The New England Comparative Effectiveness Public Advisory Council

Public Meeting – December 9, 2011

Nonpharmacologic Interventions for Treatment-Resistant Depression: Supplementary Data and Analyses to the Comparative Effectiveness Review of the Agency for Healthcare Research and Quality

FINAL MEETING REPORT – December 22, 2011

Completed by:

The Institute for Clinical and Economic Review

ICER
INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

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Introduction

To make informed healthcare decisions, patients, clinicians, and policymakers need to consider many different kinds of information. Rigorous evidence on the comparative clinical risks and benefits of alternative care options is always important; but along with this information, decision-makers must integrate other considerations. Patients and clinicians must weigh patients' values and individual clinical needs. Payers and other policymakers must integrate information about current patterns of utilization, and the impact of any new policy on access, equity, and the overall functioning of systems of care. All decision-makers, at one level or another, must also consider the costs of care, and make judgments about how to gain the best value for every healthcare dollar.

The goal of this initiative is to provide a forum in which all these different strands of evidence, information, and public and private values can be discussed together, in a public and transparent process. Initially funded by a three-year grant from the federal Agency for Healthcare Research and Quality (AHRQ), and backed by a consortium of New England state policy makers, the mission of the New England Comparative Effectiveness Public Advisory Council (CEPAC) is to provide objective, independent guidance on how information from adapted AHRQ evidence reviews can best be used across New England to improve the quality and value of health care services. CEPAC is an independent body of 19 members, composed of clinicians and patient or public representatives from each New England state with skills in the interpretation and application of medical evidence in health care delivery. Representatives of state public health programs and of regional private payers are included as ex-officio members of CEPAC. The latest information on the project, including guidelines for submitting public comments, is available online: cepac.icer-review.org.

The Institute for Clinical and Economic Review (ICER) is managing CEPAC and is responsible for developing adaptations of AHRQ reviews for CEPAC consideration. ICER is an academic research group based at the Massachusetts General Hospital's Institute for Technology Assessment. ICER's mission is to lead innovation in comparative effectiveness research through methods that integrate evaluations of clinical benefit and economic value. By working collaboratively with patients, clinicians, manufacturers, insurers and other healthcare stakeholders, ICER develops tools to support patient decisions and medical policy that share the goals of empowering patients and improving the value of healthcare services. More information about ICER is available at www.icer-review.org.

ICER has produced this set of complementary analyses to provide CEPAC with information relevant to clinical and policy decision-makers in New England. This supplement is not meant to revisit the core scientific findings and conclusions of the AHRQ review on "Nonpharmacologic Interventions for Treatment-Resistant Depression in Adults" but is intended to supplement those findings with: 1) updated information on the patient management options for treatment-resistant depression published since the AHRQ review; 2) regional and national data on prevalence, utilization, and existing clinical guidelines as well as payer coverage policies; and 3) the results of budgetary impact and cost-effectiveness analyses developed to support discussion of the comparative value of different management options. This report is part of an experiment in enhancing the use of evidence in practice and policy, and comments and suggestions to improve the work are welcome.

1. Background

1.1 The Condition

Major depressive disorder (MDD) is a common and debilitating condition; on an annual basis, it is estimated that nearly 14 million Americans will have at least one episode of MDD (Kessler, 2003). The impact of MDD is varied and complex; it has been found to negatively affect physical functioning, quality of life, productivity, and interpersonal relationships, often in an inter-related fashion (Klerman, 1992). MDD is also considered a major risk factor for Type 2 diabetes and coronary heart disease (von Knorring, 1996), and has been found to complicate the management and worsen the severity of many chronic conditions such as HIV/AIDS, Parkinson's disease, and multiple types of cancer (Cassano, 2002).

For many patients, a cornerstone of treatment for MDD is the use of antidepressant medications, such as selective serotonin reuptake inhibitors (SSRIs) and serotonin/norepinephrine reuptake inhibitors (SNRIs), typically in combination with a form of psychotherapy. While medications are effective at reducing depressive symptoms in a significant number of patients, nonresponse to medications is common. The rate of nonresponse to one or more medication attempts has been estimated to range from 30-50% among patients presenting with a first episode of MDD (Cadieux, 1998; Thase, 1997). While definitions of so-called "treatment-resistant" depression (TRD) vary, this generally refers to patients with persistent depression after attempted management with two or more medications.

The heterogeneity of patient populations with MDD, the complexities involved in managing these patients, and the lack of a universally-effective treatment all combine to make MDD one of the most significant contributors to growing healthcare costs. The total burden of depression has been estimated at over $80 billion dollars annually in the US (Greenberg, 2003), nearly two-thirds of which is a consequence of lost work productivity due to depressive symptoms. The burden is most pronounced among patients with TRD. A recent study estimated total annual costs among employees with TRD to be nearly $15,000 per employee, which was more than twofold higher than costs among depressed employees without TRD (Greenberg, 2004). Evaluated costs included direct medical costs and indirect costs such as disability and absenteeism.

Given the failure of repeated treatment efforts to evoke a clinically-significant and lasting response for many patients, along with the costs and system impacts associated with managing these patients, there is significant interest on the part of patients, clinicians, policymakers, and other stakeholders in exploring different management options for TRD. This supplementary report builds on the conclusions of the AHRQ review by: describing recommendations and payer coverage policies for selected nonpharmacologic management options for TRD; identifying any new evidence on these options published since the AHRQ review; and finally, developing a simulation model to use findings from the AHRQ review to quantify the potential clinical and economic impact to the New England region of changes in the use of nonpharmacologic therapy for TRD.

1.2 Management Options for TRD

The management options of interest for this evaluation include electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), vagus nerve stimulation (VNS), and two alternative forms of psychotherapy, cognitive-behavioral therapy (CBT), and interpersonal therapy (IPT). These interventions are described in more detail below.

Electroconvulsive Therapy (ECT)

ECT, formerly known as "electroshock therapy", has been available for use in the US for over 70 years, and has been used for depression as well as other psychiatric conditions including schizophrenia, catatonia, and mania (Greenhalgh, 2005). ECT involves passing an electric current through the brain to produce a brief convulsion or seizure. These seizures are thought to produce immediate changes in brain chemistry that reverse symptoms of certain mental illnesses. During the procedure, electrodes are placed at the bifrontal, bilateral, or right unilateral positions on the head. The procedure is performed under general anesthesia. Muscle relaxants also may be used to prevent violent seizures, and a mouth guard may also be used depending on the patient's previous reactions to ECT. The seizures induced by ECT typically last 30-60 seconds each, and are measured by EEG monitoring. The entire procedure lasts approximately 10-15 minutes. A course of ECT typically involves sessions 3 times a week for 2-4 weeks, depending on depressive severity and the patient's tolerance for the procedure (Mayo Clinic, 2011).

Immediate risks of ECT and anesthesia may include nausea, headache, jaw pain, and muscle stiffness and soreness. Patients also frequently report confusion immediately following the procedure, which may last from a few minutes to several hours. Of most concern is memory loss, which may involve periods of time before ECT, during ECT treatment, or even after treatment has stopped (Mayo Clinic, 2011); however, these symptoms appear to dissipate over time (O'Connor, 2003).

Relapse rates greater than 50% after ECT have been reported, particularly among patients without maintenance medication therapy (UK ECT Review Group, 2003). In response to this, some practitioners have recently begun performing "continuation ECT", in which patients receive ECT at a reduced frequency (e.g., once per week, once per month) but for a longer overall treatment duration (i.e., for one year or longer) (van Waarde, 2010).

Because ECT was introduced prior to U.S. Food and Drug Administration (FDA) device regulation, it was not subjected to formal review and approval as a device. It is classified as a high-risk "class III" device, indicating that insufficient information exists to provide reasonable assurance of its safety and effectiveness. Earlier this year, the agency's Neurological Devices Panel advised the FDA that ECT should retain its class III designation, despite calls from the psychiatry community to change this categorization given its longstanding use (Lowry, 2011).

Repetitive Transcranial Magnetic Stimulation (rTMS)

rTMS involves the placement of a small wire coil on the scalp that conducts a varied and powerful electric current through it, creating a magnetic field through the tissues of the head (Wassermann, 1998). The current elicited by the electromagnetic coil is thought to stimulate nerve cells in the region of the brain involved in mood regulation and depression (Walter, 2001).

The procedure is performed in an office setting without anesthesia. Once the coil is placed, the electric current is turned on and off repeatedly at various locations on the head to find the optimal location (a process called "mapping"). When the current is on, a series of loud click or taps can be heard; the patient may be given earplugs to reduce the effects of these clicks. Once the optimal location is found, the physician will increase the magnetic dose until the patient's fingers or hands twitch (known as the "motor threshold") (Mayo Clinic, 2011). This is the dose that will be used for the session. Sessions are typically 40 minutes in length, after which the patient can usually resume normal activities. Treatment is typically administered daily (excluding weekends) for 2-6 weeks (Mayo Clinic, 2011).

Immediate side effects of rTMS include headache or scalp discomfort from the procedure, tingling, spasms, or twitches in the facial muscles, lightheadedness, and hearing discomfort from the procedure noise. Most of these effects are transient and improve throughout the course of treatment (Mayo Clinic, 2011). Rarely, rTMS has been reported to invoke seizures, and may also produce mania in patients with bipolar disorder; hearing loss from procedure noise also has been reported (Belmaker, 2003).

Other forms of electromagnetic therapy have begun to emerge. Recently, a novel coil, known as the "H-coil," has been developed to enable stimulation of deeper brain regions (i.e., "deep TMS") (Rosenberg, 2010). In addition, magnetic seizure therapy (MST) has also been developed, in which magnetic energy is used to induce therapeutic seizures. In contrast to ECT, these seizures are focal and limited to the prefrontal cortex in an attempt to limit any deleterious effects on cognition or memory (Kayser, 2011).

The FDA first approved rTMS in October 2008; it is indicated for the treatment of MDD in adults who have failed to achieve satisfactory improvement from at least one prior antidepressant medication used at or above the minimum effective dose and duration (U.S. FDA, 510(k) documentation, 2008).

Vagus Nerve Stimulation (VNS)

VNS involves the surgical implantation of electrodes around the left vagus nerve and repeated stimulation of the nerve by electrical pulses. Originally studied as a means to reduce seizure activity in patients with epilepsy, the VNS device was found to improve mood and depressive symptoms in these patients (Lulic, 2009).

The procedure involves the implantation of a stopwatch-sized pulse generator in the upper left side of the chest, and guiding of the lead wires under the skin to the neck, where the electrodes are then attached to the left vagus nerve through a second incision. Surgery is done on either an outpatient basis or with an overnight hospital stay. Following recovery from surgery, the pulse generator is switched on during an office visit and programmed. Stimulation is tested at various levels, but typically occurs every 5 minutes, and each occurrence lasts for 30 seconds (Mayo Clinic, 2011). Patients are given a handheld device that allows the generator to be turned off for certain situations (e.g., public speaking, exercise). The device typically remains implanted for 10 weeks, but can be left in for longer or shorter durations depending on patient response.

Risks of VNS include those associated with any surgical procedure (e.g., pain, infection, reactions to anesthesia) as well as those specific to the surgical location, such as temporary paralysis of the vocal cords (George, 2005; Rush, 2009). Other side effects may include voice alteration, cough, neck pain, difficulty swallowing, tingling sensations, and shortness of breath (Rush, 2009).

The FDA approved VNS for TRD in July 2005, with a specific indication for "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" (U.S. FDA, PMA suppl., 2005).

Cognitive-Behavioral Therapy/Interpersonal Therapy (CBT/IPT)

Use of cognitive-behavioral techniques for psychotherapy first became popular in the 1960s. It is a structured form of psychotherapy that aims to modify negative and/or inaccurate thinking, and is used for a wide variety of conditions, including depression. The cognitive model involves four key steps: (1) identification of troubling situations or conditions; (2) awareness of the patient's thoughts, emotions, and beliefs about these conditions; (3) identification of negative and/or inaccurate thinking or behavior in relation to these beliefs; and finally (4) challenging of identified negative thoughts or beliefs (DeRubeis, 1990). With regard to depression, there is an emphasis on negatively distorted thinking and deficits in learning and memory (DeRubeis, 1990). While the duration of treatment varies by condition and severity, a course of CBT typically involves 10-20 one-on-one treatment sessions with a trained therapist lasting 45-60 minutes each (Mayo Clinic, 2011).

In contrast, IPT was developed as a treatment modality specifically for depression in the 1970s and 1980s. This approach is modeled on the identification of four key problem areas: (1) grief after the loss of a loved one or a relationship; (2) role disputes involving differing expectations for the patient and another involved in a relationship with the patient; (3) role transitions involving a change from an old to new role in the workplace or other setting; and (4) interpersonal deficits involving communication issues, social isolation, and other concerns (Swartz, 1999). Patients and their therapists may choose to explore all or only some of these problem areas. The stages of treatment typically progress from definitive diagnosis and identification of problem areas to creation of a "treatment contract" involving defined expectations for both therapist and patient (Weissman, 2006). While duration of treatment varies based on the problem areas identified, IPT is typically a focused, short-term approach employing weekly sessions over a 12 to 16-week treatment duration (Markowitz, 2004).

Neither CBT nor IPT are associated with any inherent harms. However, these approaches are intended to explore painful feelings and experiences, which may make patients emotionally uncomfortable at times (Mayo Clinic, 2011).

2. Clinical Guidelines

2.1 Electroconvulsive Therapy (ECT)

- American Psychiatric Association (APA) (2010)
  http://www.psychiatryonline.com/pracGuide/pracGuideTopic_7.aspx
  ECT is recommended for patients with severe MDD, particularly with associated psychotic or catatonic features or suicidal tendencies. Initial and maintenance ECT is also recommended in patients whose symptoms have not responded sufficiently to psychotherapy or pharmacotherapy, in patients who prefer ECT, have a previous positive response to ECT, or have functional impairment. Continuation therapy with ECT may be considered with patients responding acutely to ECT.
  NOTE: APA's Task Force on ECT is in the process of updating the specific recommendations from the group's report in 2001.

- National Institute for Health and Clinical Excellence (2009)
  http://guidance.nice.org.uk/CG90/Guidance/pdf/English
  In patients with life-threatening severe depression, or when other therapies have failed, ECT is a therapeutic option. ECT may be considered in patients with moderate depression whose disease is unresponsive to multiple medications and psychotherapy. For patients unresponsive to ECT, a subsequent trial may be undertaken after complete evaluation of the previous course along with alternative therapies. Specific considerations should be given to use of unilateral or bilateral modalities as well as assessment of effects on cognitive function. For continuous/maintenance therapy with ECT, there are no current recommendations.

- Institute for Clinical Systems Improvement (2011)
  http://www.icsi.org/depression_5/depression__major__in_adults_in_primary_care_3.html
  ECT is effective for treatment of acute phase MDD, as well as for maintenance therapy. ECT may be appropriate in depressed patients with resistance or intolerance to antidepressant medications, previous positive response to ECT, psychotic or melancholic symptoms, catatonia, suicidal ideation, concurrent pregnancy, as well as in geriatric patients and those with Parkinsonism-associated depression.

- Department of Veterans Affairs/ Department of Defense (2009)
  http://www.healthquality.va.gov/Major_Depressive_Disorder_MDD_Clinical_Practice_Guideline.asp
  For treatment of severe MDD, ECT may be considered in patients with the following characteristics: intolerance or inadequate response to multiple antidepressants, catatonia or psychotic symptoms, suicidality, previous positive response to ECT or patient preference. Significant co-morbidities, such as recent myocardial infarction or detached retina, may preclude patients from receiving ECT. Continued ECT may be considered. There are insufficient data to recommend or reject ECT for the elderly.

2.2 Repetitive Transcranial Magnetic Stimulation (rTMS)

- American Psychiatric Association (2010)
  http://www.psychiatryonline.com/pracGuide/pracGuideTopic_7.aspx
  Data are insufficient to recommend rTMS as initial therapy in MDD. TMS may be an option for patients with inadequate response to pharmacotherapy.

- National Institute for Health and Clinical Excellence (2007)
  http://guidance.nice.org.uk/IPG242
  Due to lack of sufficient data regarding clinical efficacy, rTMS should be utilized in research studies only to provide further analysis of factors such as treatment duration and frequency and intensity of application. No major safety concerns have been identified with the use of TMS in severe depression.

- Institute for Clinical Systems Improvement (2011)
  http://www.icsi.org/depression_5/depression__major__in_adults_in_primary_care_3.html
  While rTMS is recognized as an emerging therapeutic intervention in TRD, no specific recommendations are provided. Patients should be referred to specialists in psychiatry for evaluation.

2.3 Vagus Nerve Stimulation (VNS)

- American Psychiatric Association (2010)
  http://www.psychiatryonline.com/pracGuide/pracGuideTopic_7.aspx
  VNS is not recommended as initial therapy in MDD. For patients not responding to at least four trials of antidepressants and/or ECT, VNS may be considered as an alternative therapeutic choice. Maintenance therapy with VNS is appropriate for patients who have responded to this therapy.

- National Institute for Health and Clinical Excellence (2009)
  http://guidance.nice.org.uk/IPG330
  VNS may only be used in patients with treatment-resistant depression, and only after special arrangement for clinical governance, consent and audit or research. Utilization should involve multidisciplinary evaluation and management of the patient.

- Institute for Clinical Systems Improvement (2011)
  http://www.icsi.org/depression_5/depression__major__in_adults_in_primary_care_3.html
  While VNS is recognized as an emerging therapeutic intervention in TRD, no specific recommendations are provided. Patients should be referred to specialists in psychiatry for evaluation.

- Department of Veterans Affairs/ Department of Defense (2009)
  http://www.healthquality.va.gov/Major_Depressive_Disorder_MDD_Clinical_Practice_Guideline.asp
  There has been insufficient evidence on the efficacy and safety of VNS to recommend its routine use in treatment-resistant depression.

2.4 Cognitive Behavioral Therapy (CBT) or Interpersonal Psychotherapy (IPT)

- American Psychiatric Association (2010)
  http://www.psychiatryonline.com/pracGuide/pracGuideTopic_7.aspx
  For patients with mild to moderate depression, CBT or IPT is an appropriate initial therapeutic option. In patients with moderate to severe MDD, the combination of CBT/IPT with pharmacotherapy may be used. CBT and IPT may be used as continuous and maintenance therapies.

- National Institute for Health and Clinical Excellence (2009)
  http://guidance.nice.org.uk/CG90/Guidance/pdf/English
  For patients with mild to moderate depression, or persistent subthreshold depressive symptoms who lack adequate response to low-intensity psychosocial intervention, CBT or IPT may be appropriate interventions. Combination therapy with CBT or IPT and antidepressant medication may be indicated for patients with moderate to severe depression. In patients without adequate response to pharmacotherapy or psychotherapy, combination therapy with CBT and an antidepressant may be considered. Patients at risk for relapse may also consider CBT.

- Institute for Clinical Systems Improvement (2011)
  http://www.icsi.org/depression_5/depression__major__in_adults_in_primary_care_3.html
  Psychotherapy (including CBT and IPT) is effective in mild to moderate depression and may lower relapse rates. Psychotherapy may prevent relapse in patients with major depression, and maintenance therapy may assist with management of chronic MDD. For patients not responding to medication, psychotherapy may be considered as an alternative option.

- Department of Veterans Affairs/ Department of Defense (2009)
  http://www.healthquality.va.gov/Major_Depressive_Disorder_MDD_Clinical_Practice_Guideline.asp
  First-line therapies for uncomplicated major depression include CBT and IPT, delivered by specifically-trained providers. They are also first-line therapies for pregnant and post-partum women with depression. CBT is a treatment option for severe depression, particularly with a history of suicide risk. Combination therapy with CBT and pharmacotherapy is recommended in recurrent or chronic major depression. IPT and CPT may be combined with pharmacotherapy for treatment in patients who are refractory to a single form of treatment.

3. Medicare, National and New England Private Insurer Coverage Policies

3.1 Electroconvulsive Therapy

National Payers

- Centers for Medicare and Medicaid Services (CMS): Medicare has not made a national coverage decision for ECT in depression. No local coverage determinations have been made in New England, although a local coverage decision has been made in Wisconsin, where ECT is considered medically necessary when at least one of the following conditions is met:
    - Major depressive episode and/or major depressive disorder
    - Rapid resolution of depression is necessary (e.g. acute suicide risk or agitation)
    - Unresponsiveness to pharmacological therapy, or inability to medically tolerate medication, maintenance medication, or medication side effects
    - Bipolar illness with either mania or depression where medications are ineffective or not tolerated, or severe mania presenting a safety risk to the patient or to others
    - When continuation of ECT is necessary to sustain remission or improvement

  ECT is not covered for depression when a patient is responsive to antidepressants; when there is no evidence of ECT effectiveness in patients who have been treated previously; in patients tolerant to antidepressants and not at immediate risk of suicide; or in those whose treatment and/or primary diagnosis is related to alcoholism.
  https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=30493&ContrId=47&ver=8&ContrVer=1&SearchType=Advanced&CoverageSelection=Both&NCSelection=NCA|CAL|NCD|MEDCAC|TA|MCD&ArticleType=Ed|Key|SAD|FAQ&PolicyType=Final&s=All&KeyWord=Electroconvulsive+therapy&KeyWordLookUp=Title&KeyWordSearchType=Exact&kq=true&bc=IAAAABAAAAAA&

- Aetna: Aetna considers ECT medically necessary for treatment of major depression or mania when a patient is at least 12 years of age, and one of the following conditions is met:
    - Member is unresponsive to pharmacological therapy, or unable to tolerate effective medications or has a medical condition for which medication is contraindicated
    - Member has had favorable responses to ECT in the past
    - Rapid response is required for patient or others' safety
    - Member is experiencing severe mania or depression during pregnancy
    - Member prefers ECT as a treatment option in consultation with the psychiatrist

  http://www.aetna.com/cpb/medical/data/400_499/0445.html

  (NOTE: No published policies on ECT were found for other national payers, including CIGNA, UnitedHealthcare, and Wellpoint/Anthem.)

Regional Payers

- Blue Cross Blue Shield of Massachusetts: BCBSMA covers outpatient ECT when administered by a BCBSMA network-credentialed psychiatrist in a qualified acute care general hospital or contracted acute care psychiatric hospital when at least one of the following conditions is met:
    - Severe depression or mania that is unresponsive to pharmacotherapy, especially with acute suicide risk, extreme agitation, and/or catatonia
    - Intolerance to antidepressant or neuroleptic medications or their side effects, or inability to medically tolerate maintenance medication
    - Rapid resolution of depression is necessary

  ECT is only covered after receiving informed consent in writing from the patient or legal guardian, and if the patient has reasonable accommodations for transportation and assistance. Patients receiving ECT should not require inpatient medical or psychiatric treatment.

  BCBSMA does not cover outpatient ECT when a patient is responsive to mood stabilizers or is able to tolerate antidepressant or neuroleptic medications, and is not at risk of suicide; when there is no evidence of ECT effectiveness in patients who have been treated previously; when pharmacotherapy was previously effective for maintenance; when treatment is related to alcoholism; or when there is no evidence of catatonia, mania, acute suicide risk, or extreme agitation.
  http://www.bluecrossma.com/common/en_US/medical_policies/319%20Outpatient%20Electroconvulsive%20Therapy%20prn.pdf#page=1

- Blue Cross Blue Shield Rhode Island: ECT is covered in both the outpatient and inpatient settings when provided by a psychiatrist or other licensed physician.
  https://www.bcbsri.com/BCBSRIWeb/pdf/medical_policies/BehavioralHealthServices.pdf

(NOTE: No published policies on ECT were found for other regional payers, including Harvard Pilgrim Health Care, Tufts Health Plan, ConnectiCare, BCBSVT, HealthNet, Neighborhood Health Plan of RI, and MVP Health Care.)

3.2 Repetitive Transcranial Magnetic Stimulation

National Payers

- Centers for Medicare and Medicaid Services (CMS): Medicare has not made a national coverage decision on rTMS. No local coverage determinations have been made in New England, although local coverage decisions have been made in Mid-Atlantic States not to cover rTMS for depression, as it is considered investigational and not medically necessary.

- CIGNA, Aetna, and Wellpoint/Anthem do not cover rTMS for the treatment of depression because its value and effectiveness are not considered to be established.

Regional Payers

- BCBSMA, Harvard Pilgrim Health Care, Tufts Health Plan, and BCBSRI do not cover rTMS for depression because it is considered experimental, investigational, or unproven.

(NOTE: No published policies on transcranial magnetic stimulation were found for other regional payers, including ConnectiCare, BCBSVT, HealthNet, Neighborhood Health Plan of RI, and MVP Health Care.)

3.3 Vagus Nerve Stimulation

National Payers

- The Centers for Medicare and Medicaid Services (CMS): CMS has made a national coverage decision not to cover VNS for depression because it is considered experimental or investigational and therefore is not medically necessary. https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=230&ncdver=2&CoverageSelection=National&KeyWord=vagus+nerve+stimulation&KeyWordLookUp=Title&KeyWordSearchType=And&bc=gAAAABAAAAAA&

- CIGNA, Aetna, UnitedHealthcare, and Wellpoint/Anthem do not cover VNS for depression because it is considered experimental or investigational.

Regional Payers

- BCBSMA, Harvard Pilgrim Health Care, Tufts Health Plan, BCBSRI, and HealthNet do not cover VNS for depression because it is considered experimental or investigational.

- ConnectiCare: The efficacy of VNS for the treatment of depression has not been demonstrated, and all requests for this service require prior authorization. http://www.connecticare.com/provider/PDFs/New%20Technology%20Guidance.pdf

(NOTE: No published policies on VNS were found for other regional payers, including BCBSVT, Neighborhood Health Plan of RI, and MVP Health Care).

3.4 Cognitive Behavioral Therapy/Interpersonal Therapy

No published polices on CBT or IPT were found for any national or regional payer.

4. New Evidence Following AHRQ Review

4.1 Updated search

We conducted a systematic literature search of MEDLINE, Cochrane Central Register of Controlled Trials, EMBASE, and PsycInfo, utilizing the search criteria defined by the AHRQ review. The search timeframe spanned from January 1, 2010 to October 11, 2011. We identified 221 records after removal of duplicates (Figure 1). Any citations already included in the AHRQ review were removed. The remaining abstracts were screened using parameters designated by the AHRQ review (i.e., study type, patient population, treatment intervention and outcomes evaluated). Following initial screening, full-text review was performed on 54 retrieved articles. Forty-four of these were excluded for a variety of reasons, most commonly inappropriate study populations (e.g., more than 20% bipolar, patients without treatment-resistant disease) (Figure 1, p.18).

Ten articles were evaluated for new evidence (Appendix A). No randomized controlled trials (RCTs) were identified; most of the studies were small, single-center case series of relatively poor quality. For example, one series provided no details on the location, intensity, and conditions of ECT therapy (Oulis, 2011), while another did not specify the duration of follow-up (Sperling, 2011). Patient populations were heterogeneous with respect to the definition of treatment resistance, disease severity and duration of current depressive episode. Outcomes focused on examination of potential mechanisms of action of the different nonpharmacologic interventions, or assessment of predictors of response to the interventions. Two studies, described in more detail below, explored safety and quality of life (QoL) in TRD patients (Berlim, 2011, Oulis, 2011).

4.2 ECT

The AHRQ review identified four reports of two studies examining specific adverse events associated with ECT (Pridmore, 2000, McLoughlin, 2007, Eranti, 2007, Knapp, 2008). One concern is the potential for ECT to cause changes in cardiac repolarization and increase the risk of arrhythmia, as measured by a lengthened QT interval. Psychotropic medications such as antidepressants and atypical antipsychotics have been shown to have this effect, and a similar phenomenon is suspected with ECT (Tezuka, 2010). While baseline prolonged QTc may not preclude patients with TRD from receiving ECT, consideration of cardiac risk factors is an important part of the clinical evaluation prior to administration of therapy (Pullen, 2011). A small case series assessing ECT's impact on the QT interval has recently been published (Oulis, 2011). In this study, six female patients with concomitant atypical antipsychotic and antidepressant medication therapy (at least four medications in total) underwent ECT for resistant depression. Over 63 sessions of ECT, the corrected QT (QTc) interval was lengthened in all patients; changes were considered to be within normal limits. There were no reports of any arrhythmias or other major cardiac adverse events. As these findings represent a very small patient population, any conclusions drawn from these results must be done cautiously.

4.3 rTMS

In general, health-related quality of life (QoL) is under-evaluated in TRD patients. The AHRQ review identified six studies that assessed QoL, and only three of these evaluated patients undergoing rTMS. New observational data regarding QoL among patients receiving rTMS became available after publication of the AHRQ review. In a recent case series, 15 patients with treatment-resistant moderate to severe MDD, who maintained concurrent therapy with psychotropics, underwent high frequency-rTMS therapy over a four-week period (Berlim, 2011). Patients experienced significant improvement in their depressive symptoms, as measured with the HAM-D_{21} ($p=0.035$). Patients also experienced significant improvement in the World Health Organization's Quality of Life Measure – Brief Version (WHOQOL BREF) overall score ($p=0.017$), as well as in physical and psychological domain scores. This study provides limited evidence regarding improved QoL in patients with TRD but due to the inherent biases within a case series, the results should be interpreted with care.

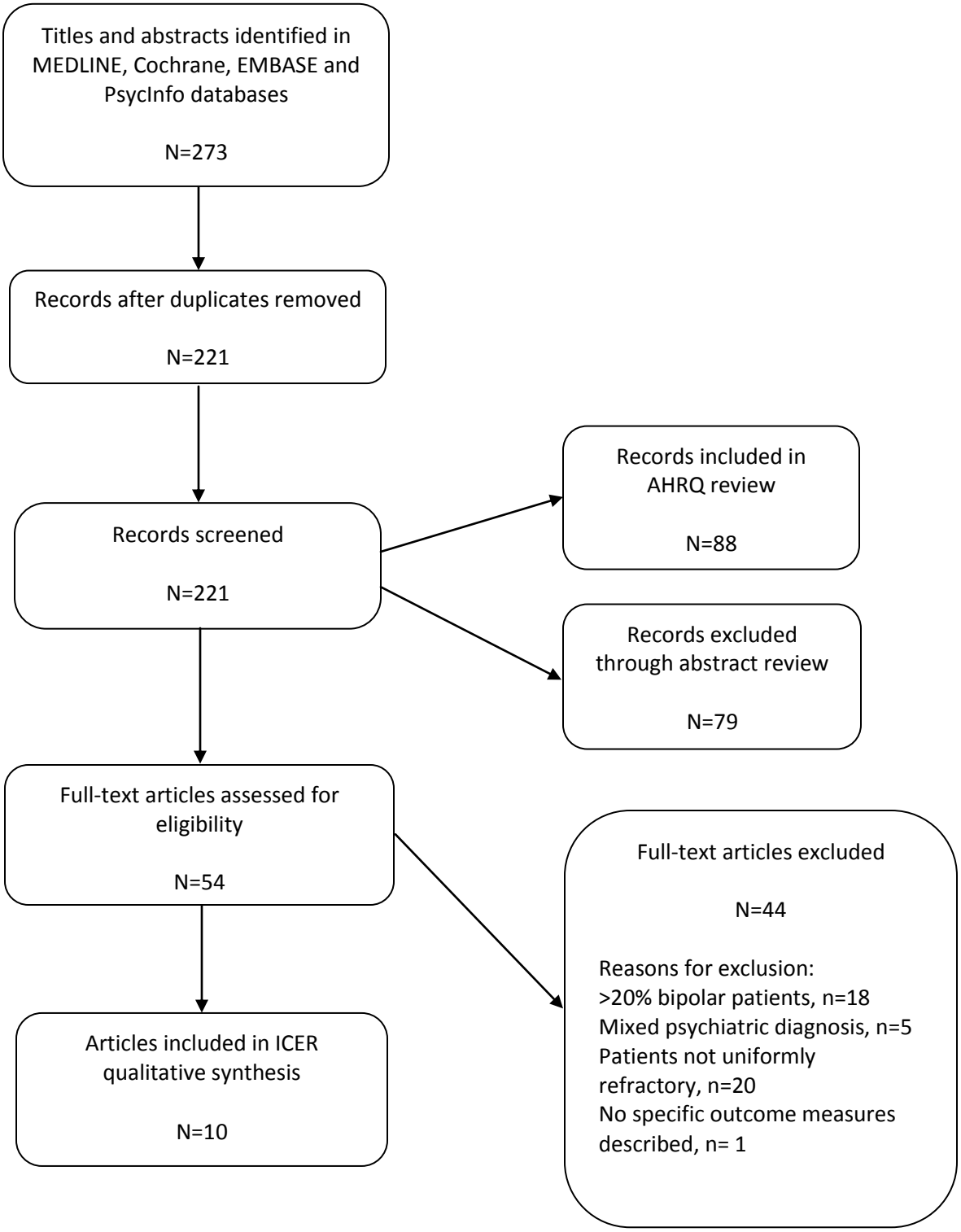
4.4 VNS

No studies have been published since the AHRQ review that provide significant new information about the impact of VNS on clinical, economic, and/or safety outcomes among patients with TRD.

4.5 CBT/IPT

No studies have been published since the AHRQ review that provide significant new information about the impact of CBT and/or IPT on clinical, economic, and/or safety outcomes among patients with TRD.

Figure 1. PRISMA flow diagram of included and excluded studies from updated literature search.



5. Analysis of Comparative Value

5.1 Methods

An economic model was developed to evaluate the comparative value of nonpharmacologic therapies for use in patients with TRD. The comparative value of these strategies was considered in two ways: the budget impact to public and/or private payers of changing coverage policy (and the associated distribution of management options utilized) and the cost-effectiveness of a given management option vs. a comparator option. Budget impact was analyzed on a population basis and considered the impact of changes in coverage, resource utilization, and cost among Medicaid beneficiaries and members of the three largest private payers in each New England state. Cost-effectiveness was evaluated in a hypothetical cohort of 1,000 patients and considered the outcomes and costs associated with each modeled treatment "pathway".

Management Options

Only nonpharmacologic interventions demonstrating sufficient evidence of effectiveness and safety in the AHRQ evaluation were considered in the economic analyses (see Table 1 on the following page). The budget impact analyses considered scenarios in which varying percentages of use of ECT and rTMS are assumed in a population of patients with TRD. Evidence for vagus nerve stimulation was found to be insufficient in the AHRQ review (Gaynes, 2011), thus it is not considered in the comparative value assessment. Psychotherapy (CBT/IPT) was also excluded as it was not possible to sufficiently differentiate resource use and costs in comparison to "usual care" (i.e., traditional psychotherapy and/or medication), given that all forms of psychotherapy share the same billing codes for individual sessions. In addition, neither the AHRQ review nor this supplementary analysis found any studies reported in which CBT/IPT was compared directly to ECT or rTMS.

Analyses of cost-effectiveness were limited to a comparison of rTMS to usual care, as this was the only comparison in the AHRQ review demonstrating sufficient evidence of a difference in net clinical benefit (Gaynes, 2011).

Key treatment parameter estimates may be found in Table 1 on the following page. Estimates for treatment response and remission were obtained from meta-analyses conducted in the AHRQ review. Estimates of response and remission for ECT and rTMS were obtained directly from head-to-head data reported in Table 11 of the AHRQ review (Gaynes, 2011). These rates are assumed equal for ECT and rTMS given the conclusions drawn in the comparative effectiveness review that there are no significant differences in changes in depressive severity, response, or remission between these two options. Estimates of the risk of relapse were also assumed to be equal based on the findings reported in Table 35 of the review (Gaynes, 2011). The corresponding usual care inputs were derived by applying the inverse of the meta-analyzed relative risk of these outcomes for rTMS vs. usual care (Figures 13 and 14, and Table 37 for response, remission, and relapse in the AHRQ review). As there were no data differentiating management alternatives in terms of relapse rates, a uniform monthly risk was assumed across all options.

Table 1. Treatment parameters.

Unit Item	Usual Care	ECT	rTMS	Unit
Response[*] to treatment	27.1%	59.1%	59.1%	Course of therapy
Remission[†] on treatment	24.9%	59.1%	59.1%	Course of therapy

[*] 20-50% change on depression scale

[†] HAM-D17 < 8, HAM-D21 < 10, or MADRS < 8

Source: Gaynes B, et al. AHRQ Comparative Effectiveness Review Number 33.

Demographic characteristics of patients with TRD, as well as estimates of resource use and payment under conditions of typical practice, were obtained from regional benchmark information provided by the proprietary LifeLink™ Health Plan Claims Database (IMS Health, Danbury, CT), which is comprised of 79.4 million privately-insured individuals from 79 health plans nationwide and includes 6.7 billion medical and pharmacy claims generated from 2001 to the present. The population was restricted to patients aged 20-64 years, who were located in the Northeast U.S. Census region, and had one or more claims with a diagnosis of depression in 2008. Utilization and cost data were generated for calendar year 2009.

Clinical and Economic Model

The model framework considers the outcomes of a population consisting of 30% men between the ages 20 and 64 years with a mean age of 45 years across the entire population. The age range was selected because (a) the AHRQ review focused on adults only; and (b) the population of most interest for decision-makers in each New England state was felt to include Medicaid and privately-insured patients only. Medicare patients were therefore excluded from consideration.

Population characteristics were consistent with those of the IMS database as described above. All patients were assumed to carry a diagnosis TRD consistent with that used in the AHRQ report (i.e., depression that is non-responsive to two or more trials of drug therapy). All costs and payments are reported in 2010 US dollars unless otherwise specified.

Key Model Assumptions about TRD Management Options (Budget Impact and Cost-Effectiveness Analyses)

- The primary measure of clinical impact is the proportion of treated patients with a "positive treatment response." Definitions of response varied by study, but generally are based on improvement of 20-50% on a standardized depression scale such as the Hamilton Rating Scale for Depression (HAM-D).
- Remission rates were applied in accordance with the definitions used in the AHRQ review, in which patients who reached a minimum threshold score (i.e., HAM-D17 < 8, HAM-D21 < 10, or MADRS < 8) were felt to have achieved full remission.
- All patients under all treatment scenarios were assumed to continue with usual care (e.g., therapy visits, prescription medications) regardless of the outcome of nonpharmacologic intervention.

- Rates of effectiveness and harm were assumed to be identical for ECT and rTMS, based on findings from head-to-head trials reported in the AHRQ review.
- rTMS was assumed to be more effective than usual care, consistent with the AHRQ review's meta-analysis of the rTMS vs. sham trials.
- Based on the reported range of course of therapy reported in the AHRQ review, ECT was assumed to involve twice-weekly sessions of 3-4 hours each over a total of four weeks, while rTMS was assumed to involve daily sessions (five days per week) of 40 minutes each over a total of four weeks. Total estimated cost for each course of therapy was assumed to be approximately $3,500 and $4,400 for ECT and rTMS respectively, including the costs of planning visits, treatment delivery, and anesthesia (ECT only).

Key Model Assumptions about TRD Management Options (Cost-Effectiveness Analysis Only)

- The patient group with a positive treatment response to nonpharmacologic intervention is assumed to benefit from fewer emergency department (ED) and inpatient admissions.
- Changes in resource use associated with a positive treatment response or relapse are applied over the course of 6 months, corresponding to the model cycle length.
- Risk of relapse is applied in the second 6-month cycle and thereafter.
- For patients that suffer a relapse, it is assumed that resource use for ED and inpatient admissions returns to the higher frequency associated with TRD.
- Among the group of patients who relapse, 50% of those previously on ECT or rTMS are assumed to retry the same nonpharmacologic strategy following relapse, whereas 100% of all patients who relapse on usual care are assumed to retry usual care.
- In calculating the impact on lost wages in the cost-effectiveness analysis, the distribution of employment status was assumed to be: employed full-time (71%), part-time (16%), unemployed (8%) or receiving disability (5%).

Key Assumptions about TRD

Major assumptions regarding the course of TRD and its treatment can be found below; detailed input parameter estimates can be found in Table 2 on the following page.

<u>Population</u>

The age and gender distribution was assumed from the data provided by IMS Health. Accordingly, 70% of TRD patients aged 20-64 years were assumed to be female, and 60% were assumed to be aged 45-64 years.

<u>Prevalence</u>

The prevalence of TRD in the private payer population was estimated to be 2.0% based on a published epidemiologic estimate (Ivanova, 2010) for males and females irrespective of age. The corresponding prevalence among Medicaid recipients was derived by applying a relative risk of 1.69 from a study comparing depression prevalence by socioeconomic status (Lorant, 2003) to the prevalence of TRD in the private payer population, resulting in an estimated prevalence of 3.4%.

Table 2. General model input parameters.

Unit Item	Input	Unit	Frequency	Unit
Population Characteristics				
Male patients	30%			
Mean age: Male/Female	45.5/45.4	Years		
Employment Status				
Full-Time	71.10%			
Part-Time	15.60%			
Unemployed	8.10%			
Disability	5.10%			
Payment Items – Private				
Outpatient Visits	$584	per visit	2.4	per year
Office Visits	$115	per visit	13.7	per year
Emergency Department	$1,089	per visit	0.3	per year
Pharmacy	$60	per script	31.2	per year
ECT	$433.58	per session	8	per course of therapy
rTMS planning	$246	per session	1	per course of therapy
rTMS delivery	$206	per session	20	per course of therapy
Inpatient Facility Admission	$11,296	per admission	0.1	admissions per year
Inpatient Professional Visit	$330	per visit	4.7	visits per admission
Indirect Cost Items				
Regional employment wage	$23.57	per hour		
Regional disability benefit	$962.58	per month		
Reason for Productivity Loss				
General depression overall	51.2	Days lost/year		
– Medically-related	13.5	Days lost/year		
– Disability	37.7	Days lost/year		
Usual care	0	Additional days lost/year		
rTMS treatment	11	Days lost/course of therapy		
Utility Items		Duration		
Baseline TRD - Male	0.708	Annual		
Baseline TRD – Female	0.708	Annual		
Death	0	Annual		
Change due to:				
– Aging	-0.00251	Annual		
– ECT	0	Per course		
– rTMS	0	Per course		
– Usual care	0	Per course		
– Response	0.0625	Per response		
– Remission	0.125	Per remission		
– Relapse	-0.0625	Per relapse		
– Serious Adverse Event	-0.1	Per event		

Mortality

Overall age and gender-specific mortality was obtained from the 2007 U.S. life tables (Arias, 2011). Hazard ratios from a published study on the association between major depression and all-cause mortality (Zheng, 1997) were applied to these data to estimate the increased risk of death among men and women with TRD. Adjusted hazard ratios of 3.1 for males and 1.7 for females were applied to the gender-specific risks in the general population. The resulting risk of death for patients with TRD was approximately 3.3% per year for males and 1.8% per year for females.

Loss of Productivity and Wages

Lost wages were estimated using data from the 2009 U.S. Census data for residents of the Northeast U.S. (U.S. Census Bureau, 2009). The proportion of patients receiving disability benefits (5.1%) and average benefit paid ($963/month) was derived from regional New England data (Office of Retirement and Disability Policy, 2009). Average hourly wages ($23.57) were obtained from the Bureau of Labor Statistics (Bureau of Labor Statistics, 2010) and used to derive a mean estimate for New England. Days of work lost due to disability or medically- related issues was obtained from a published study (Ivanova, 2010). Work loss due to the time required for ECT and rTMS treatment was assumed based on the typical course of therapy reported in the AHRQ review. Specifically, rTMS was assumed to involve four hours of work loss for each session.

Utility Estimates

Weights to adjust for changes in quality of life were obtained from the literature. The utility for men and women suffering from TRD was set to 0.708 based on data from an epidemiologic study (Sullivan, 2006). Adjustments were made to account for the general impact of aging, remission, and relapse.

Payments and Resource Utilization

The average paid amount for each resource use item was derived from the IMS LifeLink database as previously-described, and was used as the model input to represent the direct cost to a private payer (Table 3, page 23). Medicaid payments were assumed to be 60% of those received by private payers. Because patients with TRD were assumed to have more severe symptoms, routine resource use for patients with general depression was adjusted using a literature-based, resource-specific factor (Ivanova, 2010) to estimate likely resource consumption among patients with TRD. Payment estimates from prior years were inflated to 2010 using the overall medical inflation component of the consumer price index for the Northeast U.S. (Bureau of Labor Statistics, 2010). All resulting payment and frequency inputs are presented in Table 2 on page 21.

Budget Impact

The budget impact analysis estimates the regional impact of introducing coverage for rTMS in New England as determined by the number of insured adult lives covered under Medicaid and by the three largest private payers in each of the six New England states (Table 3 on the following page). The total number of patients with TRD is calculated using separate prevalence estimates for the private payer and Medicaid populations. This may be further specified by population age category and gender. Use of ECT and rTMS in the TRD population before and after introduction of a new coverage decision is specified as the percentage of patients treated with each option.

Table 3. Estimated number of enrollees in budget impact analyses, by state and payer type.

State	Medicaid[*†] (n)	Private Payer[‡] (n)
CT	163,800	1,383,791
ME	135,700	807,396
MA	690,900	2,396,386
NH	35,500	341,054
RI	78,100	1,246,212
VT	63,700	270,755

[*]Kaiser Family Foundation, State health facts. Adult covered lives with Medicaid 2008-2009
[†]Kaiser Family Foundation, State health facts. Age Distribution of Medicaid Enrollees, FY 2007
[‡]U.S. News & World Report LP; http://health.usnews.com/health-plans

The payments associated with ECT and rTMS treatment, routine care for depression, adverse events related to treatment, and resource use as a result of relapse are estimated at baseline and over multiple scenarios evaluating increased use of rTMS. Findings are reported on an annual basis. In addition, 50% of patients who relapse are assumed to retry the same strategy again within the year.

Over the one-year time horizon, the model estimates the total number of patients with TRD, the proportion treated using ECT or rTMS, the subset of treated patients who would be expected to have a positive response, and the corresponding resources consumed and associated payments. Payments are reported as total payments per patient with TRD, annual plan payments for all patients with TRD, annual payments for all services for all members, and payments per member per month (PMPM) for all members.

At baseline, 20% of TRD patients are assumed to be receiving ECT. In the first modeled scenario (Scenario 1), one-half of the patients receiving ECT are assumed to switch to rTMS. In the second scenario, (Scenario 2), the percentage of patients receiving ECT is assumed to remain constant at 20%, and an additional 10% of TRD patients are assumed to undergo rTMS treatment rather than continue with usual care for TRD. Each scenario is considered separately for Medicaid beneficiaries, privately-insured patients, and a combination of the two groups over the entire region. In addition, state-specific analyses are presented in Appendix B for the combined Medicaid/private population.

Cost-Effectiveness

The cost-effectiveness analysis considers the experience of a cohort of 1,000 hypothetical patients diagnosed with TRD who are treated with either rTMS or usual care over the course of five years. During this time, patients may respond to treatment and are at risk for early treatment withdrawal, adverse events, hospitalization, relapse among those in remission, death from any cause and TRD-related death (i.e., suicide and other excess mortality from depression) in six-month cycles. The payments associated with these outcomes and treatment accumulate over five years, yielding the estimated total direct medical cost of using rTMS vs. usual care in patients with TRD. In addition, the indirect costs associated with lost productivity due to treatment and TRD in general are taken into account providing a broader perspective. Lost wages and disability payments are estimated for patients and summed over the period of analysis. The present value of all costs accrued in the future is estimated using an annual discount rate of 3.5%, consistent with typical practice in long-term economic evaluations.

Total time alive, or life years, is estimated by summing the total number of patients alive at each time point. This outcome is weighted to estimate the total quality-adjusted life years (QALYs), which accounts for changes in quality of life determined by the experiences of the patient group and the duration over which they occur. Specifically, the amounts of time patients are in remission, relapsed, in hospital, and dead are multiplied by the "weight" associated with each of these states and summed over the population.

Effectiveness outcomes are presented for each strategy in terms of the numbers of patients with a positive treatment response or remission, relapse, inpatient stay, or death; total life years and QALYs are also reported for each cohort. Costs associated with each of these categories are presented as the total cost and by component for each strategy. Cost-effectiveness results are presented as incremental cost-effectiveness ratios (ICERs) for rTMS relative to usual care. Measures of interest included cost per life-year gained (LYG), cost per QALY gained, and cost per additional positive treatment response.

5. 2 Results

Estimated Region-wide Budget Impact – All Payers

The distribution of patients represented by Medicaid and private payers in this analysis is shown by New England state in Table 4 below along with the estimated prevalence and resulting number of patients with TRD.

Table 4. Estimated TRD population, by payer type.

	Medicaid		Private Payer		Overall
	n	%	n	%	
New England State Distribution					
CT	163,800	11%	1,383,791	89%	1,547,591
ME	135,700	14%	807,396	86%	943,096
MA	690,900	22%	2,396,386	78%	3,087,286
NH	35,500	9%	341,054	91%	376,554
RI	78,100	6%	1,246,212	94%	1,324,312
VT	63,700	19%	270,755	81%	334,455
Proportion of patients by payer (%)		15%		85%	
Covered Populations*					
Total membership (n)		1,167,700		6,445,594	7,613,294
Prevalence of TRD		3.4%		2.0%	2.2%
Patients with TRD (n)		39,468		128,912	168,380

*Note that uninsured patients are not represented in this analysis as there is no direct impact to a third party payer.

Shifting 10% of patients from ECT to rTMS in Scenario 1 resulted in no change in the number of patients having a positive treatment response relative to baseline (see Table 5 on the following page) due to the underlying assumption of equivalent efficacy for ECT and rTMS. In Scenario 2, in which 10% of the population receiving usual care at baseline was assumed to begin rTMS, an additional 3.2% of patients overall are estimated to have a positive treatment response.

Table 5. Estimated clinical impact of ECT and rTMS in an insured population.

	Baseline	Scenario 1*†	Net Change vs. Baseline	Scenario 2*‡	Net Change vs. Baseline
Summary of Covered Population					
Total membership (n)	7,613,294	7,613,294		7,613,294	
Patients with TRD (n)	168,380	168,380		168,380	
Patients with TRD receiving ECT and/or TMS (n)	33,676	33,676		50,514	
As a proportion of all members	0.4%	0.4%		0.7%	
As a proportion of patients with TRD	20.0%	20.0%		30.0%	
Outcomes & Resource Use					
Positive Treatment Response (n)	56,421	56,421	0	61,807	5,386
Positive Treatment Response (%)	33.5%	33.5%		36.7%	

*Note. This analysis is from the point of view of a third party payer, therefore, all patients are assumed to be covered.
†Scenario 1 consists of 10% of patients treated with ECT, 10% with rTMS, and 80% under usual care.
‡Scenario 2 consists of 20% of patients treated with ECT, 10% with rTMS, and 70% under usual care.

The uptake of rTMS in Scenarios 1 and 2 resulted in a net economic impact of 1.1% and 3.1%, respectively, relative to baseline due to the increased cost of rTMS therapy, corresponding to an increase in total payments of approximately $19 million in Scenario 1 and $53.5 million in Scenario 2 across the region (see Table 6 on the following page). Total cost per patient treated with nonpharmacologic therapy ranged from $10,101 – $10,419 annually, depending on the uptake of rTMS. Annual payments are estimated to increase $93 - $318 per patient given a 10% uptake of rTMS, depending on the scenario (Table 6 on the following page). On an overall basis, the PMPM was estimated to increase by $0.21 and $0.59 for scenarios 1 and 2 respectively.

Table 6. Estimated economic impact of ECT and rTMS use in an insured population.

		Scenario 1*†		Scenario 2*‡	
	Baseline	Payments	Net Change vs. Baseline	Payments	Net Change vs. Baseline
Payments per patient with TRD (n=168,380)					
ECT and/or TMS	$668	$781	$113	$1,115	$447
Outpatient Management & ER	$7,767	$7,767	$0	$7,718	($49)
Inpatient admissions	$1,666	$1,666	$0	$1,586	($80)
Total per patient	$10,101	$10,214	$113	$10,419	$318
Annual payments for all patients with TRD	$1,700,807,456	$1,719,880,131	$19,072,676	$1,754,373,736	$53,566,280
			1.1%		3.1%
Plan payments for Covered Population (n=7,613,294)					
Annual payments for all services (all patients)	$27,013,330,265	$27,032,402,940	$19,072,676	$27,066,896,545	$53,566,280
Payment per member per month - overall (PMPMo)	$295.68	$295.89	$0.21	$296.27	$0.59

*TMS and ECT are assumed to have equivalent efficacy, therefore, no cost offset is considered due to improved response.
†Scenario 1 consists of 10% of patients treated with ECT, 10% with rTMS, and 80% under usual care.
‡Scenario 2 consists of 20% of patients treated with ECT, 10% with rTMS, and 70% under usual care.

Estimated Region-wide Budget Impact – Medicaid Only

Table 7 below shows the absolute number of patients represented in the Medicaid-only analysis. Uptake of rTMS among patients receiving Medicaid resulted in a 2.6-4.6% increase in payments for all patients with TRD. Total cost per patient treated with nonpharmacologic therapy ranged from $6,688 – $6,995 annually, depending on the uptake of rTMS (Table 8 on the following page).

Table 7. Estimated clinical impact of ECT and rTMS use in the Medicaid population.

	Baseline	Scenario 1*†	Net Change vs. Baseline	Scenario 2*‡	Net Change vs. Baseline
Summary of Covered Population					
Total membership (n)	1,167,700	1,167,700		1,167,700	
Patients with TRD (n)	39,468	39,468		39,468	
Patients with TRD receiving ECT and/or TMS (n)	7,893	7,893		11,840	
As a proportion of all members	0.7%	0.7%		1.0%	
As a proportion of patients with TRD	20.0%	20.0%		30.0%	
Outcomes & Resource Use					
Positive Treatment Response (n)	13,225	13,225	0	14,488	1,263
Positive Treatment Response (%)	33.5%	33.5%		36.7%	

*Note. This analysis is from the point of view of a third party payer, therefore, all patients are assumed to be covered.
†Scenario 1 consists of 10% of patients treated with ECT, 10% with rTMS, and 80% under usual care.
‡Scenario 2 consists of 20% of patients treated with ECT, 10% with rTMS, and 70% under usual care.

Table 8. Estimated economic impact of ECT and rTMS use in the Medicaid population.

		Scenario 1*†		Scenario 2*‡	
	Baseline	Payments	Net Change vs. Baseline	Payments	Net Change vs. Baseline
Payments per patient with TRD (n=039,468)					
ECT and/or TMS	$442	$614	$172	$835	$393
Outpatient Management & ER	$5,142	$5,142	$0	$5,110	($32)
Inpatient admissions	$1,103	$1,103	$0	$1,050	($53)
Total per patient	$6,688	$6,860	$172	$6,995	$308
Annual payments for all patients with TRD	$263,949,131	$270,732,493	$6,783,361	$276,085,572	$12,136,441
			2.6%		4.6%
Plan payments for Covered Population (n=1,167,700)					
Annual payments for all services (all patients)	$2,648,406,478	$2,655,189,839	$6,783,361	$2,660,542,918	$12,136,441
Payment per member per month - overall (PMPMo)	$189.00	$189.49	$0.48	$189.87	$0.87

*TMS and ECT are assumed to have equivalent efficacy, therefore, no cost offset is considered due to improved response.
†Scenario 1 consists of 10% of patients treated with ECT, 10% with rTMS, and 80% under usual care.
‡Scenario 2 consists of 20% of patients treated with ECT, 10% with rTMS, and 70% under usual care.

Estimated Region-wide Budget Impact – Private Payer

On a percentage basis, the increases in payments for private payers managing treatment of patients with TRD (Table 9 on the following page) were predicted to be incrementally less than predicted for Medicaid (ranging from 0.9% - 2.9% in total) given the assumed lower prevalence of TRD among private payer populations (Table 10 on the following page). Total cost per patient treated with nonpharmacologic therapy ranged from $11,146 – $11,467 annually, depending on the uptake of rTMS.

Table 9. Estimated clinical impact of ECT and rTMS use in a private payer population.

	Baseline	Scenario 1*†	Net Change vs. Baseline	Scenario 2*‡	Net Change vs. Baseline
Summary of Covered Population					
Total membership (n)	6,445,594	6,445,594		6,445,594	
Patients with TRD (n)	128,912	128,912		128,912	
Patients with TRD receiving ECT and/or TMS (n)	25,782	25,782		38,674	
As a proportion of all members	0.4%	0.4%		0.6%	
As a proportion of patients with TRD	20.0%	20.0%		30.0%	
Outcomes & Resource Use					
Positive Treatment Response (n)	43,196	43,196	0	47,320	4,124
Positive Treatment Response (%)	33.5%	33.5%		36.7%	

*Note. This analysis is from the point of view of a third party payer, therefore, all patients are assumed to be covered.
†Scenario 1 consists of 10% of patients treated with ECT, 10% with rTMS, and 80% under usual care.
‡Scenario 2 consists of 20% of patients treated with ECT, 10% with rTMS, and 70% under usual care.

Table 10. Estimated economic impact of ECT and rTMS use in a private payer population.

		Scenario 1*†		Scenario 2*‡	
	Baseline	Payments	Net Change vs. Baseline	Payments	Net Change vs. Baseline
Payments per patient with TRD (n=128,912)					
ECT and/or TMS	$737	$832	$95	$1,201	$464
Outpatient Management & ER	$8,571	$8,571	$0	$8,516	($54)
Inpatient admissions	$1,839	$1,839	$0	$1,750	($88)
Total per patient	$11,146	$11,241	$95	$11,467	$321
Annual payments for all patients with TRD	$1,436,858,324	$1,449,147,639	$12,289,314	$1,478,288,164	$41,429,840
			0.9%		2.9%
Plan payments for Covered Population (n=6,445,594)					
Annual payments for all services (all patients)	$24,364,923,787	$24,377,213,101	$12,289,314	$24,406,353,627	$41,429,840
Payment per member per month - overall (PMPMo)	$315.01	$315.17	$0.16	$315.54	$0.54

*TMS and ECT are assumed to have equivalent efficacy, therefore, no cost offset is considered due to improved response.
†Scenario 1 consists of 10% of patients treated with ECT, 10% with rTMS, and 80% under usual care.
‡Scenario 2 consists of 20% of patients treated with ECT, 10% with rTMS, and 70% under usual care.

Cost-Effectiveness of TRD Management Strategies

rTMS is associated with a 13.6% increase in the number of positive treatment responses over usual care over five years; in addition, the number of full remissions was 15.9% higher under the rTMS strategy (Table 11 on page 30). Note that a reference copy of Table 2 (model input parameters) follows this table (page 31) to assist in the interpretation of Table 11.

The cumulative discounted cost associated with managing patients with TRD treated with rTMS is estimated to be $35,550 per patient over five years compared with $31,296 for patients under usual care. This is driven entirely by treatment costs and represents a 13.6% increase in payments associated with managing TRD. When indirect, non-medical costs are considered, these estimates increase to $70,205 and $76,530 for rTMS and usual care, respectively.

A cost per life-year gained could not be estimated, as survival is assumed to be the same for each strategy. Quality adjusted life years differed by a factor of 0.5% favoring rTMS and yielding a cost/QALY gained of $216,468 per patient, based on discounted direct medical costs (Table 11, page 30). Improvements in treatment response with rTMS resulted in a cost per additional treatment response gained of $11,803 for rTMS.

When indirect costs were taken into consideration, the cost per QALY gained increased to $321,880 and the cost per additional treatment response increased to $17,551. While the improved treatment response with rTMS resulted in faster return to work for those employed, the increased time away from the workplace required when undergoing rTMS treatment itself shifted the balance toward higher indirect costs in the rTMS cohort.

Threshold analyses (based on direct medical costs only) were calculated to determine at what cost per-session of rTMS therapy must be priced to achieve cost neutrality and a cost/QALY gained of $100,000. At $104 per session, the cost/QALY gained is equal to $100,000; this per-session cost is approximately one-half of that estimated in the primary analysis ($206 per session). The difference in total costs of usual care and rTMS was zero at an estimated rTMS cost per session of $16. In each analysis, all other parameters were held constant.

Table 11. Cost-effectiveness of rTMS vs. usual care in patients with TRD over 5 years.

	Usual Care	rTMS	Difference TMS relative to Usual Care
Clinical Outcomes for 1000 patients			
Positive Treatment Response*	2,632	2,993	360
Remission†	2,421	2,806	385
Deaths	69	69	0.0
Life years	4,855	4,855	0.0
Quality adjusted life years (QALYs)	3,621	3,640	19.6
Cumulative Costs for 1000 patients			
rTMS therapy	$0	$4,918,352	$4,918,352
Outpatient & ER costs	$43,320,644	$42,787,610	($533,033)
Inpatient costs	$9,668,104	$9,285,806	($382,299)
Total Direct Medical Costs only‡	$31,296,246	$35,549,730	$4,253,483
Indirect Non-Medical costs§	$17,216,215	$19,537,966	$2,321,751
Total including Indirect costs	$70,204,963	$76,529,734	$6,324,770
Total cost per Patient			
Including Indirect costs	$70,205	$76,530	$6,325
Direct Medical Costs	$31,296	$35,550	$4,253
Life years per patient	4.85	4.85	0.00
QALY per patient	3.62	3.64	0.02
Cost-Effectiveness			
Cost/LYG			N/A
Cost/QALY (direct costs only)			$216,468
Cost/QALY (including indirect costs)			$321,880
Cost/Additional Treatment Response (direct costs only)			$11,803
Cost/Additional Treatment Response (including indirect costs)			$17,551

†HAM-D17 < 8, HAM-D21 < 10, or MADRS < 8.

‡Total direct medical costs is not equal to the sum of the components as it is discounted, whereas the components are undiscounted.

§Indirect costs include lost wages and payments from disability insurance.

Table 2 (reference copy). General model input parameters.

Unit Item	Input	Unit	Frequency	Unit
Population Characteristics				
Male patients	30%			
Mean age: Male/Female	45.5/45.4	Years		
Employment Status				
Full-Time	71.10%			
Part-Time	15.60%			
Unemployed	8.10%			
Disability	5.10%			
Payment Items – Private				
Outpatient Visits	$584	per visit	2.4	per year
Office Visits	$115	per visit	13.7	per year
Emergency Department	$1,089	per visit	0.3	per year
Pharmacy	$60	per script	31.2	per year
ECT	$433.58	per session	8	per course of therapy
rTMS planning	$246	per session	1	per course of therapy
rTMS delivery	$206	per session	20	per course of therapy
Inpatient Facility Admission	$11,296	per admission	0.1	admissions per year
Inpatient Professional Visit	$330	per visit	4.7	visits per admission
Indirect Cost Items				
Regional employment wage	$23.57	per hour		
Regional disability benefit	$962.58	per month		
Reason for Productivity Loss				
General depression overall	51.2	Days lost/year		
– Medically-related	13.5	Days lost/year		
– Disability	37.7	Days lost/year		
Usual care	0	Additional days lost/year		
rTMS treatment	11	Days lost/course of therapy		
Utility Items		Duration		
Baseline TRD - Male	0.708	Annual		
Baseline TRD – Female	0.708	Annual		
Death	0	Annual		
Change due to:				
– Aging	-0.00251	Annual		
– ECT	0	Per course		
– rTMS	0	Per course		
– Usual care	0	Per course		
– Response	0.0625	Per response		
– Remission	0.125	Per remission		
– Relapse	-0.0625	Per relapse		
– Serious Adverse Event	-0.1	Per event		

5.3 Conclusions

A 10% uptake in coverage of rTMS is projected to impact payer expenditures by 1.1 - 3.1% across New England, depending on whether rTMS replaces a portion of ECT use or is additive. On a per member per month (PMPM) basis, the impact ranges from $0.21 - $0.59, or a relatively modest 0.07 - 0.2% increase. Higher PMPM estimates were observed for the Medicaid-only population (0.3 - 0.5%), but remained modest. While actual decisions regarding whether to provide coverage for rTMS will require consideration of the tradeoffs involved by individual public and private payers in each state, the overall analysis presented here and the state-specific analyses shown in Appendix B should be of some assistance.

In trials and in this economic evaluation, rTMS therapy is associated with improved clinical outcomes relative to usual care. The estimated cost of a course of rTMS is $4,366 per patient which is projected to be partially offset by a reduction in resource use associated with improved outcomes. Achievement of a cost/QALY below $100,000 requires a projected 50% decrease in the cost of each rTMS treatment session relative to the base case estimate. Cost neutrality cannot be achieved with a singular change in payments unless one is willing to accept a 97% decrease in the cost of each rTMS session.

These results are subject to the assumptions underlying the model and must be interpreted with care. The AHRQ review (Gaynes, 2011) determined that, in general, existing evidence is still insufficient to draw conclusions regarding the comparative effectiveness of nonpharmacologic therapies such as rTMS and ECT. The outcomes associated with these strategies and with usual care were determined by data from the relatively few studies that were feasible to quantitatively analyze in the AHRQ review (Gaynes, 2011). The strongest evidence was for the relative outcomes of rTMS compared with usual care based on the meta-analyzed data in the report. In the budget impact analysis, data were too sparse to draw meaningful inferences about the relative outcomes, thus ECT and rTMS are assumed to be equivalent on response, remission, and relapse.

Another limitation of the model is that the long-term data to inform the subsequent course of therapy following treatment success or failure with ECT and rTMS are generally unavailable; so many assumptions were required to predict outcomes beyond the first 6-12 months following treatment. Moreover, management of TRD is often complex and highly variable across patients, and even the definition of TRD itself was inconsistent across studies, leading to significant challenges in defining the course of patients over time. Finally, the underlying resource use and payments were determined from a population of insured patients diagnosed with depression in the Northeastern U.S.; while these data are somewhat relevant, they may not be completely generalizable to each state's target population or to a more severe cohort of patients with TRD.

Taken as a whole, the model results provide an estimate of the impact of introducing rTMS therapy for CEPAC consideration. Specific point estimates should not be interpreted as absolute, rather as a guide for consideration of various scenarios that would involve the introduction of coverage for rTMS.

5.4 Comparison of ICER Analysis to Published Cost-Effectiveness Analyses

A single published study compared the cost-effectiveness rTMS to usual care (or "sham") with results ranging from an rTMS strategy resulting in overall cost savings to a cost per QALY gained of US$36,551 (Simpson, 2009). Results were highly dependent on the source of effectiveness data – randomized control trial vs. open-label study – and the inclusion of indirect, productivity costs. The primary reason for differences between these results and ours is that Simpson and colleagues had access to primary patient level data from which to derive more specific patient response categories (i.e., category of improvement in depression score) and other key inputs, as well, an estimation of model outcomes over a one-year time horizon compared with our five-year perspective. The mean cost of rTMS therapy in this study was US$7,792 as compared to our estimated cost of $4,366. This is likely due to the longer rTMS duration assumed by Simpson and colleagues.

Other published studies (McLoughlin, 2007, Knapp, 2008) compared the cost-effectiveness of ECT to rTMS. As these were conducted from the perspective of the health system in the United Kingdom, it is difficult to draw meaningful comparisons to their estimates given the inherent differences in health-system dynamics and cost.

6. Questions and Discussion

CEPAC members voted on questions concerning the comparative clinical effectiveness of the four treatment options discussed: 1) repetitive transcranial magnetic stimulation (rTMS); 2) electroconvulsive therapy (ECT); 3) vagus nerve stimulation; and 4) cognitive behavioral therapy/interpersonal therapy (CBT/IPT).

- **Comparative clinical effectiveness: rTMS vs. usual care**

  For patients who have TRD, is the evidence adequate to demonstrate that rTMS provides a net health benefit *equivalent* or *superior* to usual care (i.e., general supportive psychotherapy with or without continued use of antidepressant medication)?
  CEPAC Vote: 10 Yes 5 No

  a. If yes:
     - Is rTMS *equivalent* or *superior* to usual care?
       5 Equivalent 5 Superior

  b. If no, is this due to:
     - Inadequate evidence with which to judge comparative net health benefit
       5 Yes
     - Adequate evidence of an *inferior* net health benefit
       0 Yes

  Comments:

  - CEPAC desired greater clarity on the ideal number of treatment failures required before rTMS is used, since standard practice differs from the FDA label (one failed trial of antidepressants).
  - Although the majority of CEPAC voted that the evidence is adequate to suggest that rTMS is more effective than usual care, comments from some CEPAC members noted the need for more data on which patients are ideal candidates for rTMS.
  - Some members expressed concern about the potential for overutilization of rTMS without a standard definition of the ideal patient population.
  - Many CEPAC members who voted that the evidence was inadequate to determine if rTMS is as effective or better than usual care cited the dearth of evidence on the benefits of rTMS beyond the initial 4-6 week treatment phase.

- **Comparative clinical effectiveness: rTMS vs. ECT**

For patients who have TRD, is the evidence adequate to demonstrate that rTMS provides a net health benefit *equivalent* or *superior* to ECT?
CEPAC Vote: 9 Yes 6 No

a. If yes:
   - Is rTMS *equivalent* or *superior* to ECT?
     9 Equivalent 0 Superior

b. If no, is this due to:
   - Inadequate evidence with which to judge comparative net health benefit
     6 Yes
   - Adequate evidence of an *inferior* net health benefit
     0 Yes

Comments:

- CEPAC emphasized the need to identify the subpopulations that would benefit more from each therapy. Some CEPAC members suggested the need to establish target subpopulations for each treatment, with more severe patients receiving ECT and less severe patients receiving rTMS.

- **Comparative clinical effectiveness: ECT vs. usual care**

For patients who have TRD, is the evidence adequate to demonstrate that ECT provides a net health benefit *equivalent* or *superior* to usual care (i.e., general supportive psychotherapy with or without continued use of antidepressant medication)?
CEPAC Vote: 3 Yes 11 No 1 Abstain

a. If yes:

   - Is ECT *equivalent* or *superior* to usual care?
     0 Equivalent 3 Superior

b. If no, is this due to:

   - Inadequate evidence with which to judge comparative net health benefit
     11 Yes
   - Adequate evidence of an *inferior* net health benefit
     0 Inferior

Comments:

- Several CEPAC members qualified their "no" vote on the evidence for ECT with recognition that ECT is an older treatment adopted in an era with far lower standards for evidence on clinical effectiveness. CEPAC members acknowledged that ECT is accepted broadly as standard of care for patients with severe depression who need immediate treatment due to features including catatonia, psychosis, active suicidal ideation, and serial failure to respond to drug treatment.
- The one abstention vote was predicated on the lack of data regarding the appropriate patient population to receive ECT.

- **Comparative clinical effectiveness: VNS vs. usual care**

For patients who have TRD, is the evidence adequate to demonstrate that VNS provides a net health benefit *equivalent* or *superior* to usual care (i.e., general supportive psychotherapy with or without continued use of antidepressant medication)?
CEPAC Vote: 0 Yes 15 No

a. If yes:
N/A

b. If no, is this due to:
- Inadequate evidence with which to judge comparative net health benefit
15 Yes
- Adequate evidence of an *inferior* net health benefit
0 Yes

- **Comparative clinical effectiveness: CBT/IPT vs. usual care**

For patients who have TRD, is the evidence adequate to demonstrate that CBT/IPT provides a net health benefit *equivalent* or *superior* to usual care (i.e., general supportive psychotherapy with or without continued use of antidepressant medication)?
CEPAC Vote: 6 Yes 9 No

a. If yes:
- Is CBT/IPT *equivalent* or *superior* to usual care?
6 Equivalent 0 Superior

b. If no, is this due to:
- Inadequate evidence with which to judge comparative net health benefit
9 Yes
- Adequate evidence of an *inferior* net health benefit
0 Yes

Comparative Value

When a majority of CEPAC votes that the evidence is adequate to demonstrate that an intervention produces patient outcomes equivalent or superior to a reference option, the Council members are also asked to vote on whether the intervention represents a "high," "reasonable," or "low" value. The value "perspective" that members of CEPAC are asked to assume is that of a state Medicaid program that must make resource decisions within a fixed budget for care. While information about hypothetical budget tradeoffs are provided, CEPAC is not given prescribed boundaries or thresholds for budget impact, PMPM changes, or incremental cost-effectiveness ratios to guide its judgment of high, reasonable, or low value. For each vote on comparative value Council members are asked to complete a multi-criteria decision analysis scoring sheet to make more transparent how they weighed different criteria in their ultimate judgment of comparative value. Only those CEPAC members who vote that the evidence is adequate to demonstrate equivalent or superior clinical effectiveness are asked to vote on comparative value.

Votes on Comparative Value

In response to public comment provided in advance of the December 9 meeting, an additional analysis was conducted prior to voting. The comment suggested that a more relevant comparison might be the use of rTMS as an *adjunct* to usual care vs. usual care with another adjunctive therapy (e.g., CBT, adding an antipsychotic drug). A simple calculation was made to address this by adding the median cost of antipsychotic therapy observed in a TRD cohort study (Ivanova, 2010) and applying it to the cost-effectiveness model; no change in effectiveness was assumed. Over 5 years, this change would be estimated to increase the direct cost of usual care to approximately $3,370 per patient, thereby decreasing the incremental cost of rTMS to approximately $1,900, and the resulting cost per QALY gained to $98,000.

1. rTMS vs. usual care
Based on reimbursement levels provided with this report, would you judge the comparative value of rTMS to be of 1) high value; 2) reasonable value; or 3) low value compared to usual care?
CEPAC Vote: 4 Low 6 Reasonable

Multi-criteria decision analysis voting was done by all voting CEPAC members in order to describe their judgment and weighting of several criteria potentially relevant to an overall rating of comparative value. The results for the vote on rTMS vs. usual care is shown in the table below on the following page:

Table of Multi-criteria decision analysis votes.

Possible Factors in Your Judgment of "Comparative Value"	Rating from lowest to highest (0 – 5) of each factor for this intervention		Rating of how important this factor was in overall judgment of comparative value	
	Vote Average	Vote Range	Vote Average	Vote Range
Magnitude of the net clinical benefit compared with other available options	2.8	0 – 5	4	3 – 5
Confidence in the evidence on comparative clinical benefit	2.2	0 - 5	4.1	3 -5
Magnitude of improvement in safety and tolerability	2.7	0 -5	3.4	0 -5
Confidence in the evidence on improvement of safety and tolerability	2.9	1 - 5	2.9	0 – 4
Magnitude of the incremental cost-effectiveness ratio (ICER)	2.4	0 -4	3.1	1 – 5
Confidence in the accuracy of the ICER	2.6	1 – 5	2.6	1 – 5
Budget impact/opportunity cost (other potential uses for $$)	3.2	1 – 5	3.4	1 – 5
Other reasonable treatment options are available	2.1	0 – 5	3.6	0 – 5
Severity of the condition	3.8	1 – 5	3.4	0 - 5
Ability of the intervention to address healthcare disparities	1.5	0 – 5	1.6	0 – 5
Support for the intervention from clinicians	2.3	0 – 5	2.0	0 – 5
Special (vulnerable) population	3.5	1 – 5	3.4	1 – 5
Risk of overuse or misuse	3.2	1 – 5	2.8	1 – 5

2. rTMS vs. ECT

Based on reimbursement levels provided with this report, would you judge the comparative value of rTMS to be of 1) high value; 2) reasonable value; or 3) low value compared to ECT?

CEPAC Vote: 5 Low 3 Reasonable 1 High

Multi-criteria decision analysis results for the comparative value votes on rTMS vs. ECT are shown in the table on the following page:

Table of multi-criteria decision analysis votes.

Possible Factors in Your Judgment of "Comparative Value"	Rating from lowest to highest (0 – 5) of each factor for this intervention		Rating of how important this factor was in overall judgment of comparative value	
	Vote Average	Vote Range	Vote Average	Vote Range
Magnitude of the net clinical benefit compared with other available options	2.5	0 – 5	3.875	1 – 5
Confidence in the evidence on comparative clinical benefit	1.6	1 – 4	3.5	1 – 5
Magnitude of improvement in safety and tolerability	3.1	0 -5	3.25	0 – 5
Confidence in the evidence on improvement of safety and tolerability	2.5	0 – 4	3.125	0 – 5
Magnitude of the incremental cost-effectiveness ratio (ICER)	2.0	0 – 5	2.5	1 – 5
Confidence in the accuracy of the ICER	2.4	1 – 5	3.125	1 – 5
Budget impact/opportunity cost (other potential uses for $$)	2.4	0 – 5	2.75	0 – 5
Other reasonable treatment options are available	3.1	0 – 5	3.5	0 – 5
Severity of the condition	3.6	0 – 5	4.25	3 – 5
Ability of the intervention to address healthcare disparities	2.3	0 – 5	2.286	0 – 4
Support for the intervention from clinicians	2.8	0 – 5	2.75	0 – 5
Special (vulnerable) population	2.8	0 – 5	2.75	0 – 5
Risk of overuse or misuse	2.7	0 – 5	3.286	0 – 5

Social value considerations for policymakers

The final question of the meeting explored broader considerations of public health, equity, and access:

- Are there any considerations related to public health, equity, disparities in access or outcomes for specific patient populations, or other social values that should be considered in medical policies related to the use of rTMS, ECT, VNS, or CBT/IPT?

CEPAC voiced concern that with no third party reimbursement for rTMS, only patients who can afford to pay out-of-pocket can obtain treatment. Therefore, there may be concerns over equity in access to rTMS for certain populations.

Roundtable Discussion
Following the CEPAC votes and deliberation of the evidence, CEPAC engaged in a roundtable discussion with a panel composed of two representatives from the clinical expert community and two representatives of regional private health plans. The goal of the roundtable was to explore the implications of CEPAC votes for clinical practice and payer policies. The topics discussed included:

Future Research
Panelists outlined the gaps in current evidence and outlined future research needs to support future coverage decisions, including evidence of the long-term health benefit and duration of effect for rTMS. Panelists also indicated their concern for the shortage of funding for these types of clinical trials.

Coverage considerations
Payer representatives and CEPAC discussed the prospect of using specific medical policies for rTMS such as coverage with evidence development, patient registries, and limited networks with centers of excellence, but voiced concern for the practicalities of each. Payers at the table cautioned that with such a significant population in need of interventions to treat resistant-depression, that centers of excellence and limited networks may not be able to accommodate the demand for these services, and that payers will have to be able to prioritize which patients receive treatment if coverage becomes available.

Payers also stressed their concerns for indication creep if rTMS became available for everyone to use, highlighting that without further evidence on the specifics of treatment duration, maintenance therapy, and selection in the appropriate patient population, that rTMS could be used inappropriately.

Policy Implications:

<u>Physician Specialty Societies</u>

- Professional societies should lead the effort in establishing training and practice standards and promote the development of registries to monitor outcomes of patients receiving treatment for TRD that can be used to guide quality improvement.
- Professional societies should develop clinical guidelines for TRD that include recommendations for : 1) the appropriate subpopulations to receive treatment with rTMS and ECT; 2) treatment duration and frequency for rTMS; 3) maintenance therapy requirements; and 4) the threshold for previously failed treatments required before considering rTMS.

<u>Hospitals and other clinical providers</u>

- Each hospital providing treatment for TRD should participate in registries to gather data on the short and long-term outcomes of patients undergoing ECT or rTMS. The data derived from these registries should be used to guide internal quality improvement and inform the

appropriateness of each therapy for various subpopulations as well as an evaluation of the long-term outcomes for patients receiving treatment for TRD.

Payers

- If payers elect to cover rTMS, they should consider limiting coverage to patients with ≥ 2 failed drug treatments during the most recent episode of depression, a higher threshold than that included in the FDA license. In addition, payers should consider options for limiting coverage to designated centers of excellence, perhaps with an additional requirement for continued evidence generation through a national registry to be organized by professional societies. These limitations would be useful to assure the following: 1) consistent, rigorous training standards are established for providers; and 2) coverage will support rather than hinder efforts to gather further evidence to help guide future patient, provider, and payer decisions regarding appropriate patient selection for both rTMS and ECT. Payers on the roundtable voiced concerns for the feasibility and practicality of a centers of excellence approach for coverage of rTMS due to the large number of patients potentially eligible for this service and the consequent difficulty of assuring equitable access. All participants on the roundtable agreed that it is difficult to find funding to support large, effective registries.

7. Public Comment

Members of the public were invited to submit public comment on the draft supplementary report during the period of November 16, 2011 to December 21, 2011. The following organizations submitted and/or presented public comments:

- David G. Brock, M.D., Medical Director, Neuronetics, Inc.
- Jeffrey C. Fetter, M.D. and Paul Holzheimer, M.D., Executive Council to the New Hampshire Psychiatric Society
- Patricia R. Recupero, J.D., M.D. President and CEO, and colleagues, Butler Hospital
- Linda Carpenter, MD, Butler Hospital

The complete statements provided to CEPAC can be accessed via the CEPAC website.

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Appendix A

Study Citation **Research Objective**	**Study Characteristics**	**Patient Population**	**Study Outcomes**	**Adverse Events** **Quality of Life**
Author, Year: Azuma H. et al., 2011 *Research Objective:* Evaluation of the association of ictal peak HR and ictal EEG markers with the efficacy of ECT	*Study Design:* Case series N=53 *Study Duration:* 20 days (10 days before and after an ECT session) *Intervention:* ECT Location: bilaterally to fronto-temporal region Intensity: minimum seizure duration of 20 sec.; if missed or abortive (<20 sec.), increased pulse wave stimuli by 10% up to 100%, for a maximum of 3 stimulations per session *Medications Allowed:* Antidepressants, which remained unchanged throughout study; benzodiazepines, antipsychotics, antiparkinson medications and antihypertensives allowed; lithium and anti-epileptics discontinued	Depressed in-patients who had not responded to at least 4 weeks of pharmacotherapy *Mean age:* 49.6 years *Gender:* 31 males, 22 females *Diagnosis:* MDD, 49 BD, 4 *Mean duration of current episode:* 21.0 months *Mean number of previous episodes:* 1.7 *Mean pre-treatment GRID-HAMD score:* 20.2	*Mean post-treatment GRID-HAMD score:* 10.2 ($p<0.001$) *Remitters* (50% reduction of baseline GRID-HAMD score, and score ≤ 7 points on post-treatment GRID-HAMD score): N=16 (30.2%) *Responders* (50% reduction of baseline GRID-HAMD score): N=26 (49.1%) Peak HR and postictal suppression index were associated with therapeutic efficacy in remitters with adequate seizures	No assessment conducted

Study Citation Research Objective	Study Characteristics	Patient Population	Study Outcomes	Adverse Events Quality of Life
Author, Year: Baeken C. et al., 2011 *Research Objective:* Assessment of impact of HF rTMS therapy on post-synaptic 5-HTA_{2A} receptor binding indices	*Study Design:* Prospective matched cohort N=42 *Study Duration:* At least 4 weeks (unspecified washout period, followed by 2 week period without antidepressants or psychotropic medications, then a 2 week period of rTMS sessions) *Intervention:* **Group 1** HF-rTMS Location: left and right DLPFC Frequency: 10 Hz Intensity: 110% of patient's resting motor threshold Number of trains: 40 Length of trains: 3.9 sec. Inter-train interval: 26.1 sec. Number of sessions: 10 daily, over 2 week *Medications Allowed:* Benzodiazepines; all antidepressants and psychotropic agents were discontinued **Group 2** No intervention	**Group 1** Unipolar depressed patients of melancholic subtype For current depressive episode, all patients had at least 2 unsuccessful trials of SSRI/SNRI medications and 1 failed trial of TCA therapy *Overall mean age:* 45.3 years *Overall gender:* 8 males, 13 females **Group 2** Healthy, age-and sex-matched individuals with no history of depression *Overall mean age:* 42.1 years *Overall gender:* 8 males, 13 females	**Group 1** *Responders* (50% reduction of baseline HDRS) *Mean baseline HDRS score:* 26.67 *Mean post HDRS score:* 9.11 *Non-responders* *Mean baseline HDRS score:* 24.75 *Mean post HDRS score:* 21.25 Compared with the control group, depressed patients had less baseline 5-HTA_{2A} receptor binding indices in the DLPFC, and higher 5-HTA_{2A} receptor binding indices in the left hippocampus Better outcomes with HF-rTMS were associated with a decrease in the right hippocampal 5-HTA_{2A} receptor binding, and positively correlated with bilateral 5-HTA_{2A} receptor binding indices in the DLPFC	No assessment conducted

Study Citation Research Objective	Study Characteristics	Patient Population	Study Outcomes	Adverse Events Quality of Life
Author, Year: Berlim M. et al, 2011 *Research Objective:* Evaluation of HF-rTMS as an augmenting therapy over a broad range of clinical and subjective outcomes in treatment-resistant MDD	*Study Design:* Case series N=15 *Study Duration:* 4 weeks *Intervention:* HF rTMS Location: left DLPFC Frequency: 10 Hz Intensity: 120% of resting motor threshold Number of trains: 75 Length of trains: 4 sec. Inter-train interval: 26 sec. Number of sessions: 5 daily per week for a total of 20 sessions *Medications Allowed:* Current stable doses of psychotropic medications, and benzodiazepines, which were titrated as needed	Patients with moderate to severe MD and current diagnosis of a moderate current major depressive episode Patients had failed to respond to at least 3 courses of antidepressants from at least 2 different classes during current episode *Mean age:* 47 years *Gender:* 7 males, 8 females *Mean duration of current episode:* 68 months *Mean number of previous episodes:* 1.53 *Mean pre-treatment HAM-D_{21}:* 29.87 *Mean pre-treatment WHOQOL-Bref – physical QOL:* 32.85 *Mean pre-treatment WHOQOL-Bref – psychological QOL:* 28.61	*Mean post-treatment HAM-D_{21}:* 25.27 (p=0.035) Significant reductions were also measured in the IDS-SR_{30}, HAM-A, BAI and CGI-S scales	1 patient withdrew because of scalp pain *Mean post-treatment WHOQOL-Bref – physical QOL:* 39.12 (p=0.028) *Mean post-treatment WHOQOL-Bref – psychological QOL:* 28.61 (p=0.041) Significant improvement was seen in the WHOQOL-Bref – overall QOL No significant changes were noted in the social and environmental domains of the WHOQOL-Bref.

Study Citation Research Objective	Study Characteristics	Patient Population	Study Outcomes	Adverse Events Quality of Life
Author, Year: Domschke K. et al., 2010 *Research Objective:* Analysis of the effects on ECT response in TRD patients with the COMT val158met genotypic polymorphism	*Study Design:* Case series N=104 *Study Duration:* Ranging from a mean of 7.6 to 8.4 weeks *Intervention:* ECT Location: right, unilateral (6 patients switched to bilateral therapy due to insufficient response) Intensity: minimum seizure duration of 25 sec.; restimulation included dosage elevation in 5-10% steps *Medications Allowed:* Antidepressants, neuroleptics and anxiolytics	Patients with current major depression with pharmacologically treatment-resistant disease, having failed at least 2 courses of antidepressant therapy *Mean age:* 56.6 years *Gender:* 33 males, 71 females *Mean number of previous episodes:* 3.7 *Mean pre-treatment HAM-D_{21}:* 22.9	*Mean post-treatment HAM-D_{21}:* 9.1 ($p < 0.0005$) *Responders:* (>50% reduction of HAM-D) 67/104 *Non-responders:* (≤ 50% decrease in HAM-D) 37/104 The more active allele of COMT 158val was significantly associated with pre-ECT severity of depression, particularly in female patients; these carriers also responded significantly better to ECT therapy	No analysis conducted

Study Citation Research Objective	Study Characteristics	Patient Population	Study Outcomes	Adverse Events Quality of Life
Author, Year: Holtzheimer P.E. et al., 2010 *Research Objective:* Evaluation of the safety and efficacy of accelerated rTMS (aTMS) in depressed patients	*Study Design:* Case series N=14 *Study Duration:* 6 weeks *Intervention:* aTMS Location: left DLPFC Frequency: 10 Hz Intensity: 100% of motor threshold Number of trains: 20 per hour-long session Length of trains: 5 sec. Inter-train interval: 25 sec. Number of sessions: 5 consecutive sessions on Day 1; 10 consecutive sessions on Day 2 *Medications Allowed:* No specific restrictions; patients needed to maintain stable dosing throughout study	Depressed patients in a current major depressive episode, with ≤ 3 adequate medication failures in current episode *Median age:* 51 years (range 20-74) *Gender:* 9 males, 5 females *Diagnosis:* MDD, 13 BD, 1 *Median duration of current episode:* 9 months (range 3-96) *Median number of previous episodes:* 4 (range 2-8) *Mean baseline HDRS24 score:* 24.6	At 6 weeks (n=9): *Mean HDRS24:* 11.1 (p< 0.001) *Responders:* (≥ 50% decrease in baseline HDRS24) 5/14 *Remitters:* (HDRS24 ≤ 10) 4/14 Significant decreases were noted in HAM-A, RBANS and BDI	1 patient discontinued the trial due to increased suicidal ideation 1 patient required a decrease in stimulation intensity due to tolerability and subsequently dropped out of the trial No seizures occurred

Study Citation Research Objective	Study Characteristics	Patient Population	Study Outcomes	Adverse Events Quality of Life
Author, Year: Jhanwar V.G. et al., 2011 *Research Objective:* Assessment of the safety and efficacy of augmenting therapy with rTMS in patients with MDD who do not respond to a standard antidepressant	*Study Design:* Case series N= 21 *Study Duration:* 4 weeks *Intervention:* rTMS Location: left DLPFC Frequency: 10 Hz Intensity: 110% of patient's motor threshold Number of trains: 25 Length of trains: 5 sec. Inter-train interval: 25 sec. Number of sessions: 20 sessions over 4 weeks *Medications Allowed:* No specific restrictions, except no changes were allowed after inclusion into the study	Patients with MDD, without psychotic features, with at least 2 adequate trials of antidepressants *Mean age:* 38 years *Gender:* 13 males, 8 females *Mean duration of current episode:* 36.57 months *Mean baseline HAM-D17 score:* 30.80	*Mean post-treatment HAM-D17 score:* 19.00 ($p< 0.001$) A significant decrease in CGI-C was also noted.	No study dropouts were due to adverse events. 4 patients reported headache and pain over left scalp during treatment that ceased with termination of rTMS No patients developed new onset of seizures There were no patient reports of memory or cognitive side effects There was no impact of rTMS on blood pressure or heart rate during treatment

Study Citation Research Objective	Study Characteristics	Patient Population	Study Outcomes	Adverse Events Quality of Life
Author, Year: Kito S. et al., 2011 *Research Objective:* Analysis of changes in cerebral blood flow following low-frequency right prefrontal stimulation (LFRS) and neuroanatomical correlates of therapeutic efficacy in patients with TRD	*Study Design:* Case series N=26 *Study Duration:* 5 weeks *Intervention:* rTMS Location: right DLPFC Frequency: 1 Hz Intensity: 100% of resting motor threshold Number of trains: 5 Length of trains: 60 sec. Inter-train interval: 60 sec. Number of sessions: 12 sessions over 3 weeks *Medications Allowed:* No specific restrictions; however no changes allowed 4 weeks prior to, and throughout study	Patients diagnosed with MDD (unipolar) with failed response to a minimum of 2 courses of antidepressants from different classes, in the current episode *Mean age:* 46.19 years *Gender:* 14 males, 12 females *Mean duration of current episode:* 11.42 months *Mean number of previous episodes:* 3.12 *Mean baseline HDRS score:* 22.65	*Mean post-treatment HDRS score:* 11.92 ($p< 0.001$) *Responders:* (50% reduction in HDRS from baseline) 11/26 *Remitters:* (HDRS <8) 4/11 responders *Non-responders:* 15/26 No areas with significantly increased cerebral blood flow were identified following LFRS Significant decreases were seen in regional cerebral blood flow, with correlation to therapeutic efficacy of LFRS in areas such as the right prefrontal cortex and the bilateral orbitofrontal cortex	No analysis conducted

Study Citation Research Objective	Study Characteristics	Patient Population	Study Outcomes	Adverse Events Quality of Life
Author, Year: Minelli A. et al., 2011 *Research Objective:* Evaluation of impact of ECT on VEGF serum levels in TRD patients	*Study Design:* Case series N=19 *Study Duration:* 1 month *Intervention:* ECT Location: bilateral frontotemporal region Intensity: NR Conditions: Max charge, 504 mC Current, 0.9 A Frequency 30-70 Hz Pulse width, 1 ms Max duration 8 sec. *Medications Allowed:* Concurrent medications maintained for 3 weeks prior to and throughout study	Patients with TRD MDD (unipolar) with failure to respond to at least 2 adequate trials of 2 or more antidepressants classes, and to an adequate trial of a TCA *Mean age:* 54.84 years *Gender:* 4 males, 15 females *Mean baseline MADRS:* 34.32	*Mean post-treatment MADRS:* 7.42 ($p< 0.001$) VEGF serum concentrations significantly increased from baseline to the end of the study A significant correlation was found between the increase in VEGF at 1 month and the decrease in MADRS score	No analysis conducted

Study Citation Research Objective	Study Characteristics	Patient Population	Study Outcomes	Adverse Events Quality of Life
Author, Year: Oulis P. et al., 2011 *Research Objective:* Investigation of QTc interval changes associated with concomitant ECT and atypical antipsychotic/antidepressant therapy	*Study Design:* Case series N=6 *Study Duration:* 10 to 11 sessions *Intervention:* ECT Location: bilateral application, location NR Intensity: NR *Medications Allowed:* All patients received antidepressant therapy along with low doses of atypical antipsychotics	Patients with MDD and resistant to combination therapy with antidepressant and atypical antipsychotic medications *Mean age:* 50 years *Gender:* 6 females	QTc interval changes remained within normal limits just prior to and throughout ECT administration (up to 10 minutes afterwards)	No adverse cardiac events occurred in patients, including arrhythmias such as torsade de pointes

Study Citation Research Objective	Study Characteristics	Patient Population	Study Outcomes	Adverse Events Quality of Life
Author, Year: Sperling W. et al., 2011 *Research Objective:* Assessment of gustatory and olfactory perception during VNS therapy in patients with refractory depression	*Study Design:* Case series N=9 *Study Duration:* NR *Intervention:* VNS Intensity: 1.25 mA Frequency: 20 Hz Pulse width: 500 µs On mode: 30 sec. on, 5 min. off Off mode: 30 min. off *Medications Allowed:* No concurrent medications allowed 2 weeks prior to and throughout study	Therapy-resistant patients with a major depressive episode *Mean age:* 51.6 years *Gender:* 6 males, 3 females *Mean baseline HAM-D17 score:* 10.89	No statistically significant changes assessed during on and off mode VNS therapy Significant changes in the intensity of taste perception were demonstrated during the on mode of VNS, particularly with "sweet" and "bitter"	No analysis conducted

Abbreviations:

5-HTA_{2A}: a serotonin receptor; A: amps; aTMS: accelerated repetitive transcranial magnetic stimulation; BAI: Beck Anxiety Inventory; BD: bipolar disorder; BDI: Beck Depression Inventory-2; CGI-C: Clinical Global Impression - change subscae; CGI-S: Clinical Global Impression-severity subscale; COMT: catechol-O-methyltransferase; DLPFC: dorsolateral pre-frontal cortex; ECT: electroconvusive therapy; EEG: electroencephalogram; GRID-HAMD: standardized administration and scoring of the HAMD; HAM-A: Hamilton Anxiety Rating Scale; HAMD: Hamilton Depression Rating Scale; HDRS: Hamilton Depression Rating Scale; HF: high frequency; HR: heart rate; Hz: herz; IDS-SR_{30}: 30 item Inventory of Depressive Symptomatology; LFRS: low-frequency right pre-frontal stimulation; MADRS: Montgomery and Asberg Depression and Rating Scale; mC: milliCoulomb; MDD or MD: major depressive disorder; ms: millisecond; NR: not reported; QOL: quality of life; QTc: corrected QT interval; RBANS: Repeatable Battery for the Assessment of Neuropsychological Status; rTMS: repetitive transcranial magnetic stimulation; TCA: tricyclic antidepressant; TRD: treatment-resistant depression; VEGF: vascular endothelial growth factor; VNS: vagus nerve stimulation; WHOQOL: World Health Organization's quality of life measure, brief version

Appendix B

Budget Impact by State

Connecticut

	Medicaid		Private Payer		Overall
	n	%	n	%	
Covered Populations*					
Total membership (n)	163,800	11%	1,383,791	89%	1,547,591
Prevalence of TRD		3.4%		2.0%	2.1%
Patients with TRD (n)		5,536		27,676	33,212

*Note that uninsured patients are not represented in this analysis as there is no direct impact to a third party payer.

Table B1. Connecticut: Estimated Clinical Impact of ECT and TMS in an Insured Population.

	Baseline	Scenario 1*†	Net Change vs. Baseline	Scenario 2*‡	Net Change vs. Baseline
Summary of Covered Population					
Total membership (n)	1,547,591	1,547,591		1,547,591	
Patients with TRD (n)	33,212	33,212		33,212	
Patients with TRD receiving ECT and/or TMS (n)	6,642	6,642		9,963	
As a proportion of all members	0.4%	0.4%		0.6%	
As a proportion of patients with TRD	20.0%	20.0%		30.0%	
Outcomes & Resource Use					
Positive Treatment Response (n)	11,129	11,129	0	12,191	1,062
Positive Treatment Response (%)	33.5%	33.5%		36.7%	

*Note. This analysis is from the point of view of a third party payer, therefore, all patients are assumed to be covered.
†Scenario 1 consists of 10% of patients treated with ECT, 10% with rTMS, and 80% under usual care.
‡Scenario 2 consists of 20% of patients treated with ECT, 10% with rTMS, and 70% under usual care.

Table B2. Connecticut: Estimated Economic Impact of ECT and TMS Use in an Insured Population (2010 US dollars).

		Scenario 1*†		Scenario 2*‡	
	Baseline	Payments	Net Change vs. Baseline	Payments	Net Change vs. Baseline
Payments per patient with TRD (n=033,212)					
ECT and/or TMS	$688	$796	$108	$1,140	$452
Outpatient Management & ER	$7,999	$7,999	$0	$7,949	($50)
Inpatient admissions	$1,716	$1,716	$0	$1,634	($82)
Total per patient	$10,403	$10,511	$108	$10,722	$319
Annual payments for all patients with TRD	$345,501,751	$349,091,659	$3,589,908	$356,098,685	$10,596,933
			1.0%		3.1%
Plan payments for Covered Population (n=1,547,591)					
Annual payments for all services (all patients)	$5,602,361,390	$5,605,951,298	$3,589,908	$5,612,958,323	$10,596,933
Payment per member per month - overall (PMPMo)	$301.67	$301.86	$0.19	$302.24	$0.57

*TMS and ECT are assumed to have equivalent efficacy, therefore, no cost offset is considered due to improved response.
†Scenario 1 consists of 10% of patients treated with ECT, 10% with rTMS, and 80% under usual care.
‡Scenario 2 consists of 20% of patients treated with ECT, 10% with rTMS, and 70% under usual care.

Maine

	Medicaid		Private Payer		Overall
	n	%	n	%	
Covered Populations*					
Total membership (n)	135,700	14%	807,396	86%	943,096
Prevalence of TRD		3.4%		2.0%	2.2%
Patients with TRD (n)		4,587		16,148	20,735

*Note that uninsured patients are not represented in this analysis as there is no direct impact to a third party payer.

Table B3. Maine: Estimated Clinical Impact of ECT and TMS in an Insured Population.

	Baseline	Scenario 1*†	Net Change vs. Baseline	Scenario 2*‡	Net Change vs. Baseline
Summary of Covered Population					
Total membership (n)	943,096	943,096		943,096	
Patients with TRD (n)	20,735	20,735		20,735	
Patients with TRD receiving ECT and/or TMS (n)	4,147	4,147		6,221	
As a proportion of all members	0.4%	0.4%		0.7%	
As a proportion of patients with TRD	20.0%	20.0%		30.0%	
Outcomes & Resource Use					
Positive Treatment Response (n)	6,948	6,948	0	7,611	663
Positive Treatment Response (%)	33.5%	33.5%		36.7%	

*Note. This analysis is from the point of view of a third party payer, therefore, all patients are assumed to be covered.
†Scenario 1 consists of 10% of patients treated with ECT, 10% with rTMS, and 80% under usual care.
‡Scenario 2 consists of 20% of patients treated with ECT, 10% with rTMS, and 70% under usual care.

Table B4. Maine: Estimated Economic Impact of ECT and TMS Use in an Insured Population (2010 US dollars).

		Scenario 1*†		Scenario 2*‡	
	Baseline	Payments	Net Change vs. Baseline	Payments	Net Change vs. Baseline
Payments per patient with TRD (n=020,735)					
ECT and/or TMS	$672	$784	$112	$1,120	$448
Outpatient Management & ER	$7,812	$7,812	$0	$7,763	($49)
Inpatient admissions	$1,676	$1,676	$0	$1,595	($81)
Total per patient	$10,160	$10,272	$112	$10,478	$318
Annual payments for all patients with TRD	$210,659,418	$212,987,121	$2,327,703	$217,259,446	$6,600,028
			1.1%		3.1%
Plan payments for Covered Population (n=0,943,096)					
Annual payments for all services (all patients)	$3,359,804,248	$3,362,131,951	$2,327,703	$3,366,404,276	$6,600,028
Payment per member per month - overall (PMPMo)	$296.88	$297.08	$0.21	$297.46	$0.58

*TMS and ECT are assumed to have equivalent efficacy, therefore, no cost offset is considered due to improved response.
†Scenario 1 consists of 10% of patients treated with ECT, 10% with rTMS, and 80% under usual care.
‡Scenario 2 consists of 20% of patients treated with ECT, 10% with rTMS, and 70% under usual care.

Massachusetts

	Medicaid		Private Payer		Overall
	n	%	n	%	
Covered Populations*					
Total membership (n)	690,900	22%	2,396,386	78%	3,087,286
Prevalence of TRD		3.4%		2.0%	2.3%
Patients with TRD (n)		23,352		47,928	71,280

*Note that uninsured patients are not represented in this analysis as there is no direct impact to a third party payer.

Table B5. Massachusetts: Estimated Clinical Impact of ECT and TMS in an Insured Population.

	Baseline	Scenario 1*†	Net Change vs. Baseline	Scenario 2*‡	Net Change vs. Baseline
Summary of Covered Population					
Total membership (n)	3,087,286	3,087,286		3,087,286	
Patients with TRD (n)	71,280	71,280		71,280	
Patients with TRD receiving ECT and/or TMS (n)	14,256	14,256		21,384	
As a proportion of all members	0.5%	0.5%		0.7%	
As a proportion of patients with TRD	20.0%	20.0%		30.0%	
Outcomes & Resource Use					
Positive Treatment Response (n)	23,885	23,885	0	26,165	2,280
Positive Treatment Response (%)	33.5%	33.5%		36.7%	

*Note. This analysis is from the point of view of a third party payer, therefore, all patients are assumed to be covered.
†Scenario 1 consists of 10% of patients treated with ECT, 10% with rTMS, and 80% under usual care.
‡Scenario 2 consists of 20% of patients treated with ECT, 10% with rTMS, and 70% under usual care.

Table B6. Massachusetts: Estimated Economic Impact of ECT and TMS Use in an Insured Population (2010 US dollars).

		Scenario 1*†		Scenario 2*‡	
	Baseline	Payments	Net Change vs. Baseline	Payments	Net Change vs. Baseline
Payments per patient with TRD (n=071,280)					
ECT and/or TMS	$640	$761	$120	$1,081	$441
Outpatient Management & ER	$7,447	$7,447	$0	$7,400	($47)
Inpatient admissions	$1,598	$1,598	$0	$1,521	($77)
Total per patient	$9,685	$9,806	$120	$10,002	$317
Annual payments for all patients with TRD	$690,377,139	$698,959,694	$8,582,555	$712,961,042	$22,583,903
			1.2%		3.3%
Plan payments for Covered Population (n=3,087,286)					
Annual payments for all services (all patients)	$10,625,552,550	$10,634,135,105	$8,582,555	$10,648,136,452	$22,583,903
Payment per member per month - overall (PMPMo)	$286.81	$287.04	$0.23	$287.42	$0.61

*TMS and ECT are assumed to have equivalent efficacy, therefore, no cost offset is considered due to improved response.
†Scenario 1 consists of 10% of patients treated with ECT, 10% with rTMS, and 80% under usual care.
‡Scenario 2 consists of 20% of patients treated with ECT, 10% with rTMS, and 70% under usual care.

New Hampshire

	Medicaid		Private Payer		Overall
	n	%	n	%	
Covered Populations*					
Total membership (n)	35,500	9%	341,054	91%	376,554
Prevalence of TRD		3.4%		2.0%	2.1%
Patients with TRD (n)		1,200		6,821	8,021

*Note that uninsured patients are not represented in this analysis as there is no direct impact to a third party payer.

Table B7. New Hampshire: Estimated Clinical Impact of ECT and TMS in an Insured Population.

	Baseline	Scenario 1*†	Net Change vs. Baseline	Scenario 2*‡	Net Change vs. Baseline
Summary of Covered Population					
Total membership (n)	376,554	376,554		376,554	
Patients with TRD (n)	8,021	8,021		8,021	
Patients with TRD receiving ECT and/or TMS (n)	1,604	1,604		2,406	
As a proportion of all members	0.4%	0.4%		0.6%	
As a proportion of patients with TRD	20.0%	20.0%		30.0%	
Outcomes & Resource Use					
Positive Treatment Response (n)	2,688	2,688	0	2,944	257
Positive Treatment Response (%)	33.5%	33.5%		36.7%	

*Note. This analysis is from the point of view of a third party payer, therefore, all patients are assumed to be covered.
†Scenario 1 consists of 10% of patients treated with ECT, 10% with rTMS, and 80% under usual care.
‡Scenario 2 consists of 20% of patients treated with ECT, 10% with rTMS, and 70% under usual care.

Table B8. New Hampshire: Estimated Economic Impact of ECT and TMS Use in an Insured Population (2010 US dollars).

		Scenario 1*†		Scenario 2*‡	
	Baseline	Payments	Net Change vs. Baseline	Payments	Net Change vs. Baseline
Payments per patient with TRD (n=008,021)					
ECT and/or TMS	$693	$800	$107	$1,146	$453
Outpatient Management & ER	$8,058	$8,058	$0	$8,007	($51)
Inpatient admissions	$1,729	$1,729	$0	$1,646	($83)
Total per patient	$10,479	$10,586	$107	$10,798	$319
Annual payments for all patients with TRD	$84,052,590	$84,909,076	$856,487	$86,613,724	$2,561,134
			1.0%		3.0%
Plan payments for Covered Population (n=0,376,554)					
Annual payments for all services (all patients)	$1,369,730,640	$1,370,587,126	$856,487	$1,372,291,774	$2,561,134
Payment per member per month - overall (PMPMo)	$303.13	$303.32	$0.19	$303.70	$0.57

*TMS and ECT are assumed to have equivalent efficacy, therefore, no cost offset is considered due to improved response.
†Scenario 1 consists of 10% of patients treated with ECT, 10% with rTMS, and 80% under usual care.
‡Scenario 2 consists of 20% of patients treated with ECT, 10% with rTMS, and 70% under usual care.

	Medicaid		Private Payer		Overall
	n	%	n	%	
Covered Populations*					
Total membership (n)	78,100	6%	1,246,212	94%	1,324,312
Prevalence of TRD		3.4%		2.0%	2.1%
Patients with TRD (n)		2,640		24,924	27,564

*Note that uninsured patients are not represented in this analysis as there is no direct impact to a third party payer.

Table B9. Rhode Island: Estimated Clinical Impact of ECT and TMS in an Insured Population.

	Baseline	Scenario 1*†	Net Change vs. Baseline	Scenario 2*‡	Net Change vs. Baseline
Summary of Covered Population					
Total membership (n)	1,324,312	1,324,312		1,324,312	
Patients with TRD (n)	27,564	27,564		27,564	
Patients with TRD receiving ECT and/or TMS (n)	5,513	5,513		8,269	
As a proportion of all members	0.4%	0.4%		0.6%	
As a proportion of patients with TRD	20.0%	20.0%		30.0%	
Outcomes & Resource Use					
Positive Treatment Response (n)	9,236	9,236	0	10,118	882
Positive Treatment Response (%)	33.5%	33.5%		36.7%	

*Note. This analysis is from the point of view of a third party payer, therefore, all patients are assumed to be covered.
†Scenario 1 consists of 10% of patients treated with ECT, 10% with rTMS, and 80% under usual care.
‡Scenario 2 consists of 20% of patients treated with ECT, 10% with rTMS, and 70% under usual care.

Table B10. Rhode Island: Estimated Economic Impact of ECT and TMS Use in an Insured Population (2010 US dollars).

		Scenario 1*†		Scenario 2*‡	
	Baseline	Payments	Net Change vs. Baseline	Payments	Net Change vs. Baseline
Payments per patient with TRD (n=027,564)					
ECT and/or TMS	$709	$811	$103	$1,166	$457
Outpatient Management & ER	$8,242	$8,242	$0	$8,190	($52)
Inpatient admissions	$1,768	$1,768	$0	$1,683	($85)
Total per patient	$10,719	$10,822	$103	$11,039	$320
Annual payments for all patients with TRD	$295,460,710	$298,290,462	$2,829,752	$304,282,619	$8,821,908
			1.0%		3.0%
Plan payments for Covered Population (n=1,324,312)					
Annual payments for all services (all patients)	$4,887,928,208	$4,890,757,960	$2,829,752	$4,896,750,116	$8,821,908
Payment per member per month - overall (PMPMo)	$307.58	$307.75	$0.18	$308.13	$0.56

*TMS and ECT are assumed to have equivalent efficacy, therefore, no cost offset is considered due to improved response.
†Scenario 1 consists of 10% of patients treated with ECT, 10% with rTMS, and 80% under usual care.
‡Scenario 2 consists of 20% of patients treated with ECT, 10% with rTMS, and 70% under usual care.

Vermont

	Medicaid		Private Payer		Overall
	n	%	n	%	
Covered Populations*					
Total membership (n)	63,700	19%	270,755	81%	334,455
Prevalence of TRD		3.4%		2.0%	2.3%
Patients with TRD (n)		2,153		5,415	7,568

*Note that uninsured patients are not represented in this analysis as there is no direct impact to a third party payer.

Table B11. Vermont: Estimated Clinical Impact of ECT and TMS in an Insured Population.

	Baseline	Scenario 1*†	Net Change vs. Baseline	Scenario 2*‡	Net Change vs. Baseline
Summary of Covered Population					
Total membership (n)	334,455	334,455		334,455	
Patients with TRD (n)	7,568	7,568		7,568	
Patients with TRD receiving ECT and/or TMS (n)	1,513	1,513		2,270	
As a proportion of all members	0.5%	0.5%		0.7%	
As a proportion of patients with TRD	20.0%	20.0%		30.0%	
Outcomes & Resource Use					
Positive Treatment Response (n)	2,536	2,536	0	2,778	242
Positive Treatment Response (%)	33.5%	33.5%		36.7%	

*Note. This analysis is from the point of view of a third party payer, therefore, all patients are assumed to be covered.
†Scenario 1 consists of 10% of patients treated with ECT, 10% with rTMS, and 80% under usual care.
‡Scenario 2 consists of 20% of patients treated with ECT, 10% with rTMS, and 70% under usual care.

Table B12. Vermont: Estimated Economic Impact of ECT and TMS Use in an Insured Population (2010 US dollars).

		Scenario 1*†		Scenario 2*‡	
	Baseline	Payments	Net Change vs. Baseline	Payments	Net Change vs. Baseline
Payments per patient with TRD (n=007,568)					
ECT and/or TMS	$653	$770	$117	$1,097	$444
Outpatient Management & ER	$7,595	$7,595	$0	$7,547	($48)
Inpatient admissions	$1,629	$1,629	$0	$1,551	($78)
Total per patient	$9,878	$9,995	$117	$10,195	$317
Annual payments for all patients with TRD	$74,755,847	$75,642,119	$886,271	$77,158,221	$2,402,374
			1.2%		3.2%
Plan payments for Covered Population (n=0,334,455)					
Annual payments for all services (all patients)	$1,167,953,229	$1,168,839,501	$886,271	$1,170,355,603	$2,402,374
Payment per member per month - overall (PMPMo)	$291.01	$291.23	$0.22	$291.61	$0.60

*TMS and ECT are assumed to have equivalent efficacy, therefore, no cost offset is considered due to improved response.
†Scenario 1 consists of 10% of patients treated with ECT, 10% with rTMS, and 80% under usual care.
‡Scenario 2 consists of 20% of patients treated with ECT, 10% with rTMS, and 70% under usual care.