

**Department of Health and Human Services
DEPARTMENTAL APPEALS BOARD
Appellate Division**

NCD 160.18, Vagus Nerve Stimulation
Docket No. A-14-3
Decision No. 2613
December 30, 2014

**DECISION THAT THE NCD RECORD IS COMPLETE AND
ADEQUATE TO SUPPORT THE VALIDITY OF
NCD 160.18(C), VAGUS NERVE STIMULATION**

The Medicare program, established under title XVIII of the Social Security Act (Act), covers a wide range of medical items and services but the benefits are defined and limited by law. Medicare generally bars coverage for items or services that “are not *reasonable and necessary* for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member” (italics added). Act § 1862(a)(1)(A). The Centers for Medicare & Medicaid Services (CMS) may issue National Coverage Determinations (NCDs), which prospectively grant, limit, or deny Medicare coverage for specific healthcare items or services. *See* Act §§ 1862(l)(6)(A), 1869(f)(1)(B); 42 C.F.R. § 405.1060.

In this case, two Medicare beneficiaries (the “Aggrieved Parties”) whose names we withhold for privacy reasons filed a complaint with the Departmental Appeals Board (Board) to challenge an NCD concerning vagus nerve stimulation (VNS). The challenged NCD, which CMS issued on May 4, 2007 and published in section 160.18(C) of the Medicare National Coverage Determinations Manual,¹ states that “effective for services performed on or after May 4, 2007, VNS is not reasonable and necessary for resistant depression.” (“Treatment-resistant” depression, or TRD, is depression that fails to respond, or that responds only partially, to standard antidepressant therapy.)

For the reasons discussed below, we reject the Aggrieved Parties’ argument that the NCD record was not complete and adequate to support the validity of NCD 160.18(C). We also conclude that the Aggrieved Parties have not shown that CMS unreasonably interpreted and applied the relevant statutory coverage requirement in deciding whether VNS should be covered for TRD. We further conclude that the NCD record continues to

¹ The Medicare National Coverage Determinations Manual is available at <http://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Internet-Only-Manuals-IOMs-Items/CMS014961.html> (last visited Dec. 22, 2014).

be complete and adequate to support NCD 160.18(C)'s validity, even in light of more recent developments. In addition, we reject the Aggrieved Parties' contention that NCD 160.18(C) must be invalidated to the extent it precludes coverage of certain "maintenance" services for Medicare beneficiaries with TRD who were implanted with the VNS pulse generator prior to the issuance of NCD 160.18(C) on May 4, 2007. Our rejection of that contention is based on CMS's representation in this proceeding that NCD 160.18(C) is inapplicable to Medicare coverage claims for those services, a representation which is consistent with a reasonable reading of the text of NCD 160.18(C).

We are mindful that some researchers, clinicians, and patients – and at least one medical society (the American Psychiatric Association) – now consider adjunctive VNS to be a last-resort treatment option for TRD patients under certain circumstances. The material presented to us includes statements from medical experts who believe that the evidence of VNS's safety and treatment effectiveness for TRD is adequate to support Medicare coverage. These experts (and other physicians) describe VNS as an essential option for severely or chronically depressed persons who have not responded to conventional treatment and who lack other realistic options to moderate the debilitating effects of their disease. We assume for purposes of this decision that a clinician may reasonably decide to prescribe VNS as a treatment option and that reports of TRD patients who have experienced improvement in depressive symptoms after being treated with VNS are true. But it does not automatically follow that CMS must find VNS to be reasonable and necessary for the treatment of TRD for purposes of Medicare coverage in light of continuing questions about its safety and whether it produces substantial and durable improved health outcomes for Medicare beneficiaries. Nor does the fact that some experts disagree with several aspects of CMS's evaluation of the studies of VNS necessarily undercut our conclusions. The Board does not make Medicare coverage policy in the first instance, and the statute and regulations require us to defer to CMS's findings of fact and conclusions of law so long as they are reasonable. Therefore, the question before us is not whether individual physicians or patients believe in the utility of VNS. Instead, we review whether CMS based NCD 160.18(C) on objectively reasonable grounds that are adequately supported by a complete NCD record and whether the NCD record continues to be complete and adequate to support the validity of the NCD, in light of the new information before us. *See* 42 C.F.R. § 426.525(c)(1)-(2). We explain below why we conclude that the NCD record was and continues to be complete and adequate.

I. BACKGROUND²

VNS is a type of brain stimulation therapy that uses a small, battery-powered generator (“Venus device”), which is similar to a pacemaker, to send mild pulses of electrical energy through the left vagus nerve, a cranial nerve that regulates various involuntary functions and “has influence over widespread brain areas.” CMS Ex. 1, at 18. The VNS device is surgically implanted inside the left chest wall, near the carotid artery; two electrodes are wrapped around the left vagus nerve and connected to the device with a subcutaneous lead wire. *Id.* at 18, 53, 703. External equipment is used to program or adjust the intensity, duration, or frequency of the device’s electrical pulses and to retrieve data. *Id.* at 18. The VNS device’s battery has a finite lifespan and must be replaced periodically. Complaint ¶ 18. The VNS device and related equipment are manufactured and marketed by Cyberonics, Inc. as the VNS Therapy System. CMS Ex. 1, at 952-54; AP Ex. 5.

In 1997, the U.S. Food and Drug Administration (“FDA”) approved the marketing of the VNS Therapy System for the treatment of epileptic seizures. CMS Ex. 1, at 18; AP Ex. 4, at 1. Medicare presently covers VNS as treatment for patients with “medically refractory partial onset [epileptic] seizures for whom surgery is not recommended or for whom surgery has failed.” AP Ex. 1, at 2.

After researchers reported that some patients receiving VNS therapy for seizure control experienced improvement in mood, Cyberonics sponsored clinical studies to determine VNS’s potential to treat depression in patients with a history of non-response to standard treatment (such as antidepressant drugs and psychotherapy). *See* AP Ex. 45, at 5; CMS Ex. 1, at 18, 956-57, 975-76. Three of those studies figure prominently in CMS’s decision to issue NCD 160.18(C), and for that reason we provide a brief, preliminary description of them.

The first is known as the D-01 pilot (or feasibility) study. CMS Ex. 1, at 20, 24, 31, 486, 957. It involved 59 subjects who received adjunctive VNS (that is, VNS in combination with other types of ongoing antidepressant treatment) for two years. The study found that its subjects “demonstrated a sustained clinical response over 2 years” with adjunctive

² The parties’ key submissions in this proceeding are cited in this decision as follows: Beneficiaries’ Complaint, dated October 13, 2013 (“Complaint”); NCD Record for Vagus Nerve Stimulation (160.18) (“CMS Ex. 1, at ___”); Aggrieved Parties’ Statement Regarding the NCD Record, dated January 10, 2014 (“AP Statement”); Response of the Secretary of Health & Human Services to the Aggrieved Parties’ Statement Regarding the NCD Record, dated February 12, 2014 (“CMS Response”); Secretary of Health & Human Services’ Supplemental Briefing, dated June 6, 2014 (“CMS Supp. Br.”); Aggrieved Parties’ Statement Regarding the Secretary’s Supplemental Response, dated July 8, 2014 (“AP Resp. to Supp. Br.”); and Factual and Analytical Errors in the Secretary’s Supplemental Response, attached to the July 8, 2014 Statement Regarding the Secretary’s Supplemental Response (“Att. to AP Resp. to Supp. Br.”). Exhibits submitted by the Aggrieved Parties are cited as “AP Ex. ___.”

VNS and that the treatment was “generally well tolerated, with a low attrition rate.” *Id.* at 493. The D-01 did not use a control group – that is, a group of persons with similar clinical and demographic characteristics who did not receive VNS – against which to compare those findings.

The results of the D-01 led to a second study called the D-02 pivotal study. CMS Ex. 1, at 975. The D-02 was a large multi-center study involving 222 outpatients with resistant depression or bipolar disorder. *Id.* at 24-31, 619, 982, 3809. The study had two phases. The initial, or “acute,” phase was a three-month, double-blind, randomized, sham-controlled trial (DBRCT). The VNS device was implanted in all 222 subjects, who were then assigned randomly to the treatment (VNS) group or a non-treatment (sham) group. Two weeks after implantation, the devices in the treatment group were turned on and set to a tolerable output level. The devices implanted in the sham-group subjects were also turned on but were programmed to emit no electrical pulses. “Concomitant treatment” – that is, any non-VNS antidepressant treatment being provided to the subjects – was supposed to be held constant during the acute phase. Subjects’ responses to treatment (relative to a baseline) were measured using one primary and three secondary rating scales to measure the severity of a subject’s depressive symptoms.

After completing the study’s acute phase, 205 of the original 222 subjects entered the D-02’s long-term “observational” phase³ and were followed for an additional nine months. *See* CMS Ex. 1, at 27, 957-59, 982-83. During the observational phase, *all* subjects received VNS (in addition to other prescribed antidepressant therapy): subjects who were in the treatment group during the acute phase continued to receive VNS; subjects in the sham group had their VNS devices activated to emit electrical pulses. *Id.* at 27. Changes in concomitant treatment were permitted during the long-term phase, and study “protocol violators could be included in the efficacy analysis.” *Id.*

The D-02 pivotal study produced mixed results. The acute-phase DBRCT found that 15 percent of subjects in the VNS group had experienced a “response” (as measured using the primary rating scale) versus 10 percent in the sham group. CMS Ex. 1, at 624, 625. However, these group differences were determined to be “not statistically significant.” *Id.* at 625. Results based on two of the three secondary scales were also not statistically significant. *Id.* at 623 (table 4). On the other hand, for subjects who completed the long-term (observational) phase, the study’s authors reported results suggesting that VNS has a long-term therapeutic effect while noting that further studies were needed to determine whether such an effect could be attributed to VNS. *Id.* at 31.

³ An “observational” trial is one in which patients receiving one type of treatment are compared with patients receiving an alternative treatment. CMS Ex. 1, at 1698.

A third Cyberonics-sponsored study, called the D-02/D-04, was based on data from the D-02 observational trial and another Cyberonics-sponsored study called the D-04. *See* CMS Ex. 1, at 34-39, 198-205, 281-90. The D-04 assessed the health “outcomes” (and other consequences) for depressed subjects who were receiving standard antidepressant treatment, which its authors called “treatment-as-usual” (“TAU”), a term that VNS researchers have continued to use. *Id.* at 198-99.⁴ The D-02/D-04 study compared one-year treatment outcomes for D-04 subjects (those who received TAU) with outcomes experienced by the D-02 observational subjects (subjects who received adjunctive VNS – that is, VNS plus TAU). *Id.* at 281-83, 976. The study found a “significant between-group difference favoring VNS+TAU over TAU alone that grew over time.” *Id.* at 287.

Relying heavily on the D-01, D-02, and D-02/D-04 studies, Cyberonics sought FDA approval to market the VNS Therapy System for patients with depression who had not responded to multiple courses of other antidepressant treatment. CMS Ex. 1, at 952, 975-76. In July 2005, the FDA granted conditional premarket approval, finding that Cyberonics had provided “reasonable assurance” of VNS’s safety and effectiveness for TRD.⁵ AP Ex. 5. The FDA approved the device specifically for the “adjunctive long-term treatment of chronic or resistant 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 antidepressant treatments.” *Id.* at 1. As a condition of its approval, the FDA required Cyberonics to conduct two long-term post-approval studies of VNS known as the D-21 dosing study and the D-23 Treatment-Resistant Depression registry study (both of which we discuss later). *Id.* at 3-4.

In July 2006, Cyberonics asked CMS to approve an NCD authorizing Medicare coverage of adjunctive VNS for a subset of depression patients who meet FDA’s premarket approval criteria.⁶ CMS Ex. 1, at 3768, 4179. On May 4, 2007, CMS rejected Cyberonics’ coverage request and issued NCD 160.18(C), finding that VNS is “not reasonable and necessary” for the treatment of resistant depression. *Id.* at 4, 12-13, 19.

⁴ TAU was defined in the D-04 study as whatever treatment strategy – *e.g.*, medication, psychotherapy – the physician and the subject chose to follow. CMS Ex. 1, at 200.

⁵ Under its regulatory scheme, the FDA grants premarket approval for “class III” medical devices, such as the VNS Therapy System, when it finds that there is “reasonable assurance” of the device’s “safety and effectiveness” after weighing “any probable benefit to health from the use of the device against any probable risk of injury or illness from such use.” 21 U.S.C. §§ 360c(a)(1)(C), 360c(a)(2)(C), 360e(d)(1).

⁶ In particular, Cyberonics asked CMS to cover the VNS device as part of an “adjunctive long-term treatment of chronic or recurrent depression for patients over the age of 18 who are experiencing a major depressive episode and have not had an adequate response to four or more adequate antidepressant treatments” and who have been either (1) previously treated with or refused treatment with electroconvulsive therapy (ECT) or (2) have been previously hospitalized for depression. CMS Ex. 1, at 3768-69, 4179-80.

CMS explained the reasons for its non-coverage determination in a document titled *Decision Memo for Vagus Nerve Stimulation for Treatment of Resistant Depression (TRD)* (“Decision Memo”). *Id.* at 14. Prior to issuing its determination, CMS invited two rounds of public comment, the second of which followed CMS’s release of a draft decision memorandum. *Id.* at 3-4, 2676.

II. CMS RATIONALE FOR NCD 160.18(C)

This section summarizes the Decision Memo’s analysis and principal findings.

A. *Depression and its treatment*

The Decision Memo begins with the following undisputed description of depression and how it is treated:

- Depression, known in diagnostic terminology as major depressive disorder (“MDD”), is a serious condition characterized by one or more “episodes” during which an individual experiences a debilitating combination of symptoms – such as depressed mood, loss of pleasure in activities, feelings of worthlessness, diminished ability to think or concentrate, fatigue, and thoughts of death or suicide. CMS Ex. 1, at 15.
- Over a patient’s lifespan, “the course of depression is marked by recurrent episodes of depression followed by periods of remission.” CMS Ex. 1, at 16 (citation and internal quotation marks omitted). “Patients with depression can experience spontaneous remission,” and, left untreated, a major depressive episode typically lasts six months or longer, according to an American Psychiatric Association practice guideline. *Id.*
- Depression is a common affliction among the elderly, affecting one in six persons 65 years or older. CMS Ex. 1, at 16-17. “Depression in older adults occurs in a complex psychosocial and medical context: the prevalence of clinically significant depression in later life is estimated to be highest (about 25%) in those with chronic illness, particularly those with ischemic heart disease, stroke, cancer, chronic lung disease, arthritis, Alzheimer’s disease, and Parkinson’s disease.” *Id.* at 16 (quotation marks and citations omitted).
- “[T]here is no consensus as to the site of pathology for depression,” but “there are many effective treatments” for the disorder, including pharmacotherapy (medication), psychotherapy, psychotherapy combined with pharmacotherapy, and electroconvulsive therapy (“ECT”) – with pharmacotherapy being the “first-line treatment for MDD” in most cases. CMS Ex. 1, at 16-17.

- It is estimated that 10 to 30 percent of depression patients do not respond, or respond completely, to treatment with antidepressant medication. CMS Ex. 1, at 17 (citing *id.* at 159). Researchers have hypothesized various reasons for this “therapy resistance,” including “occult [hidden or undetected] medical conditions causing depression, substance abuse interfering with treatment, noncompliance, abnormal metabolism, psychosocial factors, . . . other psychiatric comorbidities, [and] . . . prescribing antidepressant medication in dosages that are too low and for inadequate lengths of time.” *Id.* (citations omitted). Strategies used after the failure of a “standard first line treatment” include drug substitution, combination strategies (the addition of a second antidepressant agent), augmentation with non-antidepressant agents (such as thyroid hormone, benzodiazepines, estrogen, dexamethasone, or lithium), or ECT. *Id.* at 17, 139.

B. Medicare coverage and evidentiary criteria

The Decision Memo provides the following explanation of how CMS approached Cyberonics’ request for Medicare coverage of VNS:

- When CMS makes a national coverage determination, it evaluates whether the “relevant clinical evidence” – such as formal studies of a treatment’s safety and effectiveness – is of “*sufficient quality* to support a finding that an item or service . . . is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member.” CMS Ex. 1, at 19 (italics added).
- In order to determine whether a treatment or other medical intervention is reasonable and necessary, CMS considers, among other factors, whether “the intervention will improve *health outcomes*” for individuals in the Medicare population.⁷ CMS Ex. 1, at 19 (italics added). (In this context, the term “outcome” is clinical short-hand for what happens to a patient’s health during or after receiving a treatment – be it improvement, stasis, or deterioration of the underlying disorder, the occurrence of other positive or negative health-related events, or changes in the risk of experiencing such events.) According

⁷ Later in the Decision Memo, CMS framed the critical question as follows: “Is the evidence sufficient to conclude that, in the Medicare population, vagus nerve stimulation will improve health benefits for individuals with treatment resistant depression?” CMS Ex. 1, at 23.

to CMS, “the *outcomes of interest* for treatment with the VNS device” include changes in the severity of depressive symptoms and “implant-related adverse events,” such as complications from implantation surgery and side effects of stimulation with the implanted VNS device.⁸ *Id.* at 20 (italics added).

- CMS evaluates clinical studies and other evidence of a treatment’s medical necessity and reasonableness using the “methodological principles of study design” set forth in Appendix A of the Decision Memo (DM App. A).⁹ CMS Ex. 1, at 19. According to that appendix, three main factors guide CMS’s evaluation:

(1) “[T]he quality of the individual studies”:

“Quality” refers to a study’s “internal validity.” *See* DM App. A at 1-2. Internal validity is the extent to which the study’s conclusions about whether a treatment has caused an observed outcome can be relied upon given the circumstances under which the study was conducted. *Id.* (stating that a study’s strength depends on the “scientific validity underlying study findings regarding *causal relationships* between health care interventions and health outcomes” (italics added)).

(2) “[T]he relevance of findings from individual studies to the Medicare population”:

This factor concerns a study’s “external validity,” which generally means the degree to which a study’s findings, even if valid in the study setting, are “generalizable” to – or likely to be true for – patients who are being treated in community practice (outside the study setting). DM App. A at 2-3. “The extent to which the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study

⁸ In studies of antidepressant treatment, patient outcomes are commonly assessed using standardized instruments (typically questionnaires) completed by the patient or the clinician. CMS Ex. 1, at 20, 141. Clinical information obtained using these instruments is weighted and keyed to a numeric rating scale. *Id.* Many instruments yield a scaled score that represents the overall severity of a patient’s depressive symptoms at a given point in time; others measure quality of life, work functioning, and other health-related dimensions. *Id.*; CMS Supp. Br. (Table 2). Examples of these instruments include the Hamilton Rating Scale for Depression (HRSD), the Clinical Global Impressions Scale (CGI), the Inventory of Depressive Symptomatology (IDS), and the Montgomery-Asberg Depression Rating Scale (MADRS). *Id.*

⁹ The text of Appendix A was not reproduced in the NCD record, but it is expressly incorporated by reference in CMS’s Decision Memo. *See* CMS Ex. 1, at 19, 52. As it appears in the NCD record, the Decision Memo includes an active internet link (or URL) to Appendix A that appears just below section IX. *Id.* at 59.

characteristics,” such as the profile of the patient population being studied and the nature of the clinical setting in which study subjects receive the experimental treatment, as well as on other variables.

(3) “[O]verarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention’s risks and benefits”:

- In explaining this factor, Appendix A states that an intervention is “generally” not reasonable if its risks outweigh its benefits, and that the “[d]irection, magnitude, and consistency of the risks and benefits across all studies are also important considerations.” DM App. A at 1, 3-4. In order to weigh risks and benefits, “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.” *Id.* at 3. It is also “important that an intervention’s benefits are clinically significant and durable, rather than marginal or short-lived.” *Id.*
- Appendix A further explains that a clinical study’s internal and external validity depend on whether the study has been designed to minimize “bias” or other factors that might lead researchers to draw erroneous conclusions about (that is, overestimate or underestimate) the true effect of the treatment being studied.¹⁰ DM App. A at 1-2. Study methods or designs that enhance validity include: (1) use of “contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups”; (2) “[p]rospective (rather than retrospective) studies to ensure a more thorough and systematic assessment of factors related to outcomes”; (3) randomization of study subjects to treatment and control groups; (4) in

¹⁰ Appendix A states that “[v]arious types of bias can undermine internal validity,” including:

- 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 (**confounding**)
- Differential assessment of outcome (**detection bias**) [also known as “observer bias” – the unconscious influence of a researcher’s beliefs or expectations on a study’s subjects or observations]
- Occurrence and reporting of patients who do not complete the study (**attrition bias**)

DM App. A at 2 (emphasis added).

controlled experiments, the “blinding” of investigators and subjects to knowledge of which subjects are receiving and not receiving the experimental treatment; and (5) “[l]arger sample sizes in studies to help ensure adequate numbers of patients are enrolled to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population[.]” *Id.* at 1. Appendix A lists various study designs, ranking them from strongest to weakest in their ability to minimize “systemic bias.” *Id.* at 2. The strongest are randomized controlled and non-randomized controlled trials, and the weakest are “surveillance studies” (such as those using registries or surveys), “consecutive case series studies,” and single case reports. *Id.* at 2.

C. *Description of evidence*

After defining its analytic approach to the coverage issue, the Decision Memo describes the evidence that CMS reviewed in resolving the issue. CMS Ex. 1, at 23-42. CMS focused primarily on the three clinical studies that supported the FDA premarket approval application: the D-01 pilot, the D-02 pivotal, and the D-02/D-04 studies. *Id.* at 23-40. CMS also reviewed “evidence-based” medical practice guidelines, technology assessments of VNS by non-governmental organizations, and medical literature and other material submitted by Cyberonics. *Id.* at 20, 23-24, 40. In addition, CMS reviewed and responded to public comments from patients, researchers, academic and practicing physicians, medical organizations, and others. *Id.* at 40-53.

D. *Findings and Analysis*

As indicated, the D-01 and D-02/D-04 studies reported results suggesting that long-term adjunctive VNS may confer a treatment benefit on some persons with TRD. *See* CMS Ex. 1, at 33-34, 39. The Decision Memo indicates that CMS gave both studies little weight. In general, CMS found that the studies’ designs or methods were inadequate to minimize potential biases and account for “confounding” variables (that is, extraneous variables whose influence affects the variable being studied) that may have accented or masked the true effect of VNS, thereby skewing the reported results. *Id.* at 54-57. CMS emphasized that “[w]ell-designed clinical trials are important for accurate outcome interpretation,” and that “inclusion of an appropriate comparator [*i.e.*, a control group] facilitates study interpretation.” *Id.* at 22. In addition, said CMS, “[w]ell constructed randomization” minimizes bias. *Id.*

CMS took note of several potential “confounders” in the VNS studies, including the placebo response,¹¹ the fact that depression patients sometimes experience spontaneous remission, the influence of changes to a study subject’s concurrent non-VNS antidepressant therapy, and the statistical phenomenon of “regression to the mean” (*i.e.*, natural variability or “waxing-and-waning” of symptoms). CMS Ex. 1, at 22, 46-47, 55, 56. CMS characterized the placebo response as a “substantial, common consideration in trials of antidepressants,” and stated that “more weight will normally be accorded to studies that are designed to guard against the placebo effect.” *Id.* at 22.

CMS expressed other concerns in the Decision Memo. For example, CMS commented that “treatment-resistant depression” is a term that “lacks a standard definition that has been scientifically validated, and appears to be subject to various interpretations.” CMS Ex. 1, at 54. CMS observed that published literature, including the clinical studies of VNS, uses “varying definitions of treatment resistance, response, and remission” and noted that a “debate exists regarding whether assessment at a single time point (e.g., at the end of a clinical trial) is acceptable in defining remission or whether remission should be defined as no or few symptoms sustained over a predefined length of time.” *Id.* at 45, 46. The lack of uniform or standardized definitions of response, remission, and relapse, said CMS, makes it difficult to compare studies and identify the circumstances under which a patient might benefit from VNS. *Id.* at 22, 46. CMS stated that regardless of whether there is a standard definition of treatment resistance, the relevant published medical literature has not “clearly defined the treatment resistant group for whom VNS, if proved to be beneficial, might be indicated.” *Id.* at 52, 57.

CMS also questioned researchers’ reliance on outcome instruments that subjectively measure or report depressive symptomatology, commenting that CMS “generally accords more weight to outcomes with validated measures of patient functioning (social and work), quality of life, morbidity (such as hospitalization), and mortality.” CMS Ex. 1, at 21-22. It was also “not clear” from the clinical studies, said CMS, “which items and which scales are most sensitive at measuring changes during a patient’s treatment for depression.” *Id.* at 21.

In addition, CMS was skeptical about whether the findings of the studies upon which Cyberonics’s coverage request was based (particularly the D-01 and D-02/D-04 studies) *were valid for older adults*, the largest subgroup of the Medicare population, for whom depression “occurs in a complex psychosocial and medical context.” CMS Ex. 1, at 16.

¹¹ CMS explains in one of its submissions to the Board that the “placebo response” consists of a “study effect” – the influence of factors associated with being in the clinical trial, such as receipt of care that may be superior to that received prior to the study – and a “placebo effect” – which is a “nonspecific, psychological or psychophysiological therapeutic effect that can be attributed, at least in part, to the expectation that improvement will follow the application of a treatment.” CMS Supp. Br. at 4.

Responding to two experts who indicated that the D-01 and D-02 studies were designed to exclude patients with significant co-morbidities that may mimic antidepressant treatment resistance or reduce the likelihood of remission, CMS stated:

It is unclear how results from trials of patients without reported significant comorbidities can be generalized to many clinical populations, including older adults in Medicare. These important individual patient factors may be linked to a lower probability of remission, which is observed as a resistance to treatment. . . . CMS believes that by excluding patients with comorbidities we are unable to generalize whether VNS showed a health benefit in the Medicare population, should the clinical trial have been positive.

Id. at 45 (italics added; internal quotation marks omitted).

As for VNS's safety, CMS noted that "[a]dverse events are important medical outcomes"; that patients require information about the potential for such events in order to make well-informed treatment choices; that surgical implantation of the VNS device (an "invasive" procedure) could result in infection or tissue scarring; and that other "potential adverse outcomes" of VNS therapy include vocal cord paralysis, sleep apnea, shortness of breath, syncope, cardiac arrhythmias, and difficulty swallowing. CMS Ex. 1, at 22. CMS also stated that it had "safety concerns" based on: (1) FDA warning letters to Cyberonics about the VNS device's quality and about inadequate reporting (or under-reporting) of serious adverse events potentially associated with VNS therapy; (2) an FDA analysis of 44 reported "adverse events," including three suicides, a patient who experienced an onset of seizures, and another who had a "stroke event"; and (3) a small, one-year VNS study (Corcoran 2006, CMS Ex. 1, at 196-97) which reported several serious adverse events, including a suicide and a patient who experienced recurrent pulmonary emboli. *Id.* at 49.

Although CMS acknowledged anecdotal evidence of VNS's effectiveness, including the patient testimonials and reports from practicing psychiatrists, CMS concluded that the available evidence was not adequate on the whole to conclude that there is a "treatment benefit directly attributable to VNS therapy" for Medicare patients with resistant depression. CMS Ex. 1, at 50, 57. The relevant clinical studies, CMS said, "did not demonstrate illness resolution, nor were they designed to demonstrate a reduction in deaths." *Id.* at 50. Most importantly, CMS emphasized that the "*only well-designed trial*" of VNS for TRD, the D-02 DBRCT, "*failed to demonstrate statistically significantly superior outcomes greater than sham treatment . . .*" *Id.* at 55 (italics added).

III. THE NCD REVIEW PROCESS

Section 1869(f) of the Act authorizes the Board to review an NCD under certain conditions. The regulations in 42 C.F.R. Part 426 implement that statutory authority and specify the following review process.

A Medicare beneficiary who needs a medical item or service for which Medicare coverage is precluded under an NCD may challenge the NCD's validity by filing a written complaint. 42 C.F.R. § 426.500(a). When it receives the complaint, the Board first determines whether it meets certain threshold regulatory requirements. *See id.* § 426.510(b). If the complaint is "acceptable," the Board directs CMS to provide the complainant (or "aggrieved party") and the Board with the "NCD record." *Id.* § 426.510(d)(3). The NCD record "consists of any document or material that CMS considered during the development of the NCD" including "medical evidence considered on or before the date the NCD was issued" *Id.* § 426.518(a). After CMS produces the NCD record, the aggrieved party may submit a statement "explaining why the NCD record is not complete, or not adequate to support the validity of the [challenged] NCD under the reasonableness standard," and, in turn, CMS may submit a response "in order to defend the NCD." *Id.* § 426.525(a), (b).

The Board then "applies the reasonableness standard to determine whether the NCD record is complete and adequate to support the validity of the NCD." 42 C.F.R. § 426.525(c)(1). The Board's role at this stage of the review process is "not to assess the ultimate validity of the NCD based on an evidentiary record but simply to determine whether the information CMS considered *during the development of the NCD*, including medical evidence considered *on or before the date the NCD was issued*, supports the validity of the NCD, in light of the material submitted by the aggrieved party." *NCD 140.3, Transsexual Surgery*, NCD Ruling No. 2 (Dec. 2, 2013) (italics in original). If the Board determines that the NCD record is complete and adequate to support the validity of the NCD, the review process ends with the Board's "[i]ssuance of a decision finding the record complete and adequate to support the validity of the NCD" 42 C.F.R. § 426.525(c)(2). "If the Board determines that the NCD record is not complete and adequate to support the validity of the NCD, the Board permits discovery and the taking of evidence . . . and evaluate[s] the NCD in accordance with § 426.531" (a regulation that specifies what the Board must and may do in applying the reasonableness standard). *Id.* § 426.525(c)(3).

IV. CASE HISTORY

In accordance with the procedures in 42 C.F.R. Part 426, the Aggrieved Parties initiated this proceeding by filing a complaint. Attached to the complaint were numerous exhibits, including articles from peer-reviewed scientific and medical journals and other material whose publication or creation post-dates the issuance of NCD 160.18(C). The Aggrieved

Parties allege in the complaint that they suffer from TRD, that VNS is a reasonable and necessary treatment for that condition, and that NCD 160.18(C) is contrary to the “preponderance” of scientific and clinical evidence, the opinion of medical experts and practicing psychiatrists, and “Medicare policy concerning reasonableness and medical necessity.” Complaint ¶ 9. For these and other reasons, the Aggrieved Parties ask the Board to find that NCD 160.18(C) “should not be relied on to deny”: (1) “access to reasonable and necessary treatment related to VNS therapy for TRD”; (2) “access to physician services that allow effective use of a VNS device that was covered by Medicare when implanted”; and (3) “access to a replacement battery to enable effective use of the implanted VNS device.” *Id.* ¶¶ 97-99.

The Board found the Aggrieved Parties’ complaint to be acceptable, and CMS thereafter produced the NCD record. The NCD record (CMS Exhibit 1) includes published scientific and medical literature, technology reviews, public comments, FDA analyses, and other material considered by CMS when it issued NCD 160.18(C). The NCD record also includes the Decision Memo supporting CMS’s noncoverage determination (CMS Ex. 1, at 14-64).

Following production of the NCD record, the Aggrieved Parties filed (along with additional exhibits) a statement explaining why, in their view, the NCD record is not complete or adequate to support the validity of NCD 160.18(C). In that statement, which largely reiterates the complaint’s allegations, the Aggrieved Parties contend that NCD 160.18(C) is unsupported by the material that CMS reviewed (or that was available to CMS) prior to its issuance on May 4, 2007, and that NCD 160.18(C) also conflicts with more recent clinical studies and with current expert opinion and medical standards of care. AP Statement ¶¶ 1, 2, 5-6, 15, 18, 60, 61. The Aggrieved Parties submit that numerous peer-reviewed clinical studies clearly demonstrate that VNS is safe and effective for TRD patients. *Id.* ¶¶ 2, 15, 18, 60.

CMS initially responded to the Aggrieved Parties’ statement by contending that medical literature and other material whose publication or creation post-dates the issuance of NCD 160.18(C) is legally irrelevant at this stage of the NCD review process. In a ruling dated May 19, 2014, the Board rejected that position and ordered CMS to file a supplemental brief addressing whether the NCD record is complete and adequate in light of the post-May 2007 material submitted by the Aggrieved Parties. CMS then filed a supplemental brief to which it attached a detailed analysis of that material, stating that the

analysis “reflects the agency’s expert medical judgment as to why the new evidence does not defeat the current NCD record in support of NCD 160.18.”¹² The Aggrieved Parties filed a response to CMS’s supplemental brief along with additional exhibits.

The Board later received *amicus curiae* statements from four physicians: Francisco A. Moreno, M.D., Professor of Psychiatry at the University of Arizona College of Medicine; Charles R. Conway, M.D., Associate Professor of Psychiatry at the Washington University in St. Louis and Director of the Washington University Treatment-Resistant Depression Clinic; Scott T. Aaronson, M.D., Director of Clinical Research Programs, Sheppard Pratt Health System; and Steven Buser, M.D. Three of the amici (Aaronson, Moreno, and Conway) are researchers and two (Aaronson and Moreno) served as investigators in one or more of the relevant Cyberonics-sponsored clinical studies (such as the D-02 and the post-approval studies required by the FDA). Dr. Conway, Dr. Aaronson, and Dr. Moreno have received financial or research support from Cyberonics, and Dr. Buser is the treating psychiatrist of one of the Aggrieved Parties. See AP Exs. 2, 19 (at 1), and 66 (at 6). All four amici have multiple years of experience treating depression patients with VNS.

Finally, the Board received comments from the parties concerning each of the *amicus curiae* statements, and further submissions concerning a Medicare claims appeal (which we discuss in section VII).

V. DISCUSSION

As indicated, the Board at this stage of the NCD review process applies the “reasonableness standard” to determine whether the NCD record is “complete and adequate” to support the validity of NCD 160.18(C). Under the reasonableness standard, the Board evaluates whether the “findings of fact, interpretations of law, and application of fact to law” supporting the challenged coverage determination are “reasonable based on the . . . NCD record and the relevant record developed before . . . the Board.” 42 C.F.R. § 426.110. That standard obligates the Board to “defer” to CMS’s “reasonable” findings and conclusions in recognition of CMS’s program “expertise,” particularly “in the area of coverage requiring the exercise of clinical and scientific judgment.” Act § 1869(f)(1)(A)(iii)(III); Final Rule, *Medicare Program: Review of National Coverage Determinations and Local Coverage Determinations*, 68 Fed. Reg. 63,692, 63,703 (Nov. 7, 2003). Thus, the preamble to the final rule which established the NCD review process explained that:

¹² While the statement is not presented as the opinion of any individual witness on the issues in this case, we recognize, as do the courts and the regulation itself, that CMS has considerable substantive expertise in administering the Medicare program and we treat the analysis as a statement of agency position on the issues addressed.

So long as the outcome is one that could be reached by a rational person, based on the evidence in the record as a whole (including logical inferences drawn from that evidence), the determination must be upheld. This is not simply based on the quantity of the evidence submitted, but also includes an evaluation of the persuasiveness of the material. If . . . CMS has a logical reason as to why some evidence is given more weight than other evidence, the . . . Board may not overturn the determination simply because [it] would have accorded more weight to the evidence in support of coverage. . . .

For legal interpretations, the reasonableness standard would not be met if an interpretation is in direct conflict with the plain language of the statute or regulation being interpreted. . . . So long as an interpretation is one of the readings permitted by the plain language of the law and can be reconciled with relevant policy, however, it must be upheld, even if . . . the Board might have reached a different result if interpreting the statute or regulation in the first instance.

68 Fed. Reg. at 63,703-04.

The findings and conclusions to which we apply the reasonableness standard are spelled out in CMS’s Decision Memo for NCD 160.18(C). In that document, CMS considered whether VNS is reasonable and necessary for resistant depression by assessing the “degree” to which it was “confident” that VNS “will improve health outcomes” for Medicare beneficiaries. CMS Ex. 1, at 19. CMS concluded that it had only low or minimal confidence in that proposition:

. . . [W]e do not believe that the evidence we have reviewed is sufficient to conclude that VNS improves health outcomes in the Medicare population. Additionally, we are not convinced that the literature has clearly defined the treatment resistant group for whom VNS, if proved to be beneficial, might be indicated. The only well-designed trial did not demonstrate benefit. The observational studies have biases that make conclusions difficult.

Id. at 57. These findings are based on a detailed systematic assessment of the strengths and weaknesses of the primary relevant clinical studies whose results had been published by May 2007 (when NCD 160.18(C) was issued), including D-01 pilot, the D-02 pivotal, and the D-02/D-04 studies. *Id.* at 24-40, 53-57.

The Aggrieved Parties contend that some of those studies, together with more recently published research, convincingly demonstrate that VNS produces substantial and durable health benefits for persons with TRD. They also point to information (for example, medical practice guidelines issued by the APA) indicating that VNS has gained

acceptance in the medical community as a viable option for treating severe and chronic depression. We conclude, however, that the material and argument submitted by the Aggrieved Parties is insufficient to show that the NCD record was incomplete or inadequate to support the validity of NCD 160.18(C) as of the date of the NCD's issuance (May 4, 2007) or that the NCD record is no longer complete or adequate in light of developments since that date.

The Decision Memo indicates that CMS's primary justification for noncoverage is that the published clinical evidence has not yet established that VNS has a *beneficial effect* for TRD patients. The Decision Memo emphasizes, as well, that to the extent any beneficial effect accrues from VNS treatment, that effect has not been shown to be generalizable to Medicare beneficiaries who suffer from TRD. The Decision Memo further emphasizes (and the Aggrieved Parties do not dispute) that implantation (and subsequent explantation for maintenance and battery replacement) of the VNS device is an invasive procedure with attendant risks of harm. In addition, the Decision Memo emphasizes that the device's use poses risks, the medical literature having documented numerous significant adverse effects of VNS therapy. In light of the severity of the risks associated with implantation and explantation and the frequency of the lesser risks associated with stimulation (all of which are relevant "health outcomes"), and given that the only randomized, double-blind, sham-controlled clinical trial – the type of study best designed to ascertain whether VNS actually works – found no statistically significant evidence of causality, CMS is reasonable in insisting on stronger, more definitive evidence that VNS causes clinically significant and durable improvement in TRD patients' health outcomes as well as a better understanding of what groups of TRD patients are likely to benefit from that treatment (assuming that VNS causes such improvement).

For these and other reasons discussed below in sub-sections V.A. through V.C., we hold that the record upon which CMS issued NCD 160.18(C) is complete and adequate to support its validity. In sections VI and VII, we address other arguments advanced by the Aggrieved Parties that we find irrelevant or immaterial to that conclusion.

A. *In issuing NCD 160.18(C), CMS did not apply an unreasonable interpretation of the statutory prohibition on Medicare payment for items or services that are not "reasonable and necessary."*

Before addressing the Aggrieved Parties' primary contentions, we address their argument that CMS used improper criteria in determining whether VNS satisfied the coverage requirement in section 1862(a)(1)(A) of the Medicare statute that an item or service be "reasonable and necessary." On page one of the analysis attached to CMS's supplemental brief, CMS stated that "there is insufficient data currently available to determine that the use of vagus nerve stimulation (VNS) will provide *significant positive clinical outcomes* to the Medicare population" (italics added). Seizing on the italicized words, the Aggrieved Parties assert that "[n]either the Social Security Act, Medicare's

enabling regulations, nor any Medicare guidance document, articulates the Medicare coverage standard [*i.e.*, “reasonable and necessary”] as requiring ‘significant positive clinical outcomes.’” AP Resp. to Supp. Br. at 2. They also assert that the meaning of “significant positive clinical outcomes” is unclear because CMS “has not premised coverage” on that standard. *Id.*

This argument is without merit. First, when considered in context, the term “significant” in CMS’s analysis was likely referring to its previously-articulated concerns about whether the positive outcomes reported in the studies have statistical and clinical significance and are relevant to the elderly Medicare population. We also note that the May 4, 2007 Decision Memo, CMS’s authoritative statement of the bases for its non-coverage determination, does *not* use the phrase “significant positive clinical outcomes.” Instead, the document states that CMS determined whether VNS was reasonable and necessary by considering whether there was sufficient “relevant clinical evidence” that VNS “will improve health outcomes for patients” – by, for example, reducing mortality or the severity of depressive symptoms.¹³ CMS Ex. 1, at 19-20, 23. We do not view the terminology used in the analysis as meaningfully different from the language of the Decision Memo.

It is true, of course, that the Medicare statute – and, in particular, section 1862(a)(1)(A) – does not speak of “improved health outcomes” or contain similar language. But that fact does not render NCD 160.18(C) invalid because Congress gave CMS the authority to interpret the reasonable-and-necessary criterion through case-by-case adjudication or generally applicable rules (such as an NCD). *See* Act § 1869(a); 42 C.F.R. § 405.1060(a)(3) (stating that NCDs are “made under section 1862(a)(1)” of the Act); *Heckler v. Ringer*, 466 U.S. 602, 617 (1984) (“The Secretary’s decision as to whether a particular medical service is ‘reasonable and necessary’ and the means by which she implements her decision, whether by promulgating a generally applicable rule or by allowing individual adjudication, are clearly discretionary decisions.”); *Almy v. Sebelius*, 679 F.3d 297, 303 (4th Cir. 2012) (stating that the Medicare statute leaves discretion with the Secretary to decide coverage questions by, for example, implementing an NCD or deciding individual cases through an adjudicative process), *cert. denied*, 133 S.Ct. 841 (2013).

In this case, CMS interpreted the coverage standard in section 1862(a)(1)(A) as requiring evidence that VNS produce – that is, cause – improvement in certain dimensions of patients’ health. Under the reasonableness standard, we must uphold that interpretation

¹³ CMS noted that “[a]n improved health outcome is one of several considerations in determining whether an item or service is reasonable and necessary.” CMS Ex. 1, at 19.

unless it conflicts with the statute’s language or an applicable regulation. 68 Fed. Reg. at 63,703-04. The Aggrieved Parties do not allege any such conflict. Instead, they point to section 13.5.1 of the Medicare Program Integrity Manual (MPIM),¹⁴ which sets out criteria for CMS’s contractors to apply when making local coverage determinations and which the Aggrieved Parties suggest sets a standard different than the one CMS articulated in the Decision Memo. AP Resp. to Supp. Br. at 2.

We see no conflict between MPIM § 13.5.1 and the Decision Memo. MPIM § 13.5.1 states that for a treatment to be reasonable and necessary, it must not be investigational, and it must be “safe and effective” and “appropriate.” To be appropriate, a treatment must (according to MPIM § 13.5.1) “meet[] . . . the patient’s medical need” and be “[a]t least as beneficial as an existing and available medically appropriate alternative.” A treatment can hardly be said to meet a patient’s medical need and be “beneficial” for a patient if it does not cause an improved or “positive” health outcome for the patient.¹⁵ Consequently, we have no basis to conclude that NCD 160.18(C) is based on an unreasonable interpretation of the relevant statutory coverage requirement.

B. *As of May 4, 2007, the NCD record was complete and adequate to support the validity of NCD 160.18(C).*

The Aggrieved Parties assert that the NCD record was not complete and adequate as of May 4, 2007, the date CMS issued NCD 160.18(C). AP Statement ¶ 5. They allege two grounds for that assertion. First, they contend that NCD 160.18(C) was in conflict with the “overwhelming majority” of the scientific and medical literature that existed on May 4, 2007. *Id.* at 1 & ¶¶ 2-5, 60. Second, they contend that NCD 160.18(C) was in conflict with the then-existing “consensus of expert medical opinion” regarding VNS’s safety and effectiveness in treating resistant depression. *Id.* ¶ 19. Neither contention has factual merit, as we discuss in parts B.1 and B.2 (below). Furthermore, as we explain in part B.3, the Aggrieved Parties did not show that CMS made findings that were unreasonable based on the published medical literature and other information that existed on May 4, 2007.

¹⁴ The MPIM (CMS Pub. 100-08) is available on CMS’s website at <http://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Internet-Only-Manuals-IOMs-Items/CMS019033.html> (last visited Dec. 22, 2014).

¹⁵ Also, a treatment cannot be regarded as “effective” if it does not have the ability to produce a desired effect, and a desired effect in this context is a positive, improved, or beneficial health outcome. *See, e.g., Notice, Medicare Program; Withdrawal of Coverage of Thermography*, 57 Fed. Reg. 54,798, 54,799 (Nov. 20, 1992) (stating that CMS considers “*effectiveness* to mean that there is a *probability of benefit* to individuals *from a medical item, service, or procedure* for a given medical problem under average conditions of use; that is, in day-to-day medical practice” (italics added)).

1. Scientific and medical literature

In support of their claim that NCD 160.18(C) was in conflict with the “overwhelming majority” of the scientific and medical literature available on May 4, 2007, the Aggrieved Parties point to two groups of published articles. The first group consists of six articles – all part of the NCD record – that report the results of four clinical studies: the D-01 pilot¹⁶; the D-02/D-04¹⁷; an 11-patient European study of VNS’s safety and efficacy that we refer to as the “Corcoran study”¹⁸; and a study concerning the “durability” of antidepressant response to VNS, which we call the “Sackeim study.”¹⁹ See AP Statement ¶ 2. We discuss these four studies separately in parts B.1.(a)-(d). The second group of articles was submitted by the Aggrieved Parties and is not part of NCD record (although all of the articles in that group pre-date the issuance of NCD 160.18(C)). See *id.* ¶ 4 (citing AP Exs. 28, 30-32, 34-35, 37, 39-41, 43-45, and 47-53). We discuss them in part B.1(e).

(a) **The D-01 pilot study**

As we discussed in the background material, the D-01 pilot study followed 59 subjects who received adjunctive VNS – that is, VNS in conjunction with other ongoing antidepressant treatment – over two years. See CMS Ex. 1, at 486-88 (describing the study’s subjects and methods). The subjects had diagnoses of MDD or bipolar disorder. Upon enrollment, they were in a major depressive episode (MDE) of at least two years or were experiencing a recurrent MDE as part of a history of four lifetime MDEs. In deciding who was eligible to participate, the researchers defined treatment resistance to mean that a subject: (1) had failed to respond adequately during the current MDE to at least two antidepressant medications from different medication classes and (2) had also failed to attain a significant clinical response to a six-week-or-longer course of

¹⁶ See CMS Ex. 1, at 416-24 & AP Ex. 42 (*Marangell, L.B., et al. (2002), “Vagus Nerve Stimulation (VNS) for Major Depressive Episodes: One-year Outcomes”*); CMS Ex. 1, at 486-94 & AP Ex. 36 (*Nahas, Z., et al. (2005), “Two-year Outcome of Vagus Nerve Stimulation (VNS) for Treatment of Major Depressive Episodes”*); CMS Ex. 1, at 594-604 & AP Ex. 46 (*Rush, A.J., et al. (2000), “Vagus Nerve Stimulation (VNS) for Treatment-resistant Depressions: a Multicenter Study”*).

¹⁷ CMS Ex. 1, at 281-90 & AP Ex. 38 (*George, M.S., et al. (2005), “A One-year Comparison of Vagus Nerve Stimulation with Treatment as Usual for Treatment-resistant Depression”*)

¹⁸ CMS Ex. 1, at 196-97 & AP Ex. 33 (*Corcoran, C., et al. (2006), Vagus Nerve Stimulation in Chronic Treatment-Resistant Depression: Preliminary Findings of an Open-Label Study*).

¹⁹ CMS Ex. 1, at 649-83 & AP Ex. 73 (*Sackeim, H.A., et al. (2007), “Durability of Antidepressant Response to Vagus Nerve Stimulation (VNS)”*).

psychotherapy during the current or a previous MDE. The subjects were required to maintain a stable antidepressant medication regimen during the study's first three months (the acute phase). After three months, medications could be changed or adjusted based on the judgment of a researcher or the subject's physician.

The study used the 28-item Hamilton Rating Scale for Depression (HRSD₂₈) as the primary tool to measure disease severity at given intervals. A "response" to treatment was defined as a \geq (greater-than-or-equal-to) 50 percent reduction from the subject's baseline HRSD₂₈ score by the end of the study's acute phase (that is, after three months). "Remission" was defined as an HRSD₂₈ score of less than 11 at the end of three months. Response and remission were also assessed at the end of one and two years. A subject was considered to have sustained a response if, at a later assessment point, his HRSD₂₈ score was at least 40 percent better than the baseline score.

The study found that at the end of three months, 30.5 percent of subjects had shown a response and 15.3 percent were in remission. CMS Ex. 1, at 489. Response rates at the end of one and two years were 44 percent and 42 percent, respectively. *Id.* In addition, remission rates after one and two years were 27 percent and 22 percent, respectively. *Id.* Of the 18 subjects who responded by the end of three months, 13 were still in a state of response after one year and 9 subjects remained responders after two years. *Id.* Of the 13 subjects who were responders at one year (but not at three months), 10 were still responders after two years. *Id.* Based on these findings, the study's researchers concluded that "adjunctive VNS demonstrated a sustained clinical response over 2 years in a treatment-resistant cohort[.]" *Id.* at 493.

Because the D-01 pilot study did not involve a control group, CMS found that the study yielded only weak or inconclusive evidence that the observed improvement was due to VNS, stating that "the effectiveness of treatments for depression cannot be conclusively judged from case series data, due to regression to the mean (the waxing and waning of symptoms), spontaneous remission (which is known to occur), and placebo response, which is known to be an important confounder in studies of antidepressants." CMS Ex. 1, at 54 (citation omitted). That assessment, which the Aggrieved Parties do not expressly challenge, is plainly reasonable in part because it mirrors the following statements by the study's authors:

This study has limitations inherent in its naturalistic follow-up design. As this was a pilot study, *no control group was included in the design, which makes it difficult to compare these outcomes [of the study] with those from other continuation and maintenance studies of other antidepressant strategies.* In addition, Axis II and substance abuse comorbid diagnoses were not collected. After completion of the acute phase, the study lacked control over stimulation parameters, concomitant psychopharmacology, and ECT treatments. Although these participants were treatment resistant, . . . ,

the possibility of spontaneous partial or total remission attributable to the natural course of the disease must also be considered. The small sample size and concomitant treatments prohibit drawing any conclusions regarding the type of interventions most useful to “rescue” relapsed participants.

Id. at 492-93 (italics added); *see also id.* at 422 (indicating, in the article that reported the D-01 study’s one-year results, that the “encouraging longer-term VNS treatment results” were “not definitive” given the lack of a control group and blinding). The D-01’s authors also commented that further research was needed to define which types of patients were likely to benefit from VNS. CMS Ex. 1, at 492. Observing that “individual responses varied considerably over time, with the response rates of 9 participants decreasing to less than the 40% benchmark from 12 to 24 months” while the status of 8 participants “improved . . . from nonresponse at 12 months to response at 24 months,” the authors conceded that “[f]urther work is needed to identify predictors of treatment response at both the short (3-and 12-month) and longer (24-month) time points” and that “*controlled studies* are needed to fully address” the hypothesis that adjunctive VNS may be beneficial even after a minimal response to that treatment during the first year. *Id.* (italics added).

The authors of the D-01 pilot study indicated that the “acute benefits” experienced by the VNS subjects (that is, beneficial three-month outcomes) were probably *not* the result of a placebo response, asserting that the placebo response – the phenomenon of patients who experience health improvement upon receiving an inactive therapy – “is expected to be short-lived.” CMS Ex. 1, at 422 (emphasis and italics added). However, in the Decision Memo, CMS rejected any suggestion that it was unnecessary to account for a placebo response in this context:

Walsh et al. noted in their review of placebo response in studies of major depression, “The length of randomized controlled trials has increased, and we found, as have others, that, *the proportion of patients responding to placebo increases with trial length.* Presumably, this association reflects both the cumulative effects of the nonspecific interventions inherent in clinical trials and a longer period during which spontaneous recovery could occur” (Walsh et al., 2002). Khan et al. in their examination of FDA data from randomized controlled trials concluded, “First, *it strongly suggests that placebo-controlled trials are critical for evaluating the efficacy of treatment in this area.* If clinical trial design manipulations can change symptom reductions from less than 27% in one trial to more than 61% in another, then certainly no absolute numerical cutoff will suffice for a determination of efficacy” (Khan, Detke et al. 2003). . . .

Id. at 55 (italics added). CMS also rejected an assertion that “[i]n major depression, placebo effects are seen early and are typically transient,” stating that the “literature is inconsistent regarding this issue.” *Id.* at 48.

In their response to CMS’s supplemental brief, the Aggrieved Parties argue that CMS’s concern about the placebo response in patients with TRD has been dispelled or “refuted” by the research community. *See* Att. to AP Resp. to Supp. Br. at 5-7, 13, 14 (¶ 3), 15 (¶ 6). They claim that research “support[s] the position that a placebo response affecting the treatment effect in the TRD population is likely *de minimis*.” *Id.* at 5-7. As best we can determine, the Aggrieved Parties cite only one published study – Brunoni (2009) – to support that proposition, *see id.* at 7 & n.9, but they did not submit a copy of that study for our consideration.

The Brunoni study was published after CMS issued NCD 160.18(C) in May 2007, so the study cannot possibly be evidence that the NCD record was incomplete and inadequate as of May 2007. But even if it had been published before May 2007, it is unclear how the Brunoni study, given what the Aggrieved Parties say about it, renders CMS’s findings about the placebo response unreasonable. The Aggrieved Parties quote a short passage from the study,²⁰ but that passage does not justify their characterization of the placebo response’s influence in TRD patients as “*de minimis*.” Att. to AP Response to Supp. Br. at 7 (quoting a passage that refers merely to “low” placebo responses). Nor does the quoted passage suggest that there is consensus in the research community that the placebo response need not be accounted for in studying the efficacy of antidepressant treatment for TRD patients. The Aggrieved Parties assert that the Brunoni study discusses other research which found that the average effect of the placebo response in TRD patients is a nine (9) percent reduction in depression severity scores, “which is far from the 50% reduction required to qualify as a response.” Att. to AP Resp. to Supp. Br. at 7. It does not follow, however, that a placebo response of that magnitude need not be accounted for in studying a treatment’s effectiveness. In assessing the validity of the relevant clinical study findings, the question is not whether any individual confounder (such as the placebo response) was likely or unlikely to have materially affected the research results, but whether the cumulative influence of all plausible confounders could explain the observed improvements that the authors suggest is attributable to VNS.²¹

²⁰ The Aggrieved Parties quoted the Brunoni study as stating that “‘placebo response might also decay in refractory patients’” and that “[a]long these lines, low placebo responses were reported in a recent rTMS meta-analysis that addressed treatment-resistant patients[.]” Att. to AP Response to Supp. Br. at 7.

²¹ As CMS indicated in its response to the *amicus curiae* statement of Dr. Buser (at 3), a reliable estimate of the true beneficial effect (that is, the observed effect minus the influence of confounders, such as the placebo response) of an experimental treatment is important for weighing the treatment’s risks and benefits.

Apart from the citation to the Brunoni study, the Aggrieved Parties offered no expert opinion that supports their view that the placebo response is “de minimus” in TRD patients, nor did they directly respond to the Decision Memo’s findings regarding the placebo response. We note that a technology assessment by the Blue Cross Blue Shield Association’s Technology Evaluation Center (TEC), which provides scientific opinions regarding the clinical effectiveness and appropriateness of medical technologies, identified the placebo response as one of several concerns about the validity of the Cyberonics-sponsored clinical studies of VNS, as did the FDA’s reviewers. CMS Ex. 1, at 135 (footnote), 144, 151, 1007, 1676. Indeed, the FDA reviewers commented that a study cited by Cyberonics (Quitkin 1987) to support its claim that placebo effects occur early and diminish rapidly in patients with resistant depression “actually provided evidence to the contrary[.]” *Id.* at 1008.

The most we can infer from all these circumstances is that there was (as of May 2007) – and continues to be – a reasonable difference of medical and scientific opinion about the magnitude and persistence of the placebo response in patients with TRD. Therefore, we conclude that CMS’s findings in the Decision Memo concerning the potential influence of the placebo response were – and remain – reasonable.

(b) The D-02/D-04 study

As we indicated in the background material, the D-02/D-04 study compared one-year outcomes experienced by two (nonrandomized) groups: (1) a group of D-02 pivotal study subjects who received adjunctive VNS (that is, VNS in conjunction with other prescribed therapy that the study referred to as “treatment-as-usual” (VNS+TAU)) during that study’s observational phase; (2) a group of TRD patients from the D-04 observational study who received only TAU (or “standard of care” therapy). *See* CMS Ex. 1, at 34, 281, 976. (The D-04 group “had not originally been intended to serve as the primary benchmark for the VNS+TAU group” but, rather, “was intended to describe health care costs.” *Id.* at 281.) Adjustments in (non-VNS) antidepressant treatment were permitted during both the D-02 observational trial and the D-04 study. *Id.* at 29, 283.

Like the D-01 pilot, the D-02/D-04 study reported seemingly positive results. The primary outcome measured by the study was the change in patient scores on the 30-item Inventory of Depressive Symptomatology – Self-Rated (IDS-SR₃₀). (Lower scores on the IDS-SR₃₀ signify less severe depression.) Using a “repeated-measures” linear regression model, the investigators calculated the “*difference in IDS-SR₃₀ per month between the VNS+TAU and TAU groups interpreted as the average amount of improvement in IDS-SR₃₀ score in 1 month that VNS+TAU participants would experience beyond the improvements experienced by TAU participants.*” CMS Ex. 1, at 283 (italics added). The model yielded an “estimated average reduction in the IDS-SR₃₀ total score for VNS+TAU participants [that] was .40 points per month . . . greater than the reduction for the TAU participants.” *Id.* at 285. That difference persisted over time: IDS-SR₃₀ scores

for the VNS+TAU group were found to be 1.19, 2.38, 3.57, and 4.76 points lower than the scores for the TAU group at 3, 6, 9, and 12 months, respectively. *Id.* Secondary outcome analyses (using different depression rating scales) “found clinically important differences between the two groups, confirming the primary analysis.” *Id.* at 285, 287. The study also found that VNS therapy was associated with durability of treatment benefit: “whereas more than half of the responders in the VNS+TAU group at 3 months were also responders at 12 months, only one of the seven TAU responders at 3 months was also a responder at 12 months.” *Id.* at 287. The study’s authors concluded:

The results of this open, non-randomized comparison should be understood in the context of the chronic, recurrent, treatment-resistant nature of the sample TRD population. Little change should have been seen in either study group; however, the differences in therapeutic effects between VNS+TAU and TAU were both statistically significant and clinically important. Exploration of other possible contributing factors, including baseline covariates, intercurrent treatment, site differences, medication management, and placebo effects, failed to identify factors that could account for these group differences. Furthermore, most participants who showed benefit after 3 months of VNS exposure continued to do so after an additional 9 months, which is unlikely in TRD (Prudic et al 2004). In fact, treatment resistance is a powerful predictor of relapse after remission with ECT [citing studies]. It seems, therefore, that the most likely explanation is that VNS accounted for the superior long-term outcome of the VNS+TAU compared with the TAU-alone group. . . .

Id. at 289.

CMS criticized the D-02/D-04 study in its Decision Memo. CMS first indicated that the study’s results were compromised by weaknesses in the design or execution of the underlying D-02 observational study. CMS Ex. 1, at 56. According to CMS, the D-02 observational trial “did not include the 21 sham treated (placebo) patients whose HRSD scores improved so much that they did not meet the criteria to continue in the long-term phase, thus illustrating either the natural course of the disease, where symptoms wax and wane and there may be spontaneous remission, or the placebo effect.” *Id.* at 55. CMS also found that the D-02 trial involved “inconsistent reporting of data between publications and FDA public documents; lack of rigor in patient selection; [and] measures and endpoints that are clinically ambiguous” *Id.* In addition, CMS questioned the method by which the D-02’s researchers ascertained patients’ history of antidepressant therapy; found “problematic” the use of “various symptom scales for a total score to represent true patient benefit”; noted that patients with “clinically significant suicide risk” were excluded from the study, “rais[ing] the question of what

was intended by the study definition of treatment resistant depression”; and stated that “[s]ignificant confounding was introduced to the examination of results for the variable of interest when there was concurrent optimization of other treatments that may vary from site to site or clinician to clinician.” *Id.* at 55-56.

In evaluating the comparison study, CMS stated the following concerns (some of which were previously mentioned in its evaluation of the D-02 observational trial): potential “selection bias” stemming from the timing of patient enrollment, inconsistencies in the criteria for patient inclusion and exclusion, and “imbalance between groups in the 17 measured baseline variables”; “[u]ncertainty in poolability of results” (of the underlying studies) due to the fact that only one-half of the study sites participated in both underlying studies; the use of a depression rating scale (the IDS-SR₃₀) that possibly increased the risk of obtaining “false positive results”; and doubt about whether the primary outcome measure – a comparison of “rates of improvement over time” – “represent[ed] real clinical improvement” for individual patients. CMS Ex. 1, at 56 (italics added). CMS also emphasized that during both the D-04 and D-02 observational trials, changes in non-VNS treatment were permitted during the study period, making it “difficult to definitively attribute improvement to VNS.” *Id.* at 57. CMS noted that when FDA attempted to account for that circumstance using “censoring” analysis, no “statistically significant difference” in outcome was found between the VNS+TAU and the TAU-only groups, a result at odds with the findings reported to the FDA by Cyberonics. *Id.* In short, said CMS, “statistical manipulation of the results of the D02 and D04 studies [did] not compensate for a poorly designed study.” *Id.*

The Aggrieved Parties assert that the D-02/D-04 study demonstrates that VNS therapy results in “superior long-term outcomes compared with ongoing TAU.” AP Statement ¶ 15. However, they are virtually silent about CMS’s criticism of the study’s design and methods, including its assessment of the D-02 observational trial. As best we can tell, the Aggrieved Parties touch on only three of CMS’s concerns.

First, with respect to CMS’s finding that “[s]ignificant confounding was introduced” in the D-02 observational trial by the “optimization” of concomitant treatment, the Aggrieved Parties note that “responders treated with VNS in the open label phase of the D02 trial had fewer medication changes than non-responders and patients treated with TAU,” implying (perhaps) that VNS, rather than the concomitant treatments, was the factor accounting for observed group differences. Att. to AP Resp. to Supp. Br. at 16; *see also id.* at 18 (asserting that “VNS+TAU patients with fewer medication changes have better outcomes”). The Aggrieved Parties do not point to any data or analysis to justify such an implication. *Id.* Moreover, they do not dispute that concomitant treatment changes were potential confounders, nor do they explain how the study’s authors accounted for those changes in deriving and reporting their results and whether the methods used were adequate under the circumstances. In addition, the Aggrieved Parties do not dispute, or attempt to discount the significance of, CMS’s finding that the

censoring analysis obtained (or performed) by the FDA to account for concomitant therapy changes (among other factors) revealed no “statistically significant difference” in outcome between the VNS+TAU and the TAU-only groups. CMS Ex. 1, at 36-37, 57. That finding accurately reflects the analytical results reported in the FDA’s 2004 “Final Statistical Summary” concerning Cyberonics’ premarket approval application. *Id.* at 934, 948 (noting that “most of [the] statistical results” of the censoring and other supplemental analysis requested by FDA during the premarket approval process “**failed** to support that D-[0]2 patients showed superior IDS-SR or HRSD-24 results to those for D-[0]4 patients, except for average change from baseline comparison at 12 months for IDS-SR only” (emphasis in original)); *see also id.* at 148-49, 151 (Blue Cross Blue Shield TEC assessment, discussing the FDA’s censoring and other supplemental analysis of the D-02/D-04 and noting that the FDA “[a]nalyzes performed on subsets of patients cared for in the same sites, and *censoring observations after treatment changes*, generally showed diminished differences in apparent treatment effectiveness of VNS and *almost no statistically significant results*” (italics added)).

Second, in response to CMS’s finding that there was an “imbalance between [the VNS+TAU and TAU-only] groups in the 17 measured baseline variables,” CMS Ex. 1, at 56, the Aggrieved Parties contend that the use of “propensity scoring” in the study ensured that any differences between the treatment and control groups at baseline were “not significant.” *See* Att. to AP Resp. to Supp. Br. at 18 (asserting that “baseline demographic and illness characteristic differences are controlled in the primary repeated-measures linear regression analysis by incorporating the five-level grouped propensity score”). CMS acknowledged the study’s use of propensity scoring but indicated that the technique did not adjust for important “unmeasured variables,” a concern that the FDA reviewers also raised. CMS Ex. 1, at 56, 1009. The Aggrieved Parties do not question the reasonableness of that criticism.

Third, the Aggrieved Parties comment on CMS’s uncertainty about whether the measured group differences “represent[] real clinical improvement.” CMS Ex. 1, at 56. As indicated, the study found that VNS+TAU subjects experienced monthly improvements (that is, reductions) in IDS-SR₃₀ scores that were, on average, 0.4 points greater than those experienced by the TAU subjects. This group difference was cumulative, and thus over the course of 3, 6, 9, and 12 months, average IDS-SR₃₀ scores for VNS+TAU subjects were 1.19, 2.38, 3.57, and 4.76 points lower than those achieved by TAU subjects. In its supplemental brief, CMS explained that the practical or clinical significance of these group differences was uncertain in light of the rating scale used by the researchers. CMS Supp. Br. at 11. A subject’s total score on the IDS-SR₃₀ can range from 0-84 points, with the total score used to categorize the overall severity of the subject’s depressive disorder, as follows: 0-13 points (normal); 14-25 points (mild depression); 26-38 points (moderate depression); 39-48 points (severe depression); and 49-84 points (very severe depression). *Id.* Although the group differences found in the D-02/D04 study were “statistically significant,” CMS accurately notes that they were

small relative to the width of the severity categories (for example, “moderate depression” is associated with a score that falls within a 12-point range of 26 to 38).²² *Id.* CMS further asserts that a “0.4 difference in score over a period of a month (or even a difference in score of 4.8 points over a year [12 months x 0.4] is of unknown significance.” *Id.*

The Aggrieved Parties assert that CMS did not produce “evidence” justifying its concern about a lack of “clinical significance.” Att. to AP’s Response to Supp. Br. at 18. However, the bases for CMS’s concern about clinical significance are plainly apparent from the D-02/D-04’s published findings and the features of the IDS-SR₃₀ rating instrument. The Aggrieved Parties do not point to anything in the NCD record (or elsewhere) indicating that the concern is unfounded. We thus cannot conclude that CMS was unreasonable in questioning the clinical significance of the D-02/D-04 study’s results.

The Aggrieved Parties assert that CMS’s criticism of the D-02/D-04 study improperly implies that “clinical superiority” of adjunctive VNS over TAU is “required as a precursor to Medicare coverage.” AP Resp. to Supp. Br. at 18. Of course, a stated objective of that study was to demonstrate the clinical superiority of adjunctive VNS versus TAU for TRD patients. *See* CMS Ex. 1, at 281 (hypothesizing that “participants treated with VNS+TAU would have significantly greater improvements in depressive symptoms over the course of 12 months, as compared with those treated with TAU alone”). The study’s use of a control group – namely, TAU patients from the D-04 study – indicates that it was also intended to provide evidence of VNS’s causal effect. CMS found that the D-02/D-04 study did not achieve that goal, stating “the comparison of these two observational trials provides little evidence that a patient will experience a health benefit as a direct result of VNS therapy.” CMS Ex. 1, at 56. That finding may indeed imply that adjunctive VNS is not “clinically superior” to TAU alone, but such an implication is not necessarily inconsistent with the Medicare coverage standard. For patients with TRD, VNS is not being used as an alternative to TAU but as adjunctive therapy – a supplement to TAU. Thus, if VNS has an actual treatment effect, then it should (when used as adjunctive therapy) increase or enhance the therapeutic benefit that the patient would have experienced with TAU alone. In other words, VNS should result in outcomes superior to TAU when used as adjunctive therapy. On the other hand, if adjunctive VNS (VNS+TAU) does not lead to superior outcomes, one could reasonably question whether VNS has any beneficial treatment effect or is otherwise “reasonable *and necessary*.”

²² A patient classified as having “severe depression” and a baseline IDS-SR₃₀ score of 47 would retain that classification even if his score improved by 5 or even 8 points because the lower-boundary score for severe depression on that scale is 39.

(c) **The Corcoran study**

The Cyberonics-sponsored Corcoran study (CMS Ex. 1, at 196; AP Ex. 33) followed 11 European subjects for one year after implantation of the VNS device. Upon enrollment, the subjects had diagnoses of MDD, were in a “chronic” MDE (that is, a depressive episode whose duration was two years or longer), and had failed to respond to antidepressants from at least two different medication categories. Subjects continued to take antidepressant and mood-stabilizing drugs during the trial, and medication changes were permitted after the end of the trial’s initial three-month (acute) phase. Treatment outcomes were measured using the Hamilton Rating Scale for Depression (HRSD) and other instruments. Treatment response was defined as a ≥ 50 percent decrease in HRSD score, and remission was defined as an HRSD score of less than 10.

Although only one subject responded during the acute phase, six subjects (or 55 percent of the sample) responded to treatment after one year, and three subjects were in remission. The study’s authors stated that their results “suggest[] that [VNS] may be an effective treatment for *some* individuals suffering from chronic treatment-resistant depression.” CMS Ex. 1, at 197 (italics added). The authors acknowledged that the study had various limitations, including a *small sample size, the lack of control group and randomization, and the allowance of medication changes* during the long-term phase. *Id.* (italics added). The authors stated that the medication changes “possibly impact[ed]” the study’s findings but were “controlled for . . . statistically.” *Id.* In addition, the authors reported “several serious adverse events” that occurred during the study, including the suicide of one subject, the development of pulmonary emboli in another, and vocal cord palsies in two other subjects. *Id.*

In response to a comment that the Corcoran study showed “high efficacy,” CMS stated (in the Decision Memo) that the study was “too small to draw such sweeping conclusions.” CMS Ex. 1, at 51. CMS also expressed concern about the number and nature of the adverse events reported. *Id.* at 49. The Aggrieved Parties do not address this study in their submissions or otherwise argue that CMS’s findings and concerns about the study were unreasonable.

(d) **The Sackeim study**

The Sackeim study – another study without a control group – assessed the “durability” of antidepressant response to VNS over two years. *See* CMS Ex. 1, at 649; AP Ex. 73. It combined data from the D-01 pilot and D-02 pivotal studies. A total of 264 subjects from those studies were divided into three groups: early responders, late responders, and non-responders. Early responders were subjects who experienced a ≥ 50 percent reduction in their scores on the 28-item Hamilton Rating Scale for Depression (HRSD₂₈) after three months of VNS therapy. Late responders were subjects who met that criterion after 12

months. An early or late responder was deemed to have maintained a “response” at a later assessment if the responder’s HRSD₂₈ score at the later assessment was at least 40 percent greater than baseline (a threshold lower than one required to find an early response).²³

The study found 48 early responders (18.2 percent of the sample), 54 late responders (20.5 percent), and 162 non-responders (61.4 percent). *See* AP Ex. 73, at 3, 4. Among the 48 early responders, 32 continued to be responders after one year, and 34 after two years. *Id.* Among the 54 late responders, 37 were still responding after two years. *Id.* The study’s authors stated that the “delay in acute response” experienced by some subjects was one of the study’s “exceptional” findings, noting that because of VNS’s “delayed effects,” “the outcome of a VNS trial for an individual patient may not be fully known until 12-24 months have elapsed.” *Id.* at 7-8. However, the authors stated that they “were unsuccessful in identifying predictors of early or late benefit” and their “findings did not address whether improvement is sustained only when VNS is responsible for acute response.” *Id.*

The authors also stated that “[i]n the absence of a long-term, sham-controlled, randomized trial, one cannot conclude that the acute or sustained effects observed in the pilot and pivotal studies were attributable to VNS.” AP Ex. 73, at 8. In addition, the authors identified three potential confounders (extraneous factors that may have contributed to the observed outcomes but were not explicitly accounted for in the statistical analysis): “placebo effects”; “the action of altered medication regimens”; and “the natural history of illness” (waxing and waning of symptoms, or spontaneous remission). *Id.* Although the researchers hypothesized that these factors did not contribute to the observed patient outcomes, they did not claim that their results and methods provided sound evidence confirming their hypotheses. For example, the authors indicated that the issue of whether medication changes helped produce the observed treatment benefits was only “partially addressed” in the study. *Id.* Regarding the natural-history-of-illness factor, the authors stated that while data from another study “suggest that spontaneous recovery rates are extremely low” in patients with resistant depression, the “natural history of TRD is not well characterized[.]” *Id.*

²³ The authors stated that the “criterion for maintenance of response was reduced to an improvement of at least 40% from baseline” because this “avoided characterizing a minor decrease (e.g., from 51% to 49%) as loss of benefit.” AP Ex. 73, at 2. Given that the more accepted 50-percent-reduction criterion was used as the definition of “response” during the early (three-month) phase of the trials, the change in criterion calls into question the authors’ reporting of the rates of “maintaining response” (i.e. durability) in the later phases. CMS Ex. 1, at 640 (stating that “[t]ypically response has been defined as $\geq 50\%$ reduction in pretreatment symptom severity”). CMS reasonably raised concerns about the lack of empirical evidence for endpoints in clinical studies of depression, noting for example that, although “remission” was the recommended endpoint, use of different definitions of “remission” can lead to radically different results. CMS Ex. 1, at 22, 46.

In its Decision Memo, CMS rejected a commenter’s suggestion that “regression to the mean” (waxing and waning of symptoms, or spontaneous remission) – one of the potential confounders identified by the Sackeim study’s authors – was “less relevant” for TRD patients:

There is insufficient evidence to conclude that regression to the mean is less relevant for a particular patient. CMS notes that the natural course of untreated depression has rarely been examined, so it is difficult to understand spontaneous remission. The Surgeon General’s Report on mental health stated about major depressive disorder, “When untreated, a major depressive episode may last, on average about 9 months. Eighty to 90 percent of individuals will remit within 2 years of the first episode (Kapur & Mann, 1992). Thereafter, at least 50 percent of depression will recur, and after three or more episodes the odds of recurrence within 3 years increases to 70 to 80 percent if the patient has not had preventive treatment.” “Across the life span, the course of depression is marked by recurrent episodes of depression followed by periods of remission” (Surgeon General’s Report 1999). In D02 there was a control group, some of whom improved as measured by the symptom scale; by this, they either responded to another treatment or remitted spontaneously.

CMS Ex. 1, at 46-47. Other than pointing to the Brunoni (2009) study, which it failed to submit, and offering unsupported or speculative statements of counsel, the Aggrieved Parties make no credible attempt to rebut these CMS findings. *See* Att. to AP Resp. to Supp. Br. at 9 (citing to the Brunoni study in footnote 15), 15-16. The Aggrieved Parties also do not argue that the Sackeim study’s methods and results were sufficient to overcome CMS’s concerns about the placebo response. *Id.* at 15-16.

(e) Other studies and published articles

In addition to the six articles that report on the D-01, D-02/D-04, Corcoran, and Sackeim studies, the Aggrieved Parties cite 20 other published articles to support their contention that NCD 160.18(C) was inconsistent with the scientific and clinical evidence available to CMS on May 4, 2007. AP Statement ¶ 4 (*citing* AP Exs. 28, 30-32, 34-35, 37, 39-41, 43-45, and 47-53). Of these 20 articles – the contents of which are summarized in this decision’s appendix – three are case reports on single patients (AP Exs. 28, 34, and 37); eight review or analyze prior studies of VNS’s use in treating depression or epilepsy (AP Exs. 30, 31, 35, 47, 48, 49, 50, 52); three are studies of the anatomy of the vagus nerve or patients’ physiological responses to VNS (AP Ex. 39, 40, and 51); three report on studies of VNS’s safety or effectiveness for epilepsy (AP Ex. 41, 44, and 45); one concerns a small (14-patient) study that focused primarily on the efficacy of electroconvulsive

therapy in conjunction with VNS (AP Ex. 32); one describes a study of VNS's impact on neurocognitive performance (*e.g.*, psychomotor function, language, attention, memory, and executive function) in TRD patients (AP Ex. 43); and one examines the global "burden of disease" of TRD (AP Ex. 53).

The Aggrieved Parties do not discuss any of these articles, much less explain their significance in light of CMS's reasons for denying coverage. Although CMS did not include these articles in the NCD record, CMS did find that these *types* of articles were not strong or probative evidence that VNS produces improved health outcomes. For example, CMS stated (in the Decision Memo) that "the results of individual practitioners or patients [case reports] are less rigorous and therefore less useful for making a coverage determination," and that smaller clinical trials (such as the 11-patient Corcoran study) do not permit firm or "sweeping" conclusions about treatment effectiveness. CMS Ex. 1, at 20, 51. In addition, said CMS, "[r]eview articles and reanalysis of previous data generally do not provide additional evidence of health benefit beyond what is already known from the primary medical research literature[.]" *Id.* at 43. Concerning studies of VNS's physiological effects, CMS stated that while determining the "physiologic mechanism of VNS action is important, data on mechanism provides insufficient evidence to determine if VNS improves health outcomes and thus if VNS is reasonable and necessary." *Id.* at 45.

As our Appendix shows, these unchallenged findings are plainly applicable to the 20 additional articles cited by the Aggrieved Parties. Furthermore, some of the articles support CMS's judgment that the available clinical studies had not yet (as of May 2007) satisfactorily demonstrated VNS's benefit for TRD patients and that additional research was needed to address important unresolved issues, such as VNS's effectiveness in clinical practice and the need to identify factors that predict a positive treatment response to VNS in TRD patients. AP Ex. 30, at 10 ("Additional studies are needed to identify the patient-related factors that predict response to therapy and the parameter settings that are most effective for patients with various disease characteristics."); AP Ex. 35, at 5 ("More extensive long-term prospective data are needed to completely evaluate [VNS's] role as adjunctive treatment for drug-resistant epilepsy and depression."); AP Ex. 47, at 10 (concluding that the clinical studies of VNS were "promising" but noting there "are some concerns to be resolved regarding the full degree of treatment efficacy" and that "close scrutiny should be applied to the post-FDA approval experience with VNS to get a fuller picture of [VNS's] effectiveness in clinical practice"); AP Ex. 49, at 3 (indicating that the D-02/D-04 study's results "support the benefit of adjunctive VNS therapy for patients with TRD compared to TAU" but noting the importance of the fact that the D-02/D-04 involved a "non-randomized comparison"); AP Ex. 52, at 5 (concluding that "[f]urther work needs to be done with respect to predictors of response to VNS in TRD" and that "[g]iven that VNS does not appear to have robust acute antidepressant effects, the most appropriate place of VNS in the therapeutic armamentarium of depression remains to be determined").

2. Expert medical opinion

In support of their contention that NCD 160.18(C) was in conflict with the “consensus of expert medical opinion” that existed as of May 4, 2007, the Aggrieved Parties assert that:

- Of the 1843 public comments submitted to CMS during the review process leading the issuance of NCD 160.18(C), all but 12 comments supported coverage of VNS therapy for TRD;
- Of the 151 comments submitted by physicians, only three opposed Medicare coverage;
- Of the 84 comments submitted by “other healthcare professionals and organizations, only five were not in favor of VNS therapy coverage”;
- In 2006 and 2007, the American Association of Neurological Surgeons (“AANS”) and the American Psychiatric Association (“APA”) “indicated their support of coverage for VNS therapy.”

See id. ¶¶ 20-24 (citing AP Ex. 57 and CMS Ex. 1, at 42, 44, 50).

Some of these same points were made to CMS during the coverage review process that preceded the issuance of NCD 160.18(C), including the observation that virtually all 1843 public comments supported coverage of VNS for TRD. CMS Ex. 1, at 50. In response to that observation, CMS stated that “individual responses should not be construed as a consensus response, as is illustrated by those who actually chose to respond, which is a small percentage of the psychiatric community in the United States.” *Id.* CMS also noted that clinical practice guidelines published by specialty medical societies (such as the APA) did not mention or endorse VNS as a treatment for resistant depression. *Id.* at 40, 50 (stating that “VNS [was] not included in current guidelines such as those endorsed by consensus statements that are subject to peer review” and that an APA publication titled “Guideline Watch: Practice Guideline for the Treatment of Patients with Major Depressive Disorder, 2nd Edition” (CMS Ex. 1, at 266) stated that evidence was not yet sufficient to recommend the use of VNS in routine clinical practice). In addition, CMS implicitly found that the commenters’ support was outweighed by the fact that its review found “little data that demonstrates that VNS has benefit for the Medicare population.” *Id.* at 50 (stating that conclusion while acknowledging the large number of comments in support of VNS).

The Aggrieved Parties do not question the reasonableness of these findings as they pertain to the state of affairs on May 4, 2007. They do not, for example, claim or show that the expert commenters were actually representative of an expert “consensus.” Nor do the Aggrieved Parties dispute CMS’s findings that VNS was not included in clinical practice guidelines as of May 2007. Although the APA and AANS supported Medicare coverage of VNS for TRD in their public comments, neither challenged CMS’s judgment concerning the strength of the relevant clinical evidence, despite having an opportunity to do so.²⁴ See AP Ex. 57; CMS Ex. 1, at 2187-88.

3. The Aggrieved Parties have not demonstrated that the NCD record was not complete and adequate to support the validity of the NCD in light of information reviewed by, or available to, CMS on or before May 4, 2007.

As CMS explained in the Decision Memo, the determination to deny Medicare coverage of VNS for resistant depression rests largely on three pillars:

- The results of the only “well-designed” clinical study of adjunctive VNS – namely, the D-02 pivotal study’s DBRCT, which “failed to demonstrate statistically significantly superior outcomes greater than sham treatment” (CMS Ex. 1, at 55, 57);
- A judgment that other clinical studies of VNS therapy for TRD had design or methodological shortcomings that called into question the internal and external validity of their findings (*id.* at 57, noting that the “observational studies [such as the D-01] have biases that make conclusions difficult” and expressing uncertainty about “how results from trials of patients without reported significant comorbidities can be generalized to many clinical populations, including older adults in Medicare”); and
- The fact that VNS is an invasive treatment, with the risk of adverse effects, some of which may not have been tracked or accurately reported (*id.* at 49).

²⁴ According to the Aggrieved Parties, CMS’s Decision Memo includes a finding that “only one expert” commenter thought that additional randomized controlled studies were necessary to demonstrate VNS’s safety and efficacy for resistant depression. AP Statement ¶ 24. The Decision Memo contains no such finding. CMS merely discussed the comments of “[o]ne commenter” who “agreed that more randomized controlled clinical data concerning safety and efficacy would be informative . . . and hopefully settle the debate” without suggesting that the commenter was the only expert who held such an opinion. CMS Ex. 1, at 44.

The Aggrieved Parties do not directly challenge CMS's first rationale. In particular, they do not dispute CMS's characterization of the results of the DBRCT, nor do they deny that those results are entitled to considerable weight in evaluating the overall strength of the relevant clinical evidence. Instead, the Aggrieved Parties point to other clinical studies which suggest that VNS may produce long-term benefit in TRD patients. CMS's second rationale – that these other, longer-term studies are weak or provide questionable evidence that VNS improves health outcomes for TRD patients – is amply supported by the NCD record. Of the four pre-May 2007 studies cited by the Aggrieved Parties, three (i.e., D-01, Corcoran, and Sackeim) were uncontrolled studies, the type of study whose results CMS could reasonably assign comparatively less weight in determining whether VNS has a treatment effect.²⁵ In addition, the authors of the D-01, Corcoran, and Sackeim studies acknowledged other design and methodological shortcomings that weakened their findings, including lack of randomization and blinding. The D-02/D-04 study was larger than the other three and used a control group. But CMS reasonably determined that the D-02/D-04 study was methodologically unsound and that its results, while positive, were of doubtful clinical importance.

As our previous discussion shows, the Aggrieved Parties have not offered any effective challenge to CMS's assessment of the D-02/D-04 or of any other pre-May 2007 study. For example, they have not identified any material error in how the Decision Memo: (1) characterized the relevant studies' methods or results, (2) applied scientific or statistical principles, (3) assessed the strength of a study's findings, or (4) assigned weight to certain evidence. The Aggrieved Parties argue that the primary clinical studies of VNS for resistant depression are "well-designed." See AP Statement ¶¶ 15-16. But beyond that mere label, they fail to explain *why*, under accepted principles for evaluating scientific research, the studies should be regarded as having produced reliable, probative evidence that VNS improved health outcomes for TRD patients. The Aggrieved Parties also ignore CMS's concern about the relevance of the primary clinical studies for older Medicare beneficiaries with significant "comorbidities." See CMS Ex. 1, at 45, 57. In addition, the Aggrieved Parties do not argue that CMS's safety concerns about the VNS device were – as of May 2007 – trivial, unfounded, or outweighed by the available evidence of treatment benefit.

²⁵ See generally Kaye, D. and D. Freedman, *Reference Guide on Statistics* in Federal Judicial Center, *Reference Manual on Scientific Evidence* (3d ed.2011) ("Reference Manual") at 220 ("[D]ata from a treatment group without a control group generally reveal very little and can be misleading.") and at 222 ("Was there a control group? Unless comparisons can be made, the study has little to say about causation."). The Federal Judicial Center's *Reference Manual on Scientific Evidence*, produced in collaboration with the National Academy of Sciences, states in its preface that it is intended to "assist judges in identifying the issues most commonly in dispute in selected areas and in reaching an informed and reasoned assessment concerning the basis of expert evidence." The Manual is available at [http://www.fjc.gov/public/pdf.nsf/lookup/SciMan3D01.pdf/\\$file/SciMan3D01.pdf](http://www.fjc.gov/public/pdf.nsf/lookup/SciMan3D01.pdf/$file/SciMan3D01.pdf) (last visited Dec. 22, 2014).

The Aggrieved Parties assert that NCD 160.18(C) was not based on the “strongest evidence available.” *See* AP Statement ¶ 17. We disagree. To decide the coverage issue posed by CMS – does VNS improve health outcomes? – the strongest evidence available was the D-02 pivotal study’s DBRCT, which “failed to demonstrate statistically significantly superior outcomes greater than sham treatment[.]” CMS Ex. 1, at 55. CMS explicitly relied on that study, as well as on the absence of countervailing findings from studies of comparable rigor and quality. *Id.* at 55-57.

CMS’s judgment that there was, as of May 4, 2007, insufficient evidence of VNS’s clinical benefit for TRD patients is supported by the findings of external technology assessments performed in 2006 by the California Technology Assessment Forum,²⁶ which found the “observational” evidence of VNS’s treatment effect “not yet convincing” given the results of the DBRCT (CMS Ex. 1, at 168), and by the Blue Cross Blue Shield Association’s TEC, which characterized the primary clinical evidence as “not strong” (*id.* at 151). CMS’s judgment is further supported by the published comment of Ziad Nahas and Mark S. George, two of the principal authors of the D-01 and D-02/D-04 studies, who stated in a 2007 article there was a “critical need for a clear demonstration of [VNS’s] antidepressant efficacy.” CMS Ex. 1, at 298.

The Aggrieved Parties suggest that CMS ought to have assigned substantial weight to the FDA’s safety and effectiveness findings in resolving the Medicare coverage issue. AP Statement ¶¶ 33-34. While conceding that such findings are “not determinative of Medicare coverage,” the Aggrieved Parties assert that “CMS adopts” them. *Id.* ¶ 34.

CMS did not say in its Decision Memo how (if at all) it weighed the FDA’s findings, but we find no prejudicial error in that omission because “CMS and its contractors make coverage determinations and the FDA makes premarket approval decisions under different statutory standards”:

Whereas the FDA must determine that a product is safe and effective as a condition of approval [*see, e.g.*, 21 U.S.C. §§ 360c and 360e], CMS must determine that the product is reasonable and necessary as a condition of coverage under section 1862(a)(1)(A) of the Social Security Act. Under a premarket approval review, the FDA determines whether or not the product is safe and effective for its intended use that is stated in its proposed

²⁶ According to its website, <http://www.ctaf.org/about-ctaf> (last visited Dec. 22, 2014), the California Technology Assessment Forum is a “core program” of the non-profit Institute for Clinical and Economic Review, which is a program “with the purpose of producing objective evidence reports and holding public meetings to develop recommendations for how patients, clinicians, insurers, and policymakers can apply evidence to improve the quality and value of health care.”

labeling. Medicare evidence-based NCD reviews [on the other hand] consider the medical benefit and clinical utility of an item or service in determining whether the item or service and its expenses are reasonable and necessary under the Medicare program.

67 Fed. Reg. 66,718, 66,755-756 (Nov. 1, 2002); *see also Notice, Medicare Program; Revised Process for Making Medicare National Coverage Determinations*, 68 Fed. Reg. 55,634, 55,636 (Sept. 26, 2003) (stating that “CMS and its contractors make coverage determinations and the FDA conducts premarket review of products under different statutory standards and different delegated authority”); *Yale-New Haven Hosp. v. Leavitt*, 470 F.3d 71, 84 (2d Cir. 2006) (“‘reasonable and necessary’ is not obviously the same standard as ‘safe and effective’”); MPIM § 13.5.1 (indicating that CMS evaluates factors other than safety and effectiveness in determining whether a medical item or service is reasonable and necessary). Although an FDA-regulated product must generally receive FDA approval or clearance for at least one clinical indication in order to be eligible for Medicare coverage, “FDA approval/clearance alone does not generally entitle that device to coverage.”²⁷ 68 Fed. Reg. at 55,636.

The Aggrieved Parties allege that “the VNS therapy implant is the only device that purportedly is not covered for any Medicare beneficiaries for an FDA-approved (as opposed to FDA-cleared) indication.” AP Statement ¶ 33. That assertion is not supported by evidence, and even if it were, would be irrelevant because CMS and the FDA apply different standards in exercising their respective regulatory authority.

In light of all these circumstances, we conclude that, as of May 4, 2007, the NCD record was complete and adequate to support CMS’s determination that VNS is not reasonable and necessary for resistant depression.

²⁷ For some items, such as drugs and biologicals, CMS accepts the FDA’s safety and effectiveness findings as sufficient evidence that the item is reasonable and necessary (and thus entitled to Medicare coverage) for the FDA-approved indication. *See* 67 Fed. Reg. at 66,756; Medicare Benefit Policy Manual (CMS Pub. 100-02), ch. 15 § 50.4.1 (available at <http://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Internet-Only-Manuals-IOMs-Items/CMS012673.html>). But CMS is under no legal obligation to do so; it may, in its discretion, “choose to perform a reasonable and necessary determination” despite FDA approval. 67 Fed. Reg. at 66,756 (specifying circumstances in which CMS may elect not to accept the FDA’s findings); *Almy v. Sebelius*, 679 F.3d at 308 (noting, in a case involving the FDA 510(k) process, that “[w]hile FDA approval may . . . inform [CMS]’s decision as to whether a device is ‘reasonable and necessary,’ it cannot tie [CMS]’s hands”).

C. *The NCD record remains complete and adequate to support the validity of NCD 160.18(C), even in light of post-May 2007 developments, such as the publication of additional clinical studies of VNS.*

Referring to peer-reviewed articles and other information published or created after May 2007, the Aggrieved Parties contend that NCD 160.18(C) is “not reasonable in view of the *current* medical and scientific literature.” AP Statement ¶ 6 (emphasis and italics in original); *see also id.* ¶ 60 (asserting that the NCD “does not reflect the current published, peer-reviewed literature”). The Aggrieved Parties also contend that the NCD is in conflict with a current “consensus of expert medical opinion” regarding VNS’s safety and efficacy for TRD. *Id.* ¶¶ 19, 25, 61. The Aggrieved Parties assert that this alleged consensus, together with the medical literature and other information published since May 2007, “clearly invalidates NCD 160.18.” AP Resp. to Supp. Br. at 2.

We reject these contentions for the reasons explained in parts A through C, below. As the Board stated in *Pancreas Transplants # 35-82*, NCD Ruling No. 1 (2005), the burden is on the Aggrieved Parties to “demonstrate that the situation [that is, the state of affairs when CMS issued the challenged NCD] has changed to such a degree that the [NCD] record can no longer be considered complete and adequate to support the validity of the NCD provision under the reasonableness standard.” Overall, the post-May 2007 studies and other material submitted by the Aggrieved Parties do not meet that burden. While the Aggrieved Parties have shown that the situation has changed somewhat with respect to clinical practice and that researchers have attempted to address some of CMS’s stated concerns, the Aggrieved Parties have failed to offer a coherent explanation about how the recent studies (and other medical literature) have filled research gaps, explored and resolved all of the numerous questions that were unresolved by earlier research, or dispelled all of the specific concerns raised by CMS in its Decision Memo. In particular, we note the absence of any successful sham-controlled study and of any *clinical study findings that address VNS’s use in the primary Medicare population of persons 65 years or older.*²⁸

We also emphasize that the post-May 2007 studies and other published statements on their face actually reinforce many of CMS’s pre-existing concerns about VNS’s safety risks, including surgical complications of implantation (or explantation), side effects of stimulation, or other adverse events. In its response to one of the *amicus curiae* statements, CMS stated:

²⁸ The Aggrieved Parties correctly point out that the Medicare population includes younger adults who suffer from resistant depression and who qualify for Medicare based not on their age but on disability. *See* AP Statement at 3 n.3. That fact is not determinative here because the Aggrieved Parties’ complaint does not ask the Board to invalidate NCD 160.18(C) for only a subset of the Medicare population.

If we are to expose the Medicare beneficiary population to such harmful effects, CMS must be certain that the risk of . . . having the device implanted is worth its benefit. The means by which this can be accomplished is the use of a comparator group [a control group] in the study and preferably one that is being treated with an implanted sham or inactive device. The study design of a single group study, as used in all but one of the VNS articles to date[,] is far too limited to provide us the information we need.

CMS Response to *Amicus Curiae* Letter of Buser at 4. This risk-benefit calculation, echoed in the Decision Memo, continues to be reasonable in light of all the information before us.

The Aggrieved Parties proffer some reasons (which we discuss below) why a long-term sham-controlled study could not be easily or ethically done. They do not deny, however, that only two of the new studies (*i.e.*, Olin and Feldman) on which they rely had a control group as part of the study design. Given the negative results of the one sham-controlled study with a concurrent control group that was done and the remaining concerns about whether any long-term improvements reported in the studies were actually caused by VNS, the new studies do not render the NCD record incomplete and inadequate to support the validity of NCD 160.18(C).

1. The peer-reviewed scientific and medical literature published since May 2007 is not sufficient to call into question the reasonableness of CMS's rationale for NCD 160.18(C).

In support of its contention that NCD 160.18(C) is contrary to the post-May 2007 medical and scientific literature, the Aggrieved Parties point to the following six published articles, which report on six peer-reviewed clinical studies (we identify each article, and the study which the article describes, by the last name of its principal author):

- Aaronson (2013), AP Ex. 12: the D-21 dosing study, a FDA-mandated post-approval study which compared the safety and efficacy of different stimulation levels of VNS for treating TRD;
- Feldman (2012), AP Ex. 18: a study of Medicare claims data for beneficiaries with depression who were implanted with the VNS device during an 18-month period (prior to the May 4, 2007 issuance of NCD 160.18(C)) when some Medicare contractors covered VNS for that condition on a case-by-case basis;
- Olin (2012), AP Ex. 19: a study that assessed mortality and suicidality in persons with TRD;
- Christmas (2013), AP Ex. 15: a small European study of VNS's safety and efficacy for TRD;

- Bajbouj (2010), AP Ex. 22: a Cyberonics-sponsored European study of VNS’s safety and efficacy for TRD; and
- Berry (2013), AP Ex. 14: a Cyberonics-sponsored meta-analysis that compared treatment outcomes for persons receiving adjunctive VNS for TRD and persons who received only “treatment-as-usual” (TAU) for that condition.

See AP Statement ¶¶ 7-10, 12-13. We briefly describe each of these studies.

Aaronson (2012): As noted earlier, FDA’s premarket approval of VNS for TRD was not unconditional. As a condition of its approval, the FDA required Cyberonics to conduct two post-approval studies. The objective of the first study – known as the D-21 dosing study, and whose results we summarize here – was to assess the effectiveness and safety of different stimulation levels of VNS as well as the duration of subjects’ response to that therapy rather than to evaluate the potential long-term efficacy of VNS.²⁹ AP Ex. 5, at 3; CMS Ex. 1, at 1027. (The other FDA-mandated post-approval study, known as the D-23 Treatment-Resistant Depression registry, is ongoing and is discussed later.) A dose response would be some, and perhaps important, scientific evidence that VNS has some effect (independent or synergistic) in reducing depressive symptoms or producing other beneficial health outcomes for TRD patients.³⁰

The D-21 study enrolled 331 subjects who were assigned randomly to one of three dose groups: low, medium, or high. Both subjects and researchers were blinded to the randomized dosage assignment. The subjects were a “highly treatment-resistant population,” and all three treatment groups were “similar in terms of psychiatric history.” AP Ex. 12, at 4. The study’s primary outcome measurement was a subject’s score on the Inventory for Depressive Symptomatology – Clinician Administered (IDS-C) scale. (Outcomes were also measured using four other scales.)

After 22 weeks – the end of the study’s “acute phase” – approximately 20 percent of subjects across all three dose groups experienced a treatment “response” – defined as a \geq 50 percent reduction in IDS-C score from a baseline severity measurement. AP Ex. 12, at 6. However, “[w]hile the response rate was numerically higher in the HIGH group

²⁹ VNS dosing is modulated using various stimulation parameters, such as pulse width, frequency, and duration of stimulation. AP Ex. 12, at 2.

³⁰ A dose-response relationship exists if increasing exposure to an agent is associated with an observed change in outcome, effects, or risks. See generally Kaye, D. and D. Freedman, *Reference Manual* at 545, 603, 622, 681 (defining “dose-response relationship” or “dose-response assessment” as those terms are used in the fields of epidemiology, toxicology, and exposure science). The existence of a dose-response relationship is one of a number of factors that guide researchers in making judgments about whether an observed association reflects a causal relationship. See *id.* at 599-600.

compared with the MEDIUM and LOW groups for each measure, there were no significant differences in response rates among the treatment groups.” *Id.*

Approximately 9 to 11 percent of subjects in the medium-dose and high-dose groups experienced a “remission” (based on each of the rating scales) by the end of the acute phase, compared with 5 to 6 percent of subjects in the low-dose groups. *Id.* But, again, the discrepancy in remission rates *between dose groups* was not statistically significant. *Id.*

During the long-term phase of the study, “investigators could . . . modify concomitant antidepressant and mood stabilizer treatments . . . to improve efficacy as clinically indicated, but preferably only after adjusting VNS parameters.” AP Ex. 12, at 3. At the end of the long-term phase (that is, at 22 weeks), IDS-C and secondary-scale scores showed continued improvement for each dose group: in particular, “[a]t Week 50, response rates for the various scales ranged from 27% to 42% in the LOW group, 36% to 53% in the MEDIUM group, and 27% to 48% in the HIGH group”; in addition, “[r]emission rates were comparable between the treatment groups for each scale and ranged from 15% to 23%.” *Id.* at 6 (citations omitted).³¹ However, there were “no significant differences in response rates among the treatment groups.” *Id.*

Based on two different rating scales (the IDS-C and the Montgomery-Asberg Depression Rating Scale (MADRS)), the study calculated the “proportion of responders at the end of the acute phase who were also responders at the end of the long-term phase.” AP Ex. 12 at 7. The authors found that “[f]or both scales, the MEDIUM and HIGH groups exhibited high rates of sustained response (88.2% and 92% for the MEDIUM group, and 81.8% and 76.7% for the HIGH group on the IDS-C and MADRS, respectively),” while “[t]he sustained response rate in the LOW group was substantially less than the MEDIUM or HIGH groups on both the IDS-C (43.8%) and MADRS (68.8%) scales.” *Id.* at 8.

The study evaluated VNS’s safety by recording “adverse events” (AEs) and “serious adverse events” (SAEs) at specified intervals from implantation to the end of the long-term phase. AP Ex. 12, at 4. The study found that “[o]verall, VNS was well tolerated, as shown by the very high rate of completion (94.3%) during the long-term phase.” *Id.* at 8.

In short, the study’s authors concluded that “[w]ithin the limits of this study design, the results showed that TRD patients receiving adjunctive VNS in an open-label setting had significant improvement at study endpoint compared with baseline, and the effect was durable over 1 year (unusual for the population being studied).” AP Ex. 12, at 9.

³¹ These ranges illustrate how the choice of rating scale can affect the evaluation of whether a patient has improved enough to be considered a responder or remitter.

Feldman (2012): The Feldman study was based on historical Medicare claims data. It compared the health outcomes (including mortality), costs of care, and other “patient experience” of three groups of Medicare beneficiaries with major depressive disorder: (1) the “VNS group,” whose members received adjunctive VNS during an 18-month period, prior to the issuance of NCD 160.18(C), when some Medicare contractors covered that treatment for depression on a case-by-case basis; (2) a group of beneficiaries, called the “TRD” control group, whose members were not treated with VNS but who were considered to be treatment-resistant based on the nature and frequency of the healthcare services they received during a “2-year identification period”; and (3) the “managed depressed” control group, whose members were not likely to be treatment-resistant (based, again, on healthcare utilization history). AP Ex. 18, at 3-4.

Even though the frequency of “co-occurring psychiatric conditions” and “medical comorbidities” in the VNS group was lower than in the TRD and managed-depressed groups, the study found that VNS-group members experienced a *higher rate* of “negative events” during the two-year comparison period. AP Ex. 18, at 7 (indicating that 31 percent of the VNS group experienced negative events during the two-year post-implantation period, versus 20 percent of the TRD control group and 4 percent of the managed-depressed control group, and also indicating that the percentage of the VNS group that experienced “no negative events” was *lower* than the percentage in the two non-VNS control groups); *see also* CMS Response to *Amicus Curiae* Letter of Moreno at 2. On the positive side, the Feldman study found the annual mortality rate for the VNS group following implantation was less than one-half the rate in the two control groups (19.9 deaths per 1000 patient years versus 46-47 deaths per 1000 patient years). *Id.* at 5. However, the study’s authors acknowledged that that finding (and others) “cannot be explained without further research.” *Id.* at 11.

Olin (2012): The Olin study used data from one of the FDA-mandated post-approval studies to assess VNS’s potential efficacy in reducing mortality and suicide risks in persons with TRD. The study compared a group of subjects with TRD who received adjunctive VNS with a group who received only TAU. The study found that “all-cause mortality” and suicide rates for the adjunctive VNS group were about one-half the rates for TAU-only subjects but that these results were “not statistically lower due to the low mortality rate in both groups.” AP Ex. 19, at 5. The study also assessed suicidal ideation, or risk of suicidality, in the two groups. Based on the MADRS rating instrument, the “standardized” rates of suicidal ideation in the VNS+TAU group were 10 to 20 percent lower than rates in the TAU group. *Id.* at 7. However, the results obtained using a different scale, the Assessment of Suicidality (AOS), were “more variable . . . and indicate that there is no statistically significant difference between treatment groups.” *Id.* The authors suggested that the MADRS “may be a more sensitive indicator of suicidal ideation and is better correlated with disease state.” *Id.*

Using a “marginal structural model,” the authors calculated that the subjects who responded to any treatment (VNS+TAU or TAU only) had a “statistically significant 51% lower suicide risk than non-responders as measured by the MADRS Item 10[.]” AP Ex. 19, at 7. According to the study’s authors, this finding is “heavily weighted by the VNS+TAU group, which had the higher response rate, and a lower rate for decreased suicidal behavior, suicide and all-cause mortality.” *Id.*

Christmas (2013): This was a one-year uncontrolled study involving two small groups of subjects: a 28-person cohort, and a 13-person cohort. An apparent objective of the study was to assess VNS’s effect on persons who were, on average, more treatment-resistant than the subjects of previous studies. (The study’s authors commented that previous Cyberonics-sponsored trials had included subjects of varying levels of treatment resistance, “leaving significant remaining uncertainty about the effectiveness of VNS in patients with truly chronic, highly treatment-refractory unipolar depression.” AP Ex. 15, at 2 (citation omitted).)

Based on two depression rating instruments, the study found that 10 of the 28 subjects in the first cohort (35.7 percent) and 4 of the 13 subjects (30.8 percent) in the second cohort had “responded” after one year of adjunctive VNS. Although the study’s authors stated that their results support the use of VNS in subjects with “chronic and medication-refractory illness in whom there is poor evidence for the effectiveness of standard medication and psychological therapies,” they acknowledged that there “*continues to be uncertainty about the efficacy of VNS as a treatment for major depression*” and noted that “[t]he evidence from [other] published studies of VNS for major depression leaves unresolved a number of questions about the benefits of VNS in more refractory patients[.]” AP Ex. 15, at 4 (italics added). The authors also stated that “*there is uncertainty about optimum stimulation parameters,*” that “[i]t is not currently possible to predict who will benefit from VNS, and [that] non-responders in all clinical studies of VNS outnumber responders.” *Id.* (italics added). As for the study’s limitations, the authors noted that its sample was small, there was no control group, data were derived from other unblinded studies, and thus “*it [was] not possible to know to what extent ‘response’ can be attributed to factors other than VNS[.]*” *Id.* (italics added). The authors noted that patient outcomes were assessed at 12 months and that “less is known about longer-term outcomes.” *Id.* The authors further noted that “available evidence,” including the Bajbouj study (discussed below), “would suggest that those who achieve remission at 12-months are likely to maintain it at two-years or more,” but the authors did not discuss or assess that evidence. *Id.*

Bajbouj (2010): This article reported the two-year results of a European study known as the D-03. Partially sponsored by Cyberonics, the D-03 was designed to extend the findings of the D-01 pilot. AP Ex. 22, at 2. The study enrolled 74 subjects, of whom 70 were assessed at the end of three months. Of those 70 subjects, 60 were assessed at the end of one year, and 49 were assessed at the end of two years. The study’s primary

outcome measurement was a subject's score, at designated intervals, on the 28-item Hamilton Rating Scale for Depression (HRSD₂₈). Based on that instrument, the researchers determined whether the subjects had experienced a treatment "response" (defined primarily as a ≥ 50 percent reduction in the HRSD₂₈ score compared with the mean score obtained during two baseline visits) or a "remission" (defined primarily as a score of 10 or lower on the HRSD₂₈). Adjustments in stimulation parameters and medications were permitted during the study's long-term phase.

The study found a statistically significant reduction in HRSD₂₈ scores at three months, one year, and two years. After three months of VNS, the response rate was 37.1 percent (26 of 70 subjects), and the remission rate was 18.6 percent (13 of 70 subjects). After one year, the response rate was 53.3 percent (32 of 60 subjects), and the remission rate increased to 35 percent (21 of 60 subjects). At the end of two years, the response rate was 53.1 percent (26 of 49 subjects), and the remission rate was 38.9 percent (19 of 49 subjects). (Note that these percentages were calculated using the number of subjects still "evaluable" at each assessment point – that is, excluding subjects who had "exited" the study prior to the 24-month endpoint plus one subject for whom data was available at the 24-month endpoint but not at the 12-month endpoint. *See* AP Ex. 22, at 3 (fig. 1), 8 (fig 5, pt. A).)

Two subjects "discontinued from the study because of an adverse event," and two subjects had the VNS device explanted, one because of "aggravation of illness." AP Ex. 22, at 5. In addition, "[t]wenty seven patients reported 39 serious adverse events that resulted in hospitalization, including worsening of depression (13/39, 33.3%), infection (3/39, 7.7%), suicide attempt (2/39, 5.1%), overdose (2/39, 5.1%), mixed state (1/39, 2.6%), and manic reaction (1/39, 5.1%)." *Id.* There were two suicides, both of which occurred during the first year of the study. *Id.* at 5, 7.

The study's authors concluded that their "data suggest that long-term VNS treatment in addition to medication can offer the possibility of meaningful and sustained clinical benefit for patients who have not achieved satisfactory response with conventional treatment." AP Ex. 22, at 8. Noting that previous uncontrolled studies had reported substantial response rates after 12 or 24 months of VNS, the authors stated that their "observation that more than 50% (26/49, OC [observed cases]) . . . of the patients in our study met the criteria for response after 2 years of treatment suggests a sustained response to VNS for many patients." *Id.* at 6. The authors acknowledged that the "OC approach" – reporting results based on observed cases – "may overestimate the effect of an intervention because it does not account for the outcomes of study participants whose outcomes are unknown (*e.g.*, lost to follow-up or withdrawn from the study)." *Id.* at 7. In addition, the authors stated that their "encouraging data" had to be "interpreted with appropriate caution in the light of 2 major design limitations":

First, *the lack of a control group makes it difficult to compare the clinical outcome with those of other psychopharmacological, psychotherapeutic, or brain stimulation interventions and to disentangle the effects of VNS from the nonspecific effects of the study participation.* This shortcoming has, to an extent, been considered in a previous study in which patients who received long-term treatment with VNS were matched with comparably ill patients who were receiving treatment as usual [citing the D-02/D-04 study].

The second major limitation . . . is that neither stimulation parameters nor further antidepressant treatment were controlled, although the differences in the overall numbers of antidepressant and other psychotropic treatments did not differ significantly. Hence, *it is important that future studies should control for these parameters and include a control group.*

Id. (italics added). As for the risks associated with VNS, the authors stated that “adverse effects notably weakened with increasing treatment duration.” *Id.* at 7. However, in light of the two suicides that occurred during the study period, a three percent prevalence rate, “which is above the range one would expect in patients with treatment-resistant depression,” the authors stated that “[f]uture studies should closely evaluate possible changes in suicidality associated with VNS.” *Id.* at 7, 8.

Berry (2013): The Berry study was a sophisticated meta-analysis of data from the six multi-center clinical studies sponsored by Cyberonics (the D-01, D-02, D-03, D-02/D-04, and the D-21 and D-23 post-approval studies). The study collected and compared, at intervals up to 96 weeks, treatment outcomes from two groups: a group of 1035 subjects who received adjunctive VNS (that is, VNS+TAU); and a group of 425 patients who received only TAU. Based on the MADRS (the study’s primary outcome measurement tool), the study’s authors reported “a substantial and sustained difference in both response and remission rates” between VNS+TAU subjects and those who received only TAU. AP Ex. 14, at 11. For the VNS+TAU group, MADRS response rates at 12, 24, 48, and 96 weeks were 12, 18, 28, and 32 percent, respectively, compared to 4, 7, 12, and 14 percent for the TAU group. *Id.* at 5. MADRS remission rates for the VNS+TAU group at the same four intervals were 3, 5, 10, and 14 percent, respectively, compared to 1, 1, 2, and 4 percent for the TAU group. *Id.* The study also calculated that the odds of a MADRS-measured response in the VNS+TAU group were 3.19 times greater than for the TAU-only group, and that the odds of a MADRS-measured remission were 4.99 times greater. *Id.* at 8.

The six studies we have just described report findings suggesting that VNS may have some long-term beneficial effects in some TRD patients. At issue, of course, is not just the substance of those findings but their validity (or strength). In deciding whether VNS is reasonable and necessary for TRD, CMS applied the evaluation principles described in Appendix A to the Decision Memo. Consistent with those principles – whose relevance

and usefulness the Aggrieved Parties do not dispute – CMS has indicated that pertinent clinical evidence must permit a confident conclusion that VNS improves health outcomes for Medicare beneficiaries with TRD. CMS Ex. 1, at 19, 50. A sound basis for that conclusion, CMS explained, includes statistically significant and clinically important results from well-executed studies that do at least two things: (1) minimize bias and isolate VNS’s treatment effect from potentially confounding variables (such as the placebo response, spontaneous remission, changes in concomitant therapy during the study period, and statistical phenomena like regression to the mean); and (2) enable informed judgments about whether Medicare beneficiaries outside the study setting will experience improved outcomes from VNS. *See* DM App. A.

Viewed within that evaluative framework, the six studies tend to confirm, rather than undermine, the continuing validity of CMS’s rationale for NCD 160.18(C). In general, the studies lack at least one or more (and usually two or more) of the design elements – large sample size, randomization, concurrent control groups, prospective study designs, and blinding of researchers and patients – that enable researchers to draw reliable conclusions about whether a treatment causes improved health outcomes and, if so, whether the improvement is clinically significant. Two of the studies – Christmas and Bajbouj – were uncontrolled (or single-arm) studies, a limitation that their authors acknowledged made it difficult to isolate VNS’s true effect. Two other studies – Feldman and Olin – were large controlled studies, but neither involved randomization and blinding, and one (Feldman) was a retrospective study.

Only one of the six studies – Aaronson (the D-21 dosing study) – used randomization and blinding. However, that study did not achieve its primary objective: to demonstrate that VNS evokes a dose-response in persons with TRD.³² AP Ex. 12, at 2 (“hypothesiz[ing] that medium- and higher-range VNS ‘doses’ would be associated with superior clinical outcomes, compared with relatively ‘low dose’ stimulation”) and 8 (“we did not find significant differences between the treatment groups in antidepressant efficacy during the acute phase . . . or the chronic phase”). Although the absence of statistically significant evidence of a dose-response relationship is not, by itself, conclusive proof that VNS is not causally linked with improvement in patient outcomes, it tends to validate CMS’s concern about the overall weakness of the relevant research findings.

³² The Aggrieved Parties submit that the study’s authors did in fact report a dose-response. *See* Att. to AP Resp. to Supp. Br. at 11. They point to the study’s “post-hoc exploratory” analysis, which showed a “modest” and statistically significant “correlation between a higher charge per day and a greater antidepressant effect.” AP Ex. 12, at 9. However, the authors substantially qualified that finding, noting that the “the effect size is rather limited” and that the “the relatively low rate of responders makes it statistically difficult to draw conclusions regarding independent variables driving the response outcomes.” *Id.*

The D-21 study did find “high rates of sustained response” in subjects who were treated with high and medium doses of VNS. AP Ex. 12, at 7-8. In other words, a high proportion of subjects who received a medium or high dose of VNS and who did exhibit an initial response by the end of the study’s acute phase (at 22 weeks) still showed a response at the end of the study’s long-term phase (at 50 weeks). *Id.* However, using the study’s published data, CMS calculated that only a small percentage of the study’s *total enrolled subjects* – 17.2 percent or 12.1 percent, depending on the rating scale used – were in a state of response after 50 weeks of treatment. *See* CMS Resp. to *Amicus Curiae* Statement of Conway at 6. Moreover, the study did not compare those outcomes to those of TRD patients who did not receive VNS, a circumstance that, as earlier studies noted, makes it difficult to judge whether an observed improvement in patient outcome is actually due to VNS (rather than to other phenomena or circumstances, such as the placebo response, changes in concomitant treatment, and regression to the mean).

The Aggrieved Parties have done little to demonstrate that the most recent studies have increased the level of clinical or scientific certainty about VNS’s benefit for TRD patients (and especially for older adults in Medicare).³³ For example, the Aggrieved Parties cite the Aaronson study’s finding that patients receiving adjunctive VNS showed “significant improvement at study endpoint compared with baseline” (AP Statement ¶ 8), but they do not convincingly explain why that finding ought to be regarded as *reliable* evidence of VNS’s treatment effectiveness given that the observed outcomes were not compared to those of a comparable group of patients who did not receive VNS (a limitation of the D-01, D-03, and other previously mentioned studies). *See* Att. to AP Response to Supp. Br. at 11-12. The Aggrieved Parties implicitly respond to that criticism by contending that the D-21’s finding of improved outcomes is uninfected by potential bias or confounding. *See* Att. to AP Resp. to Supp. Br. at 1. However, they offer only brief and thinly supported assertions of counsel to support that contention. *Id.* For example, the Aggrieved Parties suggest that the placebo response was not a significant confounder in the D-21 study; however, their only support for that suggestion are the findings of a study (Brunoni 2009) that was not submitted in support of their complaint. *Id.* The Aggrieved Parties also assert that “observer bias” in the D-21 study was “negligible” because “neither the patients nor the treating physicians knew which dose was administered.” *Id.* No further explanation is given for that proposition, but additional explanation is necessary because the study’s authors indicated that the treatment (dosing) blind was not

³³ We note that the Aggrieved Parties do not cite to any new, independent assessments of VNS, such as the Blue Cross Blue Shield technology assessment on which CMS relied in the Decision Memo.

preserved for substantial percentages of the study subjects³⁴ and because it is not apparent that blinding to *dosing levels* – as opposed to blinding to subjects’ receipt of VNS (without regard to dosing level) – was sufficient to minimize the risk of observer bias in assessing long-term treatment effect. The Aggrieved Parties also state an argument about the potential influence of natural disease progression, but the argument is inadequately developed and unaccompanied by citations to the NCD record or their own exhibits. *Id.* at 11-12. We also think it noteworthy that the D-21 study’s principal author (Dr. Aaronson), who also filed an *amicus curiae* statement in this proceeding, did not express an opinion concerning the validity, or methodological strength, of the study’s findings regarding VNS’s long-term treatment effectiveness. *See* Sept. 3, 2014 *Amicus Curiae* Statement of Aaronson at 3 (stating only that the D-21 found a “statistically significant improvement in key depression outcome measures *in all three dosing groups compared to baseline*” (italics in original)).

As they do with the D-21 study, the Aggrieved Parties contend that the findings of the uncontrolled Bajbouj (D-03) study were free of potential bias and confounding. *See* Att. to AP Resp. to Supp. Br. at 12-13. To a large extent, that contention is based on assertions that we considered but found inadequate in connection with our discussion of the D-21 study. The Aggrieved Parties point to statements by the Bajbouj study’s authors that certain potentially confounding variables were unlikely to have influenced the reported results. *See, e.g., id.* at 13 (discussing the Bajbouj study’s comments regarding the placebo response). However, unless those statements are based on clear and persuasive research findings – and the Aggrieved Parties failed to show that they were – the statements cannot be regarded as anything but unproven hypotheses. We note that, in its supplemental brief, CMS commented that the Bajbouj study’s two-year results were “deeply flawed by [a] 34% attrition rate.” CMS Supp. Br. at 7. Although the Aggrieved Parties claim that this attrition rate is not unusually high for studies of antidepressant treatment, they do not discuss whether the study’s methods and design were adequate to minimize potential attrition bias. Att. to AP Resp. to Supp. Br. at 12.

We acknowledge, as CMS does, that some of the post-May 2007 studies – such as Feldman, Olin, and Berry – have strengths, such as large samples and the use of “sophisticated statistical techniques to overcome biases inherent in nonexperimental designs.” CMS Supp. Br. at 10. Nevertheless, the studies’ results are not compelling. The findings of the Olin and Feldman studies can fairly be characterized as mixed (*e.g.*, in the Olin study, group differences in suicidal ideation rates that were statistically

³⁴ The study’s authors stated that “[f]or the LOW stimulation group, the lowest settings for output current and pulse width were selected to strike a balance between the risk of unblinding with no stimulation versus the risk that even quite modest stimulation could provide some therapeutic support” AP Ex. 12, at 9. However, said the authors, “even this cautious strategy did not adequately protect the treatment blind as 73% of the LOW dose group (versus 41% of the MEDIUM and 31% of the HIGH dose groups) accurately guessed their treatment group assignment at the end of the acute phase.” *Id.*

significant on one outcome scale but not another) or uncertain (*e.g.*, the Feldman study’s mortality finding which favors VNS but which the authors were apparently unable to explain or, presumably, attribute to VNS). The Berry meta-analysis found that subjects receiving adjunctive VNS (that is, VNS+TAU) were significantly more likely to experience treatment response and remission than TAU-only subjects. However, the study reported that, over 96 weeks of treatment, the mean MADRS score in the VNS+TAU group was only 3.26 points less than the mean score in the TAU group (lower scores on the MADRS signify less severe depression). *See* AP Ex. 14, at 7. Given that the MADRS uses a 60-point rating scale,³⁵ the comparatively small between-group difference of 3.26 points highlights a concern that CMS raised about the results of the D-02/D-04 study: that the *magnitude* of observed difference in outcomes between the VNS+TAU and TAU-only groups, even where “statistically significant,” may not be *clinically* important. *See* CMS Supp. Br. at 13.

Another ongoing issue in the literature concerns “predictors of response” – a set of clinical characteristics that predict whether a patient with TRD will respond positively to VNS. *See* CMS Ex. 1, at 685. CMS found that researchers have not yet “clearly defined the treatment resistant group for whom VNS, if proved to be beneficial, might be indicated.” *Id.* at 57. Various published studies, including the 2013 Christmas study, support that finding. *See, e.g.*, AP Exs. 15 (at 4) and 73 (at 8). The Aggrieved Parties nonetheless contend that the finding is no longer valid. AP Statement ¶ 26. First, they allege that the “relevant treatment population” has been defined in publications of the Agency for Healthcare Quality and Research (AHQR) and the American Psychiatric Association (APA). *Id.* (*citing* AP Exs. 6, 7, and 8). However, the APA and AHQR materials do not specify predictors of response to VNS, contrary to the Aggrieved Parties’ suggestion. Although the APA’s publications state that *some* study subjects have shown benefit when treated with adjunctive VNS, and identify clinical indications (generally, the FDA-approved ones) for which VNS *might* be an appropriate treatment, the publications do not state that any particular patient characteristic reliably predicts whether VNS will result in a positive treatment response. *See* AP Exs. 7-8.

Apart from issues relating to treatment efficacy, three of the post-May 2007 studies appear to reinforce CMS’s concern about VNS’s adverse effects. For example, the Aaronson study reported that post-implantation adverse events occurred in significant proportions of the D-21’s sample of 331 subjects. These events included: voice alteration, 239 of 331 subjects (72.2 percent); dyspnea (shortness of breath), 107 of 331 subjects (32.3 percent); incision pain, 105 of 331 subjects (31.7 percent); paresthesia

³⁵ The 60-point MADRS scale ranks the severity of depression as follows: 0 to 6 (normal, symptom absent); 7-19 (mild depression); 20-34 (moderate depression); and 34-60 (severe depression). *See* CMS Supp. Br. at 12 n.28; AP Ex. 61, at 41.

(burning or pricking sensation usually felt in the extremities), 105 of 331 subjects (31.7 percent); increased cough, 83 of 331 subjects (25.1 percent); headache, 61 of 331 subjects (18.4 percent); depression, 60 of 331 subjects (18.1 percent); pharyngitis (sore throat), 57 of 331 subjects (17.2 percent); and numerous other events. *See* AP Ex. 12, at 8 (table 5). In addition, the Bajbouj study (the D-03) reported that 27 of its 74 subjects, or 36 percent, reported at least one “serious adverse event” resulting in hospitalization. AP Ex. 22, at 5. And the Feldman study found that VNS subjects experienced a higher rate of “negative events” during the study period than subjects in the two non-VNS groups. AP Ex. 18, at 7.

In deciding whether VNS therapy is reasonable and necessary, CMS properly weighs the overarching conclusions that can reliably be drawn from relevant clinical evidence about the treatment’s health benefits against the risks of harm it poses to the Medicare population. AP Ex. 73 (Sackeim study), at 1 (noting that in light of its safety risks, VNS is “only of value if its clinical benefits persist”). In this instance, we also consider the potential harm from VNS’s use in evaluating whether the NCD record is complete and adequate to support the validity of the NCD. It is undisputed that the risks of harm include potential surgical complications from the invasive implantation procedure as well as post-implantation side effects from electrical stimulation. There is also a risk of harm to patients associated with the surgical explantation of the VNS device if it fails to work properly or for maintenance and battery replacement. In addition, CMS identified one other relevant risk to the Medicare population stemming from the current uncertain understanding about predictors of response to VNS – namely, the risk that substantial numbers of beneficiaries will use VNS to “futile” effect, thereby delaying their receipt of potentially effective alternative treatment. CMS Ex. 1, at 52; CMS Response to *Amicus Curiae* Letter of Aaronson at 4. We note also that none of the post-May 2007 studies address the relevance of the study findings to the elderly Medicare population, and the Aggrieved Parties have not argued that the risks of VNS’s use in that population would be less than the risks in the younger populations who participated in the studies. Thus, even if we accepted the later studies as some evidence (albeit weak evidence) that long-term, durable improvement in depressive symptoms in the younger TRD populations studied were caused by VNS, we would nonetheless conclude that the NCD record continues to be complete and adequate to support the validity of the NCD because CMS could still reasonably strike the risk-benefit balance in favor of non-coverage, given the nature of the majority of the Medicare population. This balance is particularly important given that even the most optimistic readings of benefit suggest that a small percentage of patients would obtain any improvement in their symptoms as a result of the treatment while a high percentage of patients treated would experience some adverse effects, including many serious enough to cause hospitalization, based on the studies discussed in detail above.

The Aggrieved Parties suggest that CMS's inability to determine precisely who might benefit from a medical technology is an invalid basis upon which to deny coverage. They assert that "the defined lack of response to existing treatments in this patient population compels the availability of as many treatments as possible, particularly when the evidence supports positive outcomes in multiple studies for patients experiencing TRD in spite of multiple, and variable, prior unsuccessful treatments." Att. to AP Resp. to Supp. Br. at 24-25. Two of the amici (Buser and Aaronson) echo that view, noting that physicians often cannot predict patient response to Medicare-covered antidepressant treatment, such as ECT.

We disagree that an inability to predict a treatment response is irrelevant to a Medicare coverage determination. As discussed, in deciding whether a treatment is reasonable and necessary, CMS properly weighs its potential health benefit against the risks of harm it poses. The inability to predict response creates risks of harm for VNS's target population: the lower the degree of certainty in identifying TRD patients likely to benefit from VNS, the greater the likelihood that those patients will be exposed to those risks of harm without any offsetting benefit. The inability to predict TRD patients' response to VNS is particularly concerning where, as discussed above, adverse effects of VNS in those patients are frequent and can be severe. Indeed, Dr. Aaronson, one of the amici and the principal author of the D-21 study, appears to acknowledge that concern in a 2012 article, stating that "*determining variables which predict response is critical*" because VNS "*involves surgically implanting a semi-permanent system and is inefficacious in a significant subset of TRMD patients.*" AP Ex. 66, at 6 (italics added). The previously discussed safety findings of the D-21 study plainly illustrate Dr. Aaronson's point: the study reported a large number of adverse events in its sample of 331 subjects, even though only 12 to 17 percent of the subjects (depending on the outcome instrument) had registered a treatment response by the end of the 50-week study period. CMS believes, and we think reasonably, that these circumstances raise substantial concern about whether covering the VNS device without a better definition of the population likely to benefit (assuming VNS produces a treatment benefit) might result in a large number of Medicare beneficiaries receiving an ineffective treatment that causes affirmative harm. See CMS Response to *Amicus Curiae* Letter of Conway at 7 (stating that "it is difficult to justify implanting this device for so few, when its potential clinical outcome is so questionable but it is known to cause adverse events in such a large proportion of patients").

Evaluating predictors of response to adjunctive VNS is one of the key objectives of the D-23 TRD registry study mandated by the FDA. See AP Ex. 5, at 3-4. The D-23 study, which is still ongoing, is a long-term, prospective, observational, multi-center study that compares the health outcomes of patients receiving adjunctive VNS with the outcomes for patients receiving TAU. AP Ex. 61, at 6. The Aggrieved Parties have submitted the D-23's six-year and eight-year interims reports and urge us to consider the reports' findings. See AP Exs. 10, 61. The Aggrieved Parties submit that those findings (as reported to the FDA) "demonstrate the superiority of" adjunctive VNS compared to

TAU. AP Statement ¶ 36. However, these findings have not yet been published in a peer-reviewed medical or scientific journal.³⁶ In its Decision Memo, CMS made the following comment about unpublished research: “Data that is unpublished is given little weight because it has not been peer-reviewed and therefore we cannot substantiate the accuracy of the data and the appropriateness of the authors’ conclusions.” CMS Ex. 1, at 43. The Board has similarly observed that “[a] general weakness of unpublished research findings . . . is that they are untested by the scientific peer review process.” *LCD Complaint: Homeopathic Med. & Transfer Factor* DAB No. 2315, at 35 (2010) (holding, in a decision concerning a local coverage determination, that an administrative law judge “did not err in not treating unpublished research as a source of definitive scientific evidence”). The Aggrieved Parties do not disagree with CMS’s finding that unpublished research ought to be given minimal weight, nor do they argue there is a good reason to overlook that principle in this proceeding. To the contrary, we think that peer-review is especially critical here because the D-23 study is sponsored by a company (Cyberonics) with a large financial stake in its results. For these reasons, the D-23’s findings, as reported to the FDA in the study’s six and eight-year reports, do not cause us to find that the NCD record is incomplete or inadequate.

In addition to the six published studies discussed earlier in this section, the Aggrieved Parties submitted 14 other published reports or studies that post-date the issuance of NCD 160.18(C). They include: a report concerning a small (15-patient) uncontrolled study of VNS’s safety and efficacy for resistant depression (AP Ex. 21); a small (four-patient) uncontrolled study of VNS’s efficacy in treating concurrent depression and drug-refractory chronic migraines (AP Ex. 23); a small (nine-patient) non-randomized controlled study that examined VNS’s efficacy in reducing depression severity and healthcare utilization over one year (AP Ex. 25); two appraisals of primary research studies (AP Exs. 17 and 27); four case reports (AP Exs. 13, 20, 28, 29); one cost-effectiveness study (AP Ex. 26); one report on the treatment of epilepsy (AP Ex. 24); and three physiologic studies of VNS in TRD patients (AP Exs. 16, 66-67). Other than citing these articles, the Aggrieved Parties have not (with a few immaterial exceptions) explained their significance in light of CMS’s reasons for issuing NCD 160.18(C). We reviewed all the additional exhibits (summarizing their content in the decision’s Appendix) but agree with CMS that they contain the type of evidence – small clinical studies, case reports, re-analysis of existing research, and physiological studies – that does not add significant weight to the body of relevant research or help to answer the relevant coverage question (*i.e.*, does VNS improve health outcomes for Medicare patients with TRD?).

³⁶ In his September 3, 2014 *amicus curiae* submission, Scott T. Aaronson, M.D. states that he is “currently drafting what will be the first manuscript of the D-23 study.”

The material submitted by the Aggrieved Parties includes affidavits from three researchers who expressed opinions about the published clinical evidence of VNS's safety and efficacy: A. John Rush, M.D., Darin Dougherty, M.D., and Charles Conway, M.D. AP Exs. 75-76. These affidavits on their face are not significantly probative evidence that CMS's coverage denial is unreasonable. Dr. Rush is the author of several articles regarding VNS and TRD and was the principal author of the D-02 pivotal study. CMS Ex. 1, at 594, 605, 616, 636. He states that he told CMS officials in a May 29, 2014 teleconference that the "peer-reviewed published literature supports the safety and effectiveness of VNS for treatment of resistant depression" and that "VNS Therapy is durable for patients with TRD." AP Ex. 75. However, his one-page affidavit does not give reasons for that opinion, discuss any studies or medical literature, or attempt to rebut specific findings contained in CMS's Decision Memo.

Dr. Dougherty is director of the Division of Neurotherapeutics, Department of Psychiatry at Massachusetts General Hospital and Associate Professor of Psychiatry at Harvard Medical School. AP Ex. 9, at 5. Dr. Conway is Associate Professor of Psychiatry and Director of the Treatment-Resistant Depression Clinic at the Washington University in St. Louis. *Id.* at 3. They both state in their affidavits that "[s]ince 2007, the peer-reviewed literature and registry data supporting vagus nerve stimulation . . . has improved significantly," although neither indicates the precise nature of that alleged improvement. AP Ex. 76. The physicians also state that existing research, including "objective evidence of the physiological changes that occur with VNS," "clearly demonstrates the effectiveness of VNS therapy for patients with treatment resistant depression." *Id.* at 1 (¶ 6) and 2 (¶ 6) (emphasis in original). But their affidavits, like Dr. Rush's, contain no supporting analysis. Conclusory expert statements without such analysis have little probative value.

The four unsworn *amicus curiae* statements contain broad claims about clinical research concerning VNS. The amici emphasize that the most recent clinical studies show that VNS's therapeutic antidepressant effect takes considerable time to manifest itself (Buser and Aaronson). The amici also point to studies which they assert found that VNS improves the "durability" of response relative to TAU and indicate that these durability findings are significant because sustained treatment efficacy is a severe problem with all existing antidepressant treatment (Conway). Some of the amici (Dr. Buser, for example) characterize the evidence for VNS's treatment effectiveness in TRD patients as "compelling" or based on "rigorous" studies. But like the Aggrieved Parties and the affiants, the amici do not tell us *why* the available research should be regarded as *strong* or *reliable* evidence of VNS's treatment effect, or the effect's durability, under accepted standards for evaluating such evidence. The most recently published studies cited by the Aggrieved Parties do not characterize the state of relevant research in those (or comparable) terms. Indeed, Christmas (2013) and Bajbouj (2012) expressly acknowledged continuing uncertainty about VNS's treatment effect (especially for highly treatment-resistant patients) and suggested that further research, particularly controlled

studies, are needed to address that and other issues, including durability and predictors of response. *See* AP Exs. 15 (at 4) and 22 (at 8). We note also that CMS has identified reasonable concerns about the durability findings in these studies. For example, CMS accurately notes that of the 26 Bajbouj study subjects identified as responders to VNS after three months, only 10 remained as responders at 24 months. *See* CMS Resp. to *Amicus Curiae* Statement of Buser at 7; AP Ex. 22, at 8 (fig. 5(A)).

The Aggrieved Parties suggest that CMS has created an improperly high evidentiary threshold for coverage and acted arbitrarily in doing so. *See* AP Resp. to Supp. Br. at 3. Pointing to CMS’s supplemental brief, they allege that CMS has taken the position that sham or placebo-controlled studies are necessary to evaluate psychiatric treatments, such as VNS, even though it “routinely” approves coverage of other treatments, particularly surgical ones, without evidence from sham or placebo-controlled clinical studies, and even though “the psychiatric clinical research community rejects the use of placebo or sham treatments for psychiatric patients as unethical.”³⁷ *Id.* at 6. The Aggrieved Parties further assert that “CMS has not taken the position in any regulation or guidance document that studies of new treatments require sham procedures to eliminate a possible placebo response” and that “[s]uch a requirement would be contrary to fundamental principles of human subject research” and is “particularly offensive with this vulnerable population known to have high rates of suicidality already experiencing numerous unsuccessful treatment trials while an FDA-approved treatment option specifically for their illness already exists.” *Id.*

This argument seems to rest on the assumption that there is a consensus in the medical and research communities that sham-controlled trials of VNS (or other antidepressant treatment) – especially long-term studies of that type – are necessarily unethical. The Aggrieved Parties proffered nothing to support that assumption, however. Dr. Buser and Dr. Aaronson express ethical qualms about sham-controlled studies of persons with TRD in their *amicus curiae* statements, but neither claims that his views are widely shared in the medical and research communities or that sham-controlled trials of VNS would necessarily violate settled ethical norms of scientific and medical research. Indeed, Dr. Rush was an author of a 2003 article which indicates that a placebo-controlled trial using an “add-on design” would be an ethical way to assess a treatment intervention involving TRD patients. In that type of trial, the intervention being studied is added to (or augments) existing treatment; the results of the augmented treatment are then compared

³⁷ Citing to CMS’s supplemental brief, the Aggrieved Parties state that “the Secretary recognizes that the psychiatric clinical research community rejects the use of placebo or sham treatments for psychiatric patients as unethical.” AP Resp. to Supp. Br. at 6. However, CMS’s brief does not say that the research community has taken such a position, only that “[t]he administration of placebo or sham treatments in psychiatric clinical research *has come under debate.*” CMS Supp. Br. at 4 (italics added).

with the results of “placebo augmentation.” CMS Ex. 1, at 611. According to the article, a “placebo-controlled add-on design avoids ethical concerns because the placebo entails only a delay in receiving the treatment for those assigned to it.” *Id.* at 611-612. This approach was used in the D-02 pivotal study, and the Aggrieved Parties have not explained why it would be unethical to use this approach in a longer-term study.

The Aggrieved Parties’ argument also wrongly implies that CMS has imposed an overly rigid or prescriptive evidentiary standard for VNS. The Aggrieved Parties seize on a statement in CMS’s supplemental brief that “sham treatments are *necessary* to eliminate the public health risk of ineffective treatments.” CMS Supp. Br. at 4 (italics added). However, in considering whether the NCD record is complete and adequate, our focus is primarily on the May 2007 Decision Memo, which contains the authoritative statement of CMS’s rationale for NCD 160.18(C) and whose findings are the subject of our reasonableness analysis. The Decision Memo indicates that CMS’s determination of non-coverage was based on (among other things) a bottom-up assessment and weighing of relevant evidence of all types, including the opinions of researchers, clinicians, and medical societies. Although the Decision Memo quotes a 2003 article which states that FDA clinical drug trial data “strongly suggest[]” that placebo-controlled trials are “critical for evaluating the efficacy” of antidepressant treatment, CMS Ex. 1, at 55, the Decision Memo does not articulate a specific evidentiary threshold for Medicare coverage of VNS other than that studies be of “sufficient quality” and be designed to answer the relevant coverage questions. *Id.* at 19, 44 (stating that “good quality studies that show positive health outcomes are needed”). The Decision Memo does not rule out the possibility that the coverage question could be answered in favor of VNS with a mix of well-designed and executed controlled studies other than those which use sham-implanted subjects as the controls. Rather, it emphasizes that certain study design elements – such as randomization and blinding (both of which are absent from virtually all of the VNS studies conducted to date) – are important in obtaining valid results and that “more weight will normally be accorded to studies that are designed to guard against the placebo effect.” *Id.* at 22.

Even if the Decision Memo could be interpreted as containing a finding that sham-controlled trials are “necessary” to demonstrate antidepressant efficacy, that finding is not unreasonable because CMS provided a sound reason for it – namely, its expert judgment, informed by a review of relevant literature, that the placebo response is a substantial potential confounding factor in studies of antidepressant treatment. *See* CMS Ex. 1, at 22, 48, 54. As we noted in the previous section, CMS’s concern about the potential influence of the placebo response in TRD patients is not unreasonable.

Furthermore, the context here is not a complete absence of sham-controlled studies but rather that the D-02 sham-controlled trial showed no evidence that VNS produces improved health outcomes for patients with TRD. In light of that negative result from the sole “gold standard” study, CMS could reasonably insist that VNS’s treatment effect be

demonstrated with clinical studies of comparable methodological strength. That position would be fully consistent with the views of the Sackeim study’s authors (*i.e.*, George, Rush, and Mangerell, prominent researchers in this area), who expressly acknowledged the need for a “long-term, sham-controlled, randomized trial” to confirm VNS’s efficacy. *See* AP Ex. 73, at 8 (“In the absence of a long-term, sham-controlled, randomized trial, one cannot conclude that the acute or sustained effects observed in the pilot and pivotal studies were attributable to VNS.”).

We note that Dr. Aaronson raised his personal ethical concerns about sham-controlled trials in the article that reported the results of the D-21 dosing study. In that article, he suggested that another type of clinical trial would be adequate to demonstrate VNS’s effectiveness. *See* AP Ex. 12, at 9. “Rather than sham-controlled studies handicapping allowed treatment for a year in patients with a potentially life-threatening illness,” he said, “perhaps the paradigm needs to be changed to comparing aggressive treatment-as-usual to VNS” *Id.* at 10. Dr. Aaronson reiterates that thought in his *amicus curiae* statement, saying that he “feel[s] strongly that the long-term open label, real-world results from the D-23 TRD registry that we are in the process of analyzing and reporting” – a study that compares adjunctive VNS with treatment-as-usual (TAU) in large numbers of treatment-resistant patients – “need to be the standard by which [VNS] is evaluated.” *Id.* In response to that assertion, it is sufficient to note that Dr. Aaronson does not contend that there are *presently* a sufficient number of high-quality, peer-reviewed, adjunctive-VNS-versus-TAU studies to support Medicare coverage.³⁸

The Aggrieved Parties assert that the Board’s recent decision which invalidated the NCD that denied coverage for transsexual surgery (NCD 140.3) was based on evidence that was “significantly weaker” on the whole than the evidence offered to support coverage of VNS for TRD. AP Resp. to Supp. Br. at 3-5 (referring to *NCD 140.3, Transsexual Surgery*, DAB No 2576 (2014)). In support of that assertion, the Aggrieved Parties present a table that compares the evidence supporting NCD 140.3 and 160.18(C) based on, among other elements, the number and types of clinical studies having certain design and methodological features, such as randomization, blinding, and concurrent control groups. *Id.* at 5. The table indicates, for example, that the evidence upon which the Board invalidated NCD 140.3 did not include any sham or placebo-controlled trials (or, for that matter, any double-blind randomized controlled trials).

³⁸ Of all the published studies cited by Aggrieved Parties, we counted only four that compare the outcomes for TRD patients receiving adjunctive VNS to the outcomes of TRD patients who receive only TAU: the D-02/D-04, Olin, and Berry studies (AP Exs. 38, 14, and 19), and a nine-patient controlled study by Sperling (2009) (AP Ex. 25). None of these studies used randomized data or blinding, the Sperling study was small, and, as we previously explained, two of the larger studies —the D-02/D-04 and Berry – reported results of questionable clinical importance.

This rough comparison, being completely detached from each case’s context, provides little if any useful information or guidance. The Board does not evaluate the merits of an NCD challenge (as the Aggrieved Parties suggest we do) by comparing the relative methodological strength of different bodies of clinical research. Instead, as the reasonableness standard requires, the Board must (as it has done here) evaluate the adequacy of the relevant scientific and other evidence *in light of the legal and factual findings made by CMS* in support of its noncoverage determination. In any event, the Aggrieved Parties’ citation to *Transsexual Surgery* is misplaced because the two cases are far from comparable. In *Transsexual Surgery*, CMS did not contend, as it forcefully does here, that the stated rationale for the challenged NCD remained valid in light of the research published since its issuance; indeed, CMS did not defend the continuing validity of the NCD in *Transsexual Surgery*, a circumstance that the Board found significant for its decision-making. DAB No. 2576, at 8. Furthermore, the fact that there were no sham-controlled studies in *Transsexual Surgery* does not make that case analogous because such a study was likely infeasible given the highly invasive and probably irreversible nature of gender reassignment surgery. No such infeasibility was demonstrated in this case, as we have already explained. Also distinguishing this case from *Transsexual Surgery* is the fact that the D-02 sham-controlled study produced *negative* results, making it reasonable for CMS to insist on additional studies of comparable methodological strength.

2. The inclusion of VNS in treatment recommendations issued by the American Psychiatric Association, while evidence of VNS’s increasing acceptance in the medical community, is not evidence of a medical standard of practice or of a consensus in the medical community about the use of VNS for TRD.

When CMS issued NCD 160.18(C) in May 2007, it noted that medical practice guidelines – “such as those endorsed by consensus statements that are subject to peer review” – did not include VNS as a treatment option for major depressive disorder (MDD). CMS Ex. 1, at 16, 40, 60. At the time, “[p]ractice guidelines for the treatment of MDD recommend[ed] pharmacotherapy, psychotherapy, psychotherapy plus pharmacotherapy, or electroconvulsive therapy.” *Id.* at 16.

In June 2009, the APA issued a “White Paper” which states that “VNS is a treatment option for patients with treatment resistant depression” (although not a “first line therapy”) and that “VNS has been shown to be effective for *some* patients with significant treatment resistant depression and is approved by the FDA in this patient population.” AP Ex. 7 (*italics added*). In addition, the White Paper states that, although “VNS should not be considered an acute treatment for severely depressed patients” – ECT being more appropriate for the “[a]cutely ill” – “it would be reasonable to consider use of VNS in patients who refuse ECT, have failed ECT in the past or have medical

contraindications for the use of ECT (*e.g.*, are not able to undergo repeated exposure to anesthesia).” *Id.* The White Paper’s heading states that it was approved by the APA’s “Joint Reference Committee” and by the “APA Corresponding Committee on ECT and Other Electromagnetic Therapies.” *Id.*

In 2010, the APA published the third edition of its *Practice Guideline for the Treatment of Patients with Major Depressive Disorder* (Practice Guideline). *See* AP Ex. 8. In the section outlining its treatment “recommendations,” the Practice Guideline states (on page 19) that VNS “*may be an . . . option* for individuals who have not responded to at least four adequate trials of antidepressant treatment, including ECT” (italics added).³⁹

Relying heavily on these two publications, the Aggrieved Parties contend that NCD 160.18(C) is in conflict with a current “consensus of expert medical opinion.” AP Statement ¶¶ 19, 25, 26. However, neither publication purports to represent such a consensus statement about VNS, and the Practice Guideline specifically acknowledges that “[r]elative to other antidepressant treatments, the role of VNS *remains a subject of debate*” (italics added). AP Ex. 8, at 16. In addition, it appears that the treatment recommendations contained in these documents are based primarily on the clinical studies that CMS reviewed but criticized as flawed or inadequate, including the D-01 and D-02/D-04 studies. *Compare, e.g.*, AP Ex. 7 (References 2-7) *with* CMS Ex. 1, at 616, 594, 486, 416, 281, and 62 (*citing* the 2005 Rush “naturalistic” study). Neither publication indicates that the APA considered that criticism, and neither addresses whether VNS is appropriate for the Medicare population of older adults. Furthermore, the recommendation, unlike the Aggrieved Parties’ definition of TRD, speaks only to possible use for individuals who have failed ECT as well as other treatment options. We note also that the Practice Guideline suggests that the APA has “less-than-moderate” confidence in its recommendation for VNS’s use. The Practice Guideline explains that “[i]n order for the reader to appreciate the evidence base behind the guideline recommendations and the weight that should be given to each recommendation,” each recommendation is “keyed according to the *level of confidence* with which [it] is made,” with the level of confidence being based on the “strength of the available evidence.” AP Ex. 8, at 13 (italics added). The three levels of confidence used to rank APA’s treatment recommendations are designated by bracketed roman numerals: “[I] Recommended with

³⁹ This passage does not appear in the excerpts of the Practice Guideline submitted by the Aggrieved Parties. *See* AP Ex. 8. At the Board’s request, the Aggrieved Parties supplemented the record by providing the following internet link to the complete document: http://psychiatryonline.org/data/Books/prac/PG_Depression3rdEd.pdf (last visited Dec. 22, 2014).

substantial clinical confidence”; “[II] Recommended with moderate clinical confidence”; “[III] May be recommended on the basis of individual circumstances.”⁴⁰ The Practice Guidelines’ recommendation concerning VNS is designated by roman numeral [III], which is the lowest level of confidence.⁴¹

The Aggrieved Parties characterize the White Paper and Practice Guideline as representing a “current standard of medical practice.” AP Resp. to Supp. Br. at 6-7. Whether a treatment is “[f]urnished in accordance with accepted standards of medical practice” is certainly a relevant factor in determining whether the treatment is reasonable and necessary. MPIM § 13.5.1 (providing guidance to CMS contractors for developing local coverage determinations); *see also Transsexual Surgery*, DAB No. 2576, at 20 (noting that MPIM guidance is “instructive here as representing CMS’s determination of the type of evidence that may support Medicare coverage”). However, neither the White Paper nor the Practice Guideline states that it describes a “standard of practice.” In fact, the Practice Guideline states that it is “not intended to be construed or to serve as a standard of medical care” and that its recommendations “should be considered guidelines only[.]” AP Ex. 8, at 11.

3. Other arguments advanced by the Aggrieved Parties and the *amicus curiae* participants do not persuade us that the NCD record is incomplete or inadequate.

The Aggrieved Parties assert that under “Medicare reasonableness analysis and policy, beneficiaries should avail themselves of the most cost-effective medical treatment for their medical conditions.” AP Statement ¶ 45. They allege that VNS is “less expensive than alternative treatments such as ECT and various medicinal regimens.” *Id.* Continuing on that theme, Francisco A. Moreno, M.D. states in his August 18, 2014 *amicus curiae* submission that the 2012 Feldman study (AP Ex. 18) found that VNS patients had lower overall treatment costs than patients in one of the study’s control groups. These contentions are irrelevant because, as CMS stated in the Decision Memo, it does not take “costs,” or the cost-effectiveness of a treatment, into account in making national coverage determinations. CMS Ex. 1, at 52.

⁴⁰ See page 15 of the Practice Guideline, available at http://psychiatryonline.org/data/Books/prac/Pg_Depression3rdEd.pdf (last visited Dec. 22, 2014).

⁴¹ See page 19 of the Practice Guideline, available at http://psychiatryonline.org/data/Books/prac/Pg_Depression3rdEd.pdf (last visited Dec. 22, 2014).

The amici assert that their personal experience in treating patients with VNS has, in the words of one (Dr. Buser), “validated the utility of VNS for TRD.” We have no reason to think that the amici’s reports of successful treatment with VNS are untrue. Such reports, if appropriately documented, are one source of relevant clinical evidence of a treatment’s medical necessity and reasonableness. On the other hand, those reports are not necessarily indicative of VNS’s general acceptance in the medical community as a treatment for resistant depression. *See* MPIM § 13.7.1 (indicating that “[a]cceptance by individual health care providers, or even a limited group of health care providers, normally does not indicate general acceptance by the medical community”). Nor do they demonstrate that CMS’s rationale for NCD 160.18(C) is unreasonable. Applying the evaluation principles laid out in Appendix A to the Decision Memo, CMS found that unpublished anecdotal evidence, such as the amici’s testimonials, are at the lowest level of the evidence hierarchy and are ordinarily entitled to less weight than formal peer-reviewed clinical studies in making national coverage determinations. CMS Ex. 1, at 20 (“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.”). The Aggrieved Parties do not take issue with that principle (or, for that matter, with any of the evaluation principles in Appendix A). Indeed, they acknowledge that a national coverage determination must be based on the “strongest evidence available.” AP Statement ¶ 17. As we have noted, the strongest evidence in this case is the D-02 pivotal study’s sham-controlled trial, which did not show a statistically significant efficacy of VNS for subjects with TRD.

The amici suggest that the currently available evidence of VNS’s effectiveness is more than adequate given the nature of the illness being fought. They point out that patients for whom VNS is appropriate are severely and chronically ill, typically with histories of suicide attempts and psychiatric hospitalizations. They also emphasize that even the modest improvement experienced by their VNS patients, and by the subjects of published studies, can be “life-changing” or “significant” (Buser, Aaronson). In addition, they assert that it is both unreasonable and unethical for Medicare to deny coverage of an FDA-approved treatment for a highly vulnerable population who is at high risk of mortality and lack any other feasible treatment option. While these contentions may have some force in formulating coverage policy, they do not persuade us that CMS’s rationale for NCD 160.18(C) is unreasonable or that the NCD record is no longer complete and adequate under the reasonableness standard. In particular, they do not compel a finding that CMS is unreasonable in taking the position that, without stronger evidence of the existence and magnitude of VNS’s treatment effect, and a better understanding of the clinical circumstances in which Medicare beneficiaries with TRD would likely benefit from VNS (assuming it has a treatment effect), a large number of those persons might experience serious adverse health consequences from VNS without an offsetting reduction in the severity of their depression.

VI. CMS's ALLEGED FAILURE TO RESPOND PROPERLY TO NCD RECONSIDERATION REQUESTS FILED IN MAY 2013 IS IRRELEVANT TO OUR DETERMINATION REGARDING THE COMPLETENESS AND ADEQUACY OF THE NCD RECORD.

The Aggrieved Parties contend that CMS failed to respond, or respond adequately, to NCD reconsideration requests filed in May 2013 by Charles R. Conway, M.D. and Darin D. Dougherty, M.D., who are university-based physicians who conduct research on VNS and specialize in treating patients with TRD. AP Statement ¶¶ 29-30. The physicians apparently submitted medical literature or other documentation to support their reconsideration requests. *See* AP Ex. 9; AP Ex. 76 at 1 (¶ 5) and 2 (¶ 5). The Aggrieved Parties complain that CMS did not respond to the physicians' requests or "update the NCD record" with the supporting material. AP Statement ¶¶ 31-32. These omissions, say the Aggrieved Parties, violated procedures published by CMS in the *Federal Register* in 2003 and 2013. *Id.* ¶¶ 30-32; *see also* AP Resp. to Supp. Br. at 2, 8-9.

The "reconsideration" process permits any interested person (not just an aggrieved party) to ask CMS to reconsider and revise an existing NCD based on new information, including new medical or scientific evidence. *See* 68 Fed. Reg. at 55,638-639. As the Aggrieved Parties indicate, CMS has issued *Federal Register* notices, most recently in August 2013, specifying the elements of a "complete, formal" reconsideration request and indicating how it will consider and (if appropriate) respond to such a request. *Id.* at 55,636-639; Notice, *Medicare Program; Revised Process for Making Medicare National Coverage Determinations*, 78 Fed. Reg. 48,164, 48,165-67 (Aug. 7, 2013).

There is no dispute that Dr. Conway and Dr. Dougherty filed reconsideration requests concerning NCD 160.18(C) in May 2013. There is some disagreement about whether CMS responded to them.⁴² We need not resolve that factual dispute or consider whether CMS's response, assuming it occurred, complied with its published procedures because these issues are simply irrelevant here. The NCD review process conducted by the Board – an adjudicative process mandated by Congress in section 1869(f) of the Act – is distinct and separate from CMS's non-adjudicative reconsideration process. *S.Z., Aggrieved Party*, DAB No. 2482, at 6 (2012). The issue we address in this proceeding is whether the record upon which CMS based NCD 160.18(C) is adequate and complete in light of both the information available to CMS in May 2007 and more current information. Our resolution of that issue does not depend, either factually or legally, on how CMS handled the physicians' reconsideration requests.

⁴² CMS produced what purports to be its written responses to the physicians' reconsideration requests. *See* CMS Response at 4 & n.2. The letters are undated and unsigned, however, and CMS admits that it has been unable to locate the signed, dated versions. Meanwhile, the physicians state in their affidavits that they never received written responses from CMS. AP Ex. 76.

The only reconsideration-related circumstance that is even arguably relevant is CMS's alleged failure to supplement the NCD record with the material that supported the physicians' reconsideration requests. However, neither of CMS's most recent restatements of the reconsideration process (on September 26, 2003 and August 7, 2013) requires CMS to supplement the NCD record when it denies (or fails to respond to) a reconsideration request.⁴³ *See* 68 Fed. Reg. at 55,639; 78 Fed. Reg. at 48,167. Moreover, nothing prevented the Aggrieved Parties from submitting the physicians' supporting material in this proceeding. (We note that the Aggrieved Parties submitted affidavits from both physicians. *See* AP Ex. 76.)

VII. The AGGRIEVED PARTIES' CONTENTIONS REGARDING MEDICARE BENEFITS WHO WERE IMPLANTED WITH THE VNS DEVICE PRIOR TO MAY 4, 2007 PROVIDE NO BASIS FOR INVALIDATING NCD 160.18(C).

The Aggrieved Parties suggest that NCD 160.18(C) is invalid because it does not address the needs of Medicare beneficiaries with TRD who were implanted with the VNS device and received Medicare coverage for VNS prior to the issuance of NCD 160.18(C) on May 4, 2007. Statement ¶¶ 38-43; Complaint ¶¶ 90-95. With respect to those beneficiaries, say the Aggrieved Parties, the NCD does not afford coverage for: (1) "the interrogation and calibration of a VNS therapy device implanted and deemed to be reasonable and medically necessary when implanted for TRD"; or (2) "for the replacement of the implanted pulse generator device upon battery expiration, when required[.]" AP Statement ¶ 43. According to the Aggrieved Parties, those omissions conflict with: (1) "continuity of care" standards that are "widely accepted within the medical community (i.e., a physician should not discontinue treatment that is effective for a patient)"; (2) "well-accepted medical standards of care that acknowledge that it is unsafe for beneficiaries to have an implanted medical device that is not properly calibrated, monitored, or is otherwise non-functional"; and (3) "CMS policy statements wherein CMS has recognized that continuing Medicare coverage for beneficiaries who received Medicare-covered durable medical equipment (DME) before it was non-covered 'helps avoid disrupting the continuity of care for the beneficiaries . . .'" *Id.* ¶¶ 40-42 (*quoting* 78 Fed. Reg. 40,836, 40,877 (July 8, 2013)).

⁴³ In support of their claim that the published procedures required CMS to update the NCD record, the Aggrieved Parties cite to the 2002 proposed rule to create the NCD and LCD review processes. *See* AP Resp. to Supp. Br. at 8 (*citing* 67 Fed. Reg. 54,534, 57,537 (Aug. 22, 2002)). The 2002 proposed rule noted that CMS had established reconsideration procedures in an April 27, 1999 *Federal Register* notice (64 Fed. Reg. 22,619) – procedures which permitted an interested party to submit new evidence for CMS to consider. 67 Fed. Reg. at 57,537. Under the 1999 procedures, CMS would either issue a revised NCD if it thought the reconsideration request had merit or, if it thought the request lacked merit, "supplement the NCD record with th[e] new evidence and reissue the NCD with no changes." *Id.* However, the 1999 procedures were replaced by the reconsideration procedures in CMS's September 26, 2003 *Federal Register* notice. 68 Fed. Reg. at 55,634. As indicated in the text above, the 2003 reconsideration procedures did not require supplementation of the NCD record.

As the Aggrieved Parties claim, NCD 160.18(C) does not directly address the circumstances of persons who, prior to May 4, 2007, obtained Medicare coverage for VNS to treat resistant depression and who continue to receive that treatment. *See* AP Ex. 1. Instructions issued by CMS to its contractors on how to implement NCD 160.18(C) are likewise silent about those circumstances. *See* Medicare Claims Processing Manual (CMS Pub. 100-04), ch. 32, § 200 (available at <http://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/downloads/clm104c32.pdf>, last visited Dec. 22, 2014). Both NCD 160.18(C) and the related contractor instructions merely indicate that the denial of coverage of “VNS” – a term that both the NCD and the instructions use to refer to the surgically implanted pulse generator – is “effective for *services* performed on after May 4, 2007” (*italics added*) without further elaboration concerning the nature of those “services.”

During this proceeding, CMS represented to the Board that the “maintenance” of a VNS device implanted prior to May 4, 2007 is “outside of the scope of” NCD 160.18(C). *See, e.g.*, Secretary of Health and Human Services’ Response to Aggrieved Parties’ Oct. 6, 2014 Related Claim Update (Oct. 14, 2014) at 2.⁴⁴ CMS states that it “leaves decisions regarding the maintenance of already-implanted devices to contractor discretion” and that such decisions “are, appropriately, made on an ad hoc basis after the local contractor’s consideration of the applicable facts.” *Id.* We understand from these representations that CMS and its contractors do not, or will not in the future, apply NCD 160.18(C) to bar coverage of maintenance services – including replacement of the implanted VNS device upon battery expiration – for beneficiaries who received the VNS device prior to May 4, 2007.

⁴⁴ In another submission, CMS declared that it “has allowed coverage of maintenance items such as batteries or generators in certain cases,” including cases in which the beneficiary is receiving VNS for TRD. CMS Response at 5. And in its response to the *amicus curiae* statement of Steven Buser, M.D. (at page 9), CMS stated that “[w]hile National Coverage Determination 160.18 noncovers VNS implantation for the treatment of TRD, it is silent on the coverage of services related to the maintenance of the already implanted device as well as the related professional services,” leaving its contractors with “discretion . . . to cover or noncover these services.” For their part, the aggrieved parties submitted a transcript and recording of a telephone call, whose authenticity CMS does not question, in which an employee of CMS’s Coverage Analysis Group responded to a question from the physician of an aggrieved party who received the VNS device prior to May 4, 2007. The question posed by the physician (Dr. Buser) was whether Medicare will cover physician and other medical services to ensure that the Aggrieved Party can continue receiving VNS therapy; the CMS employee responded that “routine maintenance and programming visits” will “continue to be covered” by Medicare. AP Ex. 11; *see also* AP Ex. 2, ¶¶ 17, 19.

The Aggrieved Parties notified the Board that on September 30, 2014, the Medicare Appeals Council (MAC),⁴⁵ in a case titled *Family Life and Learning Center, PLLC* (MAC Dkt. No. E-14-14), held that NCD 160.18(C) unambiguously barred Medicare coverage for certain maintenance services (electronic analysis and programming) provided to beneficiaries with depression who were implanted with the VNS device prior to May 4, 2007. That holding is no longer in effect because on October 17, 2014, the MAC reopened and revised its September 30, 2014 decision in *Family Life*.⁴⁶ In doing so, the MAC concluded that “the silence of the NCD on collateral services to beneficiaries who already have VNS devices implanted indicates that the NCD is not applicable to the claims here and was applied incorrectly to bar them without further consideration,” and that CMS’s contractor “erred to the extent that it relied on NCD 160.18 as establishing” that Medicare did not cover the claimed maintenance services. The MAC further explained that NCD 160.18(C)’s inapplicability to those services “does not mean that the claims at issue are necessarily covered” because: (1) “where an NCD does not preclude coverage, [CMS’s] contractor is responsible for determining the scope of Medicare coverage in the first instance, either through issuance of a local coverage determination (LCD) or on a case-by-case basis”; and (2) the proponent of coverage must demonstrate, with “adequate documentation,” that the claimed services were actually provided and meet applicable coverage criteria (including the requirement that the services be “reasonable and necessary”).

In short, both CMS and the MAC have interpreted NCD 160.18(C) as being *inapplicable* to Medicare coverage claims for maintenance services relating to VNS devices implanted prior to May 4, 2007. In light of these circumstances, we have no basis to find that the NCD is invalid because it unreasonably denies coverage for those services.⁴⁷ If the Aggrieved Parties are contending that NCD 160.18(C) is invalid because it does not

⁴⁵ The MAC issues final determinations of the Secretary of Health & Human Services concerning Medicare coverage and payment disputes arising from the administrative appeals process described in 42 C.F.R. Part 405, subpart I. Under that process, a Medicare beneficiary or provider whose coverage or payment claim has been denied by a CMS contractor may appeal the denial to another contractor and, if necessary, to administrative law judges in the Office of Medicare Hearings and Appeals and then to the Medicare Appeals Council. *See generally* 42 C.F.R. §§ 405.960, 405.1000-1140. Such an appeal typically focuses on whether the coverage denial was justified given the beneficiary’s clinical condition and other circumstances unique to his claim for benefits. The validity of an NCD is not subject to challenge in the Medicare claims appeal process, although the applicability of an NCD to a particular claim may properly be addressed. 42 C.F.R. § 405.1060(b)(2).

⁴⁶ Order of Medicare Appeals Council Reopening Case and Remanding to Administrative Law Judge, *Family Life and Learning Ctr.*, Dkt. No. E-15-02 (formerly E-14-14).

⁴⁷ One of the legal prerequisites for an NCD challenge is that it be brought by a Medicare beneficiary (or the estate of such a beneficiary) who “[i]s in need of coverage for a service that is *denied based on*” the challenged NCD. 42 C.F.R. § 426.110 (*italics added*) (defining the term “aggrieved party”); *id.* § 426.320(a) (stating that only an “aggrieved party” may initiate a review of an NCD).

affirmatively authorize coverage for those services, we reject that contention. We discern no way in which the NCD's failure to address the circumstances of beneficiaries who received the VNS device prior to May 4, 2007 undercuts the reasons given by CMS for denying coverage of VNS for beneficiaries who do not yet have the device.

Finally, we address one other point made by the Aggrieved Parties in connection with this discussion about Medicare beneficiaries who received the VNS device prior to May 4, 2007. The Aggrieved Parties suggest that by permitting, or by not categorically denying, Medicare coverage of maintenance services (including replacement of the VNS device upon battery replacement) for that group of beneficiaries, CMS has implicitly conceded that VNS may, in appropriate circumstances, be reasonable and necessary for beneficiaries with TRD who do not have the device. *See* AP Statement ¶¶ 56-57 (implying that CMS would not permit coverage of battery replacement if VNS was not, in fact, safe and effective for TRD). The Aggrieved Parties assert that “[i]f VNS is not reasonable and necessary for TRD, as the . . . NCD holds, the Secretary’s determination to allow continued VNS treatment for TRD, which would naturally end with the expiration of the battery, while denying the same treatment to other Medicare beneficiaries, is *arbitrary and capricious*.” AP Resp. to Supp. Br. at 3 n.2 (italics added).

There are at least two reasons why this argument is without merit. First, it overlooks the fact that beneficiaries who received the VNS device prior to May 4, 2007 and who may need Medicare coverage of maintenance services to ensure the continuation of VNS therapy are in a different clinical posture than beneficiaries who do not have the device and for whom the device’s medical benefits are uncertain. As the Aggrieved Parties themselves assert, discontinuation of VNS therapy presents individualized continuity-of-care and safety concerns – concerns that obviously do not apply to a person who does not have the device. Furthermore, these beneficiaries have already undergone the risk of adverse effects from surgical implantation which would need to be considered in determining whether to cover new implantation and have presumably found any other adverse effects of treatment tolerable or offset by some perceived benefits. Second, while it may be true that the *Medicare coverage outcomes* for the two groups are different, that circumstance is hardly the result of arbitrary and capricious decision-making. To the contrary, it is the direct consequence of the timing of CMS’s reasoned determination, made after a lengthy coverage review process informed by public comment, that there is insufficient evidence that VNS improves health outcomes for Medicare beneficiaries with TRD.⁴⁸

⁴⁸ The Aggrieved Parties do not point to anything in the statute or regulation that precludes CMS from issuing an NCD that prospectively bars coverage for services that Medicare may have covered on an ad hoc or case-by-case basis prior to the NCD’s issuance.

VIII. CONCLUSION

In accordance with section 1869(f) of the Act, the Board's review of NCD 160.18(C) is narrow. In general, we must defer to findings supporting that determination "[s]o long as [that] outcome is one that could be reached by a rational person" applying the correct legal standards. 68 Fed. Reg. at 63,703. CMS determined in May 2007 that relevant scientific and clinical evidence is not strong enough to conclude that Medicare beneficiaries with resistant depression will receive health benefits from VNS that outweigh its risks. That judgment is based on reasonable findings of fact and conclusions of law that continue to be viable and sufficient, even in light of information post-dating the NCD's issuance. Accordingly, we conclude that the record upon which CMS issued NCD 160.18(C) is complete and adequate to support its validity.

/s/

Judith A. Ballard

/s/

Leslie A. Sussan

*/s/*Stephen M. Godek
Presiding Board Member

APPENDIX TO BOARD DECISION NO. 2613
NCD 160.18, Vagus Nerve Stimulation
Docket No. A-14-3

EXHIBITS SUBMITTED BY THE AGGRIEVED PARTIES

The body of the Board’s decision explains the basis for our conclusion that the NCD record is complete and adequate to support the validity of the challenged provision, even in light of the additional material submitted by the Aggrieved Parties. In reaching that conclusion, the Board carefully and thoroughly considered the entire record before us, including all exhibits submitted by the Aggrieved Parties. Overall, we found that, individually and cumulatively, those exhibits were not relevant or material or for other reasons do not persuade us that the NCD record is incomplete or inadequate to support the validity of the NCD. As discussed in the Board’s decision at pages 31-32 and 52, many of the studies reported or discussed did not involve VNS studies with Treatment Resistant Depression (TRD), involved studies with VNS that did not contain randomized control groups, were case studies with a small sample size or number of participants, were cost-benefit analysis reports, or were reviews of previously published scientific research. In addition, many of the exhibits actually support CMS’s conclusions. Below, we list all of the exhibits, providing detail about the content of those exhibits not referenced specifically in the body of the decision to show how they fit into our general analysis – for example, to identify an article as a report on a small sample of case studies or as a review of previously published research. This Appendix should be viewed as a part of the Board decision and given the same authority as material included in the body of the decision.¹

EXHIBIT 1: *National Coverage Determination (NCD) for Vagus Nerve Stimulation (VNS) (160.18)*

EXHIBIT 2: *Affidavit of Steven Buser, M.D.***

Dr. Buser, a board-certified psychiatrist and a diplomate of the American Board of Psychiatry and Neurology, states that he has used VNS therapy since 2006 to treat patients with TRD since 2006 (including one of the Aggrieved Parties). He asserts: (1) “[t]he use of VNS is clearly beyond the investigational and experimental stage”; (2) “numerous published peer-reviewed studies show its effectiveness as treatment for depression”; (3) “[t]he use of VNS is clinically beneficial and has been discussed with favor at various local, regional, and national medical meetings”; (4) published literature “clearly shows the clinical utility of VNS for patients who have treatment resistant depression”; and (5) his “professional experience” with VNS “has validated the utility of

¹ For the convenience of the reader, those exhibits that were dated, published, or created after the NCD was issued on May 4, 2007 are denoted with a double asterisk (**).

VNS in treating treatment resistant depression.” Dr. Buser further states that he has prescribed VNS therapy for patients with depression who have failed to get relief from pharmaceutical management or electroconvulsive therapy; that “in [his] experience with treating depressed patients with the VNS therapy, the patients have a markedly improved clinical outcome with fewer complications and recovery”; and that “[t]he majority of patient[s] for whom [he] prescribed VNS had a marked improvement in relief of depression and the ability to return to the activities of daily living.”

EXHIBIT 3: *Appointment of Aggrieved Parties’ representative***

EXHIBIT 4: *Documentation of the U.S. Food and Drug Administration’s July 16, 1997 decision granting premarket approval of the VNS Therapy System for medically refractory epilepsy*

EXHIBIT 5: *Documentation of the Food and Drug Administration’s July 15, 2005 decision granting premarket approval of the VNS Therapy System 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*

EXHIBIT 6: *“Nonpharmacologic Interventions for Treatment-Resistant Depression in Adults” (September 2011), prepared by RTI International-University of North Carolina Evidence-Based Practice Center for the Agency for Healthcare Research and Quality (AHRQ)***

This 2011 report reviews the available scientific evidence and medical literature in order to assess the comparative effectiveness of four non-pharmacologic treatments for patients with TRD. The four treatments reviewed in the report are: electroconvulsive therapy (ECT); repetitive transcranial magnetic stimulation (rTMS); vagus nerve stimulation (VNS); and cognitive behavioral therapy or interpersonal psychotherapy (CBT or IPT).

The exhibit contains only a three-page excerpt from the report’s introduction (in addition to the report’s cover page, preface, and table of contents). That brief excerpt describes VNS’s technology, its FDA approval status, and treatment costs for VNS. The excerpt then states:

The place in therapy for VNS may be for patients who have four or more adequate antidepressant treatment failures. Considerations also include a longer onset of antidepressant action than other treatments, as VNS benefits

for TRD may not be fully realized for 6 to 12 months. Further, VNS poses surgical risks and is associated with several side effects such as voice alteration, cough, neck pain, paresthesia, and dyspnea.

AP Ex. 6, at 19 (footnote and citations omitted).

EXHIBIT 7: *American Psychiatric Association (APA), “Vagus Nerve Stimulation (VNS) White Paper,” approved by Joint Reference Committee in June 2009***

This exhibit is discussed in section V.C.2 of the main body of the decision.

EXHIBIT 8: *American Psychiatric Association (APA), “Practice Guideline for the Treatment of Patients with Major Depressive Disorder” (3d ed. 2010)***

This exhibit is discussed in section V.C.2 of the main body of the decision.

EXHIBIT 9: *May 2013 Requests for Reconsideration of NCD 160.18 (without attachments) filed by Charles R. Conway, M.D. and Darin D. Dougherty, M.D.***

This exhibit is discussed in section VI of the main body of the decision.

EXHIBIT 10: *Cyberonics, Inc., 72-Month Post-Approval Study Report (Treatment-Resistant Depression Registry) and Affidavit of Mark Bunker, Pharm.D. (TRD Registry Study Director)***

This exhibit contains 72-month (interim) findings of the D-23 registry study requested by the FDA as a condition of premarket approval of the VNS Therapy System for the treatment of TRD. Both reports have been submitted to the FDA. The D-23 registry study “is a long-term, prospective, observational, multi-center patient outcome registry designed to collect data describing patients with treatment-resistant depression (TRD) who are currently in a major depressive episode.” AP Ex. 61, at 6.

The D-23 registry study enrolled 841 subjects, 494 of whom received adjunctive VNS (that is, VNS in conjunction with ongoing treatment-as-usual (TAU)), and 301 who received TAU only. AP Ex. 61, at 6. Patients have been followed for 60 months (or until withdrawal, death, or study completion) to assess treatment effectiveness and safety. *Id.* at 33.

The study's primary outcome measure is the patient's change from baseline score on the Montgomery-Asberg Depression Rating Scale (MADRS), with "response" defined as \geq 50 percent reduction from baseline. AP Ex. 61, at 63. The study also assessed treatment side effects (in both study populations) using the Frequency, Intensity and Burden of Side Effects-Rating (FIBSER) questionnaire. *Id.* at 84. In addition, the study assessed suicidality using three outcome variables. *Id.* at 84, 98.

The 8-year TRD Registry report states that VNS Therapy has shown "statistically significant benefits over [the] TAU group for almost all outcomes measured." AP Ex. 61, at 82. The report further states that FIBSER data (representing the collective impact of side effects) demonstrate that VNS is safe for persons with TRD. *Id.* at 84, 98, 117 (stating that "[t]he percentage of patients experiencing a score of 5 or 6 (least favorable)" on FIBSER subscales "are similar in all groups and decrease over time"). In addition, the report indicates that although "[s]uicide risks decreased over time in all treatment groups," the VNS group generally experienced greater decreases. *Id.* at 99, 100, 101.

Note: In a September 3, 2014 amicus curiae statement, Scott T. Aaronson, M.D. states that he is "currently drafting what will be the first manuscript of the D-23 study." He also states that he reported five-year results of the D-23 registry study at a June 12, 2014 meeting of the American Society for Clinical Psychopharmacology. His *amicus curiae* statement summarized those results as follows:

The cumulative response rate for the VNS group, as measured by the [MADRS], was approximately double that observed for the TAU patients at all post-baseline points. ***Statistically significant improvement with VNS*** was noted when comparing cumulative response rate at 5 years. VNS patients had statistically significantly longer median time to relapse than TAU patients (12 months vs. 7 months). These results are based on 500 patients with VNS and 300 with TAU alone. This is clearly the result of VNS intervention. I am not aware of any evidence that supports a 5-year placebo benefit in a patient population experiencing chronic, severe TRD. [italics and emphasis in original]

EXHIBIT 11: *Transcript and CD of telephone voicemail message by Beverly Lofton (CMS Coverage Analysis Group) to Steven Buser, M.D. on July 10, 2007 concerning Medicare coverage of routine maintenance and programming of a VNS pulse generator for patients who had the VNS device implanted prior to May 4, 2007***

The pertinent text of the transcribed voicemail states: "You sent me an email with a question about VNS, questioning will the routine maintenance and programming visits still continue to be covered under Medicare for VNS with TRD – and the answer to that question is 'yes, that will still be covered.'"

EXHIBIT 12: *Aaronson, S.T., et al. (2013), “Vagus Nerve Stimulation Therapy Randomized to Different Amounts of Electrical Charge for Treatment-Resistant Depression: Acute and Chronic Effects”***

This article reports the results of the FDA-mandated D-21 dosing study, which is discussed in section V.C.1 of the main body of the decision.

EXHIBIT 13: *Baweja, R., et al. (2013), “Concomitant Use of Maintenance ECT and Vagus Nerve Stimulation for More Than 10 Years in Treatment-Resistant Depression”***

This exhibit is a published letter written by two physicians who reported on the case of a 57-year-old man with a lifelong history of major depression as well as an “intractable” seizure disorder. The physicians reported that the man’s depression had been treated for 10 years with “weekly maintenance ECT” (electroconvulsive therapy), and his seizure disorder with VNS, “without any short- or long-term complications.” The physicians also stated that “[c]oncomitant maintenance ECT and VNS” had prevented further inpatient hospitalization and produced significant improvement in socio-occupational functioning. The authors stated that “[i]t is possible that VNS may have improved any possible cognitive effects of ECT,” and that “[m]aintenance ECT seems to be a safe treatment option for patients with treatment-resistant depression with VNS.”

EXHIBIT 14: *Berry, S.M., et al. (2013), “A Patient-Level Meta-Analysis of Studies Evaluating Vagus Nerve Stimulation for Treatment-Resistant Depression***

This article reports the results of a meta-analysis that is discussed in section V.C.1 of the main body of the decision.

EXHIBIT 15: *Christmas, D., et al. (2013), “Vagus Nerve Stimulation for Chronic Major Depressive Disorder”***

This article reports the results of a small uncontrolled study that was based on data from two other studies: (1) the D-03 European study (*see* AP Ex. 22); and (2) a small study conducted by a neurological treatment program in Dundee, England (the Dundee study). The study analyzed data for a subgroup of D-03 subjects (the D-03 cohort) and a separate group of Dundee study subjects (the Dundee cohort). The authors noted that earlier Cyberonics-sponsored trials included subjects of varying levels of treatment resistance, “*leaving significant remaining uncertainty about the effectiveness of VNS in patients with highly chronic, highly treatment-refractory unipolar depression.*” AP Ex. 15, at 2 (italics added).

The D-03 cohort consisted of 28 subjects (mean age of approximately 48 years) with confirmed diagnoses of chronic unipolar major depression, who were in a major depressive episode (MDE) upon entering the study, and who had failed to respond to four or more adequate antidepressant treatment trials during the current MDE. The mean number of failed treatments for this group was 7.9 ± 2.7 . The Dundee cohort consisted of 13 subjects (mean age of approximately 47 years) with unipolar depression whose mean number of failed treatments during the current MDE was 9.4 ± 3.9 .

For purposes of the study, treatment “response” was defined as ≥ 50 percent improvement on the 17-item Hamilton Rating Scale for Depression (HRSD₁₇) or the Montgomery-Asberg Depression Rating Scale (MADRS), or a score of 1 (very much improved) or 2 (much improved) on the Clinical Global Impression – Improvement (CGI-I) scale.

The study found that 35.7 percent of subjects in D-03 cohort met response criteria at 12 months, while 30.8 percent of subjects in the Dundee cohort met response criteria at 12 months. AP Ex. 15, at 2-3. The results for the D-03 cohort were “somewhat lower than the overall response rate” reported in the D-03 study. *Id.* at 3. However, the study’s authors noted that the D-03 subgroup they studied was a “substantially more chronic and refractory” sample than the complete D-03 population and “exclude[d] those with a diagnosis of bipolar disorder for whom measuring outcome using change on a depression rating scale has uncertain validity.” *Id.*

Although the authors stated that their results support the use of VNS in subjects with “chronic and medication-refractory illness in whom there is poor evidence for the effectiveness of standard medication and psychological therapies,” they acknowledged that there “*continues to be uncertainty about the efficacy of VNS as a treatment for major depression*” and “[t]he evidence from published studies of VNS for major depression leaves unresolved a number of questions about the benefits of VNS in more refractory patients” AP Ex. 15, at 4 (italics added). They also stated that “*there is uncertainty about optimum stimulation parameters*” and that “[i]t is not currently possible to predict who will benefit from VNS” *Id.* (italics added). As for the study’s limitations, the investigators noted that the study samples were small, there was no control group, data were derived from other unblinded studies, and “it [was] not possible to know to what extent ‘response’ can be attributed to factors other than VNS[.]” *Id.* The authors also noted that their study reported only 12-month outcomes and that “less is known about longer-term outcomes,” while stating that the “available evidence” (pointing to the D-03 study (AP Ex. 22) and one other study that is not part of the record) suggests that “those who achieve remission at 12-months are likely to maintain it at two-years or more.” *Id.* (citations omitted).

EXHIBIT 16: Conway, C., et al. (2013), “Association of Cerebral Metabolic Activity Changes with Vagus Nerve Stimulation Antidepressant Response in Treatment-Resistant Depression”**

This 2013 article describes a study of brain activity (*e.g.*, changes in cerebral metabolic rate for glucose, or “CMRGLu”) in selected regions (chosen because of their suspected involvement with depression and VNS) using fluorodeoxyglucose positron emission tomography. The study involved 13 subjects with TRD who received 12 months of VNS.

The principal author of the study, Charles R. Conway, submitted an *amicus curiae* statement which includes the following general description of his research about the physiologic effects of VNS in patients with TRD:

Over [the] course of the past 6 years, our research . . . has enabled us to better understand VNS in TRD. . . . [W]e have used the brain imaging method known as positron emission tomography scanning (or PET scans) to demonstrate how the immediate effects of VNS alter brain flow in TRD These studies demonstrate that regions well-established as critical in depression (*e.g.*, the prefrontal cortex and insular cortex) undergo significant immediate changes with VNS.

Regarding the study described in Exhibit 16, Dr. Conway states (in his *amicus* statement):

. . . In January of 2013, we published our most significant work . . . in which we studied the sub-acute (3 months) and chronic (12 months) effects associated with antidepressant response to VNS in TRD. We demonstrated that sub-acute VNS was associated with profound changes in regional cerebral metabolic activity in regions known to be associated with clinical depression (dorsolateral prefrontal, insular, and orbitofrontal cortices). Further, we demonstrated that chronic stimulation (12 months) was associated with increased metabolic activity in a brainstem region associated with dopamine neurotransmission (the ventral tegmental area), additionally substantiating that VNS in TRD likely works via activation of brain dopaminergic systems. We are continuing to use brain neuroimaging to study how prolonged response (18 months) of VNS brings about brain changes (data yet to be analyzed).

According to the 2013 article, the study’s findings of increased metabolic activity in the ventral tegmental area are “highly preliminary” and require replication. AP Ex. 16, at 8. In addition, the authors acknowledged that the study lacked a control group, which meant that they could not “conclusively state that . . . CMRGLu

changes occurred as a result of VNS or that the[] changes reflect the effects of VNS.” *Id.* “It is possible,” said the authors, “that the changes observed could have been unrelated to sustained VNS or an interaction coming about as a result of the clinical change.” *Id.*

EXHIBIT 17: *Cusin, C., et al. (2012), “Somatic Therapies for Treatment-Resistant Depression: ECT, TMS, VNS, DBS”****

This article is a literature review concerning “new somatic therapies utilized in the treatment of TRD,” including VNS. AP Ex. 17, at 1. The authors stated that the safety of VNS “is well established from its use in the treatment of epilepsy,” and that VNS “appears to be most effective in patients with MDD or bipolar disorder with low to moderate, but not extreme, antidepressant resistance.” *Id.* at 4-5, 7. In addition, the authors stated that “[b]ecause its effects take much longer to appear compared to antidepressants or ECT, VNS cannot be considered a treatment for acute TRD.” *Id.* at 5.

EXHIBIT 18: *Feldman, R.L., et al. (2012), “Medicare Patient Experience with Vagus Nerve Stimulation for Treatment-resistant Depression”****

This article reports the results of a study that is discussed in section V.C.1 of the main body of the decision.

EXHIBIT 19: *Olin, B., et al. (2012), “Mortality and Suicide Risk in Treatment-Resistant Depression: an Observational Study of the Long-Term Impact of Intervention”****

This article reports the results of a study that is discussed in section V.C.1 of the main body of the decision.

EXHIBIT 20: *Yuan, W., et al. (2012), “Long-Term Vagus Nerve Stimulation for Severe Refractory Depression: a Case Study with a Six-Year Follow-up”****

This exhibit contains a published case report concerning a 38 year-old woman with severe major depression, general anxiety disorder, borderline personality disorder, and other diagnoses. In December 2005, she began VNS to treat her “refractory depression.” The woman reported that her depression “immediately got better” and that she felt “totally different” after she began VNS. The case report states: “Over the 6 years since the stimulator was placed, she has rarely felt depressed, sometimes mildly depressed, and has never had suicidal ideation. Also the vagus nerve stimulator reduced her anxiety levels.”

EXHIBIT 21: *Cristancho, P., et al. (2011), “Effectiveness and Safety of Vagus Nerve Stimulation for Severe Treatment-Resistant Major Depression in Clinical Practice After FDA Approval: Outcomes at 1 Year”***

This article reports the results of a small case-series study of 15 subjects (with a mean age of 49) who received VNS at a university outpatient clinic. Ten subjects had a diagnosis of major depressive episode and five had bipolar disorder. Subjects were eligible for the study if they had a documented history of non-response to a minimum of four adequate antidepressant treatments. All 15 subjects were in a major depressive episode at the time of enrollment, and, as a group, they “had a high degree of illness severity as evidenced by the mean length of the current major depressive episode (63.8 months) and by the high percentage of ECT failure.” AP Ex. 21, at 3. The study’s objective was to assess the effectiveness of VNS in “standard conditions of clinical practice.” *Id.* at 2. Concomitant (non-VNS) antidepressant treatment was “held fixed as far as clinically possible” during the study. *Id.*

The primary clinical outcome assessed by the study was a subject’s six-month and 12-month change in score on the 21-item Beck Depression Inventory (BDI), which measures the severity of depressive symptomatology (with higher scores denoting more severe symptoms). Clinical “response” was defined in the study as ≥ 50 percent decrease in BDI score compared with subject’s baseline score; “remission” was defined as a BDI score of ≤ 9 at the end of 12 months. The investigators also measured “secondary” outcomes based on other scales such as the 24-item Hamilton Rating Scale for Depression (HRSD₂₄).

The investigators found that subjects’ average BDI score decreased from 37.8 at baseline (before VNS activation) to 24.6 at 12 months. The difference was found to be statistically significant ($SD = 11.4$ and $p < 0.1$). At the end of one year, four subjects in the sample (28.6 percent) had experienced a response and one subject (7.1 percent) had experienced a remission based on their BDI scores. Using the HRSD₂₄, the investigators found that six subjects (or 43 percent) had achieved a response and 2 subjects (14.3 percent) had achieved remission after one year. The investigators compared these findings to the one-year results of the D-01 pilot, D-02 pivotal, and D-03 European studies, concluding that “[o]verall, results achieved in our clinical practice were comparable to those in prior VNS studies, despite the fact that our patient population was more severely ill than those in previous VNS studies.” AP Ex. 21, at 6.

With respect to “secondary outcomes,” the study “did not find a significant increase in quality of life as measured by the Q-LES-Q [Quality of Life Enjoyment and Satisfaction Questionnaire], in contrast to the findings” of an earlier study. AP Ex. 21, at 6 (endnote omitted). “Interestingly,” said the authors, “our patients’ level of hopelessness did not

improve despite the measureable improvement in depressive symptoms.” *Id.* The authors also found (contrary to prediction) that “although VNS was beneficial in improving depressive symptoms, we observed no significant changes in rates of hospitalization or suicidal attempts after 1 year of VNS.” *Id.*

Adverse events were “similar to those reported in other VNS studies and included hoarseness (73%), dyspnea (47%), nausea (40%), pain (33%), and anxiety (20%)” AP Ex. 21, at 4. “There were no serious adverse events related to surgery.” *Id.* “Other side effects,” including cough, chest tightness, sore throat, dysphagia, and earache (among others), were reported, but these were “judged generally to be mild in severity and were present during stimulation only.” *Id.* at 4-5.

The investigators did not find statistically significant evidence of factors that predicted a response to VNS. AP Ex. 21, at 4.

EXHIBIT 22: *Bajbouj, M., et al. (2010), “Two-year Outcome of Vagus Nerve Stimulation in Treatment-Resistant Depression”****

This article reports the results of a study that is discussed in section V.C.1 of the main body of the decision.

EXHIBIT 23: *Cecchini, P., et al. (2009), “Vagus Nerve Stimulation in Drug-Resistant Daily Chronic Migraine with Depression: Preliminary Data”****

This article reports the results of a small case-series study which evaluated the efficacy of VNS in patients suffering from drug-refractory chronic migraine (CM) and depression. The authors applied VNS to four female patients (mean age 53) who had suffered from CM and depression for at least two years. The patients completed a daily headache diary reporting symptoms for six months prior to the implantation of the VNS device. Examinations were conducted every two weeks for the first month after implantation and monthly thereafter. The authors reported that “two [of the four] patients (50%) improved for both headache and depression 1-3 months after VNS was started.” AP Ex. 23, at 4. The authors stated that “for the two patients with limited or no improvement, long-term follow-up, more than 6 months, could be necessary in order to probe VNS efficacy.” *Id.* The authors concluded that the study’s results “support a beneficial effect of chronic VNS in patients suffering from drug-refractory [chronic daily headache] and depression, suggesting this novel treatment as a valid alternative for this otherwise intractable and highly disabling condition.” *Id.*

EXHIBIT 24: *Hixon, J., et al. (2009), “The Effects of Epilepsy and its Treatments on Affect and Motion”***

This article presents “two cases that illustrate the complex interplay of factors that may determine affective function in people with epilepsy.” AP Ex. 24, at 2. The authors discuss several different types of treatments for patients with epilepsy, including VNS. *Id.* at 2-8. The authors mention three prior studies in which VNS was used to treat epilepsy and stated that “these studies suggest an impact of VNS therapy on patient mood, though the mechanism is not yet established.” *Id.* at 8.

EXHIBIT 25: *Sperling, W., et al. (2009), “Clinical Benefits and Cost Effectiveness of Vagus Nerve Stimulation in a Long-Term Treatment of Patients with Major Depression”***

This article reports on a non-randomized controlled study that evaluated clinical aspects and cost-effectiveness of using VNS for a group of nine patients who were suffering from TRD. The study showed that, relative to their baseline assessments, the nine patients experienced a statistically significant improvement in depressive symptoms after 12 months of stimulation, while control-group patients experienced no statistically significant improvement after 12 months. AP Ex. 25, at 2, 3. In addition, the “average length of hospitalization” in the VNS group was “significantly reduced” from 65 days to 44 days, while “[i]n the control group, the average length of hospitalisation did not decrease in an equivalent observation period.” *Id.* at 3. The number of psychiatric consultations in the VNS group also “decreased significantly” (from 33 to 14) during the relevant study period, while there was no such change for control-group patients. *Id.* The authors stated that “in comparison to the findings of [other] multicenter studies, effective improvement of symptoms occurred later, mainly in the fourth quarter year after implantation.” *Id.* The authors acknowledged that “the validity of this study is limited to due to the lack of feasibility of a sham implantation, and the small sample size.” *Id.* at 4. “Therefore,” they said, “an adequate control collective might be desirable, as spontaneous remissions without direct reference to the treatment method used cannot be ruled out,” and “[f]urther investigation on the disease course after implantation on a larger patient collective including control groups is necessary.” *Id.*

EXHIBIT 26: *Cohen, L., et al. (2008), “Estimating the Potential Savings with Vagus Nerve Stimulation for Treatment-Resistant Depression: A Payer Perspective”***

This article concerns a study whose objective was to provide a formula to estimate the potential reduction in healthcare utilization costs for TRD patients as a result of receiving adjunctive VNS therapy. AP Ex. 26, at 1, 4.

EXHIBIT 27: *Milby, A., et al. (2008), “Vagus Nerve Stimulation for Epilepsy and Depression”***

This article reviews previously published literature concerning the VNS device, the procedures for implanting the device, possible mechanisms of VNS-induced seizure suppression and mood alteration, results from efficacy studies, and commonly reported adverse events in patients suffering from refractory epilepsy and TRD. AP Ex. 27, at 1, 3, 5-6. With respect to VNS’s use in treating TRD, the authors observed that “the unremarkable results of initial randomized trials of adjunctive VNS versus sham for TRMD at 10 weeks [referring to the D-02 pivotal study] were attributed in part to the limited duration of treatment.” *Id.* at 7. The authors indicated that longer-term studies (such as the D-01 pilot and the long-term phase of the D-02 pivotal study) reported “favorable response and remission rates” but noted that those “results raise the issue of placebo effects potentially associated with VNS implantation, and *suggest that additional randomized trials with longer treatment durations before crossover are needed to assess their significance.*” *Id.* (italics added).

EXHIBIT 28: *Sperling, W., et al. (2007), “Combined VNS-rTMS Treatment in a Patient with Therapy Resistant Depression”*

This article describes an eight-month case study in which VNS therapy and repetitive transcranial magnetic stimulation (rTMS) (a non-invasive technique that stimulates a region of the cerebral cortex by using very strong, short, magnetic pulses) were sequentially combined to treat a 50-year man with TRD. The authors stated that “[o]ver the course of the sequential treatment regimen (without concomitant pharmacological therapy)[,] a marked decrease in the depressive symptoms without psychotic symptoms occurred after completion of the rTMS treatment (day 10) and has since remained stable for 11 months under now ongoing VNS-treatment” AP Ex. 28, at 2. The authors “conclude[d] that in single cases, a synergism between VNS and rTMS treatment is possible, as in the [case study] described above, although other therapeutic options (e.g., VNS and ECT) should also be considered.” *Id.*

EXHIBIT 29: *Warnell, R., et al. (2007), “Introduction of Vagus Nerve Stimulation into a Maintenance Electroconvulsive Therapy Regimen: a Case Study and Cost Analysis”***

This case report concerns a 47 year-old male patient with TRD who received VNS therapy while also receiving maintenance electroconvulsive treatment (M-ECT) at two-week intervals. The case report describes the outcome of that combined treatment and also compares the costs of M-ECT and VNS.

EXHIBIT 30: *Labiner, D., et al. (2006), “Vagus Nerve Stimulation Therapy in Depression and Epilepsy: Therapeutic Parameter Settings”*

This article reviews a number of previously published scientific papers with the objective of helping physicians identify the optimum therapeutic settings of a VNS device (*i.e.*, appropriate output settings involving the pulse generator) for patients with epilepsy and depression while balancing the goals of maximizing efficacy, minimizing treatment-emergent side effects, and preserving the device’s battery life. AP Ex. 30, at 2. The authors reviewed the results of several prior studies in which different parameters, such as pulse width and frequency, were utilized during VNS therapy. The authors concluded that “[m]uch remains to be learned about the use of VNS therapy in depression and epilepsy.” *Id.* at 9 (italics added). The authors stated that “[a]lthough VNS therapy has been effective for TRD and pharmacoresistant epilepsy when other treatments have failed, as with all other treatments, VNS therapy is not effective for all patients.” *Id.* In particular, said the authors, “interactions among output current, pulse width, frequency, and duty cycle have not been fully characterized, and it is possible that some as-yet unidentified variable could be responsible for differences in treatment effects.” *Id.* The authors further stated that “the clinical studies of parameters used in VNS therapy are limited by small sample sizes, variations among patient characteristics, and in some cases, lack of sham-treatment controls.” *Id.* at 9-10. The authors concluded: “Additional studies are needed to identify the patient-related factors that predict response to therapy and the parameter settings that are most effective for patients with various disease characteristics.” *Id.* at 10 (italics added).

EXHIBIT 31: *Gross, M., et al. (2007), “Central Therapeutic Effects of Peripheral Vagus Nerve Stimulation”*

This article discusses the “anatomy and function of the vagus nerve, the history of VNS, its mechanism of action, and its current and future applications” to treat chronic neurologic and psychiatric disorders. AP Ex. 31, at 2. The authors observed that “VNS has some “unique features.” *Id.* at 4. “Unlike pharmacologic therapy, it is not dependent on patient compliance[,] and it functions according to its programmed parameters.” *Id.* In addition, “[t]here is no potential for additional drug-drug interactions.” *Id.* The authors further stated that peripheral “[VNS] has expanded our armamentarium to treat and improve the quality of life in subgroups of patients with epilepsy and depression that are the most challenging.” *Id.* at 5.

EXHIBIT 32: *Burke, M., et al. (2006), “Concomitant Use of Vagus Nerve Stimulation and Electroconvulsive Therapy for Treatment-Resistant Depression”*

This article reports on a study which used data from the D-02 pivotal study. The study compared 12-month outcomes experienced by 14 subjects in that study who received

ECT (in addition to VNS) with the 12-month outcomes experienced by subjects who received VNS but not ECT. The authors reported that the subjects who received ECT had a statistically significantly greater number of hospital admissions and suicide attempts during their lifetimes. AP Ex. 32, at 2. The authors concluded that ECT and VNS therapy are not mutually exclusive and can be used concurrently or sequentially. *Id.* at 4. The authors stated that “because of its rapid onset of effect,” ECT “is a treatment of choice for patients experiencing an acute, marked exacerbation of depressive symptoms characterized by suicidality, psychosis, catatonia, or other life-threatening impairment of self-care for which an immediate response is required.” *Id.* However, said the authors, VNS is “not a reasonable acute intervention” for patients experiencing an acute exacerbation of depressive symptoms “[b]ecause of [its] gradual onset of effect[.]” *Id.* Citing the D-01 pilot study, the authors further stated that for the population of TRD patients “with “chronic, severe symptoms” who refuse or drop out of “maintenance ECT,” VNS therapy may be considered a reasonable alternative treatment,” and that “[a]lthough the onset of VNS therapy is sometimes delayed, the benefit is maintained over time.” *Id.* The authors concluded that their study “show[s] that co-therapy with VNS and ECT can safely provide an optimal outcome for some patients . . . ECT to treat emergent symptoms and maintenance therapy and VNS as an alternative long-treatment for TRD.” *Id.*

EXHIBIT 33: *Corcoran, C., et al. (2006), “Vagus Nerve Stimulation in Chronic Treatment-Resistant Depression: Preliminary Findings of an Open-Label Study”*

This article discusses a small, uncontrolled study that is discussed in section IV.B.1 of the Board’s decision.

EXHIBIT 34: *Martinez, J., et al. (2006), “Vagus Nerve Stimulation Therapy in a Patient with Treatment-Resistant Depression: a Case Report of Long-Term Follow-Up and Battery End-of-Service”*

This article reports the first case study of a single patient who received long-term adjunctive VNS therapy to treat TRD and experienced VNS battery end-of-service. The patient was a 41-year-old female with a long history of TRD. Following a two-week period after implantation, the patient entered a 12-week acute phase followed by a long-term phase lasting almost six years. During the three years of the long-term phase, the patient’s symptoms fluctuated between no depression and moderate depression. AP Ex. 34, at 1, 4-5. The authors stated that the “effectiveness of VNS therapy in this patient appears to be related to synergistic actions between VNS therapy and psychotropic medications, and overall treatment effectiveness for this patient was still sensitive to changes in pharmacotherapy.” *Id.* at 4. The estimated battery life of the pulse generator in this patient was estimated to be 4-8 years. *Id.* In the six-month period before battery end-of-service was verified, the patient reported that she no longer felt any stimulation

from the VNS device, her depression worsened acutely, and she was unresponsive to changes in medication. *Id.* at 1, 4-5. After a replacement device was implanted and medication adjustments were made, the patient returned to a course of episodic fluctuation of depression similar to that observed prior to the end-of-battery service. *Id.* at 5. The authors concluded that “it is possible that the VNS battery [end-of-service] may have been a contributory factor in the lack of treatment response during the period immediately prior to discovering [end-of-service].” *Id.* The authors further concluded that “identifying clinical features that are associated with VNS battery [end-of-service] will be helpful in scheduling device re-implantation and avoiding unexpected lapses in VNS treatment.” *Id.*

EXHIBIT 35: *Shafique, S., et al. (2006), “Vagus Nerve Stimulation Therapy for Treatment of Drug-Resistant Epilepsy and Depression”*

This article briefly reviews the “mechanics” of VNS therapy, the clinical indications for using VNS, and the evidence of VNS’s safety and long-term effectiveness in patients with epilepsy and drug-resistant depression. The authors stated that “[o]verall, VNS therapy is well tolerated.” AP Ex. 35, at 5. However, they stated that “[*m*]ore extensive long-term prospective data are needed to completely evaluate its role as adjunctive treatment for drug-resistant epilepsy and depression.” *Id.* (italics added).

EXHIBIT 36: *Nahas, Z., et al. (2005), “Two-year Outcome of Vagus Nerve Stimulation (VNS) for Treatment of Major Depressive Episodes”*

This article reports results from the D-01 pilot study, which is discussed in section IV.B.1 of the main body of the decision. *See also* AP Exhibits 42 and 46.

EXHIBIT 37: *Husain, M., et al. (2005), “Pregnancy and Delivery While Receiving Vagus Nerve Stimulation for the Treatment of Major Depression: a Case Report”*

This article presents a case study of a single female patient who suffered from TRD and had previously participated in the acute and long-term phases of the D-01 pilot study. AP Ex. 37, at 2, 5. In 2002, the patient reported that she was pregnant with her first child. *Id.* at 3. The subject decided to continue VNS therapy during the pregnancy with no changes in parameter settings. *Id.* The patient experienced an uneventful pregnancy and delivered a healthy daughter at full-term. *Id.* at 4. When the case study was published, the child was approximately two years old and exhibited age-appropriate development. *Id.* at 5. The authors reported that during her pregnancy, the patient experienced sustained remission of her TRD. *Id.* The authors concluded that “[i]n this case, VNS therapy provided effective adjunctive treatment for the patient’s depression during pregnancy and delivery [and that] VNS was safe for the patient and child.” *Id.* at 6.

EXHIBIT 38: *George, M.S., et al. (2005), “A One-Year Comparison of Vagus Nerve Stimulation with Treatment as Usual for Treatment-Resistant Depression”*

This article reports the results of the D-02/D-04 comparison study, which is discussed in section IV.B.1 of the main body of the decision.

EXHIBIT 39: *Mu, Q., et al. (2004), “Acute Vagus Nerve Stimulation Using Different Pulse Widths Produces Varying Brain Effects”*

This article reports the results of a randomized, single-blind, repeated-measures study that was “designed to investigate the acute effects of VNS at three different PW [pulse widths].” AP Ex. 39, at 2. The study ultimately involved nine subjects with major depression who were being treated with VNS. *Id.* Each subject underwent three consecutive fMRI (functional magnetic resonance imaging) scans during the course of a single afternoon. Each scan occurred while the subject received VNS at varying PWs – between 130, 150, or 500 μ s. *Id.* The authors reported that the subjects were blind to the VNS settings used during the MRI scans “but could obviously feel the highest tolerated intensity setting.” *Id.* at 3. The authors concluded that the study’s results “confirm our hypothesis that in depressed adults, differences in VNS [power widths] produce significantly different brain activation as measured by BOLD fMRI.” *Id.* at 6. The authors reported that “a short PW of 130 produced significantly less overall activation than did the two longer PW settings . . . [but] there was no significant difference in overall brain activation between the 250 PW and 500 PW.” *Id.* The authors acknowledged that “there are numerous limitations to this study attempting to parametrically study VNS effects.” *Id.* For example, said the authors, the study used “the off VNS time as [the] control condition and did not have a truly active, non-VNS control condition. Thus, it is unclear how to interpret the small activations seen with the PW 130.” *Id.* A related concern, said the authors, was that “as the PW increased, subjects were increasingly able to detect their VNS generator activity.” *Id.* at 7. In addition, the authors acknowledged that “the subjects in this study were a heterogeneous group of depressed patients who differed in their chronic medications and VNS settings and level of depression on the day of setting and who had widely ranging lengths of VNS treatment.” *Id.* “[F]urther studies in more homogenous samples” are needed, they said, “to determine which, if any, of these differences might affect the VNS signal.” *Id.* (italics added). The authors concluded that the “data assessing the immediate brain effects of different VNS PW confirm our hypotheses and suggest that the PW is an important variable in determining VNS brain effects” but that “[f]urther work is needed to understand the immediate and longer term effects of VNS settings and how these relate to clinical effects.” *Id.* at 9.

EXHIBIT 40: *Armitage, R., et al. (2003), “The Effects of Vagus Nerve Stimulation on Sleep EEG in Depression: a Preliminary Report”*

This article reports the effects of VNS on sleep in seven female subjects who had TRD. AP Ex. 40, at 1, 2. (“[P]ersistent sleep disturbance in depressed patients is associated with a significantly higher risk of relapse or recurrence and suicide.” *Id.* at 1). “All subjects continued on their individual psychotropic medication regimes without change in type or dose throughout the study.” *Id.* at 3. The study found that “VNS was associated with significant reductions in depressive symptom severity, some overall improvement in sleep macroarchitecture and a significant increase in the amplitude of ultradian sleep EEG rhythms.” *Id.* at 5. The authors also stated that “[m]ost importantly, the patients in the present study were all women[]” because other studies have shown that “women with nontreatment-resistant depression are less likely to show reduced [sleep rhythms] or slow-wave activity or an abnormal time course over the night.” *Id.* The authors further stated that the “present results indicate that the effects of VNS on sleep in the [treatment] resistant patients is dramatic.” *Id.* The authors found that the “effects of other psychotropic medications on sleep EEG are more equivocal . . . and [t]hus, it is difficult to ascertain whether the concurrent medication use in the present study contributed to EEG changes, although it remains possible.” *Id.* at 6. Finally, the authors stated that “[w]e are continuing our studies to determine whether [VNS’s effects on sleep EEG] persist through time. With a larger sample size, we also hope to determine whether baseline sleep EEG characteristics predict treatment response.” *Id.*

EXHIBIT 41: *Krishmoorthy, E. (2003), “Treatment of Depression in Patients with Epilepsy: Problems, Pitfalls, and Some Solutions”*

This article outlines the depressive syndromes specific to epilepsy and possible treatment options based on the recommendations of the subcommission on classification of the International League Against Epilepsy. Regarding VNS therapy to treat epilepsy, the author stated that “[a]lthough the mechanism of VNS is unknown, its effects on mood have stimulated considerable interest, and there are a number of ongoing treatment trials for [epilepsy.]” AP Ex. 41, at 5. The author noted that VNS and other brain stimulation technologies are “in their infancy and a better understanding of the brain mechanisms they influence is required.” *Id.* The author concluded that “novel treatments such as VNS have the potential to improve both epilepsy and behavioral disorders, and may well gain popularity in the future. At present, however, the cliché ‘more research is necessary’ continues to ring true, and this must include evidence-based approaches such as RCTs [that is, randomized clinical trials] and diverse populations the world over.” *Id.* at 7.

EXHIBIT 42: *Marangell, L.B., et al. (2002), “Vagus Nerve Stimulation (VNS) for Major Depressive Episodes: One-Year Outcomes”*

This article reports results from the D-01 pilot study, which is discussed in section IV.B.1 of the main body of the decision. *See also* AP Exhibits 36 and 46.

EXHIBIT 43: *Sackeim, H., et al. (2001), “The Effects of Vagus Nerve Stimulation on Cognitive Performance in Patients with Treatment-Resistant Depression”*

This article reports on a study to determine whether VNS therapy leads to neurocognitive deterioration. Twenty-seven patients who had TRD were administered a battery of 13 neurocognitive tests prior to, and 10 weeks after, VNS implantation. The tests were administered to assess the domains of motor speed, psychomotor function, language, attention, memory, and executive function. The authors reported three noteworthy results. First, there was no evidence of neurocognitive deterioration during the trial period. AP Ex. 43, at 7. Second, “despite the small sample, several indications of neurocognitive improvement at the second assessment relative to baseline were shown.” *Id.* at 8. Third, “some associations (at the trend or significant level) indicated that greater symptomatic improvement was correlated with improved neurocognitive performance, and there was no exception to this pattern.” *Id.* The authors concluded that “cognitive improvement seen after VNS may show reversal of the baseline deficits associated with major depression.” *Id.* However, noting that their sample was small, the authors characterized the results as “tentative.” *Id.* “Although many of the neurocognitive tests in the battery have shown minimal practice effects [of clinicians] . . . with weekly administration to healthy individuals (data not shown),” said the authors, “the possibility cannot be ruled out that practice effects substantially contributed to the findings of improved neurocognitive performance after 10 weeks of VNS.” *Id.* The authors raised an additional concern that an “off-on paradigm” of VNS had been used and that the “extent to which active VNS during the follow-up assessment enhanced or impaired performance on the cognitive measures is unknown.” *Id.* at 8-9. The authors further stated that “*in future work, it will be important to evaluate the effects of long-term VNS on neuropsychological measures using a sham-or-dosage controlled design to evaluate the contribution of practice effects and with an off-off-paradigm to determine potential long-term effects on neuropsychological function.*” *Id.* at 9 (italics added).

EXHIBIT 44: *Hoppe, C., et al. (2001), “Self-Reported Mood Changes Following Six Months of Vagus Nerve Stimulation in Epilepsy Patients”*

This article reports the results of a study that evaluated patient-reported mood changes in 28 epilepsy patients following six months of VNS treatment. The authors reported that the “self-report questionnaires revealed a differentiated profile of improved and unchanged aspects of mood and well-being.” AP Ex. 44, at 5. The authors stated that

“[s]ignificant improvements could be revealed in scales that address unspecific aspect of anxiety[], such as tenseness and negative arousal, and dysphoria []. These changes were intercorrelated and aim at a more variable and unspecific level of emotional well-being.” *Id.* In contrast, said the authors, “more complex and more stable emotional states including cognitive and behavioral aspects such as depression . . . appeared unchanged.” *Id.* The authors observed that this “finding differs from earlier studies that reported an anti-depressive of VNS.” *Id.* However, the authors noted that “[d]ifferent measures focus on different aspects of well-being, and, therefore, different findings must not necessarily indicate a contradiction.” *Id.* The authors concluded that their data showed “self-reported mood improvements in epilepsy patients following 6 months of VNS treatment” – changes which “indicate a mild antidysphoric effect of VNS.” *Id.* at 6-7. The authors noted that that this finding “does not contradict earlier reports of a pronounced antidepressive effect of VNS” because “the depression baseline scores were low in our sample.” *Id.* at 7.

EXHIBIT 45: *Harden, C., et al. (2000), “A Pilot Study of Mood in Epilepsy Patients Treated with Vagus Nerve Stimulation”*

This article reports the results of a non-randomized controlled study to determine VNS’s effect on the mood and anxiety of epilepsy patients whose regimen of anti-epileptic drugs (AED) was supplemented with VNS therapy. The authors found that VNS “may be associated with improved mood in epilepsy patients as demonstrated by significant decreases in all mood scale scores across time. This did not occur in the comparison group.” AP Ex. 45, at 5. However, there was no change in the anxiety ratings of the patients in the VNS group. *Id.* The authors stated that the “failure of anxiety ratings to change in the VNS subjects despite the [improvement of the] mood ratings raises the question of a differential effect of the [VNS] device; obviously this finding requires replication.” *Id.* The authors further stated that “the outcome of this study is limited by the fact that most of the subjects had only mild depression at the outset,” and that “[s]ince the initial mood scale scores are consistent only with mild depression and not major depression, any possible effect of the VNS on improving mood is limited by a ‘floor’ effect; that is, scale scores in our study do not have much room to improve compared with our control group.” *Id.* The authors recognized that there also “may have been a placebo effect on improving mood in the VNS group simply from patients choosing to be proactive in treating their epilepsy.” *Id.* In addition, the authors acknowledged the possibility that “nonspecific effects of physician contact [during the trial period] accounted for an improvement in mood scale scores.” *Id.* at 6. The authors concluded that “while our results are clearly preliminary, they provide some indication that the VNS improves mood in patients with seizure disorders, suggesting that the VNS could potentially be a new and novel treatment modality for depression.” *Id.*

EXHIBIT 46: *Rush, A.J., et al. (2000), “Vagus Nerve Stimulation (VNS) for Treatment-Resistant Depression: a Multicenter Study*

This article reports results from the D-01 pilot study, which is discussed in section IV.B.1 of the main body of the decision. *See also* AP Exhibits 36 and 42.

EXHIBIT 47: *O’Reardon, J., et al. (2006), “Vagus Nerve Stimulation (VNS) and Treatment of Depression: To the Brainstem and Beyond”*

This article describes the clinical studies that led to the FDA’s approval of VNS for TRD, explains the “controversy” surrounding FDA’s approval, addresses critiques of that decision, discusses VNS’s “safety and tolerability,” and reviews other issues pertinent to VNS’s use in the clinical setting, including contraindications, special precautions, programming of stimulation levels (“dosing”), and combining VNS with other treatment such as ECT. The authors concluded that although the initial clinical studies of VNS indicate that “efficacy is promising, . . . *there are some concerns to be resolved regarding the full degree of treatment efficacy,*” and “*close scrutiny should be applied to the post-FDA approval experience with VNS to get a fuller picture of its effectiveness in clinical practice.*” *Id.* at 10 (italics added).

EXHIBIT 48: *Nemeroff, C., et al. (2006), “VNS Therapy in Treatment-Resistant Depression: Clinical Evidence and Putative Neurobiological Mechanisms”*

This article reviews the medical literature regarding the physiology of the vagus nerve, the mechanics of VNS treatment, and VNS’s safety and efficacy for pharmaco-resistant epilepsy and TRD. In discussing VNS’s use for the latter condition, the authors stated that VNS therapy requires “an invasive surgical procedure to implant the device . . . [and] the [u]se of traditional placebo controls is neither applicable nor ethical under these circumstances.” AP Ex. 48, at 5. Consequently, said the authors, “the findings of medical device trials, including VNS therapy, should be interpreted with the understanding that, by design, they do not include a placebo arm . . . [but instead] involve before and after comparison or comparison to historical controls.” *Id.* In discussing the D-02/D-04 study, which compared one-year outcomes of TRD patients who received adjunctive VNS with the outcomes for TRD patients who received only TAU, the authors stated that although that study’s results were “promising,” an “extrapolation of the 1-year findings to clinical practice may be limited because the TAU group was not randomized and the TAU therapies were not restricted in either group after the first 3 months.” *Id.* at 6. The authors also reported that there is “an emerging literature [about the mechanism of action of VNS in TRD patients] that, at present, is difficult to interpret” for a number of reasons, including “heterogeneity in imaging methods, small sample sizes, assorted diagnoses . . . , differing types of antidepressant therapies,” and different study timeframes. *Id.* at 6-7. In addition, the authors observed that one “key limitation to the

general study of [TRD] is the lack of a validated and universally accepted definition of treatment resistance.” *Id.* at 7. They suggested that “a general research model is needed to meet the dual goals of elucidating the mechanism of action of VNS therapy and improving clinical outcomes[]” and posed several questions for future preclinical and clinical research. *Id.* at 7-8.

EXHIBIT 49: *Marangell, L.B., et al. (2007), “Neurostimulation Therapies in Depression: a Review of New Modalities”***

This article reviews published literature regarding the clinical use of VNS, transcranial magnetic stimulation (TMS), and deep brain stimulation (DBS) in patients with psychiatric disorders, with a particular focus on patients with TRD. Based on their review of the literature, the authors found that long-term use of VNS therapy for TRD patients is well-tolerated and may improve the course of depressive symptoms for these patients. AP Ex. 49, at 2-3. The authors noted, however, that there were “[f]ew data sets” containing “longitudinal data on patients with severe treatment-resistant affective disorders, making the open long-term results [of studies like the D-01 pilot] difficult to interpret.” *Id.* at 3. The authors indicated that the D-02/D-04 was intended to address this shortcoming and that while that study’s results “support the benefit of adjunctive VNS therapy for patients with TRD compared to TAU, it is important to note that [the D-02/D-04] is a non-randomized comparison.” *Id.* The authors stated that “[s]tudies in such severely ill patients are ethically, scientifically and financially challenging.” *Id.* “Nonetheless,” they stated that, “an additional controlled trial, perhaps comparing VNS to best available non-VNS treatment (as opposed to community treatment or sham treatment) would be very useful.” *Id.*

EXHIBIT 50: *Ansari, S., et al. (2007), “Vagus Nerve Stimulation: Indications and Limitations”***

This article reviews published literature regarding the history of VNS and its use in treating patients with epilepsy and depression. The article also reviews a pilot study that assessed whether VNS improves the cognitive function of patients with Alzheimer’s disease. The authors stated that “[p]reliminary data suggest a sustained antidepressant effect [of VNS] in moderately resistant major depression” and that “[f]urther insights into the mechanisms of its action” in treating depression and other disorders “are expected.” AP Ex. 50, at 5. The authors also stated that “[t]echnical issues need to be investigated, such as how to tailor each patient’s individual treatment with respect to stimulation frequency, intensity, and duration.” *Id.* In addition, the authors stated that “implantation of a VNS system is an invasive method and it needs a clear indication every time [it] is applied.” *Id.*

EXHIBIT 51: *Park, M.C., et al. (2007), “Vagus Nerve Stimulation for Depression: Rationale, Anatomical and Physiological Basis of Efficacy and Future Prospects”****

This article reviews published literature regarding the use of VNS to treat TRD. The authors discuss the various rationales for investigating VNS as a possible treatment for TRD (including animal models, neuroimaging studies, demonstrated efficacy as a mood stabilizer, and similarities between ECT and VNS treatments), the anatomical and physiological bases for VNS’s presumed effect, and the clinical studies that have assessed VNS’s safety and efficacy (including the D-01 pilot, D-02 pivotal, and D-02/D-04 comparison studies). Based on their review of the literature, the authors concluded that the “optimal stimulation parameters for antidepressant effects are still unknown.” AP Ex. 51, at 8. The authors cautioned that care should be taken to manage the “expectations of . . . depressed patients for dramatic symptom recovery or even cure from severe psychiatric illness [that] may be fueled by the introduction of new technology and the highly interventional nature of the device implantation surgery.” *Id.* Finally, the authors noted that “ongoing preclinical and clinical studies of VNS should further refine the role of VNS in the treatment of TRD.” *Id.*

EXHIBIT 52: *Kennedy, S., et al. (2007), “Treatment Resistant Depression – Advances in Somatic Therapies”****

This article reviews evidence for the use of nonpharmacological ECT, magnetic seizure therapy (MST), repetitive transcranial magnetic stimulation (rTMS), VNS, and deep brain stimulation (DBS) in treating TRD. Regarding VNS therapy, the authors noted that although some studies found evidence of VNS’s long-term efficacy for TRD, “*it is unclear whether the long-term benefits should be attributed to VNS or to the concomitant medication changes that were permitted during the follow-up periods in these studies.*” AP Ex. 52, at 5 (italics added). The authors noted, however, that findings of a neurobiological study “support[] consistent clinical observations that the antidepressant efficacy of VNS demonstrates an extended latency before becoming clinically effective.” *Id.* The authors concluded that “[f]urther work needs to be done with respect to predictors of response to VNS in TRD.” *Id.* (italics added). And “[g]iven that VNS does not appear to have robust acute antidepressant effects,” said the authors, “the most appropriate place of VNS in the therapeutic armamentarium of depression remains to be determined.” *Id.*

EXHIBIT 53: *Greden, J. (2001), “The Burden of Disease for Treatment-Resistant Depression”*

This article does not address VNS therapy but instead assesses the global consequences (or burden) of TRD in terms of two measures: years lived with disability (YLD); and disability-adjusted life years (DALY). The author observed that “[i]nvestigators

operationally define treatment-resistant depression in various ways . . . [and] [s]ome clinical studies combine one or more of these definitions.” AP Ex. 53, at 1. The author further stated that “[e]ach definition unfortunately is confounded by innate variability, such as differences in the initial severity of the disorder, standardized rating scales used, [different] versions of a specific rating scale (e.g. the 17-item vs. the 21-item [Hamilton Rating Scale for Depression (HAM-D)], length of time that treatment is given, kinds of treatments, providers of treatments, and determinations of treatment ‘adequacy.’” *Id.* at 1-2. In addition, the author stated that “[w]e need to clarify and standardize operational definitions of treatment-resistant depression” and that “[i]mproved clarity for treatment-resistant depression is needed if we are to better understand and minimize its high burden.” *Id.* at 2, 5.

EXHIBIT 54: *Vonck, K. (2005), “Generator Replacement in Epilepsy Patients Treated with Vagus Nerve Stimulation”*

This article discusses a study that investigated the circumstances of 14 epilepsy patients whose VNS devices were replaced after of the end of the devices’ battery life. The authors concluded: “In patients treated with VNS, seizure control can be lost acutely or gradually following EOES [end of effective stimulation] or EOBL [end of battery life]. From this report, it appears that once seizure control is lost, it cannot always be regained after generator replacement. In order to prevent this avoidable risk, an effort should be made to estimate battery life in individual patients.” AP Ex. 54, at 10.

EXHIBIT 55: *Tatum, W.O., et al. (2004), “Vagus Nerve Stimulation for Pharmacoresistant Epilepsy: Clinical Symptoms with End of Service”*

This article reports the results of a study that evaluated the clinical course of 18 patients with pharmacoresistant epilepsy whose VNS devices were approaching the end of battery life. The authors found: “[O]ur results suggest that the presence of seizure increase or change in seizure pattern in epilepsy patients using VNS may indicate generator battery EOS [end of service]. When symptoms begin within 4 months of estimated EOS, battery function of the earlier VNS models may be clinically insufficient to maintain the existing seizure threshold. If recognized, this clinical change in seizure pattern should prompt clinicians to consider new generator battery reimplantation, if VNS therapy is to be maintained.” AP Ex. 55, at 5.

EXHIBIT 56: *Rakofsky, J., et al. (2009), “Emerging Targets for Antidepressant Therapies”****

This article reviews published research on “novel” therapeutic interventions for depression and their potential clinical applications. The authors focused on three types of interventions: (1) medications that modulate monoaminergic neurotransmission; (2) medications that target nonmonoamine neurotransmitter and neuromodulatory systems;

and (3) devices, such as VNS, that produce focal electrical brain stimulation that targets brain regions implicated in the pathophysiology of depression. The authors found that the “sham-controlled study” of VNS for TRD (that is, the D-02 study) “did not demonstrate significant antidepressant effects after a 10-week treatment course” but that “open-label” studies (such as the D-01 pilot study) “suggested an acute benefit for VNS in TRD patients with longer duration of treatment associated with higher response rates.” *Id.* at 5. Citing the D-02/D-04 comparison and Sackeim studies (AP Ex. 73), the authors further stated that “VNS plus TAU over one year was more effective as compared with TAU alone,” and “the same is true with regard to the maintenance of response over an additional year” *Id.* However, the authors cautioned that “[i]nterpretation of these results [from the longer term studies] is *limited by the lack of randomization, absence of a placebo-controlled group, and differences in samples when comparing the data from the VNS plus TAU maintenance of response study with data from the two-year naturalistic TAU study.*” *Id.* (italics added).

EXHIBIT 57: *September 6, 2006 comment submitted by the American Psychiatric Association (APA) concerning Cyberonics’ July 2006 reconsideration request for National Coverage Determination 160.18(C)*

In this public comment, the APA provided the following recommendation in favor of Medicare coverage of VNS for TRD: “Given the existence of this population of Medicare patients with TRD, who have a clinical history that clearly shows that there are no other medically beneficial treatment alternatives available to them, and given the FDA’s approval of the safety and effectiveness of VNS for the treatment of major depressive disorder, it is our medical opinion that VNS is, as defined by §1862(a)(1)(A) of the Social Security Act, ‘reasonable and necessary’ for the treatment of those Medicare patients with treatment resistant depression.” The APA indicated that this recommendation was based on the views of its “Council on Research, whose members comprise many of the world’s leading psychiatrists and psychiatric researchers” (excluding the views of any Council expert with a conflict of interest).

EXHIBIT 58: *February 9, 2012, CDRH (FDA)/Cyberonics “consensus summary”***

This exhibit provides the following summary of Cyberonics’ conditional premarket approval status following its submittal of the D-21 dosing study:

Safety

- Based on the D-21 dosing study results, FDA believes the rates of adverse events are representative of those provided in the premarket studies for depression.

Effectiveness

- The evidence from the D-21 dosing study does not change the effectiveness or risk-benefit profile known at the time of the approval order.

Moving Forward

- FDA will continue to monitor the safety and effectiveness of VNS for TRD in the literature and adverse event reporting, and will periodically assess the need for additional post-market data collection.
- Based on the available evidence, FDA does not intend to withdraw the indication for depression.
- FDA acknowledged the completion of the D-21 dosing study through a formal response letter dated February 7, 2012 and requested labeling changes to include the final study results with adequate description of study strengths and limitations.
- The second post-approval study for depression, as required in the conditions of approval as a prospective, observational, registry study, will continue as ordered (TRD Registry).

EXHIBIT 59: *Thase, M., et al., Chapter 92, “Treatment Resistant Depression,” in Psychopharmacology: The Fourth Generation of Progress (1995)*

This “chapter reviews the literature on the definition, assessment, and treatment of treatment-resistant depression.” AP Ex. 59, at 3. The chapter begins with a discussion of “common definitions relevant to the concept of treatment resistance,” noting that “[t]he definition of an adequate treatment trial of antidepressant medication has varied widely over the years” and that “substantial variability exists as to the definition of an acceptable treatment response [to TRD].” *Id.* The chapter then discusses “correlates of treatment resistance,” “research strategies” for evaluating treatment efficacy in TRD patients, and various treatment strategies. *Id.* at 4-16. (The article does not discuss VNS therapy.) The authors observed that “[w]hereas mood disorders have generally been viewed as episodic and of good prognosis, a large subset of this population (45% to 50%) can be expected to either be intolerant to or fail to respond to an initial medication trial.” *Id.* at 16. The authors further stated that the “[e]vidence to date” indicates that a “second monotherapy will effectively treat about 40% to 50% of those who have failed with the initial treatment, especially if the second drug has a pharmacological profile distinct from the initial medication.” *Id.* In addition, the authors stated that “[t]he need for randomized controlled studies utilizing innovative designs to identify the preferred

therapies for those patients with varying degrees of treatment resistance is clear. Even now, however, present evidence argues for carefully controlled sequenced medication trials in patients who do not respond satisfactorily to the initial treatment.” Id. (italics added).

EXHIBIT 60: *Greenberg, P., et al. (2004), “Economic Implications of Treatment Resistant Depression among Employees”*

This article describes the results of a health and disability insurance claims analysis of more than 100,000 employees, age 18-65, of a large, national (U.S.) Fortune 500 company in order to assess the cost burden of TRD. AP Ex. 60, at 1, 4-5. The study examined claims data from 1996 through 1998. *Id.* at 4. The study found that the average annual (1998) employer cost of an employee considered “TRD likely” was more twice the annual cost of a depressed employee who was “TRD-unlikely.” *Id.* at 8. The authors concluded: “The TRD-likely MDD employees used significantly more healthcare resources, had significantly more claims for diseases of different body systems, and had significantly higher direct and indirect expenditures than employees classified as TRD-unlikely. The cost differential was primarily due to the much greater costs for hospital inpatient care and pharmaceutical drugs for TRD-likely employees that were approximately three times those of the TRD-unlikely patients.” *Id.* at 10.

EXHIBIT 61: *Cyberonics, Inc., 8-Year Post-Approval Study Report (Treatment-Resistant Depression Registry) and Affidavit of Mark Bunker, Pharm.D. (TRD Registry Study Director)***

This exhibit contains the eight-year (interim) findings of the D-23 registry study requested by the FDA as a condition of premarket approval of the VNS Therapy System for the treatment of TRD. For a description of the study and a summary of its findings, see the discussion under AP Exhibit 10.

EXHIBIT 62: *VNS Therapy® Physician’s Manual; Implantation Procedure (2010)***

EXHIBIT 63: *Request for reconsideration of NCD 160.18 filed by Cyberonics, Inc. with CMS on February 8, 2013***

In this request for reconsideration, Cyberonics cited the guidelines, reports, and published studies contained in AP Exhibits 6, 7, 8, 12, 14, 18, and 19.

EXHIBIT 64: *Harris, E.C., et al. (1997), “Suicide as an Outcome for Mental Disorders”*

This article describes the results of a meta-analysis of medical literature concerning the mortality risk of mental disorders. The article does not discuss VNS therapy or provide any new analysis of data or conclusions regarding VNS therapy. Instead, based on their review of the medical literature, the authors determined a “standardized mortality ratio” (SMR) for 44 different types of mental disorders. AP Ex. 64, at 1, 18-19. The authors concluded that of the 44 disorders that were considered, 36 have significantly higher SMRs for suicide. *Id.*

EXHIBIT 65: *April 26, 2012 FDA letter notifying Cyberonics that it had fulfilled the post-approval study requirement to conduct the D-21 dosing study for the VNS Therapy System***

EXHIBIT 66: *Conway, C., et al. (2012), “Pretreatment Cerebral Metabolic Activity Correlates with Antidepressant Efficacy of Vagus Nerve Stimulation in Treatment-Resistant Major Depression: a Potential Marker for Response?”****

This article reports the results of a neuroimaging study that examined whether pretreatment (pre-VNS) metabolic activity in selected regions of interest (ROI) in the brain is associated with an antidepressant response following 12 months of VNS therapy in 15 patients with TRD. AP Ex. 66, at 1-2. The authors stated that “[t]he mechanism of action of VNS is poorly understood” and that prior “VNS neuroimaging studies [had] not examined associations between pretreatment brain activity and antidepressant response over time.” *Id.* at 2. Here, the authors used positron emission tomography (PET), a neuroimaging technique, to assess cerebral metabolic rate for glucose (CMR_{glu}) in the anterior insular, orbitofrontal, anterior cingulate, and dorsolateral prefrontal cortices. *Id.* CMR_{glu} rates were measured to establish a baseline level and then measured again after 12 months of VNS therapy. *Id.* The authors stated that these results were “suggestive of a potential marker – pretreatment CMR_{glu} in the combined AIC [anterior insular cortex] and OFC [orbitofrontal cortex] regions – for antidepressant response in the TRMD [treatment-resistant major depression] patients considering VNS therapy” and that the results were also “instructive regarding brain regions that may be implicated in the mechanism of action VNS in TRMD.” *Id.* at 4. The authors further stated that their “preliminary” results “suggest the possibility of pre-surgical guidance regarding VNS response likelihood.” *Id.* at 6 (italics added). The authors acknowledged that the “overall sample size was small, and the number of non-responders was smaller, which limited statistical power[,] . . . [and] participants remained on their psychotropic medication

regimen during the study.” *Id.* at 5. In addition, they stated that “[l]arger, controlled studies of the relationships between pre-treatment brain activity and VNS response are warranted” and that “[s]tandardized and reproducible neuroimaging metrics are also needed.” *Id.* at 6 (italics added).

EXHIBIT 67: *Conway, C., et al. (2012), “Brain Blood-Flow Change with Acute Vagus Nerve Stimulation in Treatment-Refractory Major Depressive Disorder”***

This article reports the results of a neuroimaging study using PET to identify changes in regional cerebral blood flow (rCBF) in response to immediate use of VNS therapy in 13 subjects with TRD. AP Ex. 67, at 1, 3. The authors reported that “relative to resting state (*i.e.*, VNS ‘off’), acute VNS was associated with statistically significant rCBF decreases in the left and right lateral orbitofrontal cortex . . . and the left inferior temporal region.” *Id.* at 5. “Significant rCBF increases were found in the dorsal anterior cingulate . . ., left ventrolateral and ventromedial cerebellum, left posterior limb of internal capsule/medical putamen, and right superior temporal gyrus.” *Id.* Post hoc analysis found small-to-moderate, but non-statistically significant, correlations between baseline acute change in rCBF and antidepressant response after 12 months of VNS therapy. *Id.* at 1, 5-6, 7. However, several regions – previously “identified as important in VNS in TRMD” – “demonstrated correlations which exceeded $r=0.20$,” a finding which, the authors said, suggested the possibility of finding a statistically significant correlation with a “higher-powered (larger n) study and greater immediate stimulation parameters.” *Id.* at 7. The authors acknowledged that “[t]here are several limitations to this study[, which] include small sample size [which limited statistical power], low VNS parameter settings at scanning, the presence of concomitant psychotropic medications, not varying the order of the stimulation sequences, and limited spatial resolution of the PET scans.” *Id.* at 7 (italics added). The authors also indicated that “to decrease the potential for confounding brought about by subject awareness of the delivery order of ‘on’ and ‘off’ stimulations, as well as decreasing anxiety/novelty of the stimulus, a randomized ordering of ‘on’ and ‘off’ stimulation patterns would have been preferable.” *Id.* Finally, the authors stated that “[f]uture research is needed to generalize these findings to larger [TRD] samples and to determine whether VNS-induced brain changes are prospectively associated with VNS antidepressant response.” *Id.* (italics added).

EXHIBIT 68: *May 28, 2013 Cyberonics press release announcing that it had received a letter from CMS declining the company’s request to reconsider the May 2007 NCD for TRD***

EXHIBIT 69: *Redacted Qualified Independent Contractor reconsideration decision (2012) which found that “Medicare does not consider vagus nerve stimulators [to be] reasonable and necessary when used in the treatment of resistant depression; this includes the related service of electronic analysis of the implanted neurostimulator pulse generator system.” AP Ex. 69, at 5.***

EXHIBIT 70: *Congressional correspondence dated October 25, 2013 and several posts to www.vnstherapy.wordpress.com***

EXHIBIT 71: *November 26, 2013 FDA letter approving Cyberonics’ premarket approval application (PMA) supplement, which requested approval for a labeling update to include the results of the D-21 post-approval study***

EXHIBIT 72: *Redacted e-mails regarding requests for Medicare coverage of battery replacement for an implanted VNS device (2013)***

EXHIBIT 73: *Sackeim, H.A., et al. (2007), “Durability of Antidepressant Response to Vagus Nerve Stimulation (VNS)”*

This article reports the results of a study that is discussed in section IV.B.1 of the body of the decision.

EXHIBIT 74: *Reserved by the Aggrieved Parties*

EXHIBIT 75: *Affidavit of John Rush, M.D.(2014)***

Dr. Rush’s affidavit is discussed in section V.C.1 of the main body of the decision.

EXHIBIT 76: *Affidavit of Darin Dougherty, M.D. (2014)**
Affidavit of Charles Conway, M.D. (2014)***

Dr. Dougherty is director of the Division of Neurotherapeutics, Department of Psychiatry at Massachusetts General Hospital and Associate Professor of Psychiatry at Harvard Medical School. See AP Ex. 9, at 5. Dr. Conway is Associate Professor of Psychiatry and Director of the Treatment-Resistant Depression Clinic at the Washington University in St. Louis. See AP Ex. 9, at 3.

These physicians state that they have treated patients with TRD for many years (more than 20 years in Dr. Dougherty's case, and more than 14 in Dr. Conway's). They both further state that "[s]ince 2007, the peer-reviewed literature and registry data supporting vagus nerve stimulation . . . has improved significantly." AP Ex. 76, at 1 (¶ 3) and 2 ¶ (3).

The physicians assert that they submitted reconsideration requests concerning NCD 160.18(C) in May 2013. About those requests, the physicians state:

- They have not received "a written response from CMS, either by hard copy or email, to [their] request[s] for reconsideration of NCD 160.18."
- CMS has never "advised [them], either orally or in writing, that [their] reconsideration request[s] contained insufficient information to warrant a reconsideration of NCD 160.18."
- "Further, CMS never advised [them] that the evidence that [they] submitted, coupled with the current literature, was insufficient to warrant a reconsideration."

AP Ex. 76, at 1 (¶¶ 7-9) and 2 (¶¶ 7-9). Dr. Dougherty states that in support of his reconsideration request, he submitted a "review of the peer-reviewed literature describing the various treatments for treatment-resistant depression, including VNS." AP Ex. 76, at 1 (¶ 5). He further states that "this review," along with "the prior existing peer-reviewed literature registry data and FDA approval, clearly demonstrate the effectiveness and role VNS therapy has for patients with treatment resistant depression." *Id.* (¶ 6).

Dr. Conway states that in support of his reconsideration request, he submitted "supporting documentation showing the physiological changes (as demonstrated by brain neuroimaging data) that occur in the brains of depressed patients treated with vagus nerve stimulation." AP Ex. 76, at 2 (¶ 5). He further states that this "objective" evidence, "in view of the existing peer-reviewed literature, registry data, and FDA approval, clearly demonstrates the effectiveness of VNS therapy for patients with treatment resistant depression." *Id.* (¶ 6).

EXHIBIT 77: *Screenshots of Microsoft Word file creation information (2014)***