differences in healing in favor of pulsed electromagnetic field group (50% of patients with some radiographic evidence of healing, pulsed electromagnetic field; 8% control); double-blinded; no significant differences between groups on clinician assessment of pain or movement.
 - b. Simonis study, 2003 – in 1 RCT of pulsed electromagnetic field stimulation for established tibial nonunions, radiographic and clinical evaluation showed that 89% of the pulsed electromagnetic field group fractures united versus only 50% of placebo group. Pulsed electromagnetic field stimulation was associated with significant increase in rate of union, but only before adjustment for smoking.
 - c. Scott and King study, 1994 – in a small RCT of 21 patients with established non-unions of the tibia, ulnar, or femur, 60% of actively managed patients and no controls achieved union by radiographic and clinical criteria, a statistically significant difference.
 - d. Molan, 2008 – meta-analysis did not find any statistically significant treatment (or therapy) effect of electromagnetic stimulation for improving radiographic outcomes for nonunion or delayed union fractures, fresh fractures, or tibial osteotomy. Electromagnetic stimulation treatment (or therapy) generally did not improve clinical outcomes, although 1 of 4 studies noted reduction of pain in a subgroup of patients. Evidence regarding the effect of electromagnetic stimulation on bone densitometry measures varied both across and within studies.
 - e. Punt, 2008 – retrospective, before-and-after, blinded analysis of pulsed electromagnetic field for salvage treatment (or therapy) of nonunion of traumatic fractures. Compared with clinical conditions at the time of initiation of bone growth stimulation, patients with a diagnosis of nonunion experienced substantial clinical improvement and radiographic evidence of healing. Overall clinical and radiographic success was similar for long bone-fracture and nonlong bone fracture.
- 1.6 Committee agreed that efficacy evidence identified in the technology assessment report was of overall low quality and insufficient.

Ultrasound –

- 1.7 Committee reviewed and discussed two low-intensity pulsed ultrasonography RCT systematic reviews that assessed ultrasound bone growth stimulators. Systematic reviews assessed the effectiveness and safety of ultrasound bone growth stimulators used alone or in combination with another treatment (or therapy) for fresh, delayed union, and nonunion fractures. Below is a description of both of the RCTs reviewed and discussed by the committee from the technology evidence report:
- a. Heckman, 1994 & Kristiansen, 1997 – Data from 2 RCTs, 96 patients (Heckman) and 83 patients (Kristiansen), indicate that low-intensity ultrasound accelerates healing of fresh

- tibial shaft and distal radius fractures and decreases incidence of nonunion in tibial fractures in selected patients.
- b. Non-operative versus operative: Busse, 2009 – 6 reviewed studies with measures of radiographic healing; low-intensity pulsed ultrasonography appears to accelerate healing time by 33.6%. Meta-analysis by type of fracture indicated a significant reduction in healing time with low-intensity pulsed ultrasonography treatment (or therapy) for non-operative management fresh fractures and bone grafting for nonunions, but not for operative management fresh fractures. However, meta-analysis did not find a significant effect of low-intensity pulsed ultrasonography treatment (or therapy) on functional recovery for any type of fracture, including non-operative management fresh fractures, non-operative management stress fractures, or operative management fresh fractures.
- 1.8 Committee agreed that efficacy evidence identified in the technology assessment report for ultrasound was also of overall low quality, though it included the highest level of evidence of the different stimulator types.

1. Evidence about the technology's value and cost-effectiveness

The committee discussed multiple key factors that were important for consideration in their overall decision on whether the technology has value and is cost-effective. Summary of committee considerations follows.

- 1.9 The committee discussed the evidence report cost information. Articles on cost were available for ultrasound bone growth stimulation for fresh fractures. No economic evaluations for electrical stimulation for the treatment of bone fractures were identified in the literature search. One limitation to the economic articles is that there is low quality effectiveness information.
- 1.10 The Hayes (2003) review included a 2001 systematic review that evaluated the cost-effectiveness of low-intensity ultrasound (LIPUS) to treat fresh tibia, radius, and scaphoid fractures. The analysis indicated that the total cost of treatment per patient, incorporating both direct and indirect costs, was higher for ultrasound treatment than for standard non-operative treatment for all three fracture types. Treating fresh fractures with ultrasound was far less cost effective than interventions for other common health problems. At the time of the review, there was insufficient evidence regarding the effectiveness of ultrasound treatment for delayed and nonunion fractures to permit a cost-effectiveness analysis for these indications.
- 1.11 In 2005, Busse, et al. conducted a burden of illness (BOI) study from the perspective of both local government (the Ontario Ministry of Health and Long-Term Care) and society, and concluded that reamed intramedullary nailing was most cost effective. Ultrasound with casting was judged possibly economical, but additional clinical effectiveness and actual cost information was needed.
- 1.12 Washington agency cost data ranged from \$2,800 for ultrasound to \$3,700 for electrical non-invasive.

Medicare Decision and Expert guidelines

Committee reviewed and discussed the Medicare coverage decision and expert guidelines as identified and reported in the technology assessment report.

- Centers for Medicare and Medicaid Services (2005) –
 - *Electrical Noninvasive and Invasive Stimulator device is covered only for the following indications:*
 - Nonunion of long bone fractures (3 or more months ceased healing, 2 radiographs minimum 90 days apart);

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- Failed fusion, where a minimum of 9 months has elapsed since the last surgery; or adjunct to fusion for patients with a previously failed fusion and high risk of psuedarthrosis;
 - Congenital psuedarthrosis (noninvasive only).
 - *Ultrasonic stimulator:*
 - Nonunion confirmed by 2 radiographs minimum 90 days apart and physician statement of no clinical evidence of fracture healing.
 - *Non Covered Indications:*
 - Nonunion of skull, vertebrae or tumor related;
 - Ultrasonic stimulator – fresh, delayed fractures and concurrent use with other noninvasive stimulator.
- Guidelines – two guidelines were stated in the technology assessment evidence report, those included:
 - American Association of Neurological Surgeons / Congress of Neurological Surgeons (AANS / CNS), 2009, guideline regarding BGS and lumbar fusion – Treatment standard: Insufficient evidence. Treatment guideline: electrical stimulation recommended as an adjunct to spinal fusion for patients at high risk for arthrodesis; PMEF stimulation recommended as adjunct to increase fusion rates in similar patients treated with lumbar interbody fusion procedures.
 - Agency for Healthcare Research and Quality (AHRQ), 2005, evidence review for CMS – Overall evidence quality low; treatment effect of device could not be distinguished from possible therapeutic effects of concurrent treatments.

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, input from a clinical expert, and agency and state utilization information. 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.

The committee concluded unanimously that the current evidence on Bone Growth Stimulators demonstrates that there is sufficient evidence to indicate that the bone growth stimulators are equally safe as alternatives. A majority found that the evidence on Bone Growth Stimulators for all stimulator types and all bone types is unproven as to clinical effectiveness and cost effectiveness based on overall low quality evidence for each indication and stimulator type, though ultrasound for fresh fractures did have the strongest low level of supporting evidence. Key data limitations included the overall available body of evidence was limited to small sample sizes, few studies per indication, no RCT's for some indications, substantial loss to follow up, difficulty separating treatment effect of stimulation from placebo effect or other effects where multiple interventions used, and no assessment of pain or functional outcomes in most studies. Studies of application to fresh fractures were further weakened by the use of radiographic fusion as the only measure of healing. The appropriate clinical and patient oriented endpoints are not clearly identified or agreed upon and the number of surgical interventions avoided is a central question, but not adequately reported.

However, a National Medicare Coverage Decision exists that is based on CMS' evidence review from 2005 and the committee acknowledged its responsibility to be consistent with Medicare, unless based on its review of the systematic assessment, substantial evidence exists about safety, efficacy, or cost-effectiveness to support a contrary determination. The committee found that it did not have significant

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evidence to support a contrary determination because evidence about the effectiveness and cost-effectiveness are unproven and thus may support CMS' decision, or ultimately when additional evidence is available, may not.

Given equipoise, a finding of equivalent safety, and a recent and evidence based Medicare national decision, the committee voted to cover Bone Growth Stimulators with conditions equivalent to the national Medicare coverage decision, with one exception. Ultrasonic stimulation for fresh fractures is specifically non-covered in Medicare's policy, however the committee found that the technology assessment report identified the highest level of evidence (though still unproven overall) for this indication and stimulation type, and therefore there is sufficient evidence to include this indication in the covered conditions.

Bone Growth Stimulators Vote

The clinical committee utilized their decision tool to first gauge committee judgment on the status of the evidence in the three primary areas of safety, efficacy, and cost.

Bone Growth Stimulators Evidentiary Votes:

Is there sufficient evidence under some or all situations that Bone Growth Stimulators for Fresh Fractures are:

	Unproven (no)	Equivalent (yes)	Less (yes)	More (yes)
Effective	5	0	0	4
Safe	0	9	0	0
Cost-effective Overall	9	0	0	0

Is there sufficient evidence under some or all situations that Bone Growth Stimulators for Long Bone Non-union:

	Unproven (no)	Equivalent (yes)	Less (yes)	More (yes)
Effective	7	0	0	2
Safe	0	9	0	0
Cost-effective Overall	9	0	0	0



Is there sufficient evidence under some or all situations that Bone Growth Stimulators for Spinal Fusion:

	Unproven (no)	Equivalent (yes)	Less (yes)	More (yes)
Effective	9	0	0	0
Safe	0	9	0	0
Cost-effective Overall	9	0	0	0

Bone Growth Stimulators Vote: Based on the evidence provided and the information and comments presented, the committee moved to a vote on coverage.

HTCC COMMITTEE COVERAGE DETERMINATION			
	Not covered	Covered Unconditionally	Covered Under Certain Conditions
Bone Growth Stimulators	0	0	9

- Outcome: The committee chair directed HTA staff to prepare a Findings and Decision document on Bone Growth Stimulators reflective of the majority vote for final approval at the next public meeting.

Bone Growth Stimulators are conditionally covered. Conditions for BGS treatment are limited to those in the Medicare National Coverage Decision as of August 2009, with the addition of ultrasonic stimulation for fresh fractures at high risk of non-union.

Medicare National Coverage is summarized below:

- *Electrical Noninvasive and Invasive Stimulator device is covered only for the following indications:*
 - ✓ Nonunion of long bone fractures (3 or more months ceased healing, minimum of 2 radiographs separated by minimum 90 days prior to start of treatment);
 - ✓ Failed fusion, where a minimum of 9 months has elapsed since the last surgery; or adjunct to fusion for patients at high risk of psuedarthrosis due to previously failed spinal fusion at the same site;
 - ✓ Congenital psuedarthrosis (noninvasive only).
- *Ultrasonic stimulator:*
 - ✓ Nonunion fractures confirmed by 2 sets of radiographs minimum 90 days apart prior to start of treatment with written physician interpretation of no clinically significant evidence of fracture healing.
- *Non Covered Indications:*
 - ✓ Nonunion of skull, vertebrae or tumor related;
 - ✓ Ultrasonic stimulators may not be used concurrently with other non-invasive osteogenic devices
 - ✓ Ultrasonic stimulators for delayed fractures

Note: The committee voted 7-2 regarding the specific coverage conditions including the Medicare National Coverage guidelines plus ultrasound for fresh fractures.

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