

Public Comments Received through December 21, 2011

Date: November 23, 2011 Submitted by: David G. Brock, M.D.

[Note: emphasis author's own]

I am providing in this email information for the Public Meeting of New England CEPAC regarding NeuroStar TMS Therapy, an FDA-cleared treatment for major depressive disorder. The attached Medical Technology Dossier provides a detailed summary of the available data, analyzed in the context of standard evidence-based criteria.

In 2008, the NeuroStar TMS Therapy system (Neuronetics, Inc.) received FDA clearance for the treatment of adult patients with Major Depressive Disorder (MDD) who have failed to receive satisfactory improvement from one prior antidepressant medication at or above the minimal effective dose and duration in the current episode. TMS (transcranial magnetic stimulation) is a noninvasive, non-systemic therapy that uses pulsed magnetic fields to induce an electric current in the brain that, when focused to the left prefrontal cortex which an area of the brain involved in mood regulation, results in localized neuronal depolarization and beneficial effects on the symptoms of depression. When used as an antidepressant treatment, TMS produces clinical benefit without the side effects typical of drug therapy. TMS is distinct from electroconvulsive therapy (ECT), which induces a generalized motor convulsion, requires general anesthesia and is associated with significant morbidity. In contrast, TMS is an outpatient procedure that requires no anesthesia or seizure induction and is not associated with the significant side effects of ECT. The most common medical risk associated with the use of TMS is pain or discomfort at the site of TMS application and the rare risk of inadvertent seizure induction, occurring with an incidence of <0.001% in clinical practice.

FDA clearance of the NeuroStar TMS Therapy system was based on a sham controlled randomized study that showed that NeuroStar TMS is a safe and effective treatment for certain patients with major depression. Over the past two years additional studies have been published that further validate the findings of this FDA registration study. These publications include:

• A second similarly designed randomized study whose results further validate the results of the NeuroStar TMS registration trial (George 2010). This independent study was sponsored by the NIMH. There are now two Level 1 studies reporting the safety and effectiveness of NeuroStar TMS Therapy for the treatment of major depression.

• A number of meta-analyses of TMS have been published, with the most recent and complete published in 2010 (Slotema 2010). This meta-analysis reported an effect size of 0.55 (95% confidence interval 0.38-0.72) for the use of TMS in acute depression and concluded that **TMS** "*deserves a place in the standard toolbox of psychiatric treatment methods.*"

• Demitrack (2009) published an indirect comparison of TMS Therapy and drug therapy by comparing clinical outcomes data from registration trials of TMS and antidepressant drug therapy. This comparison is negatively biased against TMS, because TMS is indicated for patients who have failed a prior adequate trial of antidepressant drug therapy, while the drug registration trials focus on first line treatment of depression. **Despite this negative bias, TMS appears to be at least equivalent to antidepressant drug therapy in terms of efficacy with fewer and non-systemic side effects.**

• The clinical use of NeuroStar TMS Therapy since its FDA clearance has steadily grown and now encompasses over 325 psychiatric practices and providing 100,000 treatments to greater than 3000 patients.

This growing body of literature and evidence of clinical use supports the medical necessity of TMS Therapy in patients who have failed an initial trial of antidepressant drug therapy.

Thank you for the opportunity to provide you with further background information on TMS and the NeuroStar TMS Therapy system, in particular. I hope this information is helpful to you in your deliberation at the Public Meeting of New England CEPAC.

I look forward to the opportunity to present in person at the Public Meeting to review this material, and to address any questions that may remain.

In the meantime, please let me know if there are any additional questions that you have on the information that I have provided in this communication.

Sincerely, David G. Brock, M.D. Medical Director Neuronetics, Inc.

Date: December 8, 2011 Submitted by: NH Psychiatric Society

Thank you for inviting comment on reimbursement policy as part of the New England Comparative Effectiveness Public Advisory Council process.

Treatment-resistant depression (TRD) is a prevalent, disabling and costly condition affecting a substantial percentage of patients diagnosed with Major Depressive Disorder or a Bipolar Disorder. Members of the NH Psychiatric Society treat patients with TRD routinely, and individual comment, as well as expert guidance, was sought in preparing this document.

Introductory remarks

Before considering the individual treatments reviewed in the report, we provide several comments on the process and assumptions.

First, evidence-based practice is a highly laudable goal and we should continue to strive for this. However, it must be recognized that the absence of (high quality) evidence is not evidence of absence (of effectiveness). This is especially important to consider when assessing the effectiveness of treatments in use long before the current standard of the large, randomized, controlled trial was adopted as the "best evidence". For certain of these treatments (such as electroconvulsive therapy and psychoanalysis), the likelihood of such high-quality trials being conducted in the current era is low. However, in lieu of "best evidence", there are numerous converging datasets (including, importantly, decades of anecdotal experience) that support the continued use of these interventions.

Second, it should be recognized that the treatment of depression has two distinct phases: (1) acute, i.e., bringing a patient out of a depressive episode; and (2) maintenance, i.e., preventing relapse/recurrence. The majority of treatment studies in depression have focused on acute treatment with little attention to maintenance treatment. As more studies have investigated maintenance treatment, we have discovered that our current interventions may not be very effective for this. However, it may indeed be that treatments for an acute depressive episode may not be ideal for maintenance therapy. Similar to the treatment of epilepsy, certain interventions may play a key role in the acute management of depression while others are better for maintenance. To expect a treatment to be effective in both treatment phases may be unrealistic.

Third, the ICER report's cost analysis does not account for the fact that major depressive disorder greatly increases the costs of caring for comorbid medical disorders, in some cases on the order of doubling costs. The ICER report points out TRD complicates the management and worsens the severity of conditions such as HIV, Parkinson's disease, and cancer, and is an independent risk factor for Type 2 diabetes and coronary heart disease.

Lastly, the ICER report's assumption of the rate of usage of both ECT and TMS of 10% of patients receiving treatment in Scenario 1 and 20% in Scenario 2 likely both overestimate the percent of patients who will receive both these treatments. Obstacles to treatment include both the limited availability of

ECT/TMS services offered in the community, as well as stigma around receiving treatment for depression in general, and these procedures in particular.

Comments on specific treatments

Electroconvulsive therapy (ECT). Introduced in 1938, ECT continues to be the most effective treatment for an acute depressive episode with remission rates up to 90% in patients with non-resistant depression and at least 50%-70% in patients with highly treatment-resistant depression. ECT is especially effective in patients with severe suicidal ideation, psychotic depression, and catatonia. Downsides of ECT include cognitive and other side effects (though most patients tolerate the treatment very well) and a relatively high relapse rate (as high as 50%-75% in patients with TRD, though the relapse rate following successful medication treatment in TRD patients is equally high). In sum, ECT is, and should remain, an important treatment for an acute depressive episode. Research to identify better maintenance treatments for TRD is still needed.

Vagus nerve stimulation (VNS). VNS has shown no statistically significant benefit for treating depression acutely. Therefore, VNS is not intended for only 10 weeks implantation. Instead, open-label data suggest that VNS may have longer-term antidepressant effects, though these data are difficult to interpret. The long-term relapse rate following successful VNS is also unclear and may be as high as 50% within the first 1-2 years.

Transcranial magnetic stimulation (TMS). Repetitive TMS has consistently demonstrated statistically significant antidepressant effects as described in numerous meta-analyses and two large, sham-controlled trials. The absolute response and remission rates in patients with TRD are relatively low, though not much different from these rates in similarly resistant patients treated with pharmacotherapy (cf. STARD data). Importantly, the published data suggest that TMS may not be as effective in patients with a higher degree of treatment resistance.

In considering the cost-effectiveness of TMS, the comparison to "usual care" may be misleading. An assumption in the model is that all patients continued on usual care regardless of the nonpharmacologic treatment employed. However, in clinical practice, TMS is often used *instead of* an adjunctive treatment. Therefore, the best cost comparison for the use of TMS would be usual care *plus* another medication and/or psychotherapy (e.g., an atypical antipsychotic, such as aripriprazole, or cognitive-behavioral therapy).

It is important to note that the current FDA approval of TMS does not take into consideration specific groups for whom TMS might be reasonably effective when used off-label. These might include patients that do not tolerate medications (and thus fail to achieve and adequate dose for an adequate duration), peri-partum and post-partum women who are reluctant to take antidepressant medications.

Cognitive behavioral therapy (CBT) and Interpersonal Therapy (IPT) are indicated for mild to moderate depression, and for severe depression a combination with pharmacotherapy is recommended by the American Psychiatric Society Practice Guidelines for Major Depressive Disorder.

Policy Implications

- 1. We call attention to certain limitations of the methodology of this analysis, which would tend to underestimate the cost of usual care.
- 2. Electroconvulsive therapy is a well-established efficacious treatment for TRD, and is covered by local insurance providers. It should continue to be reimbursed for both inpatient and outpatient management of TRD.
- Transcranial Magnetic Stimulation has been proven effective in controlled trials but is likely less efficacious than electroconvulsive therapy. It is part of the American Psychiatric Association's algorithm for treatment of Major Depressive Disorder. It should be considered for coverage in New England.
- 4. If the Advisory Council does not find TMS cost effective for all patients with TRD, a procedure should be made available to make it available to those in certain sub-populations for whom it may be particularly suitable, such as pregnant or nursing women, and patients who do not tolerate medications or ECT.
- 5. The literature on VNS is less robust than that on TMS or ECT.
- 6. CBT and IPT in combination with pharmacotherapy should be reimbursed for treatment of TRD, in accord with national guidelines.

Respectfully Submitted,

Jeffrey C. Fetter, MD President New Hampshire Psychiatric Society

Paul Holzheimer, MD Professor of Psychiatry Dartmouth Medical School Expert Consultant to NHPS

Executive Council of NH Psychiatric Society

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Sarah K. Emond, MPP Chief Operating Officer Institute for Clinical and Economic Review 101 Merrimac Street, 10th Floor Boston, MA 02114

RE: Written comments regarding CEPAC Public Meeting - Dec 9, 2011

Dear Ms. Emond,

Thank you very much for allowing me the opportunity to present to the CEPAC Public Advisory Council on transcranial magnetic stimulation for the treatment of patients with major depression. In addition to some general comments on TMS and the AHRQ report, I specifically address two issues that were raised by the CEPAC reviewers, namely the issues of patient blinding in the Neuronetics randomized clinical controlled trial, and the analysis of the Moog (2008) article.

The primary conclusions of the Agency for Healthcare Research and Quality Comparative Effectiveness Report on Non-Pharmacologic Treatments for Treatment Resistant Depression regarding the strength of evidence for efficacy of TMS are among the most definitive and positive statements to date. Given that the AHRQ review is conducted to a rigorous and independent standard of scientific integrity, and peer-review, these conclusions are particularly noteworthy.

Overall, the Panel concluded that there is a substantial and well-replicated body of evidence from randomized, sham-controlled clinical trials that provide a "high strength of evidence", their words, that TMS produces significantly greater decreases in depression severity, response rate and remission rate when compared to a sham treatment. I specifically highlight the general conclusion articulated in the Overview of Main Findings on Page 155, where the Panel summarizes that in the most stringent subset of studies, for the patients meeting the strict definition of treatment resistant depression:

"Specifically, rTMS averaged a decrease in depressive severity measured by the Hamilton Rating Scale for Depression (HAM-D) of more than 5 points relative to sham control, <u>and this change</u> <u>meets the minimum threshold of the 3-point HAM-D difference that is considered clinically</u> <u>meaningful</u>. Response rates were greater with rTMS than sham (also high strength of evidence); those receiving rTMS were more than three times as likely to achieve a depressive response as patients receiving sham procedure. Finally, rTMS was also more likely to produce remission than the control procedure (moderate strength of evidence); patients receiving rTMS were more than 6 times as likely to achieve remission as those receiving the sham."

What is also notable in this report is that the clinical trial evidence for TMS dwarfs the extant body of evidence for any of the other non-pharmacologic treatments considered, including electroconvulsive therapy, vagal nerve stimulation and psychotherapy, by a wide margin. The data for Tier 1 studies of TMS was comprised of 15 clinical trials involving nearly five hundred patients. By comparison, there were <u>no</u> eligible studies of ECT compared to a sham control condition, and only one fair trial of ECT compared head-to-head with TMS, which failed to find a difference in outcome between these two treatments (see Table A, Page ES-4 of the Executive Summary).

I would like to correct a misinterpretation of the NeuroStar TMS development program as presented during the CEPAC review of the AHRQ report. The initial randomized clinical trial (O'Reardon, 2007) was a double-blind sham controlled trial, with both the TMS treater, and the patient blinded. In addition, the clinical study ratings were performed by other blinded personnel who did not have access to the treatment session. As noted in the O'Reardon article: "Scalp discomfort with active TMS did not correlate with treatment outcome. Thus, unblinding of the active condition is an unlikely explanation for the therapeutic advantage of active TMS."

While there have been several random-assignment, open-label studies that have directly compared the clinical outcomes of patients assigned to either TMS or ECT for treatment of severe major depression, these studies were generally small in size, often performed at one investigative site, and usually diagnostically heterogeneous. The TMS treatment protocols used in these studies are therapeutically suboptimal with regard the to both TMS treatment parameters used, for example, number of pulses per treatment session, as well as employing limited duration treatment courses. None of these studies were performed using the FDA cleared NeuroStar system. The Moog (2008) article cited by the CEPAC review team during their presentation is an example of this problem, as it was a single site study, performed between 2002-2004, administering less than 10% of the number of TMS pulses employed in the Neuronetics' clinical trials, was of limited treatment duration, and is confounded by concomitant medication administration.

For most patients, the choice of TMS Therapy would come well in advance of more invasive therapeutic options such as ECT. Based on clinical trial evidence of safety and effectiveness TMS Therapy should also be considered in advance of more complex medication combination or augmentation approaches such as lithium or thyroid hormone that are not FDA approved for use in such patients.

I believe the conclusions arrived at by the AHRQ Panel are extremely significant. Indeed, they are consistent with the prevailing conclusions in the broader scientific literature regarding the safety and efficacy of the use of TMS in pharmacoresistant major depression.

Sincerely,

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David G. Brock, MD, CIP Medical Director Neuronetics, Inc.

Patricia R. Recupero, J.D., M.D.

Clinical Professor of Psychiatry, Brown University Executive Vice President for Behavioral Health, Care New England Health System President/CEO, Butler Hospital

December 21st 2011

Sarah K. Emond, MPP Chief Operating Officer Institute for Clinical and Economic Review 101 Merrimac Street, 10th Floor Boston, MA 02114 email: <u>info@icer-review.org</u>

RE: Public Comment from Butler Hospital regarding ICER draft supplementary report "Nonpharmacologic Interventions for Treatment-Resistant Depression"

Dear Ms. Emond and Members of the New England Comparative Effectiveness Public Advisory . (CEPAC) Council,

Transcranial Magnetic Stimulation (TMS) Therapy is currently offered by Butler Hospital to patients in Rhode Island and surrounding areas. Since our TMS clinic opened in January of 2009, we have delivered over 2000 treatments and observed excellent rates of response and remission among patients whose symptoms of major depression were not relieved by antidepressant medications. All of the patients treated with TMS in our facility had undertaken psychotherapy and numerous past trials of medications; about one third had already tried ECT, several had contraindications for ECT, and many found the risk/benefit ratio for ECT to be unfavorable or unacceptable. Despite the wellknown health consequences of long-term use of antipsychotic medications (such as weight gain, glucose intolerance, and risk for movement disorders) and the fact that none of the patients treated with TMS at Butler Hospital had psychotic symptoms, nearly all of them had undertaken past treatment trials with antipsychotic medications. Antipsychotic medications are the only class of drugs specifically studied in, and FDA-approved for, treatment resistant depression. We have observed that patients responding to TMS are able to continue working, reduce or avoid use of medications and hospital stays, and become more fully engaged in health-promoting behaviors such as exercise and stress management. It may be useful for CEPAC members to be aware that in our experience, the majority of insurance reimbursement or pre-authorization requests submitted through all levels of the appeals process are ultimately approved for payor support by external reviewers or adjudicators. The actions of physician reviewers and judges who overturn initial coverage denials and ultimately determine "TMS is medically necessary" for our patients reflect widespread support for the treatment, despite the current paucity of national TMS coverage policies. In the absence of formal coverage policies, the pursuit of health insurance coverage for TMS is a time-consuming, complicated, and expensive undertaking for severely depressed patients and their advocates; unfortunately many who need it the most do not have the resources to pursue it.



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Our review of the published evidence base as summarized by the Agency for Healthcare Research and Quality (AHRQ) report entitled "Nonpharmacologic Interventions for Treatment-Resistant Depression in Adults" confirms that TMS is a safe and efficacious option for patients with treatment-resistant forms of depression. The enormity of the database for the efficacy of TMS, including two recent, multisite, sham-controlled clinical trials, should be emphasized; we believe the evidence for TMS is now substantial and convincing. We have found TMS to be an important and valuable new treatment that improves the options and outcomes for the patients we serve. In light of the compelling scientific evidence and our institution's experience to date, the Butler Hospital clinicians whose signatures appear below encourage the CEPAC Council to develop a final report that accurately and favorably summarizes the benefit TMS therapy brings to the arena of mental health care. We support an immediate recommendation for federal and commercial health insurers to implement coverage policies for TMS so individuals with TRD in our community who have few or no viable options to battle a severe and disabling condition may access this new treatment.

Sineerely Yours,

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December 21, 2011

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RE: Public Comment from Butler Hospital regarding ICER draft supplementary report "Nonpharmacologic Interventions for Treatment-Resistant Depression"

December 21, 2011

Dear Ms. Emond and Members of the New England Comparative Effectiveness Public Advisory (CEPAC) Council,

In addition to the letter submitted by the physician staff of Butler Hospital, I have several additional comments regarding the recent AHRQ review and in response to the New England Comparative Effectiveness Public Advisory Council (CEPAC) public meeting held on Friday December 9, 2011.

I recognize that this was only the second public CEPAC meeting so in many ways, the process which was highlighted in the December 9th meeting reflects an important and imperfect "work in progress." The initial portion of the program, which I did not attend in full, was related to the CEPAC interpretation of the AHRQ document. However, a number of observations by myself and by others in attendance suggested that most of the panel members had not fully read or digested the CEPAC report or the AHRQ report. Several comments made by panel members highlighted the fact that understanding about major depression in general (features describing course of illness over time, standard rating scores, etc.) and specifically about Treatment Resistant Depression (TRD) was lacking or suboptimal for the task at hand. Unfortunately, most panel members seemed unfamiliar with STAR*D, the largest study of TRD outcomes, which is unequivocally the most relevant source for understanding what happens to patients with TRD in naturalistic treatment setting when they get the best-possible delivery of current standard-of-care therapy for TRD.

Although the AHRQ report evaluated several important non-pharmacologic treatments for TRD, it seems the CEPAC session really became a review of Transcranial Magnetc Stimulation (TMS); in essence, an analysis of a meta-analysis. For reasons that are not entirely clear to those

who attended or read the publicly-posted documents, there was almost no substantial discussion of ECT or VNS at the panel meeting.

The CEPAC discussion focused on several perceived issues that have been raised by previous TEC reviews of TMS research data, e.g. criticism that many of the studies contained small sample sizes, were conducted at single sites, contained diagnostically heterogeneous populations, there were a variety of different TMS treatment parameters used, and emphasizing that there is an apparent lack of support from payers, and there appears to be a "lukewarm" reception or lack of acceptance by some of the higher profile technology review agencies or professional practice guidelines.

Several comments and points made during the meeting merit clarification. The main data slide CEPAC presented contained an incorrect interpretation of the data in the O'Reardon et al (2007) paper, with some blurring of research methods from study 101 with those used in studies 102 and 103. During the CEPAC presentation, it was stated that participants or others in the randomized controlled trial (RCT; described in the O'Reardon et al 2007 report) were unblinded at time points after week 4 of the acute phase, when in fact the study blind was maintained through the completion of the taper phase at week 9. Also, a statement was made suggesting that the clinical raters in the study were unblinded, but that is also not accurate. Please be aware that there is ample evidence to the contrary, that the study blinding integrity was adequately maintained in the randomized controlled trial. CEPAC staff called out the differences in baseline depression severity between treatment groups, pointing to subsequent statistical correction as a potential confounding flaw in the study analysis. However, consultation with a statistician or more discussion with an expert in clinical trials methodology prior to the meeting would likely have put such concerns to rest and helped participants to achieve a more accurate and informed summary assessment of the data. The CEPAC panel referenced a published report a TMS study in 59 patients by Mogg (2008) which was excluded by AHRQ, asserting that it should be included, yet there was no discussion of the reasons for the AHRQ exclusion of the Mogg study, or the fact that it was not a sham-controlled trial, or acknowledgement of the fact that it employed subtherapeutic TMS treatment parameters and treatment duration.

CEPAC proposed a cost effectiveness model that seemed to seriously disadvantage TMS, but to me the model reflects more misunderstanding about the current standard of care and outcomes for patients with TRD. The model assumed that if patients failed pharmacotherapy, they just continued on with treatment as usual, without incurring any increased cost or worsening QALY, and that these TRD patients without successful therapy remained employed. The final QALY gained by TMS over care as usual over 5 years was 0.02 in the CEPAC model. Several of the CEPAC panel members apparently highlighted this methodologic concern at the meeting and it was acknowledged that area merits further consideration. I urge you to consult the necessary experts as you further deliberate this analysis, since cost effectiveness is the most critical consideration for healthcare policy decisions in a era of scarce and decreasing resources.

The panel then voted on key questions, and responses were tallied. Many panel members indicated the questions did not fit well with the various considerations about current standard of care, especially in light of the differences between the treatments and the patients who receive them.

<u>Comparative Clinical Effectiveness: For patients who have TRD, is the evidence adequate to demonstrate that rTMS provides a net health benefit equivalent or superior to the following comparators:</u>

1. Usual care (i.e., general supportive psychotherapy with or without continued use of antidepressant medication)? **(10 yes, 5 no)**

a. If yes, then subsequent questions posed:

(i.) Is rTMS equivalent (5 yes) or superior (5 yes) to usual care?

(*ii*.) Are there standards for provider training, outcome measures, and optimal treatment duration that should also be considered? (**5 no**),

b. If no, then subsequent question posed: *is this due to:*

(*i.*) *Inadequate evidence with which to judge comparative net health benefit?* **(5 endorsed)** *or* (*ii.*) *Adequate evidence of an inferior net health benefit?* **(0 endorsed)**

2. *Electroconvulsive therapy* (*ECT*)? (9 yes, 6 no, 1 abstain)

a. If yes (9 yes), then subsequent question posed:

(*i.*) Is rTMS equivalent **to ECT? (9)** or superior to ECT? **(0)** (*ii*). Are there standards for provider training, outcome measures, and optimal treatment duration that should also be considered?

b. If no (6 no), then subsequent question posed: is this due to

(*i.*) *Inadequate evidence with which to judge comparative net health benefit?* **(6 endorsed)** *or* (*ii.*) *Adequate evidence of an inferior net health benefit?* **(0 endorsed)**

Based on reimbursement levels provided with this report, would you judge the comparative value of rTMS to be: 1) high value; 2) reasonable value; or 3) low value for the following comparisons: 1.) rTMS vs. usual care? 2.) rTMS vs. ECT?

On this last question question, the panel was divided with the comparative value split between "reasonable" and "low," with one noting "high" value. I found the voting section of the CEPAC meeting to be interesting, because it did seem that a majority favorably supported TMS when the questions posed contrasted TMS against currently available treatments. However, during the subsequent discussion, panel members raised multiple concerns, including the need for longer term follow up data (12 months to 18 months), better primary data for efficacy, a national post marketing registry, and guidelines on how to decide which patients are appropriate for TMS. For ECT, a national registry was also recommended.

While all of the scientists studying TRD treatments, and the clinicians rendering treatments each day to TRD patients also embrace a large "wish-list" as was suggested for future TMS data collection and future TMS research trial designs, I would like to remind the CEPAC panel that we also are required to make decisions each day with the data we have available. As a physician and researcher, I am keenly aware of the merits of future scientific inquiry into many important questions about TMS for TRD as well as about treatments for other common and disabling medical and psychiatric disorders. However as a researcher who is also a taxpayer and a healthcare consumer, I am likewise aware that we don't live and work in a world of unlimited resources. It's rarely the case that someone has conducted the ideal scientific experiment to generate the ideal data about any health intervention. As a physician, I must treat my TRD patients with the treatments available to us today, making the best decisions possible based on the available evidence today.

I hope you will work as a panel to highlight and correct your misreading of the methodologic integrity of the O'Reardon (2007) report, and that such effort will be clear in the public record for this important process. I believe you can obtain substantial evidence about the adequacy of

blinding procedures through resources readily available and in the public domain (see, for example, results of analyses requested by FDA of the study sponsor Neuronetics, available on the FDA 2007 Panel Meeting website). I should point out that the results from the O'Reardon study are consistent with findings produced by nearly all other studies with TMS-naïve populations, i.e., the ability of a patient to guess correct treatment assignment is no better than chance. Furthermore, the OPT-TMS study (funded by NIH without involvement of the TMS device manufacturer) employed a much more elaborate and successful active sham blinding methodology, and arrived at quantitatively identical results to the Neuronetics study.

To achieve it's stated goals, the CEPAC panel should receive an updated health economic model that uses a more appropriate treatment-as-usual (TAU) comparator condition and assumes an appropriate larger incremental benefit of TMS vs TAU as supported by the data. This would likely to lead to a substantially lower estimate of the cost per QALY than is currently reported. The panelists should be wholly familiar with the fact that the addition of atypical antipsychotic medications to antidepressant therapy comprises the standard-of-care for most TRD patients today, based on the robust data generated by recent clinical trials with drugs in that pharmacological class. Long-term side effects associated with many medications used for TRD include chronic and expensive health problems such as obesity, diabetes and hypertension.

Finally, the relatively large size of the current database for the efficacy of TMS, including two recent, multisite, sham-controlled clinical trials, should be reiterated. It appeared that the CEPAC panel generally agreed the evidence for TMS is substantial and convincing. Despite these considerations, a number of CEPAC panelists appeared perplexed as to how the Payor panel members could arrive at diametrically opposite conclusions to those summarized by the AHRQ experts and by the voting members of CEPAC. To me, this puzzling refusal of the Payors to acknowledge the maturity and replicated nature of the evidence base for TMS should be noted and appropriately challenged. Recommendations about desirable future research studies are much appreciated in the appropriate context, but do not contribute substantively to the task at hand: development of "objective" guidance on implementation of AHRQ reviews.

Thank you for consideration of my comments, and for permitting me to participate in this process.

Sincerely,

Linda L Carpenter, M.D.