Vagal Nerve Stimulation for Epilepsy and Depression

Draft key questions: public comment and response

November 13, 2019

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Vagal Nerve Stimulation for Epilepsy and Depression

Draft Key Questions

Public Comment and Response

Provided by:

Center for Evidence-based Policy
Oregon Health & Science University

November 13, 2019

Responses to Public Comment on Draft Key Questions

The Center for Evidence-based Policy is an independent vendor contracted to produce evidence assessment reports for the Washington Health Technology Assessment (HTA) program. For transparency, all comments received during the public comment periods are included in this response document. Comments related to program decisions, process, or other matters not pertaining to the evidence report are acknowledged through inclusion only.

Draft key question document comments received:

- Edward J. Novotny, Jr., Head, Epilepsy Program, Seattle Children's Hospital, Professor of Neurology, University of Washington, and Chair, Professional Advisory Board of Epilepsy Foundation of Washington
- Eliza Hagen, U.S. Medical Director, and Ryan Verner, Medical Affairs and Research Manager, Neuromodulation, LivaNova
- Nicole Curtis, patient

Specific responses pertaining to submitted comments are shown in Table 1.

Table 1. Responses to Comments on Draft Key Questions for Vagal Nerve Stimulation for Epilepsy and Depression

Comments		Response
Commenter:	**Edward J. Novotny, Jr., Head, Epilepsy Program, Seattle Children's Hospital, Professor of Neurology, University of Washington, and Chair, Professional Advisory Board of Epilepsy Foundation of Washington**	
General Comments:		
As Director of the Epilepsy Program at Seattle Children's Hospital and current Chair of the Professional Advisory Board of Epilepsy Foundation of Washington, I am addressing the key questions on the use of the neurostimulation device, vagus nerve stimulator (VNS), for the treatment of epilepsy. I will focus on the use of this device in children and young adults with epilepsy.		Thank you for your comments. Please see detailed responses to your specific comments below.
Specific Comments:		
Clinical Criteria for Use of VNS	The criteria for considering VNS at Seattle Children's Hospital are: (1) medically refractory seizures; (2) adequate trials of at least 2 AEDs; (3) exclusion of nonepileptic events; and (4) ineligibility for epilepsy surgery. All people being considered for VNS are presented at our Epilepsy Surgery conference following completion of a comprehensive epilepsy evaluation to investigate alternatives to medical therapy.	Thank you for this information on the use of VNS at Seattle Children's Hospital.
Supporting Evidence	1. Alexopoulos AV, Kotagal P, Loddenkemper T, Hammel J, Bingaman WE. Long-term results with vagus nerve stimulation in children with pharmacoresistant epilepsy. Seizure. 2006;15(7):491-503. doi: 10.1016/j.seizure.2006.06.002. 2. Ben-Menachem E, Hellstrom K, Verstappen D. Analysis of direct hospital costs before and 18 months after treatment with vagus nerve stimulation therapy in 43 patients. Neurology. 2002;59(6 Suppl 4):S44-47. doi: 10.1212/wnl.59.6_suppl_4.s44. 3. Boon P, D'Have M, Van Walleghem P, et al. Direct medical costs of refractory epilepsy incurred by three different treatment modalities: a prospective assessment. Epilepsia. 2002;43(1):96-102. doi: 10.1046/j.1528-1157.2002.40100.x. 4. Englot DJ, Hassnain KH, Rolston JD, Harward SC, Sinha SR, Haglund MM. Quality-of-life metrics with vagus nerve stimulation for epilepsy from provider survey data. Epilepsy Behav. 2017;66:4-9. doi: 10.1016/j.yebeh.2016.10.005. 5. Graves N. Anticonvulsants: choices and costs. Am J Manag Care. 1998;49. https://www.ajmc.com/journals/supplement/1998/1998-09-vol4-n9suppl/sep98-1085ps463-s474. 6. Helmers SL, Griesemer DA, Dean JC, et al. Observations on the use of vagus nerve stimulation earlier in the course of pharmacoresistant epilepsy:	Thank you for your review of VNS, along with supporting references. We will check the references against our inclusion and exclusion criteria for this updated report.

Comments		Response
Commenter: Edward J. Novotny, Jr., Head, Epilepsy Program, Seattle Children's Hospital, Professor of Neurology, University of Washington, and Chair, Professional Advisory Board of Epilepsy Foundation of Washington		
	patients with seizures for six years or less. Neurologist. 2003;9(3):160-164. https://www.ncbi.nlm.nih.gov/pubmed/12808412. 7. Klinkenberg S, Aalbers MW, Vles JS, et al. Vagus nerve stimulation in children with intractable epilepsy: a randomized controlled trial. *Dev Med Child Neurol*. 2012;54(9):855-861. doi: 10.1111/j.1469-8749.2012.04305.x. 8. Morris GL, 3rd, Gloss D, Buchhalter J, Mack KJ, Nickels K, Harden C. Evidence-based guideline update: vagus nerve stimulation for the treatment of epilepsy: report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology*. 2013;81(16):1453-1459. doi: 10.1212/WNL.0b013e3182a393d1. 9. Ryvlin P, So EL, Gordon CM, et al. Long-term surveillance of SUDEP in drug-resistant epilepsy patients treated with VNS therapy. *Epilepsia*. 2018;59(3):562-572. doi: 10.1111/epi.14002.	

Abbreviation. VNS: vagal nerve stimulation.

Comments	Response
Commenter: Eliza Hagen, U.S. Medical Director, and Ryan Verner, Medical Affairs and Research Manager, Neuromodulation, LivaNova	
General Comments:	
Vagus Nerve Stimulation (VNS) Therapy has helped U.S. patients living with drug-resistant epilepsy since 1997 and difficult-to-treat depression (a.k.a treatment-resistant depression) since 2005, and continues to improve the lives of patients suffering from these chronic diseases. LivaNova PLC is pleased to offer comment on your proposed questions for the upcoming health technology assessment regarding VNS therapy for epilepsy and depression, with hopes that patients in Washington will continue to benefit from this potentially life changing therapy. Since your full technology assessment for VNS therapy in 2009 and updated literature search conducted by Hayes in 2013, investigators have continued to explore the efficacy of this therapy with an evolving understanding of efficacious dosing based on therapeutic indication and mechanism, and we are confident that a holistic review of the newly available data will yield a favorable view of the therapy.	Thank you for your comments. Please see detailed responses to your specific comments below.
We have reviewed the key questions and scope of your investigation and are pleased with the design and rigor.	

Comments		Response
Commenter: Eliza Hagen, U.S. Medical Director, and Ryan Verner, Medical Affairs and Research Manager, Neuromodulation, LivaNova		
We thank you for examining the available evidence regarding the safety and efficacy of VNS therapy once again and we look forward to participating in the process and providing comments on your draft technology assessment. Should you have any questions or need additional information, please let us know.		
Specific Comments:		
Safety	Prior to addressing comments on the key questions and scope of your investigation, we would like to comment on your "high concerns" for the safety of VNS. VNS Therapy has been implanted in over 100,000 patients worldwide and has developed a well-characterized safety record for over 25 years. The primary procedure-related adverse event is infection, which occurs in approximately 0.7-8.4% (depending on the review/hospital) of patients. Stimulation-related adverse events, such as voice alteration, coughing, pharyngitis, paresthesia, dyspnea, dyspepsia, and nausea, are mild and often diminish with time. Further, such adverse events are often limited to when the device actively delivers stimulation. The mild nature of these side-effects, in combination with the device's clinical benefit for the patient, result in the vast majority of patients (~80% in Epilepsy) electing to have their device replaced after the original device's battery is depleted.	Thank you for your comments and the summary information on the safety of VNS. We will review the adverse effects of VNS therapy as part of the updated report.
Background	Additionally, in the background of your memo you reference the decision of the Center for Medicare and Medicaid Services (CMS) to re-evaluate VNS therapy for Depression based upon the strength of the data that has emerged since the non-coverage decision in 2007. As part of that decision to cover VNS therapy for TRD through Coverage with Evidence Development, CMS also added coverage for replacement of generators/leads for those Medicare beneficiaries previously implanted with VNS for TRD. This is not part of the RECOVER clinical trial, but coverage is effective February 15th, 2019 and applies to all Medicare beneficiaries in both FFS and Medicare Advantage plans.	Thank you for your comments. This clarification has now been added to the Background section.

Comments		Response
Commenter: Eliza Hagen, U.S. Medical Director, and Ryan Verner, Medical Affairs and Research Manager, Neuromodulation, LivaNova		
Population	1. Populations. The populations studied should be consistent with FDA-approved VNS Therapy is FDA-approved indications: a. The VNS Therapy System is indicated for use as an adjunctive therapy in reducing the frequency of seizures in patients 4 years of age and older with partial onset seizures that are refractory to antiepileptic medications. i. Thus, the population for epilepsy should be modified to "Adults and children (aged 4 and older)" with epilepsy ii. The population should not exclude patients who also have status epilepticus along with other seizure types. Patients with very severe, drug-resistant epilepsy may also have status epilepticus. iii. Studies that exclusively study patients who only experience psychogenic non-epileptic seizures, aka pseudoseizures, should be excluded. As written, pseudoseizures are included. b. The VNS Therapy System is indicated for the adjunctive long-term treatment of chronic or recurrent depression for patients 18 years of age or older who are experiencing a major depressive episode and have not had an adequate response to four or more adequate antidepressant treatments. i. Thus, the population for TRD should be modified to clearly state the definition of TRD that is consistent with the VNS Therapy indications, e.g., patients suffering from major depressive disorder	Thank you for your comments. a. We have not restricted the review to any specific type of epilepsy. However, we will note any studies included in the updated review that evaluate the use of VNS for nonFDA-approved indications (other than status epilepticus alone). i. See above ii. We will include studies in people with epilepsy who also have status epilepticus, but we will exclude studies where the focus of VNS treatment is only for status epilepticus. iii. We did plan to exclude studies in people with psychogenic non-epileptic seizures however, we have amended the text to make this more explicit. b. We have restricted the review to treatment-resistant depression, regardless of how this is defined in the studies. However, we will note any studies included in the updated review that evaluate the use of VNS for nonFDA-approved indications.
Population	4. Please note that the clinical definition of TRD differs slightly from our indication for use. The clinical definition of TRD requires failures of 2 sufficient courses of adequately tolerated therapies. Our indication for VNS Therapy in Depression is for adjunctive longterm treatment of chronic or recurrent depression patients who have failed 4 or more therapies.	Thank you for your comment. We have restricted the review to treatment-resistant depression, regardless of how this is defined in the studies. However, we will note any studies included in the updated review that evaluate the use of VNS for nonFDA-approved indications.
Population	6. For our CMS-approved trial in depression, we are excluding patients with acute suicidal risk or	Thank you for your comment.

Comments		Response
Commenter: Eliza Hagen, U.S. Medical Director, and Ryan Verner, Medical Affairs and Research Manager, Neuromodulation, LivaNova		
	recent suicide attempt (<6 months), active primary diagnosis of obsessive-compulsive disorder, eating disorder, or post-traumatic stress disorder, and presence or history of rapid-cycling bipolar disorder, personality disorder, dementia, or psychiatric disorder. Thus, the study population for VNS in Depression should reflect these exclusions. We note that this is consistent with other non-pharmacological treatments, such as rTMS, whose safety and effectiveness has not been established in these populations.	We acknowledge that other studies may have different exclusion criteria, and these will be reported in detail in the evidence tables. We will also note how the studies included in the updated review vary in their patient populations. We will also note any studies included in the updated review whose populations differ from those meeting FDA-approved indications.
Intervention	5. Transcutaneous VNS systems are not FDA approved or cleared for use in Epilepsy or Depression and should not be included in the scope of this study.	Thank you for your comment. We do note that the use of transcutaneous VNS systems is not FDA-approved and this will be explicitly noted in the updated report.
Comparator(s)	2. As such, the assessment of VNS monotherapy, as included in your current scope, would assess off-label application of the therapy and potentially make such analysis irrelevant. We would recommend that such comparisons are removed from the proposal.	Thank you for your comment. We have not restricted the review to FDA-approved indications alone. However, we will note any studies included in the updated review that evaluate the use of VNS for nonFDA-approved indications (e.g., VNS monotherapy).
Comparator(s)	3. The FDA approved indication for VNS therapy in depression is broader than the proposed definition used in the inclusion criteria. VNS Therapy must be an adjunctive therapy per the labeling, but it can be delivered with any other non-contraindicated treatment-as-usual (TAU) therapy, not just pharmacotherapies. Thus, comparisons of the therapy should always be considered as VNS + TAU versus TAU alone	Thank you for your comment. We have amended this in line with your suggestion.
Comparator(s)	7. Comparator studies: a. Epilepsy i. Should explicitly include Responsive Neurostimulation (RNS) and Deep Brain Stimulation (DBS), as these are the only other device-based therapies indicated for drug-resistant epilepsy. b. Depression i. Patient population should be carefully selected to approximate the patient	Thank you for your comments. a. We will include any studies comparing VNS with any other form of brain stimulation (invasive or noninvasive), including RNS and DBS. We will note any comparator that is not FDA-approved for epilepsy in the updated report. b. We have restricted the review to treatment-resistant depression,

Comments		Response
Commenter: Eliza Hagen, U.S. Medical Director, and Ryan Verner, Medical Affairs and Research Manager, Neuromodulation, LivaNova		
	population in studies of VNS Therapy. VNS Therapy is indicated after 4 or more treatment failures. In the D-23 study patients had failed nearly 9 treatments, in other words were significantly more severe and refractory than the clinical definition of TRD which is 2 or more failures. Thus, patient inclusion criteria will be important so as not to introduce bias in any comparison made. c. Studies of comparator therapies can be quite short in duration (<6 weeks). Direct comparison of other therapies with VNS on the same timeline may result in an opinion that VNS therapy is less effective or ineffective. Please note that VNS Therapy requires a post-operative recovery period and titration period, and evidence suggests that the anti-convulsive and anti-depressive benefit builds with time and is quite durable. Based on available data, we recommend at least a 1 year follow-up for comparison studies.	regardless of how this is defined in the studies. However, we will note any studies included in the updated review that evaluate the use of VNS for nonFDA-approved indications. We will also explore any differences in effectiveness and harms by patient characteristics (e.g., severity of depression). c. We have not restricted the review by study duration. We will explore any differences in effectiveness and harms by study duration, in order to address key question 3 for epilepsy and depression.
Outcome(s)	8. Outcomes: a. Epilepsy i. Please add Seizure Severity (SSQ) and Duration of Seizure as efficacy outcomes b. Depression i. Please specify which depression severity scale(s) you intend to use to clarify what remission means. ii. Please include duration of response, duration of remission, long-term compliance with therapy, suicidality, and overall mortality as secondary outcomes as these have emerged in the literature as important considerations in the evaluation of VNS therapy. c. Health benefits outcomes should also consider the high burden these severely refractory patients place on the healthcare system. This is especially true in cases of difficult-to-treat depression. Further, given that many severely refractory patients don't have access or are not quickly referred for surgical or device-based therapies, consideration should be	Thank you for your comments. a. We have added in the outcomes of seizure severity and duration as suggested. b. Studies may use different validated tools to assess depression severity. We will therefore include any measure of depression severity, if assessed using a validated tool. We have also added in the suggested outcomes of duration of responses and remission, compliance, suicidality, and mortality, if assessed by a validated tool or method. c. We will capture issues of resource use when addressing key question 4 for epilepsy and depression

Comments		Response
Commenter: Eliza Hagen, U.S. Medical Director, and Ryan Verner, Medical Affairs and Research Manager, Neuromodulation, LivaNova		
	made of the economic impact of an untreated patient	
Outcome(s)	9. Assessment of harms should be fair and balanced. If harms are assessed for VNS Therapy, harms associated with other similar therapies should also be examined.	Thank you for your comment. We will report adverse events for both the intervention of VNS and the comparator interventions.
Outcome(s)	10. We would prefer a distinction between direct "harms" and "side-effects". We feel that listing intermittent voice alteration or coughing as a "harm" may be disingenuous to the severity of the event.	Thank you for your comment. We use the term 'direct-harm' to describe effects that are directly related to the intervention or comparator in the included studies. This could include mild effects, such as coughing, or more serious effects, such as infection. We will discuss the impact of the full range of adverse effects in the updated review.
Sources	11. Sources: a. Clinicaltrials.gov should be included as a source for efficacy and harms data as data are presented in accordance with the CONSORT statement and the protocol and reviewed by trained personnel at the Department of Health and Human Services. b. Labeling approved by FDA as part of a PMA should be considered as a source of data.	Thank you for your comments. a. We will report efficacy and harm data as reported in the published literature. We will search Clinicaltrials.gov for ongoing studies and studies that have recently completed. b. We will not use the PMA report as a source of effectiveness or harms, but we will report efficacy and harm data from the published literature. However, we will include information on the FDA-approved indications (as specified in the labelling documentation).

Abbreviations. PMA: pre-marketing approval; rTMS: repetitive transcranial magnetic stimulation; VNS: vagal nerve stimulation.

Comments	Response
Commenter: Nicole Curtis	
General Comments:	
On 11/5/2018 I was under " conscious sedation" for a very minor procedure in a hospital....because I refused to have it done in office. At the end of the biopsy, I suddenly went bradycardic and then went into Asystole, full code blue. I have had nothing but road blocks and denials in trying to determine cause of my SCA. The VNS company IGNORED request from the anesthesiologist to come to the ICU and interrogate the device. They ignored my primary doctors. I had to date more than 6 months and spend a days travel and more expense to go to down town Seattle to Swedish Cherry Hill. The VNS tech's would NOT EVEN MAKE EYE CONTACT WITH ME! I happen to know about the recalls on model 106. I have model 102. I got mine back in Illinois. Once I moved out here...I found follow up care impossible. I am still seeking answers. Was my SCA related to VNS?.... was is long QTC syndrome?...was it anaphylaxis??? I have seen 3 specialists....AND NONE OF THEM DID ANY TESTS...ONE DID A MINOR EXAM. each sending me back to the other. I am the proverbial HOT POTATO! I am more than disappointed in the "healthcare" i have received in the Washington state area.	Thank you for your comments.

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To whom it may concern:

Vagus Nerve Stimulation (VNS) Therapy® has helped U.S. patients living with drug-resistant epilepsy since 1997 and difficult-to-treat depression (a.k.a treatment-resistant depression) since 2005, and continues to improve the lives of patients suffering from these chronic diseases. LivaNova PLC is pleased to offer comment on your proposed questions for the upcoming health technology assessment regarding VNS therapy for epilepsy and depression, with hopes that patients in Washington will continue to benefit from this potentially life changing therapy. Since your full technology assessment for VNS therapy in 2009 and updated literature search conducted by Hayes in 2013, investigators have continued to explore the efficacy of this therapy with an evolving understanding of efficacious dosing based on therapeutic indication and mechanism, and we are confident that a holistic review of the newly available data will yield a favorable view of the therapy.

Prior to addressing comments on the key questions and scope of your investigation, we would like to comment on your "high concerns" for the safety of VNS. VNS Therapy has been implanted in over 100,000 patients worldwide and has developed a well-characterized safety record for over 25 years. The primary procedure-related adverse event is infection, which occurs in approximately 0.7-8.4% (depending on the review/hospital) of patients. Stimulation-related adverse events, such as voice alteration, coughing, pharyngitis, paresthesia, dyspnea, dyspepsia, and nausea, are mild and often diminish with time. Further, such adverse events are often limited to when the device actively delivers stimulation. The mild nature of these side-effects, in combination with the device's clinical benefit for the patient, result in the vast majority of patients (~80% in Epilepsy) electing to have their device replaced after the original device's battery is depleted.

Additionally, in the background of your memo you reference the decision of the Center for Medicare and Medicaid Services (CMS) to re-evaluate VNS therapy for Depression based upon the strength of the data that has emerged since the non-coverage decision in 2007. As part of that decision to cover VNS therapy for TRD through Coverage with Evidence Development, CMS also added coverage for replacement of generators/leads for those Medicare beneficiaries previously implanted with VNS for TRD. This is not part of the RECOVER clinical trial, but coverage is effective February 15th, 2019 and applies to all Medicare beneficiaries in both FFS and Medicare Advantage plans.

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We have reviewed the key questions and scope of your investigation and are pleased with the design and rigor. In order to clarify some points and to help identify additional comparators and outcomes for VNS Therapy, we have the following comments:

1) Populations:
   The populations studied should be consistent with FDA-approved VNS Therapy is FDA-approved indications:
   a. The VNS Therapy System is indicated for use as an ***adjunctive*** therapy in reducing the frequency of seizures in patients 4 years of age and older with partial onset seizures that are refractory to antiepileptic medications.
      i. Thus, the population for epilepsy should be modified to "Adults and children (aged 4 and older)" with epilepsy
      ii. The population should not exclude patients who also have status epilepticus along with other seizure types. Patients with very severe, drug-resistant epilepsy may also have status epilepticus.
      iii. Studies that exclusively study patients who **only** experience psychogenic non-epileptic seizures, aka pseudoseizures, should be excluded. As written, pseudoseizures are included.

   b. The VNS Therapy System is indicated for the ***adjunctive*** long-term treatment of chronic or recurrent depression for patients 18 years of age or older who are experiencing a major depressive episode and have not had an adequate response to four or more adequate antidepressant treatments.
      i. Thus, the population for TRD should be modified to clearly state the definition of TRD that is consistent with the VNS Therapy indications, e.g., patients suffering from major depressive disorder

2) As such, the assessment of VNS monotherapy, as included in your current scope, would assess off-label application of the therapy and potentially make such analysis irrelevant. We would recommend that such comparisons are removed from the proposal.

3) The FDA approved indication for VNS therapy in depression is broader than the proposed definition used in the inclusion criteria. VNS Therapy must be an adjunctive therapy per the labeling, but it can be delivered with any other non-contraindicated treatment-as-usual (TAU) therapy, *not just pharmacotherapies*. Thus, comparisons of the therapy should always be considered as VNS + TAU versus TAU alone.

4) Please note that the clinical definition of TRD differs slightly from our indication for use. The clinical definition of TRD requires failures of 2 sufficient courses of adequately tolerated therapies. Our indication for VNS Therapy in Depression is for ***adjunctive*** long-term treatment of chronic or recurrent depression patients who have failed 4 or more therapies.

5) Transcutaneous VNS systems are not FDA approved or cleared for use in Epilepsy or Depression and should not be included in the scope of this study.

6) For our CMS-approved trial in depression, we are excluding patients with acute suicidal risk or recent suicide attempt (<6 months), active primary diagnosis of obsessive-compulsive disorder, eating disorder, or post-traumatic stress disorder, and presence or history of rapid-cycling bipolar disorder, personality disorder, dementia, or psychiatric disorder. Thus, the study population for VNS in Depression should reflect these exclusions. We note that this is consistent with other non-pharmacological treatments, such as rTMS, whose safety and effectiveness has not been established in these populations.

7) Comparator studies:
    a. Epilepsy
        i. Should explicitly include Responsive Neurostimulation (RNS) and Deep Brain Stimulation (DBS), as these are the only other device-based therapies indicated for drug-resistant epilepsy.
    b. Depression
        i. Patient population should be carefully selected to approximate the patient population in studies of VNS Therapy. VNS Therapy is indicated after 4 or more treatment failures. In the D-23 study patients had failed nearly 9

treatments, in other words were significantly more severe and refractory than the clinical definition of TRD which is 2 or more failures. Thus, patient inclusion criteria will be important so as not to introduce bias in any comparison made.

c. Studies of comparator therapies can be quite short in duration (<6 weeks). Direct comparison of other therapies with VNS *on the same timeline* may result in an opinion that VNS therapy is less effective or ineffective. Please note that VNS Therapy requires a post-operative recovery period and titration period, and evidence suggests that the anti-convulsive and anti-depressive benefit builds with time and is quite durable. Based on available data, we recommend at least a 1 year follow-up for comparison studies.

8) Outcomes:
   a. Epilepsy
      i. Please add Seizure Severity (SSQ) and Duration of Seizure as efficacy outcomes
   b. Depression
      i. Please specify which depression severity scale(s) you intend to use to clarify what remission means.
      ii. Please include duration of response, duration of remission, long-term compliance with therapy, suicidality, and overall mortality as secondary outcomes as these have emerged in the literature as important considerations in the evaluation of VNS therapy.
   c. Health benefits outcomes should also consider the high burden these severely refractory patients place on the healthcare system. This is especially true in cases of difficult-to-treat depression. Further, given that many severely refractory patients don't have access or are not quickly referred for surgical or device-based therapies, consideration should be made of the economic impact of an untreated patient.

9) Assessment of harms should be fair and balanced. If harms are assessed for VNS Therapy, harms associated with other similar therapies should also be examined.

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10) We would prefer a distinction between direct "harms" and "side-effects". We feel that listing intermittent voice alteration or coughing as a "harm" may be disingenuous to the severity of the event.

11) Sources:
    a. Clinicaltrials.gov should be included as a source for efficacy and harms data as data are presented in accordance with the CONSORT statement and the protocol and reviewed by trained personnel at the Department of Health and Human Services.
    b. Labeling approved by FDA as part of a PMA should be considered as a source of data.

We thank you for examining the available evidence regarding the safety and efficacy of VNS therapy once again and we look forward to participating in the process and providing comments on your draft technology assessment. Should you have any questions or need additional information, please let us know.

Sincerely,

[redacted]

Eliza Hagen, M.D., M.B.A.
U.S. Medical Director, Neuromodulation

[redacted]

Ryan Verner, Ph.D.
Medical Affairs and Research Manager, Global Medical Affairs

Enclosed:
Copy of the CMS Decision Memo
VNS Therapy Safety Information

Proposed Decision Memo for Vagus Nerve Stimulation (VNS) for Treatment Resistant Depression (TRD) (CAG-00313R2)

Links in PDF documents are not guaranteed to work. To follow a web link, please use the MCD Website.

Decision Summary

CMS is proposing changes to the vagus nerve stimulation (VNS) NCD (160.18) for VNS for treatment resistant depression (TRD) that would expand Medicare coverage. The scope of this reconsideration is limited to VNS for TRD.

A. The Centers for Medicare & Medicaid Services (CMS) proposes to cover FDA approved vagus nerve stimulation (VNS) devices for treatment resistant depression (TRD) through Coverage with Evidence Development (CED) when offered in a CMS approved, double-blind, randomized, placebo-controlled trial with a follow-up duration of at least one year with the possibility of extending the study to a prospective longitudinal study when the CMS approved, double-blind, randomized placebo-controlled trial has completed enrollment, and there are positive interim primary endpoint findings.

B. Covered Indications

Each study must be approved by CMS and as a fully-described, written part of its protocol, must address if VNS improves health outcomes for individuals with TRD through the following research questions below. The details of the prospective longitudinal study must be described in the original protocol for the double-blind, randomized, placebo-controlled trial.

Primary Outcomes:

- What is the rate of remission score achievement per subject month (four weeks) of follow-up as measured by a guideline recommended depression scale assessment tool?
- What is the time from treatment until remission scores are first achieved for a consecutive two-month (eight-week) duration?
- Of those patients that achieved remission scores for a consecutive two-month period, how many consecutive months were these remission scores maintained?
- What are the patient variables associated with successful treatment of TRD with VNS?
- What are the observed harms?

Secondary Outcomes:

- What are the changes in disability and quality of life?
- What are the changes in general psychiatric status?
- What are the changes in suicidality?

Patient Criteria

- The following criteria must be used to identify patients demonstrating TRD:
  - The patient must be in a major depressive disorder (MDD) episode for ≥ two years or have had at least four episodes of MDD, including the current episode. In order to confirm the patient has MDD, accepted diagnostic criteria from the most current edition of the Diagnostic and Statistical Manual for Mental Disorder (DSM) and a structured clinical assessment are to be used.
  - The patient's depressive illness meets a minimum criterion of four prior failed treatments of adequate dose and duration as measured by a tool designed for this purpose.
  - The patient is experiencing a major depressive episode (MDE) as measured by a guideline recommended depression scale assessment tool on two visits, within a 45-day span prior to implantation of the VNS device.
- Patients must not have had a substantial response to at least six weeks of psychotherapy during any

MDE.

- Patients must maintain a stable medication regimen for at least four weeks before device implantation.
- Patients must not have:
  - Current or lifetime history of atypical or psychotic features in any MDE;
  - Current or lifetime history of any non-mood psychotic disorder (e.g., schizophrenia);
  - Current or lifetime history of bipolar disorder;
  - Current secondary diagnosis of delirium, dementia, amnesia, or other cognitive disorder;
  - Current suicidal intent; or
  - Treatment with another investigational device or investigational drugs.
- Individuals who receive placebo VNS will be offered active VNS at the end of the trial.

In addition, CMS will review studies to determine if they meet the 13 criteria listed below. If CMS determines that they meet these criteria, the study will be posted on CMS' CED website (https://www.cms.gov/Medicare/Coverage/Coverage-with-Evidence-Development/index.html).

a. The principal purpose of the study is to test whether the item or service meaningfully improves health outcomes of affected beneficiaries who are represented by the enrolled subjects.
b. The rationale for the study is well supported by available scientific and medical evidence.
c. The study results are not anticipated to unjustifiably duplicate existing knowledge.
d. The study design is methodologically appropriate and the anticipated number of enrolled subjects is sufficient to answer the research question(s) being asked in the National Coverage Determination.
e. The study is sponsored by an organization or individual capable of completing it successfully.
f. The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found in the Code of Federal Regulations (CFR) at 45 CFR Part 46. If a study is regulated by the Food and Drug Administration (FDA), it is also in compliance with 21 CFR Parts 50 and 56. In addition, to further enhance the protection of human subjects in studies conducted under CED, the study must provide and obtain meaningful informed consent from patients regarding the risks associated with the study items and/or services, and the use and eventual disposition of the collected data.
g. All aspects of the study are conducted according to appropriate standards of scientific integrity.
h. The study has a written protocol that clearly demonstrates adherence to the standards listed here as Medicare requirements.
i. The study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Such studies may meet this requirement only if the disease or condition being studied is life threatening as defined in 21 CFR §312.81(a) and the patient has no other viable treatment options.
j. The clinical research studies and registries are registered on the www.ClinicalTrials.gov website by the principal sponsor/investigator prior to the enrollment of the first study subject. Registries are also registered in the Agency for Healthcare Quality (AHRQ) Registry of Patient Registries (RoPR).
k. The research study protocol specifies the method and timing of public release of all prespecified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early. The results must be made public within 12 months of the study's primary completion date, which is the date the final subject had final data collection for the primary endpoint, even if the trial does not achieve its primary aim. The results must include number started/completed, summary results for primary and secondary outcome measures, statistical analyses, and adverse events. Final results must be reported in a publicly accessibly manner; either in a peer-reviewed scientific journal (in print or on-line), in an on-line publicly accessible registry dedicated to the dissemination of clinical trial information such as ClinicalTrials.gov, or in journals willing to publish in abbreviated format (e.g., for studies with negative or incomplete results).
l. The study protocol must explicitly discuss beneficiary subpopulations affected by the item or service under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria effect enrollment of these populations, and a plan for the retention and reporting of said populations in the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must

discuss why these criteria are necessary.

m. The study protocol explicitly discusses how the results are or are not expected to be generalizable to affected beneficiary subpopulations. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicaid eligibility.

Consistent with section 1142 of the Act, the Agency for Healthcare Research and Quality (AHRQ) supports clinical research studies that CMS determines meet the above-listed standards and address the above-listed research questions.

The principal investigator must submit the complete study protocol, identify the relevant CMS research questions that will be addressed and cite the location of the detailed analysis plan for those questions in the protocol, plus provide a statement addressing how the study satisfies each of the standards of scientific integrity (a. through m. listed above), as well as the investigator's contact information, to the address below. The information will be reviewed, and approved studies will be identified on the CMS website.

Director, Coverage and Analysis Group
Centers for Medicare & Medicaid Services (CMS)
7500 Security Blvd., Mail Stop S3-02-01
Baltimore, MD 21244-1850

C. Nationally Non-Covered Indications

VNS is non-covered for the treatment of TRD when furnished outside of a CMS approved CED study.

All other indications of VNS for the treatment of depression are nationally non-covered.

D. Other

Patients implanted with a VNS device for TRD may receive a VNS device replacement if it is required due to the end of battery life, or any other device-related malfunction.

See Appendix B for the proposed manual language.

CMS is seeking comments on our proposed decision. We will respond to public comments in a final decision memorandum, as required by §1862(l)(3) of the Social Security Act (the Act).

ProposedDecision Memo

TO: Administrative File: CAG-00313R2

FROM: Tamara Syrek Jensen, JD
Director, Coverage and Analysis Group

Joseph Chin, MD, MS
Deputy Director, Coverage and Analysis Group

Lori Ashby, MA
Director, Division of Policy and Evidence Review

Daniel Arthur Caños, PhD, MPH
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Epidemiologist

SUBJECT: Proposed National Coverage Determination for Vagus Nerve Stimulation (VNS) for Treatment Resistant Depression (TRD) Reconsideration

DATE: November 19, 2018

I. Proposed Decision

CMS is proposing changes to the vagus nerve stimulation (VNS) NCD (160.18) for VNS for treatment resistant depression (TRD) that would expand Medicare coverage. The scope of this reconsideration is limited to VNS for TRD.

A. The Centers for Medicare & Medicaid Services (CMS) proposes to cover FDA approved vagus nerve stimulation (VNS) devices for treatment resistant depression (TRD) through Coverage with Evidence Development (CED) when offered in a CMS approved, double-blind, randomized, placebo-controlled trial with a follow-up duration of at least one year with the possibility of extending the study to a prospective longitudinal study when the CMS approved, double-blind, randomized placebo-controlled trial has completed enrollment, and there are positive interim primary endpoint findings.

B. Covered Indications

Each study must be approved by CMS and as a fully-described, written part of its protocol, must address if VNS improves health outcomes for individuals with TRD through the following research questions below. The details of the prospective longitudinal study must be described in the original protocol for the double-blind, randomized, placebo-controlled trial.

Primary Outcomes:

- What is the rate of remission score achievement per subject month (four weeks) of follow-up as measured by a guideline recommended depression scale assessment tool?
- What is the time from treatment until remission scores are first achieved for a consecutive two-month (eight-week) duration?
- Of those patients that achieved remission scores for a consecutive two-month period, how many consecutive months were these remission scores maintained?
- What are the patient variables associated with successful treatment of TRD with VNS?
- What are the observed harms?

Secondary Outcomes:

- What are the changes in disability and quality of life?
- What are the changes in general psychiatric status?
- What are the changes in suicidality?

Patient Criteria

- The following criteria must be used to identify patients demonstrating TRD:
  - The patient must be in a major depressive disorder (MDD) episode for ≥ two years or have had at least four episodes of MDD, including the current episode. In order to confirm the patient has MDD, accepted diagnostic criteria from the most current edition of the Diagnostic and Statistical Manual for Mental Disorder (DSM) and a structured clinical assessment are to be used.

- The patient's depressive illness meets a minimum criterion of four prior failed treatments of adequate dose and duration as measured by a tool designed for this purpose.
- The patient is experiencing a major depressive episode (MDE) as measured by a guideline recommended depression scale assessment tool on two visits, within a 45-day span prior to implantation of the VNS device.

- Patients must not have had a substantial response to at least six weeks of psychotherapy during any MDE.
- Patients must maintain a stable medication regimen for at least four weeks before device implantation.
- Patients must not have:
  - Current or lifetime history of atypical or psychotic features in any MDE;
  - Current or lifetime history of any non-mood psychotic disorder (e.g., schizophrenia);
  - Current or lifetime history of bipolar disorder;
  - Current secondary diagnosis of delirium, dementia, amnesia, or other cognitive disorder;
  - Current suicidal intent; or
  - Treatment with another investigational device or investigational drugs.
- Individuals who receive placebo VNS will be offered active VNS at the end of the trial.

In addition, CMS will review studies to determine if they meet the 13 criteria listed below. If CMS determines that they meet these criteria, the study will be posted on CMS' CED website (https://www.cms.gov/Medicare/Coverage/Coverage-with-Evidence-Development/index.html).

a. The principal purpose of the study is to test whether the item or service meaningfully improves health outcomes of affected beneficiaries who are represented by the enrolled subjects.
b. The rationale for the study is well supported by available scientific and medical evidence.
c. The study results are not anticipated to unjustifiably duplicate existing knowledge.
d. The study design is methodologically appropriate and the anticipated number of enrolled subjects is sufficient to answer the research question(s) being asked in the National Coverage Determination.
e. The study is sponsored by an organization or individual capable of completing it successfully.
f. The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found in the Code of Federal Regulations (CFR) at 45 CFR Part 46. If a study is regulated by the Food and Drug Administration (FDA), it is also in compliance with 21 CFR Parts 50 and 56. In addition, to further enhance the protection of human subjects in studies conducted under CED, the study must provide and obtain meaningful informed consent from patients regarding the risks associated with the study items and/or services, and the use and eventual disposition of the collected data.
g. All aspects of the study are conducted according to appropriate standards of scientific integrity.
h. The study has a written protocol that clearly demonstrates adherence to the standards listed here as Medicare requirements.
i. The study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Such studies may meet this requirement only if the disease or condition being studied is life threatening as defined in 21 CFR §312.81(a) and the patient has no other viable treatment options.
j. The clinical research studies and registries are registered on the www.ClinicalTrials.gov website by the principal sponsor/investigator prior to the enrollment of the first study subject. Registries are also registered in the Agency for Healthcare Quality (AHRQ) Registry of Patient Registries (RoPR).
k. The research study protocol specifies the method and timing of public release of all prespecified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early. The results must be made public within 12 months of the study's primary completion date, which is the date the final subject had final data collection for the primary endpoint, even if the trial does not achieve its primary aim. The results must include number started/completed, summary results for primary and secondary outcome measures, statistical analyses, and adverse events. Final results must be reported in a publicly accessibly manner; either in a peer-reviewed scientific journal (in print or on-line), in an on-line publicly accessible registry dedicated to the dissemination of clinical trial information such as ClinicalTrials.gov, or in journals willing to publish in abbreviated format (e.g., for studies with

negative or incomplete results).

l. The study protocol must explicitly discuss beneficiary subpopulations affected by the item or service under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria effect enrollment of these populations, and a plan for the retention and reporting of said populations in the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary.

m. The study protocol explicitly discusses how the results are or are not expected to be generalizable to affected beneficiary subpopulations. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicaid eligibility.

Consistent with section 1142 of the Act, the Agency for Healthcare Research and Quality (AHRQ) supports clinical research studies that CMS determines meet the above-listed standards and address the above-listed research questions.

The principal investigator must submit the complete study protocol, identify the relevant CMS research questions that will be addressed and cite the location of the detailed analysis plan for those questions in the protocol, plus provide a statement addressing how the study satisfies each of the standards of scientific integrity (a. through m. listed above), as well as the investigator's contact information, to the address below. The information will be reviewed, and approved studies will be identified on the CMS website.

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All other indications of VNS for the treatment of depression are nationally non-covered.

D. Other

Patients implanted with a VNS device for TRD may receive a VNS device replacement if it is required due to the end of battery life, or any other device-related malfunction.

See Appendix B for the proposed manual language.

CMS is seeking comments on our proposed decision. We will respond to public comments in a final decision memorandum, as required by §1862(l)(3) of the Social Security Act (the Act).

II. Background

Throughout this document we use numerous acronyms, some of which are not defined as they are presented in direct quotations. Please find below a list of these acronyms and corresponding full terminology:

AANS - American Association of Neurological Surgeons
AFSP - American Foundation for Suicide Prevention
AHRQ - Agency for Healthcare Research and Quality
APA - American Psychiatric Association
ASSFN - American Society for Stereotactic and Functional Neurosurgery

AOS - Assessment of Suicidality
ATHF - Antidepressant Treatment History Form
BP - Bipolar disorder
CDRH - Center for Devices and Radiological Health (CDRH)
CGI - Clinical Global Impression Scale
CI - Confidence interval
CMS - Centers for Medicare & Medicaid Services
CNS - Congress of Neurological Surgeons
DoD - Department of Defense
DSM-4 - The Diagnostic and Statistical Manual for Mental Disorder (Fourth Edition)
DSM-5 - The Diagnostic and Statistical Manual for Mental Disorder (Fifth Edition)
ECT - Electroconvulsive therapy
FDA - Food and Drug Administration
HAMD, HAM-D, HDRS, HRSD: Hamilton Depression Rating Scale or Hamilton Rating Scale for Depression
IDS-C - Inventory of Depressive Symptomatology - Clinician Administered
IDS-SR - Inventory of Depressive Symptomatology - Self-report
ITT - Intent to treat
MAC – Medicare Administrative Contractor
MADRS - Montgomery-Asberg Depression Rating Scale
MDD - Major Depressive Disorder
MDE - Major Depressive Episode
MDMA - Medical Device Manufacturers Association
MGH-s - Massachusetts General Hospital Staging Model
MHA - Mental Health America
MINI - Mini-International Neuropsychiatric Interview
MSM - Maudsley Staging Model
NCA - National Coverage Analysis
NCD - National Coverage Determination
PMA - Premarket approval
QIDS - Quick Inventory of Depressive Symptomatology
Q-LES-Q-SF - Quality of Life Enjoyment and Satisfaction Questionnaire Short Form
QoL - Quality of Life
SD - Standard deviation
TRSM - Thase and Rush Staging Model
TAU - Treatment as usual
TA - Technology Assessment
US - United States
VA - Veterans Affairs
VNS - Vagus nerve stimulation
WHODAS - World Health Organization Disability Assessment Schedule

Depression/Treatment Resistant Depression

Depression refers to a range of disorders which have in common the presence of sad, empty or irritable mood, accompanied by cognitive and somatic changes that significantly affect an individual's ability to function (American Psychiatric Association, 2013). Depression is a very common mental illness with a highly recurrent nature, affecting approximately 350 million people around the world (Sheehan, Nagakome, Asami, Pappadopulos & Boucher, 2017). The past year prevalence in 2016 demonstrates that an estimated 16.2 million adults aged 18 or older in the United States experienced at least one major depressive episode (MDE). This number represents 6.7% of all US adults (Major Depression, National Institute of Mental Health).

Depression commonly starts at a younger age; adults aged 18 to 25 are 60% more likely to experience depression than those older than 50 years of age. Women are 70% more likely to experience depression than men (VA/DoD Clinical Practice Guideline for the Management of Major Depressive Disorder, 2016).

The majority of depressive episodes are part of major depressive disorder (MDD), experienced by approximately 13 million people in this country (Gaynes et al., 2018). The prevalence of MDD in the United States in those 18 to 29 years of age is three fold higher than the prevalence in individuals 60 and older (American Psychiatric Association, 2013). There may however be a poorer prognosis for MDD in older patients, as compared to those who are younger (Schaakxs et al., 2018).

Depression is well known to be a major risk factor for suicide. Men are more likely to complete suicide than women, but women are more likely to attempt suicide (American Psychiatric Association, 2013). In 2016, the highest rate of suicide deaths among women was found between those aged 45 – 54; the highest rate in men occurred in those aged 65 and older (Suicide, National Institute of Mental Health). Between 1999 and 2016, suicide rates in most states of the United States rose sharply, with 25 states experiencing increases greater than 30% (Stone et al., 2018).

The course of MDD is variable. Some individuals demonstrate few or no symptoms for many years between discrete episodes of the disease, while others rarely, if ever, experience remission (two or more months with no symptoms or only one or two symptoms to no more than a mild degree). It is important to identify patients who present with symptoms of recent onset from those who present during an exacerbation of chronic depressive illness; the presence of chronicity increases the possibility of underlying personality, anxiety and substance use disorders and decreases the chance that treatment will accomplish full symptom resolution (American Psychiatric Association, 2013).

Recovery typically begins within three months of onset for two of five individuals with MDD and within one year for four of five individuals. The risk of recurrence becomes less likely as the duration of remission lengthens. Recent onset is a strong determinant of the likelihood of near-term recovery. In addition to the duration of the episode, lower recovery rates are associated with psychotic characteristics, prominent anxiety, personality disorders and symptom severity. Risk of recurrence is higher in those individuals who are younger, whose preceding episode was severe, who have persisting depressive symptoms in remission, and who have already experienced multiple episodes of the disease (American Psychiatric Association, 2013).

The criteria for the diagnosis of MDD according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) require that five (or more) of the following symptoms be present during the same two week period and represent a change from previous functioning:

- Depressed mood most of the day, nearly every day;
- Markedly diminished interest or pleasure in all, or almost all activities, most of the day, nearly every day;
- Significant weight loss or gain, or decrease or increase in appetite nearly every day;
- Insomnia or hypersomnia nearly every day;
- Observable psychomotor agitation or retardation nearly every day;
- Fatigue or loss of energy nearly every day;
- Feelings of worthlessness or excessive or inappropriate guilt nearly every day;
- Diminished ability to think or concentrate or indecisiveness nearly every day;
- Recurrent thoughts of death, recurrent suicidal ideation without a specific plan or a suicide attempt or a specific plan for committing suicide.

The above symptoms should cause clinically significant distress or impairment in social, occupational, or other important areas of functioning and not be attributable to the physiologic effects of a substance or to another medical

condition. At least one of the symptoms should be either depressed mood or loss of interest or pleasure. The occurrence of the episode should not be better explained by an illness on the schizophrenia spectrum or other psychotic disorder. Also, under most circumstances, there must never have been a manic or hypomanic episode (American Psychiatric Association, 2013).

Only one half of the 13 million individuals in the United States with MDD seek help for this condition and only one in five of those individuals receive adequate acute-phase treatment. Even for patients receiving such treatment, only 30% reach full recovery or remission. Of the remaining 70% of patients with MDD, about 20% will respond without remission; 50% will not respond at all (Gaynes et al., 2018).

Notably, a substantial proportion of individuals who are initially thought to have MDD are subsequently diagnosed with a bipolar condition as several bipolar disorders may begin with one or more depressive episodes (American Psychiatric Association, 2013). Bipolar disorder affects 2.6 percent of the U.S. adult population each year. Much like MDD, bipolar depression can be difficult to treat. More than 30 percent of those experiencing bipolar disorder and receiving treatment do not experience sustained remission of depressive symptoms. Even among those who do achieve recovery for lengthy periods, depressive relapses are common; more than 20 percent of individuals with successfully treated bipolar depression will experience a depressive relapse within a year (Gaynes et al., 2018).

Patients with residual depressive symptoms despite treatment may be demonstrating treatment resistant depression (TRD). A universally accepted definition of treatment resistant depression has yet to be achieved (Al-Harbi, 2012; De Carlo, Calati, & Seretti, 2016; Gaynes et al., 2018; McIntyre et al., 2014; Medicare Evidence Development & Coverage Advisory Committee convened April 27, 2016; Milev et al., 2016).

Outcomes for TRD

Various types of outcome measures exist to assess the success or failure of treatment in clinical studies of TRD. They broadly include depression-specific measures, general psychiatric status measures, and functional scales (Gaynes et al., 2018).

The desired outcome of the depression disease process is that of remission, defined in various ways, e.g., as either minimal residual symptoms measured by a ≥ 80% reduction in symptomatology using an accepted rating scale or as an absolute cut off score on an outcome measure (Culpepper, Ruskin, & Stahl, 2015); as a complete recovery as measured by a score on a depressive severity instrument below a threshold, using a standardized and validated measure (Gaynes et al., 2018); as a ≥ 50% decrease in a severity rating scale score and a very low final score indicating minimum residual symptoms (Carreno & Frazer, 2017); or a period of two or more months with no symptoms, or only one or two symptoms to no more than a mild degree (American Psychiatric Association, 2013).

Response, defined as ≥ 50% reduction in symptom severity, is also used as an outcome (Culpepper, et al., 2015; Gaynes et al., 2018). However, patients who attain a full remission are more likely to return to normal psychosocial functioning; those individuals who have responded to treatment are more likely to have significant functional impairment (Culpepper et al., 2015) and have a higher likelihood of recurrence of a full depressive syndrome (Zimmerman et al., 2006).

However, the outcome of depression treatment is not as clear cut as might be inferred from the above. Even if remission is achieved, MDD is a highly recurrent disease process, with at least 50% of those who recover from a first episode having one or more additional episodes during their lifetime (Burcusa & Iacono, 2007).

In 1988, the MacArthur Foundation Research Network on the Psychobiology of Depression formed a task force in

order to propose standard definitions for terms used in research. Frank et al., (1991) then developed an empirically defined conceptual scheme for the various terms, among them recovery, relapse and recurrence. Though not necessarily agreed upon by all over the years, many investigators utilize these definitions (Burcusa & Iacono, 2007).

Specifically, per Frank et al. (1991):

- Recovery is conceptualized as a period of full remission lasting at least a certain number of days. Importantly, the term designates recovery from an episode of depression, not the illness in its entirety.
- Relapse is conceptualized as a return of symptoms to the full syndrome criteria for an episode during remission but before recovery has occurred (e.g. within eight weeks).
- Recurrence is conceptualized as an appearance of a new episode of MDD during a period of recovery (e.g. after eight weeks).

Remission, response and therefore recovery, relapse and recurrence, are measured by a number of instruments that are used to collect clinically important information. As already noted, they broadly include depression-specific measures, general psychiatric status measures, and functional scales. Depression specific measures may rely on patient report (e.g. the Beck Depression Inventory [BDI]), clinician report (e.g. the Hamilton Rating Scale for Depression [HAM-D] and the Montgomery-Äsberg Depression Rating Scale [MADRS]) or both (e.g. the Quick Inventory of Depressive Symptomatology [QIDS]). They are useful in research trials to measure severity of illness as well as to evaluate the success or failure of treatment efforts. Differing versions of the same tool may exist. For example there are multiple versions of the HAM-D, which is the most commonly reported depression specific tool, delineated by the number of items to be completed (HAM-D_{17}, HAM-D_{21}, etc) (Gaynes et al. 2018).

Tools that are utilized to evaluate depression also include those that assess general psychiatric illness and severity. An example is the clinician rated Clinical Global Impression Scale (CGI).

It is also important to note that many studies have reported that the clinical condition of the depressed patient may be characterized by traits beyond depressive symptomatology, such as difficulties with mobility, communication, self-care and interpersonal relations. If success or failure of an intervention is based only on reduction of depressive symptomatology, without consideration of patient function, an overestimation of a treatment's ability to foster improvement may occur. Therefore, it is important to consider functional outcomes in the assessment of the depressive disorder. (Kamenov, Cabello, Coenen, & Ayuso-Mateos, 2015). The American Psychiatric Association currently suggests that the World Health Organization Disability Assessment Schedule (WHODAS 2.0) be used as a measure of disability (Gaynes et al., 2018)

Short descriptions of the measures most relevant to this NCD are found in Appendix D.

<u>Neuromodulation and Vagus Nerve Stimulation</u>

Treatment management options for TRD include both pharmacologic and nonpharmacologic interventions (Al-Harbi, 2012; McIntyre, 2014). The landmark Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study funded by the National Institutes of Health, demonstrated that there is no clear drug treatment regimen for patients whose depression did not remit with one or more aggressive medication trials (Gaynes et al., 2009). Thus, other treatment modalities are important to consider as potential therapies for this disease.

Among the nonpharmacologic options for the treatment of depression is the category of remedies that provide neurostimulation (also known as neuromodulation). Neurostimulation therapy targets specific regions of the brain

using both non-invasive and invasive techniques. Such devices have been used to treat patients who have failed to respond to standard therapies for depression (Milev et al., 2016).

Vagus nerve stimulation (VNS) is an example of such therapy. VNS provides indirect modulation of brain activity through the stimulation of the vagus nerve. The vagus nerve, the tenth cranial nerve, has parasympathetic outflow that regulates the autonomic (involuntary) functions of heart rate and gastric acid secretion, and also includes the primary functions of sensation from the pharynx, muscles of the vocal cords, and swallowing. It is a nerve that carries both sensory and motor information to/from the brain. Importantly, the vagus nerve has influence over widespread brain areas (Groves and Brown 2005). It is believed that the stimulation of this cranial nerve alters various networks of the brain in order to treat psychiatric disease. Until recently, all VNS systems required surgical implantation. Recently there has been the development of purported similar devices that allow for noninvasive stimulation of the vagus nerve, thereby foregoing the need for surgery. This is known as transcutaneous vagal nerve stimulation, however these devices do not have an FDA approved indication for TRD (Cimpianu, Strube, Falkai, Palm & Hasan, 2017; Howland, 2014).

Surgically implanted VNS has been studied as a treatment for a variety of conditions, including TRD, refractory epilepsy, Prader-Willi syndrome, fibromyalgia, refractory migraine and cluster headaches, heart failure, Alzheimer's Disease and various psychiatric disorders (Ben-Menachem, Revesz, Simon & Silberstein, 2015; Cimpianu et al., 2017; Howland, 2014). The implanted VNS system includes a pulse generator, which is surgically inserted underneath the skin of the chest. For treatment of TRD, it is subcutaneously connected to an electrode attached to the left vagus nerve in the neck. The system delivers pulsed electrical signals to the vagus nerve. A hand held computer is used to program the pulse generator stimulation parameters, including the current charge (measured in milliamperes), pulse width (measured in microseconds), pulse frequency (measured in Herz), and the on/off stimulus time, also known as the on/off duty cycle (measured in seconds or minutes). Initial settings can be adjusted to enhance the tolerability of the device as well as its clinical effects on the patient. The generator runs continuously, but patients can temporarily turn off the device by holding a magnet over it. The VNS device can also be turned on/off by the programmer. The pulse generator battery life depends on the stimulus parameters and it can be replaced or permanently removed in a surgical procedure (Howland, 2014).

The therapy has been associated with harms related to the surgical implantation of the device (e.g. infection in 3-6% of patients, vocal cord paresis in 1% of patients, lower facial weakness in 1% of patients, bradycardia and asystole) as well as the electrical stimulation it produces (e.g. voice alteration, cough, dyspnea, paresthesia, headache and pain). The frequency of these adverse events usually declines with continued treatment. However, cardiac adverse events (e.g. bradycardia, ventricular asystole, complete heart block), which mainly occur in the operating room as the device is first being tested, have infrequently appeared years after the initiation of VNS treatment. It has also been reported that voice alteration may continue in nearly 19% of patients at five years (Ben-Menachem et al., 2015).

Other serious harms associated with (but not necessarily caused by) VNS therapy include suicide, attempted suicide and treatment-emergent hypomania or mania (Ben-Menachem et al., 2015; Milev et al., 2016)

This national coverage analysis (NCA) will examine the evidence related to the use of surgically implanted VNS in order to determine if this therapy is reasonable and necessary for the treatment of TRD in the Medicare population.

III. History of Medicare Coverage

CMS issued a NCD in 1999 to provide coverage for VNS for patients with medically refractory partial onset seizures, for whom surgery is not recommended or for whom surgery has failed. VNS is not covered for patients with other types of seizure disorders which are medically refractory and for whom surgery is not recommended or for whom

surgery has failed.

Prior to May 4, 2007, Medicare did not have a NCD on VNS for treatment of TRD and coverage was determined by local Medicare Administrative Contractors (MACs).

In 2006, CMS received a complete, formal request to reconsider the NCD to include coverage of VNS for TRD for patients who had either (1) been previously treated with or refused electroconvulsive therapy (ECT) for the treatment of depression, or (2) had been previously hospitalized for depression. The specific indication requested for VNS coverage was for the adjunctive long-term treatment of chronic or recurrent depression in patients over the age of 18 who were experiencing a major depressive episode and had not had an adequate response to four or more adequate depression treatments. On May 4, 2007, CMS determined that there was sufficient evidence to conclude that VNS was not reasonable and necessary for TRD and it has remained non-covered since then.

A. Current Request

CMS received a complete, formal request to reconsider the NCD to remove non-coverage of VNS therapy for TRD. The formal request letter can be viewed via the tracking sheet for this NCA on the CMS website at https://www.cms.gov/medicare-coverage-database/details/nca-tracking-sheet.aspx?NCAId=292.

The scope of this review is limited to surgically implanted VNS only for the treatment of TRD.

B. Benefit Category

Medicare is a defined benefit program. For an item or service to be covered by the Medicare program, it must fall within one of the statutorily defined benefit categories outlined in the Social Security Act.

VNS qualifies as:

- Physicians' services
- Hospital services
- Durable medical equipment

This may not be an exhaustive list of all applicable Medicare benefit categories for this item or service.

IV. Timeline of Recent Activities

Date	Action
May 30, 2018	CMS posts a tracking sheet announcing the opening of the NCA. The Initial 30-day public comment period begins.
June 29, 2018	First public comment period ends. CMS receives 36 comments
November 19, 2018	Proposed Decision Memorandum posted. 30-day public comment period begins.

V. Food and Drug Administration (FDA) Status

The FDA granted approval for the VNS Therapy System on July 15, 2005. This device is indicated for the adjunctive long-term treatment of chronic or recurrent depression for patients eighteen years of age or older who are experiencing a major depressive episode and have not had an adequate response to four or more adequate antidepressant treatments.

The complete FDA approval and labeling can be accessed at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P970003S050.

VI. General Methodological Principles

When making national coverage determinations under section 1862(a)(1) of the Social Security Act, CMS generally evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. The critical appraisal of the evidence enables us to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for beneficiaries. An improved health outcome is one of several considerations in determining whether an item or service is reasonable and necessary.

A detailed account of the methodological principles of study design that the Agency utilizes to assess the relevant literature on a therapeutic or diagnostic item or service for specific conditions can be found in Appendix A.

Public comments sometimes cite published clinical evidence and give CMS useful information. Public comments that give information on unpublished evidence such as the results of individual practitioners or patients are less rigorous and therefore less useful for making a coverage determination. Public comments that contain personal health information will not be made available to the public or will be redacted. CMS responds in detail to the public comments on a proposed national coverage determination when issuing the final national coverage determination.

VII. Evidence

A. Introduction

CMS last reconsidered the VNS NCD (see Appendix C for § 160.8 of the NCD Manual) in May of 2007. CMS has opened this national coverage analysis (NCA) to reconsider non-coverage of VNS for TRD. For this reconsideration, we reviewed the published medical literature from May of 2007 to 2018 to determine if VNS for TRD is reasonable and necessary.

B. Discussion of Evidence

1. Evidence Question(s)

Our review and analysis of the evidence concerning the clinical utility of VNS for TRD, and thus whether VNS for TRD is reasonable and necessary to treat certain Medicare patients, is guided by the following question:

Is the evidence sufficient to conclude that VNS improves health outcomes for Medicare patients with TRD?

2. External Technology Assessments

CMS did not request an external technology assessment (TA) on this issue. However, a related TA, which attempted to define TRD and to clarify how trials on this topic might be best designed and conducted, was requested. As this TA is related to the topic of the NCA, it will be discussed below.

Gaynes BN, Asher G, Gartlehner G, et al. Definition of Treatment-Resistant Depression in the Medicare Population. Technology Assessment Program. Project ID: PSYT0816. (Prepared by RTI–UNC Evidence-Based Practice Center under Contract No. HHSA290201500011I_HHSA29032006T). Rockville, MD: Agency for Healthcare Research and Quality. February 2018. http://www.ahrq.gov/clinic/epcix.htm.

The goal of this TA was to inform future discussions in the stakeholder community regarding the definition of TRD and the identification of important outcomes to be evaluated in related research studies. The TA further attempted to clarify how research trials might be best designed and conducted in order to inform clinical practice and health care policy in this field.

In order to accomplish these aims, a narrative review of the pertinent literature published from January, 1995 through August, 2017 was examined. These references consisted of practice guidelines, consensus statements, government materials and the like. Systematic reviews published from 2005 onwards were also analyzed. Additionally, a systematic review of pertinent published interventional trials from January, 2005 through August, 2017, was accomplished. The materials for the systematic review were indexed in MEDLINE, EMBASE, PsycINFO and the Cochrane Library.

The results of the narrative review indicated that no consensus exists for the best definition of TRD. However, the literature indicated that the commonly used definitions of TRD are based on treatment of MDD patients whose depression fails to respond (a decrease in depressive severity of at least half) or does not go into remission (complete recovery as measured by a score on a depressive severity index below a threshold) following two or more treatment attempts of an adequate dose and duration. The most common TRD definition for bipolar disorder required one prior treatment failure. No definition of adequate dose or adequate duration of therapies was found. Duration of psychotherapy treatments tended to be six weeks or longer. Minimum duration of other treatments was frequently cited as four and sometimes as six weeks. No consensus on whether pharmacologic treatment attempts require the use of different classes of antidepressants was observed.

It was concluded by the authors that the heterogeneity in the criteria that define TRD impedes the ability of researchers to combine their data and translate the findings of this field into clinical practice recommendations.

The authors of the TA also stated the diagnosis of TRD is a three-step process. It entails (1) confirmation of the diagnosis of MDD or bipolar disorder; (2) determination of the degree of resistance to meet a TRD definition; and (3) confirmation of current depression.

For substantiation of a current major depressive episode as part of MDD or bipolar disorder, the TA noted that the literature emphasizes a structured clinical assessment and diagnosis, based on widely accepted diagnostic criteria (DSM, International Classification of Diseases or Research Diagnostic Criteria) or a structured diagnostic assessment (Mini International Neuropsychiatric Interview, Structured Clinical Interview for the DSM, or Schedule for Affective Disorders and Schizophrenia). However, the literature generally did not describe or use formal tools to clarify treatment resistance. The TA did note that to determine whether the depressive illness met criteria for treatment

resistance, a history of the number of prior pharmacologic trials of adequate dose/duration that did not produce remission and/or an appropriate staging tool (Antidepressant History Treatment Form [ATHF], Thase and Rush Staging Model [TRSM], Massachusetts General Hospital Staging Model [MGH-s], or Maudsley Staging Model [MSM]) should be used to assess the spectrum of disease resistance. The TA further observed that patients were frequently confirmed as being currently depressed using a defined threshold on a validated depression monitoring measure. Both the HAM-D and the MADRS were commonly employed for this purpose.

The TA also noted that the literature emphasizes certain characteristics of study design that can improve the research in this field. In particular, the TA indicated there is a consistent recommendation for the standard use of a TRD definition as well as consistent use of validated tools to improve the quality of the evidence base. Moreover, there is a consensus that prospective randomized trial design is a valuable technique by which to minimize the role of bias in clinical trials.

Further, it was highlighted that since 2005, a consensus has been developing that the preferred definition of treatment failure is the failure to achieve remission, as evaluated by a validated instrument. However, no measure is regarded as the best to use. Both patient and clinician report tools are available. The HAM-D was most often reported as the outcome measure that evaluated depressive severity in the reviewed studies; however the MADRS was also frequently utilized for this purpose. The CGI scale was the most common general psychiatric outcome reported. Though functional impairment and quality-of-life outcomes were infrequently reported, the TA stated that the APA now suggests that the World Health Organization Disability Assessment Schedule (WHODAS 2.0) be used as a measure of disability.

In their discussion and conclusions, the authors of the TA endorsed the idea of an agreed upon core group of outcome measures to allow comparisons between trials including at least one measure of depressive severity, one measure of general psychiatric status, one measure of functional impairment/quality of life, a measure of adherence to medications and other treatment regimens, and a measure of suicidality. Further, they advised a consensus regarding standard length of treatment in order to ensure adequacy of dose and duration of treatment strategies. Standardized accounting for potential confounders (e.g., including at a minimum: depressive severity, duration of current episode, prior treatment intolerance, prior use of augmentation or combination therapy, prior psychotherapy and psychiatric comorbidities) was also believed to be important. The TA also emphasized that both compliance and consideration of prior psychotherapy use are important to assess and control for in an experimental design.

3. Internal Technology Assessment

Literature Search Methods

We searched OVID and EMBASE databases as well as the Cochrane Library. Search terms included vagus/vagal nerve stimulation, depression and treatment resistant depression. We identified studies with and without randomized control trial (RCT) design. Of the references found, we read through the abstracts and titles to find those that met the criteria below. We also reviewed references submitted to us by the requester and commenters and performed a hand search of bibliographies to identify other pertinent articles.

For the purpose of this analysis, we reviewed clinical studies published since the prior NCD (2007), with the following inclusion criteria:

Human adults with depression identified as being treatment resistant;

Studies with ten or more subjects in each arm who have failed at least two treatment courses for their depression;

Prospective trials with well-defined comparators with a goal to examine the effects of VNS therapy versus non-VNS therapy on patients' state of depression;

Results have been based on original data collected to obtain the original goal of the study, meaning that post hoc analyses of previously collected data were not considered.

Furthermore, systematic reviews and meta-analyses of comparative studies published from 2007 – 2018, but including investigations performed before that time period, were included in the NCA for historical perspective.

Randomized Controlled Trials

Aaronson ST, Carpenter LL, Conway CR, et al. Vagus Nerve Stimulation Therapy Randomized to Different Amounts of Electrical Charge for Treatment-Resistant Depression: Acute and Chronic Effects. Brain Stimul. 2013; 6(4):631-40. doi: 10.1016/j.brs.2012.09.013. PMID: 23122916.

This double-blind, randomized, multicentered study had as its goal to compare the clinical outcomes of three VNS dose response curves with variable output current and pulse width, but with the same duty cycle and pulse frequency, in patients with TRD. Groups were designated high, medium and low dose. Enrollment criteria included: individuals 18 years of age or older with a diagnosis of a chronic (> 2 years) or recurrent (≥ 2 prior episodes) MDD or bipolar disorder and a current diagnosis of MDE as defined by the DSM-4 and determined using the Mini-International Neuropsychiatric Interview; a history of failure to respond to four or more adequate dose/duration of antidepressant treatment trials from at least two different antidepressant treatment categories as documented through medical history and record review; a minimum pre-study and baseline score of 24 on the MADRS, with no greater than a 25% decrease between the pre-study and baseline visits; current recipient of at least one antidepressant treatment (medication or ECT); and a stable regimen of all current antidepressant treatments for at least four weeks before the baseline visit. Furthermore, patients with bipolar disease had to be receiving a mood stabilizer at baseline.

Exclusion criteria included a history of psychotic disorder, a history of rapid cycling bipolar disorder, a current history of bipolar disorder mixed phase, a history of borderline personality disorder, clinically significant suicidal intent at the time of screening, a history of drug/alcohol dependence in the last year, and a previous history of use of VNS. The only study personnel un-blinded to the assignment of treatment groups were study programmers at each site and clinical engineers who were employed by the sponsor to monitor the programmers.

Eligible patients were implanted with a VNS device and then randomized to low, medium or high target settings. The low dose was chosen to deliver active stimulation at the lowest available setting for amplitude of output current with a narrow pulse width (0.25 mA; 130 μs). The high dose was chosen to be consistent with higher levels of stimulation, often seen in the treatment of epilepsy (1.25-1.5mA; 250 μs). The medium dose was chosen to track closely to the high dose, but without overlap (0.5-1.0 mA; 250 μs), potentially providing a better opportunity to demonstrate efficacy versus the low dose.

After a period of recovery from the surgery, each patient began VNS dose titration to achieve the target setting. If during the allotted period of time the patient experienced intolerable side effects related to the stimulation, the highest tolerable dose for that patient was continued during the acute phase of the trial. The authors noted that dose related protocol deviations were reported in all groups.

Consistent with patient welfare, investigators were instructed to refrain from adding, discontinuing or changing the intensity of non-VNS treatments before week 22, the end of the acute phase of the investigation. During that time period, 12% - 16% of patients across all treatment groups had a mood disorder treatment added; 13% - 15% of

patients had a mood disorder treatment removed. The authors reported that changes in treatment were evenly distributed across all groups in the study.

Following week 22, there was a 28 week long-term phase of the study. During this period, the blinded investigator increased VNS dosage if clinically warranted to improve antidepressant efficacy. Investigators could also modify other antidepressant and mood stabilizer treatments if indicated.

The primary outcome of interest was the score on the Inventory of Depressive Symptomatology Clinician Administered Version (IDS-C). Patients were evaluated at baseline (up to seven days before implantation) and then at Weeks 10, 14, 18, 22 (end of acute phase), 26, 32, 38, 44 and 50 (end of long-term phase). Three hundred thirty-one individuals were enrolled in the study. The acute phase was completed by 316 patients; the long-term phase was completed by 298 patients. The defined intent to treat population included 310 patients.

Average age for all patients was 47.9 ± 10.8 years. Females comprised 67.7% of the total participants; 95.8% of the study population was Caucasian. The treatment groups were similar in terms of psychiatric history. Greater than 97% of the patients had experienced at least six unsuccessful mood disorder treatments during their lifetime. Almost half of all patients had attempted suicide at least once and on average, patients had experienced three to four prior hospitalizations for mood disorders. Approximately 80% of patients across all treatment groups had experienced six or more unsuccessful adequate dose/duration antidepressant treatments during the current depressive episode. Over fifty percent of patients across all treatment groups had received ECT.

The authors reported that in neither the acute nor the long-term phase, were there any significant differences in response or remission rates among the treatment groups (response was defined as ≥ 50% improvement from baseline; remission was defined as ≤ 14 on the IDS-C). However, they state that though effect sizes were limited, statistically significant decreases in mean depression scores (based on IDS-C) were observed in all groups. Mean IDS-C scores decreased approximately 15 points from baseline through week 50.

The below denotes the numbers of patients who had responded to treatment at week 22 and who went on to sustain response at week 50 (per IDS-C scores):

	22 weeks	**50 weeks**
LOW	16/111	7/111
MEDIUM	17/107	15/107
HIGH	22/113	18/113

Of the patients who did not respond to therapy by week 22, the following demonstrated a response at week 50 (per IDS-C scores):

	Approximate % of responders at 50 weeks	Sample Size

LOW	20	N= 81
MEDIUM	25	N= 80
HIGH	12	N=83

Further, at week 50, the IDS-C scores demonstrated that approximately 15% - 18% of individuals in each of the low, medium and high dose groups remitted.

Serious harms were reported in 66/331 patients (19.9%). Suicide attempts were reported more frequently in the low dose group (6.3%), than the medium (0.9%) or high dose (3.5%) groups. Depression was reported slightly more frequently in the low dose group (7.2%) compared with the medium (5.6%) or high dose (3.5%) groups. The prevalence of implantation related adverse effects at ≥ 1% incidence totaled 172 (n = 331). The prevalence of post-implant harms at ≥ 10% incidence was 1281 (n = 331).

The authors concluded that within the limits of this study, VNS provided as adjunctive treatment to patients with treatment resistant depression as described above, offers significant improvement at study endpoint as compared with baseline and that the effect is durable over one year. They also stated that higher electrical dose parameters were associated with response durability.

Observational Studies

Aaronson ST, Sears P, Ruvuna F, et al. A 5-Year Observational Study of Patients With Treatment – Resistant Depression Treated With Vagus Nerve Stimulation or Treatment as Usual: Comparison of Response, Remission, and Suicidality. Am J Psychiatry.2017; 174(7):640-648. doi: 10.1176/appi.ajp.2017.16010034. Epub 2017 Mar 31.

This investigation was a prospective, multicenter, open label, nonrandomized, longitudinal, naturalistic, observational post marketing FDA surveillance study for which a registry was designed to follow the clinical response and outcome over five years of patients with MDD, including those with unipolar or bipolar depression.

Patients participating in this study were recruited by physician referral and received treatment as usual (TAU) and VNS or just TAU. Subjects included those who were being evaluated for surgery or anesthesia to undergo VNS implantation, patients who had signed consent forms to receive a VNS device, patients who had scheduled VNS implantation surgery, and patients who had completed participation in a previous study termed the D-21 study [NCT 00305565: Study Comparing Outcomes for Patients With Treatment Resistant Depression Who Receive VNS Therapy at Different Doses].

The VNS arm included 335 patients without prior VNS treatment as well as 159 patients who received VNS treatment in the previous D-21 investigation. The TAU arm contained 301 patients. Eligibility criteria for the study included: age 18 years or older; a current major depressive disorder diagnosed according to DSM-IV-TR criteria and confirmed by the Mini International Neuropsychiatric Interview of at least two years in duration (unipolar or bipolar depression) or a history of at least three depressive episodes including the current major depression episode; and a history of inadequate response to at least four depression treatments (including maintenance pharmacotherapy, psychotherapy and ECT). Maintenance pharmacotherapy was defined as dosage per Physician's Desk Reference labeling for a minimum of four weeks. Exclusion criteria included a history of schizophrenia, schizoaffective disorder, other psychotic disorder, current psychosis, history of rapid cycling bipolar disorder and a CGI score < 4. Other than the patients from the D-21 study, the individuals in the study had not previously experienced VNS.

All patients (except those who participated in the D-21 study) were allowed to choose the treatment arm of their choice. However, the patients could be assigned to receive the alternate treatment due to various reasons (e.g. availability of surgical implantation at a site, failure to receive insurance coverage for the procedure, availability of donated VNS devices, etc.).

There were no restrictions on concomitant treatments.

Post baseline follow up visits for all patients were scheduled to occur at 3, 6, 9, 12, 18, 24, 30, 36, 42, 48, 54 and 60 months. During these scheduled visits, data was collected on medical status, need for adjustment of mood disorder therapy and concomitant treatments. Also various depression scale ratings were collected as well as data concerning mortality and suicidality. Central raters (un-blinded nurses with special training) conducted an assessment of suicidality via telephone after each patient visit.

Propensity scores were used to adjust for imbalance of baseline prognostic factors between treatment arms. The ITT population included those study participants who completed a baseline visit, received their respective treatment and completed at least one post-baseline treatment.

Of the 494 patients in the VNS arm, 300 (61%) completed all five years of data. It is noted that the D-21 patients rolled over into this study at various time points after implantation. Of the 301 TAU patients, 138 (46%) completed all five years of data.

Approximately 70% of all study participants were female and over 90% were Caucasian in both groups. A diagnosis of severe recurrent major depressive disorder was reported in 46% of the patients in the VNS arm and 32% in the TAU arm. A diagnosis of primary bipolar I or bipolar II disorder was reported in 28% of patients in the VNS arm and 24% in the TAU arm. Other psychiatric diagnoses included moderate recurrent major depression, moderate single episode major depression, severe recurrent major depression, and severe single episode major depression. Fifty-seven percent of the VNS group and 40% of the TAU group had experienced past treatments of ECT.

Of the patients who withdrew early, 40% (195) were from the VNS group and 54% (163) were from the TAU group. The investigators observed that reasons for early withdrawal were similar between the treatment arms. It was also noted that after premature closure of a study site where 48 patients were participating in the TAU group, most of the patients at that site were either lost to follow up or were dropped from the study for non-adherence.

The primary efficacy measure was a response rate, defined as a decrease of ≥ 50% in baseline MADRS score at any post-baseline visit during the study. The authors report a five year cumulative response rate of 67.6% [95% CI = 63.4, 71.7] in the VNS group and 40.9% [95% CI = 35.4, 47.1] in the TAU group ($p < 0.001$). Also they note that the cumulative percentage of first-time responders in the VNS group was approximately double that in the TAU arm at all post-baseline points in time through the five years of the study.

Among the secondary outcomes, the authors state that cumulative remission (based on a MADRS total score ≤ 9 at any post-baseline visit) demonstrated that over time, patients in the VNS arm were significantly more likely to experience remission than those in the TAU arm (43.3% [95% CI = 38.9, 47.7] and 25.7% [95% CI = 20.7, 31.1] respectively; $p < 0.001$).

The authors also state that the median time to first response was significantly shorter for patients in the VNS arm than for those in the TAU arm (12 months compared with 48 months; $p < 0.001$). Furthermore, median time to first remission (defined as a decrease to a score ≤ 9 on the MADRS at any post-baseline visit), in the VNS arm was significantly shorter in the VNS group than the TAU group (49 months compared to 65 months; $p < 0.001$). The duration of remission based on MADRS data was longer for VNS patients than those in the TAU arm (40 months compared with 19 months); however the difference did not reach

statistical significance (p = 0.10). Similarly, the duration of remission based on the QIDS-SR data was longer for those individuals in the VNS arm than for those in the TAU arm (30 months compared to 18 months), but the difference did not reach statistical significance (p = 0.20).

Based on several measures of suicidality, both treatment arms of the study exhibited an improvement from baseline over the course of the study. Furthermore the authors state that those individuals who were treated with VNS showed a greater reduction in their suicidality profiles and their all-cause mortality, than those individuals in the TAU group. However, this result was not always statistically significant across the different testing measures.

The authors concluded that adjunctive treatment with VNS resulted in superior outcomes in both effectiveness and mortality over a five year period compared with treatment as usual for patients with chronic, severe treatment resistant depression.

Conway CR, Kumar A, Xiong W, et al. Chronic Vagus Nerve Stimulation Significantly Improves Quality of Life in Treatment-Resistant Major Depression. J Clin Psychiatry. 2018; 79:e1-e7.

The goal of this study was to compare quality of life (QoL) changes associated with VNS + TAU versus TAU in patients with unipolar and bipolar treatment resistant depression. QoL data was gathered on all patients using the patient reported Quality of Life Enjoyment and Satisfaction Questionnaire Short Form (Q-LES-Q-SF), as well as the clinician reported CGI-I scale. The data was collected as part of the five year registry described in Aaronson et al. (2017), noted above. However the patient population analyzed was somewhat different, in that patients who rolled over from the previous D-21 study (Aaronson et al., 2013 also described above) were excluded so that all subjects had the same follow-up period. Furthermore, patients who were not depressed at baseline according to their MADRS scores, were also excluded. Therefore the data from 328 patients treated with VNS + TAU and 271 patients treated with TAU were analyzed.

Females comprised 68.6% of the VNS + TAU group and 70.8% of the TAU group; 97% of the VNS + TAU group and 90.8% of the TAU group were Caucasian. Major depressive disorder was diagnosed in 70.4% of the VNS + TAU group and 78.2% of the TAU group. Bipolar I or II disorder (most recent episode depressed) was diagnosed in 29.6% of the VNS + TAU group and 21.7% of the TAU group.

Paired data analysis (e.g. change in Q-LES-Q-SF versus percent change in MADRS score) were matched by assigned visit number; however these assessments for any given month might have taken place on separate visits (visit window was ± 45 days until one year of follow-up; thereafter ± 90 days). The authors report that the time difference between the paired measures was similar between the two groups and was a median of four weeks. Missing data were excluded if one component of a paired observation was lacking.

Among the results, the authors reported that on average, there was a comparative QoL advantage observed for the VNS + TAU group as early as three months which was sustained throughout the five year study. The VNS + TAU group demonstrated a significantly greater improvement in Q-LES-Q-SF scores than the TAU group for the same percentage drop in MADRS score from baseline. The authors reported a similar pattern when the CGI score was used. A post hoc analysis detailed the various domains in which either the VNS + TAU group or TAU group showed greater improvements.

The authors also modeled that improvements in QoL in the VNS group could occur even when the total change in MADRS score from baseline was less than 50%, the classical definition of depression response. Specifically they reported that there could be a clinically meaningful increase in Q-LES-Q-SF percent max score when the MADRS drop from baseline was 34%. Further, they stated that on average, the TAU group achieved the same clinically meaningful increase in Q-LES-Q-SF percent max score when the MADRS score drop from baseline was higher, at

least 56%.

The authors concluded that adjunctive VNS provided greater and sustained improvements in QoL as compared to TAU. Further, TRD patients treated with VNS experienced clinically meaningful QoL improvements even with symptom reduction less than the traditional 50% reduction used to describe a "response" to treatment.

Olin B, Jayewardene AK, Bunker M, Moreno F. Mortality and Suicide Risk in Treatment-Resistant Depression: An Observational Study of the Long-Term Impact of Intervention. PLOS ONE. 2012; 7(10): e48002. https://doi.org/10.1371/journal.pone.0048002.

The goal of this investigation was to characterize all-cause mortality rate and suicide risk in patients with TRD who were treated with standard TAU and those treated with VNS + TAU.

The study was an observational, open label, longitudinal, multi-center registry. The registry was a post-market surveillance study required by the FDA as a condition of approval of the TRD indication for VNS therapy to evaluate long term patient outcomes. Patients were followed for 60 months, until withdrawal from the study, death or study completion.

Patients in the VNS + TAU group had been followed for an average of 3.2 years; those in the TAU group had been followed for 2.1 years. Because baseline characteristics of each group showed areas of imbalance, the use of propensity score modeling was required.

Suicide ideation was evaluated by a central ratings group using both the Assessment of Suicidality (AOS) [*Has the patient made a suicidal gesture or attempt since the last visit; yes or no*] and MADRS Item 10, score ≥ 4, [*"Probably better off dead. Suicide thoughts are common, and suicide is considered a possible solution, but without specific plans or intention"*]. Among other criteria, eligible patients for the Registry were: individuals who had been diagnosed with a current MDE according to the DSM-IV-TR criteria; individuals who had been in the current depressive episode for at least two years or had experienced at least three lifetime MDEs (including the current episode); individuals who had an inadequate response to four or more adequate anti-depressive treatments; and individuals who had a CGI-S of four or greater. Exclusion criteria included schizophrenia, schizoaffective disorder, any other psychotic disorder, a history of rapid cycling bipolar disorder, or previous use of VNS.

After completing a screening visit, patients self-selected the treatment course that they believed was the best medical option. However after the study started, there were some treatment arm changes due to the implementation of a Medicare non-coverage policy and subsequent lack of reimbursement for the VNS procedure. The authors stated that they believed that the majority of individuals who chose VNS + TAU did so as a final alternative when all other treatments failed.

There were 335 subjects in the VNS + TAU group and 301 subjects in the TAU group. Average age of all patients was between 48 and 50 years. In the VNS + TAU group, 68.4% patients were female; 96.4% were Caucasian. In the TAU group, 70.1% of the patients were female; 91% were Caucasian. Major depressive disorder was diagnosed in 71.1% of the VNS + TAU group and 76.4% of the TAU group. Bipolar disorder was diagnosed in in 28.9% on the VNS + TAU group and 23.6% of the TAU group. In the VNS + TAU group, 58.2% of patients had a history of ECT; in the TAU group, 45.2% had a history of ECT treatment.

The authors found that the standardized all-cause mortality (4.46 vs. 8.06 per 1000 person years) and suicide rates (0.88 vs 1.61 per 1000 person years) for patients treated with VNS + TAU were approximately half that of the patients treated only with TAU. However the specific results were not statistically different due to the low mortality

rates in both groups. Similar results were noted when stratifying by propensity score quintiles.

Both groups however had a significantly higher rate of suicide relative to the US population; VNS + TAU 5.72 (95% CI; 0.07, 31.82) and TAU 9.98 (95% CI; 0.13, 55.55). The authors stated that individuals treated with VNS + TAU had a 10% - 20% reduction in the risk of suicidality as compared to individuals treated with TAU alone, as measure by the MADRS Item 10 score. However, when the Assessment of Suicidality was used, no statistical difference was noted between treatment groups.

The authors further noted that the side effects profiles as measured by the Frequency, Intensity and Burden of Side Effects Rating questionnaire demonstrated that the percentage of unacceptable side effects for VNS + TAU was higher than that of TAU; however this difference lessens over time.

The authors concluded that treatment with adjunctive VNS in this population can potentially lower the risk of all-cause mortality, suicide and suicide attempts.

Meta-Analyses/Systematic Reviews

Berry SM, Broglio K, Bunker M, Jayewardene A, Olin B, Rush AJ. A patient-level meta-analysis of studies evaluating vagus nerve stimulation therapy for treatment-resistant depression. Med Devices (Auckl). 2013;6:17-35. doi: 10.2147/MDER.S41017. PMID: 23482508.

The authors conducted a Bayesian meta-analysis of patient level data from six clinical studies that had been previously performed and supported by the manufacturer of VNS Therapy (Cyberonics). The investigations included in the meta-analysis were two single arm studies of VNS + TAU , a randomized trial of VNS + TAU versus TAU, a single arm study of patients receiving only TAU, a randomized trial of VNS + TAU comparing different VNS intensities, and a nonrandomized registry of patients who received either VNS + TAU or TAU.

The MADRS and CGI-I were selected as the primary endpoints for the meta-analysis, though they were not necessarily the primary outcome measures in the individual studies analyzed. Outcomes of interest were response, remission and sustained response based on these scales of disease severity. Response was assessed across five of the six studies using the MADRS and defined as a follow up score of at least a 50% reduction compared to baseline score. Response per the CGI Improvement subscale (CGI-I) was defined as a follow up score of 1-"very much improved" or 2-"much improved." Remission was assessed using the MADRS (score at follow up <10 points). The study designs of the original investigations included in the meta-analysis necessitated that the TAU group data be limited to two trials for the CGI-I scale and one trial for the MADRS scale.

Because only one of the studies randomized patients to VNS + TAU or TAU groups, the authors used propensity scores to control for potential differences between treatment groups. The researchers calculated propensity scores using standard methods and included the score in mixed effects repeated measures models to account for the fact that the patients in all of the different studies arrived at their assessment points at different points in real time.

In the final analysis, there were 425 TAU patients, and 1035 VNS + TAU patients. Females comprised 66.2% of the VNS + TAU group and 69.7% of the TAU group. Over 90% of patients in both groups were Caucasian. The average age was approximately 48 years in both groups. Major depressive disorder was diagnosed in 77.7% of the VNS + TAU group and 79.8% of the TAU group. The remaining patients were diagnosed with bipolar disorder.

The two groups differed on several major baseline characteristics with the VNS + TAU group exhibiting more unsuccessful types of prior drugs treatment trials, more prior use of ECT, and more lifetime depression related

hospitalizations than the individuals receiving TAU alone. Overall, withdrawal rates were similar between the two groups, being 23.6% for the VNS + TAU group and 22.2% for the TAU group. It was noted that 2.3% of the VNS + TAU patients withdrew due to lack of efficacy; none of the TAU patients withdrew for this reason.

The authors reported that while outcomes for both groups tended to improve, those who were treated with VNS + TAU demonstrated better outcomes over 96 weeks of treatment. The repeated measures analysis showed that compared to patients who received TAU only, those who received VNS + TAU had lower MADRS scores (mean difference -3.26 points; 95% CI: -3.99,-2.54). The odds of a MADRS response in the VNS + TAU group was 3.19 times greater (95% CI: 2.12, 4.66) and the odds of a MADRS remission was 4.99 times greater (95% CI: 2.93, 7.76) than those individuals who received TAU alone. Similarly, those in the VNS + TAU group had lower CGI-I scores (mean difference of -0.49 points; 95% CI: -0.59, - 0.39) and had seven times the odds of a CGI-I response (95% CI: 4.63, 10.83) compared to individuals receiving TAU alone. Analyses were repeated within subgroups defined by propensity score quintiles and similar results were obtained.

At 96 weeks, 104 individuals who received VNS + TAU were evaluated. Seventy exhibited a sustained MADRS response. At 96 weeks, 21 individuals receiving TAU were evaluated. Ten exhibited a sustained MADRS response.

Adverse events that occurred in greater than or equal to 10% of the participants who were treated with VNS were reported where the information was available. During the first year of VNS therapy, four studies documented this information; 700 patients exhibited 2637 adverse events. In year two, when only three of the included studies collected such data, there were 697 adverse events that occurred in ≥ 10% of 344 individuals (Note: each patient is only counted once per adverse event within each year. Some patients may have reported multiple occurrences of the same event, but this information was not captured). These events included depression, dysphagia, nausea, hypertonia and insomnia.

The authors concluded that the Bayesian meta-analysis demonstrated consistent superiority of VNS + TAU as compared to the use of TAU alone. They stated that for patients with TRD, VNS + TAU has greater response and remission rates that are more likely to persist than TAU.

Cimpianu C, Strube W, Falkai P, Palm U, Hasan A. Vagus nerve stimulation in psychiatry: a systematic review of the available evidence. J Neural Transm (Vienna). 2017;124:145-158. doi: 10.1007/s00702-016-1642-2.

This systematic review summarized the evidence regarding the use of invasive and non-invasive VNS for the treatment of TRD and other psychiatric disorders. The authors searched through the PubMed/MEDLINE database (up to September 2016). Literature that derived data from animal studies, trials without health related outcomes, case reports, congress proceedings, single session studies and reviews was excluded from evaluation.

The authors noted that very few studies exhibited a double-blind randomized sham controlled design; instead the majority were single blinded, open label observational or cohort investigations. Nonetheless, the text of the review pertaining to invasive VNS in the treatment of depressive disorders focused on those studies that used a randomized double blind design in at least one period (beginning) of a trial. However of those investigations described, the authors observed that for the most part, effect sizes were either not reported at all or were not reported in detail.

The authors also noted that the application of VNS in treatment resistant depression received a mixed recommendation in national guidelines. They stated that there is a consensus in the field that further randomized controlled studies as well as long term naturalistic studies are needed for the future evaluation of the efficacy of VNS for the treatment of depression.

Daban C, Martinez-Aran A, Cruz N, Vieta E. Safety and efficacy of Vagus Nerve Stimulation in treatment–resistant depression. A systematic review. J Affect Disord. 2008; 110(1-2):1-15. doi: 10.1016/j.jad.2008.02.012. Epub 2008 Mar 28. PMID: 18374988

The authors conducted a systematic review of studies published between 2000 and September 2007, found in the Medline, Psychological Abstracts and Current Content databases, that evaluated the safety and efficacy of VNS therapy in TRD patients. The criteria for inclusion were: an original study; a prospective study with follow up assessments; a study where subjects were patients with current non-psychotic TRD (unipolar or bipolar); standardized diagnostic criteria and outcome measures were utilized; statistical methods were clearly reported; and studies were reported in English.

The authors reviewed six short term studies and 12 long term- studies. One short term study was a double blind randomized controlled study comparing VNS treatment to a sham device; all other studies were naturalistic. Sample size ranged from one subject to a study investigating 205 subjects receiving VNS + TAU compared with 124 individuals receiving TAU. The short term studies performed active treatment for 10 weeks; the long term studies provided active treatment for 11 to 69 months.

The authors noted that in general, the studies selected for their systematic review shared many of the same characteristics, including: Patients were in a MDE of either MDD or of bipolar disorder; HDRS scores were ≥ 20; the current MDE had lasted at least two years or longer or more than four MDEs had occurred during the patient's lifetime; patients were determined to exhibit TRD according to the Antidepressant Treatment History Form (ATHF) with the current MDE not responding to at least two adequate antidepressant medication treatment trials with at least two different medication classes; concomitant pharmacologic therapy was allowed during the study, however dosages had to be stable for four weeks prior to study entry, during the recovery period and during the acute study phase; and the patients had not had any substantial improvement with at least six weeks of psychotherapy.

Exclusion criteria included a history of atypical depression, psychotic symptoms, schizophrenia, schizoaffective disorder, delusional disorders, rapid cycling bipolar disorder, acute suicidality and substance abuse within the last six months.

The measured outcomes consisted of baseline depression severity compared to ratings two weeks after implantation and after 3 months in acute and long term studies and also after 6, 9, 12 and subsequent months in long term studies. The primary outcome measure was the HDRS with secondary measures of the MADRS and IDS-SR. The authors further noted that in all studies, patients were considered to be responders if they experienced a reduction of more than 50% in baseline HDRS total score at the end of the trial. Those who "remitted" were individuals whose HDRS total score was ≤ 10 at study endpoint.

The authors stated their review demonstrated that VNS therapy has been reported to have antidepressant effects in open and long term studies and that these effects may be sustained. However, they also noted that the evidence base is weak and the only blinded randomized trial was inconclusive. They further observed that although serious side effects (e.g. cardiac) of VNS are rare (3%), other adverse effects, while not permanent, are numerous and "…cannot be ignored." In light of the potential advantages of VNS therapy (e.g. anti-depressant effect, compliance with treatment, etc.) they suggest more double blinded, sham controlled, randomized studies be conducted.

Martin JLR and Martin-Sanchez E. Systematic review and meta-analysis of vagus nerve stimulation in the treatment of depression: Variable results based on study designs. Eur Psychiatry. 2012; 27(3):147-55. doi: 10.1016/j.eurpsy.2011.07.006. PMID: 22137776.

The systematic review was performed to determine the efficacy of VNS for treatment of depression. In order to

achieve this goal, a review of the pertinent scientific literature available until December 2010 was conducted. The databases searched were Medline/PubMed, Embase, The Cochrane Controlled Trials Register, Pascal Biomed and CINAL. References found on the webpages of ongoing clinical trials were also examined. Selection criteria included any RCT or pre/post design study, in which depressive symptomatology was measured and the intervention studied was VNS. The outcomes assessed were levels of depression severity as measured by depression symptomatology scales and percentage of responders, defined as subjects whose symptomatology scores demonstrated ≥ 50% change from baseline. The outcomes were analyzed in the short term (≤ 12 weeks), medium term (> 12 and < 48 weeks) and long term (> 48 weeks).

In an ad hoc analysis, severe adverse effects of the intervention were also examined. To determine if severe adverse events were the result of the VNS intervention or due to the natural course of depression in the pre/post studies without a control group, a meta-analysis was performed on the incidence density of the unfavorable occurrences (subjects treated x follow up time). These results were then compared to the incidence density of the same events in the active intervention arms of clinical trials of selective serotonin reuptake inhibitors found in recently published systematic reviews.

In their literature search, the authors found only one randomized controlled trial involving VNS for treatment of depression. The primary outcome was a response rate as measured by the Hamilton Depression Rating Scale. No statistically significant differences between the active and the placebo group were noted. However, the meta-analysis of efficacy for the uncontrolled pre/post studies, showed a significant reduction in HDRS scores and the percentage of responders was 31.8% ([23.2% - 41.8%]. $p < 0.001$). To study the cause of this heterogeneity, a meta-regression was performed, which implied that an 84% variation in effect size across the studies was explained by baseline severity of depression ($p < 0.0001$).

In their analysis of adverse effects in the single RCT, the authors noted that the three subjects who withdrew from the sole randomized controlled trial, did so due to hoarseness, infection (resulting in explantation) and suicide. Higher frequencies of other adverse events were reported in the VNS group, including increased cough, dyspnea, dysphagia, vomiting, laryngismus, wound infection and palpitations.

In the uncontrolled pre/post studies that were meta-analyzed, the incidence density of suicide or attempted suicides was practically identical in the studies of VNS and selective serotonin reuptake inhibitors. Therefore the authors stated that VNS did not appear to provoke suicide conduct any more than treatment with the comparator anti-depressant.

The authors concluded that insufficient data exists to describe VNS as an effective treatment for depression. Moreover they stated that the ability of the uncontrolled studies to show causality is limited and positive outcomes might be caused by placebo effect, regression to the mean, spontaneous remission, differences in patient characteristics or the Hawthorn effect (the alteration of behavior by subjects in a study because they are aware of being observed). They stated that evidence to determine the benefit (or not) of VNS therapy, should be based on long term clinical trials with a control group aimed at monitoring the possible latency involved in the effect of VNS as well as the associated adverse effects. At present, the authors concluded, it was not clear whether the potential benefit of this treatment outweighed possible harm.

4. Medicare Evidence Development & Coverage Advisory Committee (MEDCAC)

The full transcript of the MEDCAC deliberations and its voting results can be accessed at: https://www.cms.gov/medicare-coverage-database/details/medcac-meeting-details.aspx?MEDCACId=71

A MEDCAC meeting was convened on April 27, 2016 to obtain recommendations regarding the definition of TRD as

well as to advise CMS on the use of that definition in the context of clinical studies, coverage with evidence development, and treatment outcomes. Like the external TA, the MEDCAC did not specifically discuss the application of VNS for the treatment of TRD. However the meeting attempted to characterize TRD and to clarify how treatment trials for this disease might be best designed and conducted. As this topic is related to the subject matter of this NCA, the outcome of the meeting will be summarized below.

At the MEDCAC, the panel voted on questions about key components of a definition of TRD, and how that definition could be put to clinical use in a variety of settings. Overall, the general opinion of the MEDCAC panel members was that a standard definition of TRD can be applied to the Medicare population, in both general and specialty psychiatric settings. Furthermore, the type of depression (e.g., unipolar, bipolar, psychotic) experienced, as well as the specifics of any pharmacologic therapies (e.g., dose, duration, number of trials) were noted as characteristics that should be among the important components of a TRD definition used in a research trial. Non-pharmacological therapies (e.g., electroconvulsive therapy) however, were not generally recognized for the purpose of defining TRD.

Moreover, the MEDCAC panel had high intermediate confidence that improvement or decline in depression as measured by depression scales (overall voting average = 4.62; voting member average = 4.44), improvement or decline in function (overall voting average = 4.38; voting member average = 4.56) and improvement or decline in quality of life (overall voting average = 4.38; voting member average = 4.56) were reliable, valid and meaningful health outcome for Medicare beneficiaries in a trial of an intervention for TRD. Finally, the panel had high intermediate confidence that a randomized sham-controlled double blinded study design when applied to Medicare beneficiaries, represents a meaningful and realistic study design in research investigations performed to evaluate interventions for TRD (overall voting average = 4.69; voting member average = 4.78), but low intermediate confidence in a randomized controlled un-blinded study design (overall voting average = 2.62; voting member average = 2.44).

5. Evidence-Based Guidelines

The pertinent evidence-based guidelines are summarized below.

Cleare A, Pariante CM, Young AH, et al. Evidence-based guidelines for treating depressive disorders with antidepressants: A revision of the 2008 British Association for Psychopharmacolgy guidelines. J Psychopharmacol. 2015; 29(5):459-525. doi: 10.1177/0269881115581093.

The guidelines considered the use of antidepressants to treat unipolar depressive episodes in adults as well as the place of antidepressants within the range of treatments available for depression.

In order to review and revise previous guidelines prepared in 2008, the British Association for Psychopharmacology (BAP) held a consensus meeting in 2012. Attending were experts in the field of depression along with user representatives and staff from pharmaceutical companies. Presentations were made on key topics, with an emphasis on the evidence found in systematic reviews and randomized controlled trials as searched through MEDLINE, EMBASE, the Cochrane Database and previously prepared major guidelines. After discussion with the entire group about the quality of evidence and its implications, the main topic authors revised the previous 2008 literature review with new recommendations where warranted. This information was circulated to all participants, user groups and interested parties for comment before incorporation into the final version of the guidelines.

Vagus nerve stimulation was not recommended as a first line treatment for depression. Though it has limited evidence of efficacy and no positive double blind randomized controlled trials, the guidelines stated that the therapy could be considered in patients with chronic and/or recurrent depression who have failed to respond to four or more antidepressant treatments. However the therapy was only recommended to be undertaken in specialist centers with

the availability of prospective outcome evaluation and the provision of long term follow up.

Gelenberg AJ, Freeman MP, Markowitz JC, et al. Practice Guideline for the Treatment of Patients With Major Depressive Disorder, Third Edition. 2010.

In 2010, under the direction of the Steering Committee on Practice Guidelines of the American Psychiatric Association, the above guideline was approved and published. It summarizes specific approaches to the treatment of individuals with major depressive disorder. Key features of the process that produced the Guideline included: a comprehensive literature review to identify relevant randomized and nonrandomized clinical trials; initial drafting of the guideline by a workgroup that included psychiatrists with clinical and research experience in major depressive disorder; widespread review of the document drafts by individuals and organizations including a review for potential conflicts of interest; and approval by the American Psychiatric Association Assembly and the Board of Trustees.

The guideline includes recommendations for the formulation and implementation of a treatment plan for persons with major depressive disorder. Specifically it states that tailoring the treatment plan to match the needs of the individual requires a careful and systematic assessment of the type, frequency and magnitude of psychiatric symptoms as well as ongoing determination of the therapeutic benefits and side effects of treatment. It was recommended with moderate clinical confidence that such assessments can be facilitated by the integration of clinician and/or patient administered rating scale measurements into the initial and ongoing evaluation. Examples of such evaluations commonly used in research were noted to be the Inventory of Depressive Symptoms (IDS), the Hamilton Rating Scale for Depression (HAM-D), and the Montgomery Asberg Depression Rating Scale (MADRS).

Further, the guideline states that there is no use for VNS in acute phase treatment of depression. The guideline also notes that though the role of VNS remains a subject of debate, this therapy could be considered as an option for patients with substantial symptoms that have not responded to repeated trials of antidepressant treatment.

Milev RV, Giacobbe P, Kennedy SH, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder. Can J Psychiatry.2016; 61(9): 561-575. doi: 10.1177/0706743716660033. PMID: 27486154.

The CANMAT conducted a revision of its 2009 guidelines by performing a systematic literature search to inform the management of adults with unipolar major depressive disorder. The literature search focused on systematic reviews and meta-analyses published in English between January 2009 and December 2015. Informational sources were found through a search of PubMed, PsychInfo, and Cochrane Register of Clinical Trials, as well as searches of bibliographies and review of other guidelines and major reports.

The authors noted that a meta-analysis of seven open label studies of VNS found a response rate of 31.8%. However, only one RCT had evaluated the efficacy of VNS versus a sham-control device and that investigation demonstrated no significant differences in efficacy between groups at twelve weeks.

The authors also observed that a patient level meta-analysis of all randomized and open labeled studies with VNS demonstrated that there were significantly higher odds ratios for response (OR, 3.19) and remission (OR, 4.99) for VNS + treatment as usual versus treatment as usual. However, absolute rates were noted to be low; e.g. remission rates for the VNS + treatment as usual group versus treatment as usual were:

Remission rates	**12 Weeks**	**24 Weeks**	**48 Weeks**	**96 Weeks**

VNS + treatment as usual	3%	5%	10%	14%
Treatment as usual	1%	1%	2%	4%

In another VNS study of 74 patients, the authors noted that 35% of patients had achieved a response at three months, but 61.5% and 50% of these individuals maintained that response at 12 and 24 months, respectively.

Based on the above, the guidelines state that the longer term results of VNS appear encouraging and that VNS can be considered for patients with chronic depression, particularly in situations where treatment adherence may be problematic.

The authors also note that most patients using VNS are also on antidepressant medications, so reported adverse effects are for the combined treatment. The most commonly reported adverse effects after twelve months of VNS for TRD are voice alteration (69.3%), dyspnea (30.1%), pain (28.4%) and increased cough (26.4%). The tolerability of VNS appears to improve over time. Other events associated with the use of VNS have been reported as including suicide and suicide attempts (4.6%) and treatment emergent hypomania or mania (2.7%).

6. Professional Society Recommendations / Consensus Statements / Other Expert Opinion

The Guidelines of the American Psychiatric Association, Canadian Network for Mood and Anxiety Treatments and the British Association for Psychopharmacology are presented above.

7. Public Comment

Public comments sometimes cite the published clinical evidence and give CMS useful information. Public comments that give information on unpublished evidence such as the results of individual practitioners or patients are less rigorous and therefore less useful for making a coverage determination.

CMS uses the initial public comments to inform its proposed decision. CMS responds in detail to the public comments on a proposed decision when issuing the final decision memorandum. All comments that were submitted without personal health information may be viewed in their entirety by using the following link https://www.cms.gov/medicare-coverage-database/details/nca-view-public-comments.aspx?NCAId=292.

Initial Comment Period: 5/30/2018 – 6/29/2018

During the initial 30-day public comment period CMS received 36 comments. Of these 36 comments, one was omitted from publication on the CMS website due to excessive personal health information content. Nearly all of the comments asked CMS to cover VNS for TRD, with several commenters citing research that has been completed since the last reconsideration of this policy in 2007. Several commenters also mentioned the lack of viable treatments available for patients with TRD. One comment that did not support CMS coverage of VNS for TRD mentioned how the medical literature is incomplete and does not sufficiently address the risks associated with the procedure.

The majority of comments were provided by psychiatrists and other healthcare professionals. There were five comments that represented seven professional associations, including the American Psychiatric Association (APA),

Mental Health America (MHA), American Foundation for Suicide Prevention (AFSP), Medical Device Manufacturers Association (MDMA), American Association of Neurological Surgeons (AANS), Congress of Neurological Surgeons (CNS), and the American Society for Stereotactic and Functional Neurosurgery (ASSFN). Additional group comments represented Anthem, Inc., and LivaNova.

VIII. CMS Analysis

Introduction: National coverage determinations are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally by Medicare (§1869(f)(1)(B) of the Act). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage. Moreover, with limited exceptions, items or services must be reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member (§1862(a)(1)(A) of the Act).

In addition to §1862(a)(1)(A) of the Act, a second statutory provision may permit Medicare payment for items and services in some circumstances. That statute, section 1862(a)(1)(E) of the Act, provides, in pertinent part, that:

> (a) Notwithstanding any other provision of this title, no payment may be made under part A or part B for any expenses incurred for items or services—
> . . .
> (1)(E) in the case of research conducted pursuant to section 1142, which is not reasonable and necessary to carry out the purposes of that section.

Section 1142 of the Act describes the authority of the Agency for Healthcare Research and Quality (AHRQ) to conduct and support research on outcomes, effectiveness, and appropriateness of services and procedures to identify the most effective and appropriate means to prevent, diagnose, treat, and manage diseases, disorders, and other health conditions. That section includes a requirement that the Secretary assure that AHRQ research priorities under Section 1142 appropriately reflect the needs and priorities of the Medicare program.

CED is a paradigm whereby Medicare covers items and services on the condition that they are furnished in the context of approved clinical studies or with the collection of additional clinical data. In making coverage decisions involving CED, CMS decides after a formal review of the medical literature to cover an item or service only in the context of an approved clinical study or when additional clinical data are collected to assess the appropriateness of an item or service for use with a particular beneficiary.

The 2014 CED Guidance Document is available at https://www.cms.gov/medicare-coverage-database/details/medicare-coverage-document-details.aspx?MCDId=27.

Evidence Review Summary:

For this reconsideration, CMS focused on the following question:

Question: Is the evidence sufficient to conclude that, VNS improves health outcomes for Medicare patients with TRD?

No. A total of four individual research studies were reviewed as well as one external technology assessment, four systematic reviews and meta-analyses, and three evidence based guidelines since our last national coverage analysis. Systematic reviews and meta-analyses included studies performed before our cut-off date, but were included for the sake of historical perspective. All studies reported some positive findings. However, significant issues were present in these studies that either reduced the overall quality and strength of evidence and/or the

clinical significance of the outcome. However, some of the published evidence suggests that VNS is a promising treatment for patients with TRD and therefore, we are proposing coverage with evidence development (CED).

Quality and strength of evidence

Based on the evidence and consistent with the MEDCAC voting, we believe that randomization of a study population and blinding of both the subjects and their treating physicians/providers is the most effective way to minimize bias and help assure that differences in outcomes are due to the intervention itself, rather than confounding factors. However, as noted in the reviewed literature, since 2005, when the randomized double blinded ten week study by Rush et al. (2005a) was published and failed to demonstrate statistically significant superior outcomes of VNS + TAU compared to a sham implanted VNS device, no further studies of the same design have been conducted [Rush et al., 2005a is summarized in the Decision Memo for Vagus Nerve Stimulation for Treatment of Resistant Depression (TRD) (CAG-00313R)]. The lack of randomized controlled double blinded investigations in subsequent research has led to the potential of methodologically biased analyses, making conclusions uncertain.

We understand that researchers of VNS treatment believe the study by Rush et al. (2005a) may have been too short to demonstrate effect upon TRD. A naturalistic study of VNS (i.e. open study, without a control/comparison group) followed up the short term Rush investigation and suggested that 12 months of treatment with the device was associated with clinically meaningful antidepressant effects. But the authors of this study also stated that without a control or comparison group, it was not a certainty that such longer term benefits were attributable to the VNS treatment (Rush, et al., 2005b). Further, several of the reviews summarized above have concluded the evidence base overall is weakened by the lack of investigation(s) of sufficiently rigorous design and duration to allow a determination of the possible benefits and harms of VNS treatment.

The study by Aaronson et al., (2013) was a double-blind, randomized investigation of VNS dosage, but there was no non-treatment control group. In this investigation, three groups of patients were randomized to three different target ranges of electrical charge (low, medium and high). Patients and pertinent treating practitioners were unaware of the group assignments of their patients. The hypothesis of the investigation was that medium and higher range VNS dosing (defined by amplitude of output current and a standardized pulse width) would be associated with better clinical outcomes when compared with stimulation of relatively low dosage (as defined by the lowest amplitude of output current and a narrower pulse width). However, no significant differences between treatment groups in terms of antidepressant efficacy were found over a period of 50 weeks.

Meaningful Health Outcomes

While survival (for example, decrease in suicides or all-cause mortality) is a well-accepted health outcome, it is difficult to show statistically significant improvements in clinical trials of patients with TRD. For example, the Olin et al. (2012) investigation, reported that the MADRS Item 10 demonstrated that patients treated with VNS + TAU exhibited a 10% - 20% reduction in the risk of suicidality as compared to those treated with TAU. But it was also found that there was no statistical difference between the treatment groups when the Assessment of Suicidality was tracked. Further, standardized all-cause mortality and suicide rates between the groups were not statistically different, possibly due to the low mortality rates in both groups. Similar results were reported after propensity score stratification. Therefore, no definitive positive outcomes of treatment with VNS + TAU as compared with TAU can be derived from this study.

As emphasized by the MEDCAC voting, improvement in depression (for example remission and response to therapy) is a reliable, valid and meaningful health outcome for Medicare beneficiaries in a trial of an intervention for TRD. However, results from published studies have been inconclusive. In the study by Aaronson et al. (2017), the median duration of remission (for those patients who remitted) based on MADRS data was 40 months for those in the VNS

group and 19 months for those in the TAU group; this difference was not statistically significant. Similarly the duration of remission based on QIDS-SR scores was 30 months in the VNS arm and 18 months in the TAU arm; again a difference that did not reach statistical significance. The authors also provide no information as to whether or not repeat remissions can be induced in patients who cycled out of an improved state. Thus we remain uncertain as to meaningfulness of the outcomes reported in this paper.

Aaronson et al. (2013) reported that lower depressive severity scores were similarly achieved in all three groups, but further stated that the effect sizes were limited. We note that mean IDS-C scores (primary outcome measure) decreased approximately 15 points from baseline over the course of 50 weeks. That the scoring method (IDS-C) ranges from 0 - 84 and the reported values were averaged, makes us uncertain as to the clinically meaningful changes in patients' lives that were represented by these scores. The lack of a dose-response suggests that an effective treatment range has not been determined. The lack of a non-treated control group does not inform as to whether the improvement experienced by all three dose groups was due to the VNS device.

Further, in the Aaronson et al., (2013) study, only 15% - 23% (depending on the depression severity scale recorded) of study participants (n = 298) achieved remission at week 50 (remission rates were comparable between treatment groups). This result is contrasted with the finding that the prevalence of implantation related harms occurring at ≥ 1% incidence, totaled 172 in 331 subjects. The prevalence of post – implant harms that occurred at ≥ 10% incidence in the total study population, was 1281 in 331 subjects. These latter events included depression, dyspnea, dysphagia and hypertonia. Serious harms were reported in 66 of 331 (19.9%) subjects. Two patients committed suicide during the study; one from the low dose group and one from the high dose group. Suicide attempts were reported more frequently in the low dose as opposed to the medium or high dose groups. The frequency of harms needs further assessment, especially in light of the low percentages of subjects that achieve remission in this and other studies.

In the Berry et al. (2013) person-level meta-analysis, the authors demonstrated that over time, a repeated measures analysis that compared patients who were receiving VNS + TAU to patients who received TAU only, exhibited lower MADRS scores (mean difference -3.26 points). Additionally, those in the VNS + TAU group had lower CGI-I scores (mean difference of -0.49 points) compared to individuals receiving TAU alone. However, we note that the MADRS is a 60-point scale and the CGI-I is a 7-point scale. Though the differences reported by these authors are statistically significant, we are unsure if they are clinically meaningful to patients. In addition, the authors were using data from non-randomized registries with substantial methodological problems.

In the study by Conway et al. (2018), the five year registry data was examined to document QoL in those individuals with TRD, treated with and without VNS. Though this investigation reminds us that desired outcomes include both the diminution of clinical symptoms as well as improvement in patient function, the lack of blinding and randomization weakens the results as does the median time difference of four weeks between MADRS and Q-LES-Q-SF assessments.

Overall, our analysis indicates that the reviewed studies have flaws. Because of the flaws, the true benefits and harms of VNS for treatment resistant depression in the Medicare population is uncertain. Therefore, we propose the evidence that has been generated since the last reconsideration of this policy remains insufficient to confidently determine whether VNS improves the health outcomes of Medicare beneficiaries with TRD. Thus CMS proposes that VNS for TRD is not reasonable and necessary under §1862(a)(1)(A) of the Act.

Coverage with Evidence Development (CED)

Despite the concerns that have been expressed above, the published evidence suggests that VNS is a promising treatment for patients with TRD. At least one publication stated that *"Before we can consider VNS as a routine part*

of depression management, we do need prospective data from a randomized, blinded, controlled trial with an improved design that incorporates what we have learned about the device from previous studies," (Zagorski, 2017).

We agree with this conclusion. It is noteworthy that in the studies discussed above, both patients who received VNS + TAU as well as those who received "only" TAU responded to their respective therapeutic programs. This indicates that even after multiple failed attempts, traditional treatments can still successfully ameliorate the symptoms of severe and chronic depression for some. Therefore, it is important to randomize patient selection and to blind those receiving and providing treatment and evaluation, so that bias is minimized.

As above, there has been only one randomized controlled, double-blinded study comparing VNS + TAU with TAU for the treatment of TRD (Rush et al., 2005a). That study showed no significant differences in clinical benefit to patients with TRD when treated with or without VNS. However active treatment with VNS was only studied for 10 weeks.

The findings of the MEDCAC describe randomization, blinding, and the use of sham controls as important features of study designs that would most likely advance knowledge in this field. The findings of naturalistic studies noted above indicate improvement in patients with TRD after 12 months of VNS treatment. Therefore, we believe that it is important to conduct a randomized controlled, double blinded study of at least one year's length in order to determine whether or not VNS conveys significant positive health benefits to individuals with TRD. We also believe, as did the MEDCAC panel, that reliable, valid and meaningful health outcomes for Medicare beneficiaries are improvement in depression scale scores, function and quality of life and should be included in such an investigation.

Therefore, based on the research and findings presented in the evidentiary review above, CMS proposes that the evidence is sufficient to cover VNS for TRD through Coverage with Evidence Development (CED) when offered in a CMS approved, double-blind, randomized, placebo-controlled trial that include the criteria discussed below. We recognize that waiting for the published results of such a trial may limit access at the completion of study enrollment. CMS believes that appropriate access to VNS for TRD should be maintained if initial primary endpoint findings in the respective trial are positive. Therefore, CMS proposes to also cover, in prospective longitudinal studies, FDA approved VNS devices for TRD that have completed enrollment of a CMS approved, double-blind, randomized, placebo-controlled trial and have demonstrated positive initial primary endpoint findings. We believe this proposal strikes an appropriate balance of providing patient access while also ensuring the appropriate data collection and analysis to address CMS' questions.

The proposed criteria for the double-blind, randomized, placebo-controlled study reflect methodology that has been successfully used in prior completed and published trials. To aid in the clarification of the elements of a methodologically appropriate study, our proposed CED criteria contains modifications of prior trials to strengthen the evidence base. We recognize the evolution of the knowledge base in this subject area and believe these modifications will facilitate evidence generation and allow for consistency in research studies.

Primary Outcomes

Because patients who attain a full remission are more likely to return to normal psychosocial functioning than those individuals who respond to treatment (Culpepper et al., 2015), we propose that depressive severity outcomes (i.e., depression scales) in all protocols submitted under this CED be based on remission. As we have noted, there are multiple definitions of remission in the context of major depression. We believe that use of structured measures of depression severity will aid in the description of a patient's response to treatment (MEDCAC, 2016; Gelenberg et al., 2010). We propose that the definition of remission be based on the depression scales that are recommended in the APA Practice Guidelines (Gelenberg et al.,2010) and that have been previously used in VNS and TRD research. We propose that at least two clinician reported and one patient reported measure be used, such as:

- $HDRS_{24}$ ≤ 10 (Schlaepfer et al., 2008);
- MADRS ≤ 9 (Aaronson et al., 2017); or
- $IDS\text{-}SR_{30}$ ≤ 14 (Dunner et al., 2006)

In addition to the rate of remission scores described above, for the purposes of data collection, we propose CMS approved CED studies also report the time from treatment until a remission score (as described above) is first achieved for a consecutive period of two months (8 weeks). This outcome would capture true remission, which is a very important supplement to the rate that remission scores were achieved at any point in the study. We also believe it is important to capture the length of true remission in the study. Therefore, we propose that for those patients that achieved remission scores for a consecutive two month period, studies should report how many consecutive months those remission scores were maintained.

As the effects of VNS upon TRD may require significantly more time to appear than the 10 weeks in the Rush et al. (2005a) study, we propose that the studies performed under this CED must be maintained for at least one year, as was done in Rush et al., 2005b, noted above.

We appreciate that improvement in symptoms is important to the disease process, but as noted above, patients who achieve a response to treatment are more likely to have significant functional impairment than patients who achieve remission. The latter group are more likely to return to normal psychosocial functioning (Culpepper et al., 2015). We believe the durability of remission is important to those patients whose anti-depressive treatments require hardware to be embedded in their bodies. Any research protocol submitted for CED needs to consider remission of disease as well as the durability of remission as its main outcome measures.

The technology assessment by Gaynes et al. (2018) noted that for most risk factors that might influence treatment effect, data was either insufficient to determine a treatment effect or reflected no statistically significant impact on study results. CMS is interested in specific patient characteristics that may influence the success or failure of TRD treatment with VNS. We believe such information is important to practicing physicians who consider which patients are most likely to benefit from such a therapy. For example, in the study by Aaronson et al., 2017, a subgroup analysis was performed on the registry patients who had completed a defined course in electroconvulsive therapy or who experienced comorbid anxiety or bipolar depression. In order to attempt to identify a subgroup(s) of patients either responsive or resistant to VNS treatment of TRD, we propose to require that research proposals include in their statistical analysis plans, appropriate subgroup analyses of potential risk factors (not including the characteristic of bipolar disease) such as depression severity, prior treatments, and comorbid psychiatric conditions such as anxiety, gender, and age.

Secondary outcomes

A standard core package of outcome measures would be helpful to decrease the heterogeneity of the literature. In addition to the measures of depressive symptomatology above, a measure of general psychiatric status and a measure of functional impairment /quality of life have been recommended (Gaynes et al., 2018). Assessment tools such as the DSM-5 recommended WHODAS 2.0 should be added to the outcome measures of all studies performed under this CED. Additionally, the CGI-S and the CGI-I that were used in the Rush et al. (2005a) are examples of tools that can measure general psychiatric status.

Consistent with previous research, we believe it is important to capture changes in suicidality. An example of an appropriate measure of suicidality would be the MADRS Item 10, as used in Aaronson et al. (2017).

Patient Criteria

A universally accepted definition of treatment resistant depression has yet to be achieved (Al-Harbi, 2012; De Carlo, Calati, & Seretti, 2016; Gaynes et al., 2018; McIntyre et al., 2014; Medicare Evidence Development & Coverage Advisory Committee, 2016; Milev et al., 2016). This circumstance results in difficulty when attempting to synthesize information across various medical trials. Therefore we are proposing specific criteria to define TRD.

The three stage diagnostic process described in the technology assessment (Gaynes et al, 2018) corresponds closely to that of the Rush et al. (2005a) study, is feasible to administer, and will aid in the standardization of all the CED studies. Similar to the requirements of Rush et al. (2005a), we propose that all subjects must have been in a MDD episode for ≥ two years or have had at least four lifetime episodes of MDD, including the current episode. We propose that MDD in all subjects must have been confirmed by using accepted diagnostic criteria from the most current edition of the DSM. We are also proposing that a structured clinical assessment, such as the Mini International Neuropsychiatric Interview (MINI), also confirm the diagnosis, as was suggested in Gaynes et al. (2018) and performed in Aaronson et al. (2017).

Rush et al. (2005a) required that subjects also have had an unsatisfactory response to at least two classes of antidepressant medications, but not more than six, with trial adequacy being determined by the ATHF. We are proposing to modify this requirement to be consistent with the FDA indication for VNS in the treatment of depression. We propose that adequate dose and duration of antidepressant treatments be determined by a tool designed for that purpose, such as the ATHF used by Rush et al. (2005a).

To confirm that a patient is in a major depressive episode, participants in Rush et al. (2005a) had to score ≥ 20 (the average of two baseline measurements) on the Hamilton Rating Scale for Depression-24 ($HRSD_{24}$) on two visits, over a 45 day span before implantation of the VNS device. Therefore, we propose that patients demonstrate a current major depressive episode (MDE) measured by a guideline recommended depression scale assessment tool, such as the $HRSD_{24}$, on two visits, within a 45-day span prior to implantation of the VNS device.

Because of its historical importance and the rigor of its design, the remaining patient criteria listed in this proposed decision memorandum were primarily based on the Rush et al. (2005a) study. It is important to note that patients with current or a history of bipolar disease are excluded from this research study. TRD within bipolar disorder is a distinct entity from MDD (Burcusa & Iacono, 2007; Gaynes et al, 2018) and thus will not be considered in this CED.

Study Blinding

Rush et al. (2005a) described specific stimulation parameters for the ten week study. Since the proposed CED study is of a much longer duration, stimulation parameters are not specified at any time after the surgical recovery period. To preserve the blind, the un-blinded programmer, who has no other patient care responsibilities, obtains the randomization assignment for each patient The programmer administers the initiation and follow-up parameters of the stimulation for those with an active VNS as well as simulates the same in those participants with placebo VNS. The programmer also turns off the device at clinic visits to prevent the occurrence of voice alterations during periods of assessment.

Health Disparities

Previous studies have shown that minority groups are less likely to be screened for depression and other mental disorders when compared to non-Latino whites, and are also less likely to access mental health treatment (Alegria et al., 2008; Hahm, Cook, Ault-Brutus, & Alegria, 2015). It has also been shown that men are less likely to be screened for mental health disorders or to access mental health than women (Hahm et al., 2015). Studies examining disparities in gender for the treatment of depression have revealed that women experience depression at a higher rate than men earlier in life, however this difference has been shown to subside around age 55 and

continues to be insignificant into later adulthood (Bebbington et al., 2003; Pachana, McLaughlin, Leung, Byrne, & Dobson, 2012).

Additionally, there is considerable heterogeneity in studies of TRD (Gaynes et al., 2018). Some of this may result from the lack of study of socio-cultural factors that may influence the course and treatment of depression (e.g. age, gender, marital status, etc). We encourage investigators to study these factors which may be relevant to improving the evidence base.

Summary

TRD is a concerning condition for the Medicare population as well as the general population. While there are suggestions in the literature that VNS may be a useful strategy for select individuals with this disease, we must consider that approximately 11% of the 59 million Medicare beneficiaries have claims submitted on their behalf for the diagnosis of depression (CMS Chronic Conditions Data Warehouse). Of these approximately six million individuals, it has been estimated that 10% to 33% will likely exhibit characteristics of TRD (Fava & Davidson, 1996; Kubitz, Mehra, Potluri, Garg & Cossrow, 2013; Mrazek, Hornberger, Altar & Degtiar, 2014).

Based on the evidence, we believe that VNS for TRD seems promising but not convincing. Coverage in the context of ongoing clinical research helps assure that the technology is provided to appropriate patients in controlled settings while developing evidence that the treatment improves health outcomes. To ensure benefits to Medicare beneficiaries we are proposing to cover VNS for the treatment of TRD when offered in double-blind, randomized, placebo-controlled studies.

IX. Conclusion (Proposed Decision)

CMS is proposing changes to the vagus nerve stimulation (VNS) NCD (160.18) for VNS for treatment resistant depression (TRD) that would expand Medicare coverage. The scope of this reconsideration is limited to VNS for TRD.

A. The Centers for Medicare & Medicaid Services (CMS) proposes to cover FDA approved vagus nerve stimulation (VNS) devices for treatment resistant depression (TRD) through Coverage with Evidence Development (CED) when offered in a CMS approved, double-blind, randomized, placebo-controlled trial with a follow-up duration of at least one year with the possibility of extending the study to a prospective longitudinal study when the CMS approved, double-blind, randomized placebo-controlled trial has completed enrollment, and there are positive interim primary endpoint findings.

B. Covered Indications

Each study must be approved by CMS and as a fully-described, written part of its protocol, must address if VNS improves health outcomes for individuals with TRD through the following research questions below. The details of the prospective longitudinal study must be described in the original protocol for the double-blind, randomized, placebo-controlled trial.

Primary Outcomes:

- What is the rate of remission score achievement per subject month (four weeks) of follow-up as measured by a guideline recommended depression scale assessment tool?
- What is the time from treatment until remission scores are first achieved for a consecutive two-month (eight-week) duration?
- Of those patients that achieved remission scores for a consecutive two-month period, how many

consecutive months were these remission scores maintained?
- What are the patient variables associated with successful treatment of TRD with VNS?
- What are the observed harms?

Secondary Outcomes:

- What are the changes in disability and quality of life?
- What are the changes in general psychiatric status?
- What are the changes in suicidality?

Patient Criteria

- The following criteria must be used to identify patients demonstrating TRD:
  - The patient must be in a major depressive disorder (MDD) episode for ≥ two years or have had at least four episodes of MDD, including the current episode. In order to confirm the patient has MDD, accepted diagnostic criteria from the most current edition of the Diagnostic and Statistical Manual for Mental Disorder (DSM) and a structured clinical assessment are to be used.
  - The patient's depressive illness meets a minimum criterion of four prior failed treatments of adequate dose and duration as measured by a tool designed for this purpose.
  - The patient is experiencing a major depressive episode (MDE) as measured by a guideline recommended depression scale assessment tool on two visits, within a 45-day span prior to implantation of the VNS device.
- Patients must not have had a substantial response to at least six weeks of psychotherapy during any MDE.
- Patients must maintain a stable medication regimen for at least four weeks before device implantation.
- Patients must not have:
  - Current or lifetime history of atypical or psychotic features in any MDE;
  - Current or lifetime history of any non-mood psychotic disorder (e.g., schizophrenia);
  - Current or lifetime history of bipolar disorder;
  - Current secondary diagnosis of delirium, dementia, amnesia, or other cognitive disorder;
  - Current suicidal intent; or
  - Treatment with another investigational device or investigational drugs.
- Individuals who receive placebo VNS will be offered active VNS at the end of the trial.

In addition, CMS will review studies to determine if they meet the 13 criteria listed below. If CMS determines that they meet these criteria, the study will be posted on CMS' CED website (https://www.cms.gov/Medicare/Coverage/Coverage-with-Evidence-Development/index.html).

a. The principal purpose of the study is to test whether the item or service meaningfully improves health outcomes of affected beneficiaries who are represented by the enrolled subjects.
b. The rationale for the study is well supported by available scientific and medical evidence.
c. The study results are not anticipated to unjustifiably duplicate existing knowledge.
d. The study design is methodologically appropriate and the anticipated number of enrolled subjects is sufficient to answer the research question(s) being asked in the National Coverage Determination.
e. The study is sponsored by an organization or individual capable of completing it successfully.
f. The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found in the Code of Federal Regulations (CFR) at 45 CFR Part 46. If a study is regulated by the Food and Drug Administration (FDA), it is also in compliance with 21 CFR Parts 50 and 56. In addition, to further enhance the protection of human subjects in studies conducted under CED, the study must provide and obtain meaningful informed consent from patients regarding the risks associated with the study items and/or services, and the use and eventual disposition of the collected data.
g. All aspects of the study are conducted according to appropriate standards of scientific integrity.
h. The study has a written protocol that clearly demonstrates adherence to the standards listed here as Medicare requirements.

i. The study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Such studies may meet this requirement only if the disease or condition being studied is life threatening as defined in 21 CFR §312.81(a) and the patient has no other viable treatment options.
j. The clinical research studies and registries are registered on the www.ClinicalTrials.gov website by the principal sponsor/investigator prior to the enrollment of the first study subject. Registries are also registered in the Agency for Healthcare Quality (AHRQ) Registry of Patient Registries (RoPR).
k. The research study protocol specifies the method and timing of public release of all prespecified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early. The results must be made public within 12 months of the study's primary completion date, which is the date the final subject had final data collection for the primary endpoint, even if the trial does not achieve its primary aim. The results must include number started/completed, summary results for primary and secondary outcome measures, statistical analyses, and adverse events. Final results must be reported in a publicly accessibly manner; either in a peer-reviewed scientific journal (in print or on-line), in an on-line publicly accessible registry dedicated to the dissemination of clinical trial information such as ClinicalTrials.gov, or in journals willing to publish in abbreviated format (e.g., for studies with negative or incomplete results).
l. The study protocol must explicitly discuss beneficiary subpopulations affected by the item or service under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria effect enrollment of these populations, and a plan for the retention and reporting of said populations in the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary.
m. The study protocol explicitly discusses how the results are or are not expected to be generalizable to affected beneficiary subpopulations. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicaid eligibility.

Consistent with section 1142 of the Act, the Agency for Healthcare Research and Quality (AHRQ) supports clinical research studies that CMS determines meet the above-listed standards and address the above-listed research questions.

The principal investigator must submit the complete study protocol, identify the relevant CMS research questions that will be addressed and cite the location of the detailed analysis plan for those questions in the protocol, plus provide a statement addressing how the study satisfies each of the standards of scientific integrity (a. through m. listed above), as well as the investigator's contact information, to the address below. The information will be reviewed, and approved studies will be identified on the CMS website.

Director, Coverage and Analysis Group
Centers for Medicare & Medicaid Services (CMS)
7500 Security Blvd., Mail Stop S3-02-01
Baltimore, MD 21244-1850

C. Nationally Non-Covered Indications

VNS is non-covered for the treatment of TRD when furnished outside of a CMS approved CED study.

All other indications of VNS for the treatment of depression are nationally non-covered.

D. Other

Patients implanted with a VNS device for TRD may receive a VNS device replacement if it is required due to the end of battery life, or any other device-related malfunction.

See Appendix B for the proposed manual language.

CMS is seeking comments on our proposed decision. We will respond to public comments in a final decision memorandum, as required by §1862(l)(3) of the Social Security Act (the Act).

APPENDIX A
General Methodological Principles of Study Design

(Section VI of the Decision Memorandum)

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service is reasonable and necessary. The overall objective for the critical appraisal of the evidence is to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients.

We divide the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the generalizability of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention's potential risks and benefits.

The methodological principles described below represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has its unique methodological aspects.

Assessing Individual Studies

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

- Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.
- Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.
- Prospective (rather than retrospective) studies to ensure a more thorough and systematical assessment of factors related to outcomes.
- Larger sample sizes in studies to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.
- Masking (blinding) to ensure patients and investigators do not know to that group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the primary criterion for methodological strength or quality is to the extent that differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

- Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias).

- Co-interventions or provision of care apart from the intervention under evaluation (performance bias).
- Differential assessment of outcome (detection bias).
- Occurrence and reporting of patients who do not complete the study (attrition bias).

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, in general, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The design, conduct and analysis of trials are important factors as well. For example, a well-designed and conducted observational study with a large sample size may provide stronger evidence than a poorly designed and conducted randomized controlled trial with a small sample size. The following is a representative list of study designs (some of that have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

Randomized controlled trials
Non-randomized controlled trials
Prospective cohort studies
Retrospective case control studies
Cross-sectional studies
Surveillance studies (e. g., using registries or surveys)
Consecutive case series
Single case reports

When there are merely associations but not causal relationships between a study's variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in that confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess and consider the evidence.

Generalizability of Clinical Evidence to the Medicare Population

The applicability of the results of a study to other populations, settings, treatment regimens and outcomes assessed is known as external validity. Even well-designed and well-conducted trials may not supply the evidence needed if the results of a study are not applicable to the Medicare population. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to that the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease and presence of co-morbidities) and the care setting (primary to tertiary level of care, as well as the experience and specialization of the care provider). Additional relevant variables are treatment regimens (dosage, timing and route of administration), co-interventions or concomitant therapies, and type of outcome and length of follow-up.

The level of care and the experience of the providers in the study are other crucial elements in assessing a study's external validity. Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings. For example, an investigator's lengthy and detailed explanations of the potential benefits of the intervention and/or the use of new equipment provided to the academic center by the study sponsor may raise doubts about the applicability of study findings to community practice.

Given the evidence available in the research literature, some degree of generalization about an intervention's potential benefits and harms is invariably required in making coverage determinations for the Medicare population. Conditions that assist us in making reasonable generalizations are biologic plausibility, similarities between the populations studied and Medicare patients (age, sex, ethnicity and clinical presentation) and similarities of the intervention studied to those that would be routinely available in community practice.

A study's selected outcomes are an important consideration in generalizing available clinical evidence to Medicare coverage determinations. One of the goals of our determination process is to assess health outcomes. These outcomes include resultant risks and benefits such as increased or decreased morbidity and mortality. In order to make this determination, it is often necessary to evaluate whether the strength of the evidence is adequate to draw conclusions about the direction and magnitude of each individual outcome relevant to the intervention under study. In addition, it is important that an intervention's benefits are clinically significant and durable, rather than marginal or short-lived. Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits.

If key health outcomes have not been studied or the direction of clinical effect is inconclusive, we may also evaluate the strength and adequacy of indirect evidence linking intermediate or surrogate outcomes to our outcomes of interest.

Assessing the Relative Magnitude of Risks and Benefits

Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits. Health outcomes are one of several considerations in determining whether an item or service is reasonable and necessary. CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses. The direction, magnitude, and consistency of the risks and benefits across studies are also important considerations. Based on the analysis of the strength of the evidence, CMS assesses the relative magnitude of an intervention or technology's benefits and risk of harm to Medicare beneficiaries.

APPENDIX B
Medicare National Coverage Determinations Manual

Draft

We are seeking public comments on the proposed language that we would include in the Medicare National Coverage Determinations Manual. This proposed language does not reflect public comments that will be received on the proposed decision memorandum, and which may be revised in response to those comments.

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(Rev.)

[XXX.X]

A. General

VNS is a pulse generator, similar to a pacemaker, that is surgically implanted under the skin of the left chest and an electrical lead (wire) is connected from the generator to the left vagus nerve. Electrical signals are sent from the battery-powered generator to the vagus nerve via the lead. These signals are in turn sent to the brain. FDA approved VNS for treatment of refractory epilepsy in 1997 and for resistant depression in 2005.

B. Nationally Covered Indications

Effective for services performed on or after July 1, 1999, 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.

Effective for services performed on or after [Month/XX][Day/XX], [20XX] CMS proposes to cover FDA approved vagus nerve stimulation (VNS) devices for treatment resistant depression (TRD) through Coverage with Evidence Development (CED) when offered in a CMS approved, double-blind, randomized, placebo-controlled trial with a follow-up duration of at least one year with the possibility of extending the study to a prospective longitudinal study when the CMS approved, double-blind, randomized placebo-controlled trial has completed enrollment, and there are positive interim primary endpoint findings.

Each study must be approved by CMS and as a fully-described, written part of its protocol, must address if VNS improves health outcomes for individuals with TRD through the following research questions below. The details of the prospective longitudinal study must be described in the original protocol for the double-blind, randomized, placebo-controlled trial.

Primary Outcomes:

- What is the rate of remission score achievement per subject month (four weeks) of follow-up as measured by a guideline recommended depression scale assessment tool?
- What is the time from treatment until remission scores are first achieved for a consecutive two-month (eight-week) duration?
- Of those patients that achieved remission scores for a consecutive two-month period, how many consecutive months were these remission scores maintained?
- What are the patient variables associated with successful treatment of TRD with VNS?
- What are the observed harms?

Secondary Outcomes:

- What are the changes in disability and quality of life?
- What are the changes in general psychiatric status?
- What are the changes in suicidality?

Patient Criteria

- The following criteria must be used to identify patients demonstrating TRD:
  - The patient must be in a major depressive disorder (MDD) episode for ≥ two years or have had at least four episodes of MDD, including the current episode. In order to confirm the patient has MDD, accepted

diagnostic criteria from the most current edition of the Diagnostic and Statistical Manual for Mental Disorder (DSM) and a structured clinical assessment are to be used.
    - The patient's depressive illness meets a minimum criterion of four prior failed treatments of adequate dose and duration as measured by a tool designed for this purpose.
    - The patient is experiencing a major depressive episode (MDE) as measured by a guideline recommended depression scale assessment tool on two visits, within a 45-day span prior to implantation of the VNS device.
- Patients must not have had a substantial response to at least 6 weeks of psychotherapy during any MDE.
- Patients must maintain a stable medication regimen for at least 4 weeks before device implantation.
- Patients must not have:
    - Current or lifetime history of atypical or psychotic features in MDE;
    - Current or lifetime history of any non-mood psychotic disorder (e.g., schizophrenia);
    - Current or lifetime history of bipolar disorder;
    - Current secondary diagnosis of delirium, dementia, amnesia, or other cognitive disorder;
    - Current suicidal intent; or
    - Treatment with another investigational device or investigational drugs.
- Individuals who receive placebo VNS will be offered active VNS at the end of the trial.

In addition, CMS will review studies to determine if they meet the 13 criteria listed below. If CMS determines that they meet these criteria, the study will be posted on CMS' CED website (https://www.cms.gov/Medicare/Coverage/Coverage-with-Evidence-Development/index.html).

a. The principal purpose of the study is to test whether the item or service meaningfully improves health outcomes of affected beneficiaries who are represented by the enrolled subjects.
b. The rationale for the study is well supported by available scientific and medical evidence.
c. The study results are not anticipated to unjustifiably duplicate existing knowledge.
d. The study design is methodologically appropriate and the anticipated number of enrolled subjects is sufficient to answer the research question(s) being asked in the National Coverage Determination.
e. The study is sponsored by an organization or individual capable of completing it successfully.
f. The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found in the Code of Federal Regulations (CFR) at 45 CFR Part 46. If a study is regulated by the Food and Drug Administration (FDA), it is also in compliance with 21 CFR Parts 50 and 56. In addition, to further enhance the protection of human subjects in studies conducted under CED, the study must provide and obtain meaningful informed consent from patients regarding the risks associated with the study items and/or services, and the use and eventual disposition of the collected data.
g. All aspects of the study are conducted according to appropriate standards of scientific integrity.
h. The study has a written protocol that clearly demonstrates adherence to the standards listed here as Medicare requirements.
i. The study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Such studies may meet this requirement only if the disease or condition being studied is life threatening as defined in 21 CFR §312.81(a) and the patient has no other viable treatment options.
j. The clinical research studies and registries are registered on the www.ClinicalTrials.gov website by the principal sponsor/investigator prior to the enrollment of the first study subject. Registries are also registered in the Agency for Healthcare Quality (AHRQ) Registry of Patient Registries (RoPR).
k. The research study protocol specifies the method and timing of public release of all prespecified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early. The results must be made public within 12 months of the study's primary completion date, which is the date the final subject had final data collection for the primary endpoint, even if the trial does not achieve its primary aim. The results must include number started/completed, summary results for primary and secondary outcome measures, statistical analyses, and adverse events. Final results must be reported in a publicly accessibly manner; either in a peer-reviewed scientific journal (in print or on-line), in an on-line publicly accessible

registry dedicated to the dissemination of clinical trial information such as ClinicalTrials.gov, or in journals willing to publish in abbreviated format (e.g., for studies with negative or incomplete results).

l. The study protocol must explicitly discuss beneficiary subpopulations affected by the item or service under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria effect enrollment of these populations, and a plan for the retention and reporting of said populations in the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary.

m. The study protocol explicitly discusses how the results are or are not expected to be generalizable to affected beneficiary subpopulations. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicaid eligibility.

Consistent with section 1142 of the Act, the Agency for Healthcare Research and Quality (AHRQ) supports clinical research studies that CMS determines meet the above-listed standards and address the above-listed research questions. All other indications are nationally non-covered.

The principal investigator must submit the complete study protocol, identify the relevant CMS research questions that will be addressed and cite the location of the detailed analysis plan for those questions in the protocol, plus provide a statement addressing how the study satisfies each of the standards of scientific integrity (a. through m. listed above), as well as the investigator's contact information, to the address below. The information will be reviewed, and approved studies will be identified on the CMS website.

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Baltimore, MD 21244-1850

C. Nationally Non-Covered Indications

Effective for services performed on or after July 1, 1999, VNS is not reasonable and necessary for all other types of seizure disorders which are medically refractory and for whom surgery is not recommended or for whom surgery has failed.

VNS is non-covered for the treatment of TRD when furnished outside of a CMS approved CED study.

All other indications of VNS for the treatment of depression are nationally non-covered.

D. Other

Also see §160, "Electrical Nerve Stimulators."

Patients implanted with a VNS device for TRD may receive a VNS device replacement if it is required due to the end of battery life, or any other device-related malfunction.

APPENDIX C – NCD 160.18 (Effective 5/4/2007)

A. General

VNS is a pulse generator, similar to a pacemaker, that is surgically implanted under the skin of the left chest and an electrical lead (wire) is connected from the generator to the left vagus nerve. Electrical signals are sent from the battery-powered generator to the vagus nerve via the lead. These signals are in turn sent to the brain. FDA approved VNS for treatment of refractory epilepsy in 1997 and for resistant depression in 2005.

B. Nationally Covered Indications

Effective for services performed on or after July 1, 1999, 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.

C. Nationally Non-Covered Indications

Effective for services performed on or after July 1, 1999, VNS is not reasonable and necessary for all other types of seizure disorders which are medically refractory and for whom surgery is not recommended or for whom surgery has failed.

Effective for services performed on or after May 4, 2007, VNS is not reasonable and necessary for resistant depression. (Information on the national coverage analysis leading to this determination can be found at: http://www.cms.gov/mcd/viewnca.asp?where=index&nca_id=195.)

D. Other

Also see §160, "Electrical Nerve Stimulators."

(This NCD last reviewed May 2007.)

APPENDIX D – Depressive Measures

Measure		Reference
CGI-S and CGI-I	The Clinical Global Impressions Scale provides a clinician's assessment of two measures. The first is the CGI-Severity (CGI-S) which asks the clinician to evaluate the severity of the psychopathology manifested by the patient (scale of 1-7). The second is the CGI-Improvement (CGI-I), which assesses the global improvement or change demonstrated by the patient (scale 1-7). The score of 1 in both assessments indicates the best possible circumstance; the score of 7 indicates the worst possible circumstance.	Clinical Global Impression (CGI).
HDRS, HAMD,HAM-D	Hamilton Depression Rating Scale is a commonly used outcome scale in depression treatment studies. It is a clinician rated measure. Various versions exist, including those that contain 17, 21, 24, and 25 items that are summed to yield a total score. Higher scores indicate more severe disease.	Gaynes et al., 2018

IDS	Inventory of Depressive Symptomatology investigates 30 items which are believed to correlate with the symptoms of depression. Twenty-eight of these items are summed for scoring. The IDS can be administered as either a clinician-rated (IDS-C) tool or a self-report (IDS-SR) scale. The seven-day period prior to assessment is the usual time frame for assessing symptom severity. More severe depression is represented by higher scores.	Inventory of Depressive Symptomatology (IDS) and Quick Inventory of Depressive Symptomatology (QIDS), IDS/QIDS.
MADRS	The Montgomery–Åsberg Depression Scale is a 10-item clinician-rated scale measuring severity of depressive symptoms. Items are rated on a 7-point Likert scale (from 0 to 6) and added to provide a total score (range 0–60). Like the HDRS, it is a clinician rated outcome measure. Higher scores indicate more severe disease.	Bondolfi et al., 2010
WHODAS 2.0	The World Health Organization Disability Assessment Scale Schedule 2.0 is a patient self-report assessment tool that generates a global disability score through the evaluation of six domains of functioning over the previous 30 days. The domains include: cognition (including communication); mobility; self-care; social and interpersonal functioning; home, academic and occupational functioning; and participation in family, social and community activities. Higher scores indicate more difficulty performing an activity. The WHODAS also provides a proxy administered and clinician obtained tool, that is not being required in the CED decision.	Gold, 2014 Measuring Health and Disability, Manual for WHO Disability Assessment Schedule WHODAS 2.0.

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Brief Summary[1] of Safety Information for the VNS Therapy® System [Epilepsy and Depression Indication] June 2017

1. INTENDED USE / INDICATIONS

Epilepsy (US)—The VNS Therapy System is indicated for use as an adjunctive therapy in reducing the frequency of seizures in patients 4 years of age and older with partial onset seizures that are refractory to antiepileptic medications. (Models 102, 102R, 103, 104, 105, 106)

Depression (US)—The VNS Therapy System is indicated for the adjunctive long-term treatment of chronic or *recurrent depression* for patients 18 years of age or older who are experiencing a major depressive episode and have not had an adequate response to four or more adequate *antidepressant treatments*. (Models 102, 102R, 103, 104, 105)

2. CONTRAINDICATIONS

Vagotomy—The VNS Therapy System cannot be used in patients after a bilateral or left cervical vagotomy.

Diathermy—Do not use short-wave diathermy, microwave diathermy, or therapeutic ultrasound diathermy on patients implanted with a VNS Therapy System. Diagnostic ultrasound is not included in this contraindication.

3. WARNINGS — GENERAL

Physicians should inform patients about all potential risks and adverse events discussed in the physician's manuals. This document is not intended to serve as a substitute for the complete physician's manuals.

The safety and efficacy of the VNS Therapy System have not been established for uses outside the “Intended Use/Indications” section of the physician's manuals.

The safety and effectiveness of the VNS Therapy System in patients with predisposed dysfunction of cardiac conduction systems (re-entry pathway) have not been established. Post-implant electrocardiograms and Holter monitoring are recommended if clinically indicated.

Postoperative bradycardia can occur among patients with certain underlying cardiac arrhythmias.

It is important to follow recommended implantation procedures and intraoperative product testing described in the *Implantation Procedur*e part of the physician's manuals. During the intraoperative System Diagnostics (Lead Test), infrequent incidents of bradycardia and/or asystole have occurred. If asystole, severe bradycardia (heart rate < 40 bpm), or a clinically significant change in heart rate is encountered during a System Diagnostics (Lead Test) or during initiation of stimulation, physicians should be prepared to follow guidelines consistent with Advanced Cardiac Life Support (ACLS).

Difficulty swallowing (dysphagia) may occur with active stimulation, and aspiration may result from the increased swallowing difficulties. Patients with pre-existing swallowing difficulties and those with a history of drooling or hypersalivation are at greater risk for aspiration. Use of the magnet to temporarily stop stimulation while eating may mitigate the risk of aspiration.

Dyspnea (shortness of breath) may occur with active VNS Therapy. Any patient with underlying pulmonary disease or insufficiency such as chronic obstructive pulmonary disease or asthma may be at increased risk for dyspnea.

Patients with obstructive sleep apnea (OSA) may have an increase in apneic events during stimulation. Lowering stimulus frequency or prolonging “OFF” time may prevent exacerbation of OSA. Vagus nerve stimulation may also cause new onset sleep apnea in patients who have not previously been diagnosed with this disorder.

Device malfunction could cause painful stimulation or direct current stimulation. Either event could cause nerve damage. Patients should be instructed to use the magnet to stop stimulation if they suspect a malfunction, and then to contact their physician immediately for further evaluation.

Patients with the VNS Therapy System, or any part of the VNS Therapy System, implanted should have MRI procedures performed only as described in the *MRI with the VNS Therapy System* instructions for use. In some cases, surgery will be required to remove the VNS Therapy System if a scan using a transmit RF body coil is needed.

Excessive stimulation at an excess duty cycle (that is, one that occurs when “ON” time is greater than “OFF” time) and high frequency stimulation (i.e., stimulation at ≥ 50 Hz) has resulted in degenerative nerve damage in laboratory animals.

Patients who manipulate the pulse generator and lead through the skin (Twiddler’s Syndrome) may damage or disconnect the lead from the pulse generator and/or possibly cause damage to the vagus nerve.

Cardiac arrhythmia (Model 106 only)—The AutoStim Mode feature should not be used in patients with clinically meaningful arrhythmias currently being managed by devices or treatments that interfere with normal intrinsic heart rate responses (e.g., pacemaker dependency, implantable defibrillator, beta adrenergic blocker medications). Patients also should not have a history of chronotropic incompetence [commonly seen in patients with sustained bradycardia (heart rate < 50 bpm)].

Pre-surgical Surface Assessment (Model 106 only)—For anticipated use of the AutoStim feature, it is important to follow the recommended pre-surgical surface assessment described in the Implantation Procedure to determine a location for the pulse generator to reside in which it can accurately detect heart beats

4. WARNINGS — EPILEPSY

The VNS Therapy System should only be prescribed and monitored by physicians who have specific training and expertise in the management of seizures and the use of this device. It should only be implanted by physicians who are trained in surgery of the carotid sheath and have received specific training in the implantation of this device.

The VNS Therapy System is not curative. Physicians should warn patients that the VNS Therapy System is not a cure for epilepsy and that since seizures may occur unexpectedly, patients should consult with a physician before engaging in unsupervised activities, such as driving, swimming, and bathing, and in strenuous sports that could harm them or others.

Sudden unexplained death in epilepsy (SUDEP): Through August 1996, 10 sudden and unexplained deaths (definite, probable, and possible) were recorded among the 1,000 patients implanted and treated with the VNS Therapy device. During this period, these patients had accumulated 2,017 patient-years of exposure. Some of these deaths could represent seizure-related deaths in which the seizure was not observed, at night, for example. This number represents an incidence of 5.0 definite, probable, and possible SUDEP deaths per 1,000 patient-years. Although this rate exceeds that expected in a healthy (nonepileptic) population matched for age and sex, it is within the range of estimates for epilepsy patients not receiving vagus nerve stimulation, ranging from 1.3 SUDEP deaths for the general population of patients with epilepsy, to 3.5 (for definite and probable) for a recently studied antiepileptic drug (AED) clinical trial population similar to the VNS Therapy System clinical cohort, to 9.3 for patients with medically intractable epilepsy who were epilepsy surgery candidates.

5. WARNINGS — DEPRESSION

This device is a permanent implant. It is only to be used in patients with severe depression who are unresponsive to standard psychiatric management. It should only be prescribed and monitored by physicians who have specific training and expertise in the management of treatment-resistant depression and the use of this device. It should only be implanted by physicians who are trained in surgery of the carotid sheath and have received specific training in the implantation of this device.

Physicians should warn patients that VNS Therapy has not been determined to be a cure for depression.

Patients being treated with adjunctive VNS Therapy should be observed closely for clinical worsening and suicidality, especially at the time of VNS Therapy stimulation parameter changes or drug or drug dose changes.

Excessive stimulation: *Note:* Use of the magnet to activate stimulation is not recommended for patients with depression.

6. PRECAUTIONS — GENERAL

Physicians should inform patients about all potential risks and adverse events discussed in the VNS Therapy physician's manuals.

Prescribing physicians should be experienced in the diagnosis and treatment of depression or epilepsy and should be familiar with the programming and use of the VNS Therapy System.

Physicians who implant the VNS Therapy System should be experienced performing surgery in the carotid sheath and should be trained in the surgical technique relating to implantation of the VNS Therapy System.

The safety and effectiveness of the VNS Therapy System have not been established for use during pregnancy. VNS should be used during pregnancy only if clearly needed.

[1] The information contained in this Brief Summary for Physicians represents partial excerpts of important prescribing information taken from the physician’s manuals. (Copies of VNS Therapy physician’s and patient’s manuals are posted at www.cyberonics.com.) The information is not intended to serve as a substitute for a complete and thorough understanding of the material presented in all of the physician’s manuals for the VNS Therapy System and its component parts nor does this information represent full disclosure of all pertinent information concerning the use of this product, potential safety complications, or efficacy outcomes.

The VNS Therapy System is indicated for use only in stimulating the left vagus nerve in the neck area inside the carotid sheath. The VNS Therapy System is indicated for use only in stimulating the **left vagus nerve below where the superior and inferior cervical cardiac branches separate from the vagus nerve**.

It is important to follow infection control procedures. Infections related to any implanted device are difficult to treat and may require that the device be explanted. The patient should be given antibiotics preoperatively. The surgeon should ensure that all instruments are sterile prior to the procedure. Children 4-11 years of age may have a greater risk for infection when compared to adolescent and adult patients (≥ 12 years). Careful monitoring for site infection as well as the avoidance of manipulation of the surgical site post implant in children should be stressed.

The VNS Therapy System may affect the operation of other implanted devices, such as cardiac pacemakers and implanted defibrillators. Possible effects include sensing problems and inappropriate device responses. If the patient requires concurrent implantable pacemaker, defibrillatory therapy or other types of stimulators, careful programming of each system may be necessary to optimize the patient's benefit from each device.

Reversal of lead polarity has been associated with an increased chance of bradycardia in animal studies. It is important that the electrodes are attached to the left vagus nerve in the correct orientation. It is also important to make sure that leads with dual connector pins are correctly inserted (white marker band to + connection) into the pulse generator's lead receptacles.

The patient can use a neck brace for the first week to help ensure proper lead stabilization.

Do not program the VNS Therapy System to an "ON" or periodic stimulation treatment for at least 14 days after the initial or replacement implantation.

For Models 102 and 102R do not use frequencies of 5 Hz or below for long-term stimulation.

Resetting the pulse generator disables or turns the device OFF (output current = 0 mA). For Models 102 and 102R resetting the pulse generator will result in device history loss.

Patients who smoke may have an increased risk of laryngeal irritation.

U**nintended Stimulation (Model 106 only)**—Because the device senses changes in heart rate, false positive detection may cause unintended stimulation. Examples of instances where the heart rate may increase include exercise, physical activity, and normal autonomic changes in heart rate, both awake and asleep, etc. Adjustments to the AutoStim feature's detection threshold should be considered; which may include turning the feature OFF.

Device Placement (Model 106 only)—The physical location of the device critically affects the feature's ability to properly sense heart beats. Care must be taken to follow the implant location selection process outlined in the Implantation Procedure.

Battery Drain (Model 106 only)—Talk to your patient about use of the AutoStim feature since use of the feature will result in faster battery drain and the potential for more frequent device replacements. The physician's manual describes the impacts to the battery life. The patient should return to their physician at appropriate intervals to further evaluate whether they are receiving benefit from the current AutoStim settings.

7. Environmental and Medical Therapy Hazards

Patients should exercise reasonable caution in avoiding devices that generate a strong electric or magnetic field. If a pulse generator ceases operation while in the presence of electromagnetic interference (EMI), moving away from the source may allow it to return to its normal mode of operation.

VNS Therapy System operation **should always be checked** by performing device diagnostics after any of the procedures mentioned in the physician's manuals.

For clear imaging, patients may need to be specially positioned for mammography procedures, because of the location of the pulse generator in the chest.

Therapeutic radiation may damage the pulse generator's circuitry, although no testing has been done to date and no definite information on radiation effects is available. Sources of such radiation include therapeutic radiation, cobalt machines, and linear accelerators. The radiation effect is cumulative, with the total dosage determining the extent of damage. The effects of exposure to such radiation can range from a temporary disturbance to permanent damage, and may not be detectable immediately.

External defibrillation may damage the pulse generator.

Use of electrosurgery [electrocautery or radio frequency (RF) ablation devices] may damage the pulse generator.

Magnetic resonance imaging (MRI) should not be performed using a transmit RF body coil for certain VNS therapy device configurations or under certain specific conditions. In some cases, heating of the lead caused by the transmit RF body coil during MRI may result in serious injury. Static, gradient, and radio frequency (RF) electromagnetic fields associated with MRI may change the pulse generator settings (i.e., reset parameters) or activate the VNS device if the Magnet Mode output remains "ON". Note that certain magnetic resonance (MR) system head coils operate in receive-only mode and require use of the transmit RF body coil. Other MR systems use a transmit/receive RF head coil. Local or surface coils may also be receive-only RF coils that require the transmit RF body coil for MRI. **The use of a receive RF coil does not alter hazards of the transmit RF body coil.** Exposure of the VNS Therapy System to any transmit RF coil must be avoided. Do not perform MRI scans using any transmit RF coil in the defined exclusion zones. See *MRI with the VNS Therapy System* instructions for use for details or further instructions for special cases such as lead breaks or partially explanted VNS Therapy systems.

Extracorporeal shockwave lithotripsy may damage the pulse generator. If therapeutic ultrasound therapy is required, avoid positioning the area of the body where the pulse generator is implanted in the water bath or in any other position that would expose it to ultrasound therapy. If that positioning cannot be avoided, program the pulse generator output to 0 mA for the treatment, and then after therapy, reprogram the pulse generator to the original parameters.

If the patient receives medical treatment for which electric current is passed through the body (such as from a TENS unit), either the pulse generator should be set to 0 mA or function of the pulse generator should be monitored during initial stages of treatment.

Routine therapeutic ultrasound could damage the pulse generator and may be inadvertently concentrated by the device, causing harm to the patient.

For complete information related to home occupational environments, cellular phones, other environmental hazards, other devices, and ECG monitors, refer to the physician's manuals.

8. Adverse Events — Epilepsy

Adverse events reported during clinical studies as statistically significant are listed below in alphabetical order: ataxia (loss of the ability to coordinate muscular movement); dyspepsia (indigestion); dyspnea (difficulty breathing, shortness of breath); hypesthesia (impaired sense of touch); increased coughing; infection; insomnia (inability to sleep); laryngismus (throat, larynx spasms); nausea; pain; paresthesia (prickling of the skin); pharyngitis (inflammation of the pharynx, throat); voice alteration (hoarseness); vomiting.

9. Adverse Events — Depression

Implant-related adverse events reported during the pivotal study in ≥ 5% of patients are listed in order of decreasing occurrence: incision pain, voice alteration, incision site reaction, device site pain, device site reaction, pharyngitis, dysphagia, hypesthesia, dyspnea, nausea, headache, neck pain, pain, paresthesia, and cough increased.

Stimulation-related adverse events reported during the acute sham-controlled study by ≥ 5% of VNS Therapy-treated patients are listed in order of decreasing occurrence: voice alteration, cough increased, dyspnea, neck pain, dysphagia, laryngismus, paresthesia, pharyngitis, nausea, and incision pain.

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[redacted]

From: Nicole Curtis <nicole1nct@sbcglobal.net>
Sent: Monday, October 28, 2019 4:10 AM
To: HCA ST Health Tech Assessment Prog
Subject: VNS and SCA , manufacturers avoiding issue

Hello,

On 11/5/2018 I was under " conscious sedation" for a very minor procedure in a hospital....because I refused to have it done in office. At the end of the biopsy, I suddenly went bradycardic and then went into Asystole, full code blue.

I have had nothing but road blocks and denials in trying to determine cause of my SCA. The VNS company IGNORED request from the anesthesiologist to come to the ICU and interrogate the device. They ignored my primary doctors. I had to date more than 6 months and spend a days travel and more expense to go to down town Seattle to Swedish Cherry Hill. The VNS tech's would NOT EVEN MAKE EYE CONTACT WITH ME!

I happen to know about the recalls on model 106.

I have model 102. I got mine back in Illinois. Once I moved out here...I found follow up care impossible.

I am still seeking answers.

Was my SCA related to VNS?.... was is long QTC syndrome?...was it anaphylaxis??? I have seen 3 specialists....AND NONE OF THEM DID ANY TESTS...ONE DID A MINOR EXAM. each sending me back to the other. I am the proverbial HOT POTATO!

I am more than disappointed in the "healthcare" i have received in the Washington state area.

Nicole Curtis