Evidence-based Practice Center Systematic Review Protocol

Project Title: *Non-Pharmacologic Interventions for Treatment-resistant Depression in Adults*

I. Background and Objectives for the Systematic Review

Treatment-resistant Depression (TRD) is common, costly, and chronic. Over the course of one year, between 13.1 and 14.2 million people will experience major depressive disorder; approximately half of these people seek help for this condition, and only 1/5 of those receive adequate treatment.[1] For those that receive adequate treatment, 1/2 will have TRD.[2] Given this burden and prognosis, stakeholders are looking for other options beyond pharmacologic therapy.

Biologic treatments, which may involve use of a pharmacologic intervention or a device, are common considerations for TRD. Antidepressant medications (the most commonly used intervention) are less likely to produce recovery after two failures and often have side effects. Newer non-pharmacologic options and psychotherapy options are available, but little evidence exists to guide decisions about use, and choice among these options by patients, clinicians, or payors. Stakeholders have called for clear comparative effectiveness recommendations, especially in regard to non-pharmacologic interventions.

A lack of clear consensus exists on defining and staging TRD which interferes with targeted and effective treatment, thus reducing the opportunity to improve primary and secondary outcomes. We recognize that there are many definitions being used in research and practice, but for the purposes of this review we are proposing to use the common understanding of two or more failed adequate trials of a biologic (medication or device) intervention(s). The word "adequate" is to indicate a trial that employs at least a minimal clinically-relevant dose and duration of treatment.

ECT is currently viewed by clinicians and APA guidelines as the treatment of choice among non-pharmacologic interventions for most patients with TRD who fail multiple antidepressant trials, with or without augmentation and/or psychotherapy. The specific treatments that have sufficient research to merit a comparative review would be limited to rTMS and VNS, cognitive behavioral therapy, as well as more complex and algorithm-driven medication strategies (e.g., STAR-D). The FDA approved VNS and rTMS for use in depression in 2005 and 2008, respectively.

II. The Key Questions

1. For adults with treatment-resistant depression (TRD, defined as two or more failed adequate trials of a biologic intervention), do non-pharmacologic interventions such as electroconvulsive therapy (ECT), vagus nerve stimulation (VNS), repetitive transcranial

magnetic stimulation (rTMS), or demonstrated effective psychotherapy (e.g., cognitive therapy [CBT or IPT]) differ in efficacy or effectiveness in treating acute phase depressive symptoms (e.g., response and remission), whether as a single treatment or part of a combination treatment?

a. How do these non-pharmacologic treatments compare with pharmacological treatments in efficacy or effectiveness in treating acute phase depressive symptoms after two or more failed adequate trials?

Note: KQ1 was revised to add this subquestion in response to feedback from our Technical Expert Panel (representing clinicians, researchers, policy makers, and consumers). Both clinicians and patients want clarification of the context of the decision they are confronted with when the patient is treatment resistant. "Should I try a medication approach again (the default), or should I try something else?" The panel confirmed that a medication comparator arm was needed to make the results of this comparative effectiveness review relevant to clinical and policy decision-making.

- **Population(s):** Adults with a current episode of treatment-resistant depression (TRD, defined as two or more failed adequate trials of a biologic intervention)
- **Interventions:** Non-pharmacologic interventions at any stimulus parameters, frequency, schedule or target area (eg., bilateral, unilateral):
  - Electroconvulsive therapy (ECT)
  - Vagus nerve stimulation (VNS)
  - repetitive Transcranial Magnetic Stimulation (rTMS)
  - demonstrated effective psychotherapy (e.g., cognitive therapy, interpersonal therapy [CBT or IPT])
- **Comparators:** ECT, rTMS, VNS, psychotherapy, pharmacologic treatments
- **Outcomes for each question**
  - Response
  - Remission
- **Timing:** Acute phase and continuation phase treatments
- **Settings:** Mental Health Inpatient, Mental Health Outpatient, Primary Care Outpatient

2. For adults with TRD, do non-pharmacologic interventions differ in their efficacy or effectiveness for maintaining response or remission (e.g., preventing relapse or recurrence) whether as a single treatment or part of a combination treatment?

- **Population(s):** Adults with a current episode treatment-resistant depression
- **Interventions:** Non-pharmacologic interventions (ECT, rTMS, VNS, demonstrated effective psychotherapy)

- **Comparators:** ECT, rTMS, VNS, demonstrated effective psychotherapy
- **Outcomes for each question**
  - Relapse
  - Recurrence
- **Timing:** Acute phase, continuation phase, and maintenance phase treatments
- **Settings:** Mental Health Inpatient, Mental Health Outpatient, Primary Care Outpatient

3. Do non-pharmacologic interventions (single or combination) differ in their efficacy or effectiveness for treating TRD as a function of particular symptom subtypes (e.g., catatonic (frozen or hyper) or psychotic symptoms)?

- **Population(s):** Adults with symptom subtypes of treatment-resistant depression
- **Interventions:** Non-pharmacologic interventions (ECT, rTMS, VNS, demonstrated effective psychotherapy)
- **Comparators:** ECT, rTMS, VNS, demonstrated effective psychotherapy
- **Outcomes for each question**
  - Remission
  - Response
- **Timing:** Acute phase and continuation phase treatments
- **Settings:** Mental Health Inpatient, Mental Health Outpatient, Primary Care Outpatient

4. For adults with treatment-resistant depression, do non-pharmacologic interventions differ in safety, adverse events, or adherence? Adverse effects of interest include but are not limited to: amnesia, memory loss, headaches, post-operative complications.

- **Population(s):** Adults with a current episode treatment-resistant depression
- **Interventions:** Non-pharmacologic interventions (ECT, rTMS, VNS, demonstrated effective psychotherapy)
- **Comparators:** ECT, rTMS, VNS, demonstrated effective psychotherapy
- **Outcomes for each question**
  - Safety
  - Adverse Events
  - Adherence
- **Timing:** Acute phase and continuation phase treatments
- **Settings:** Mental Health Inpatient, Mental Health Outpatient, Primary Care Outpatient

5. How do the efficacy, effectiveness, or harms of treatment with non-pharmacologic treatments for treatment-resistant depression differ for the following subpopulations?
    - Elderly or very elderly patients; other demographic groups (defined by age, ethnic or racial groups, and sex);
    - Patients with medical comorbidities (e.g., seizure history, stroke, diabetes, dementia, perinatal, ischemic heart disease, cancer).

- **Population(s):** Demographic and medical comorbities subgroups of adults with a current episode treatment-resistant depression
- **Interventions:** Non-pharmacologic interventions (ECT, rTMS, VNS, demonstrated effective psychotherapy)
- **Comparators:** ECT, rTMS, VNS, demonstrated effective psychotherapy
- **Outcomes for each question**
- Quality of Life
- Other
- **Timing:** Acute phase and continuation phase treatments
- **Settings:** Mental Health Inpatient, Mental Health Outpatient, Primary Care Outpatient

6. For adults with treatment-resistant depression, do non-pharmacologic interventions differ in regards to other health-related outcomes (e.g., quality of life)?

- **Population(s):** Adults with a current episode treatment-resistant depression
- **Interventions:** Non-pharmacologic interventions (ECT, rTMS, VNS, demonstrated effective psychotherapy)
- **Comparators:** ECT, rTMS, VNS, demonstrated effective psychotherapy
- **Outcomes for each question**
    - Quality of Life
    - Other
- **Timing:** Acute phase and continuation phase treatments
- **Settings:** Mental Health Inpatient, Mental Health Outpatient, Primary Care Outpatient

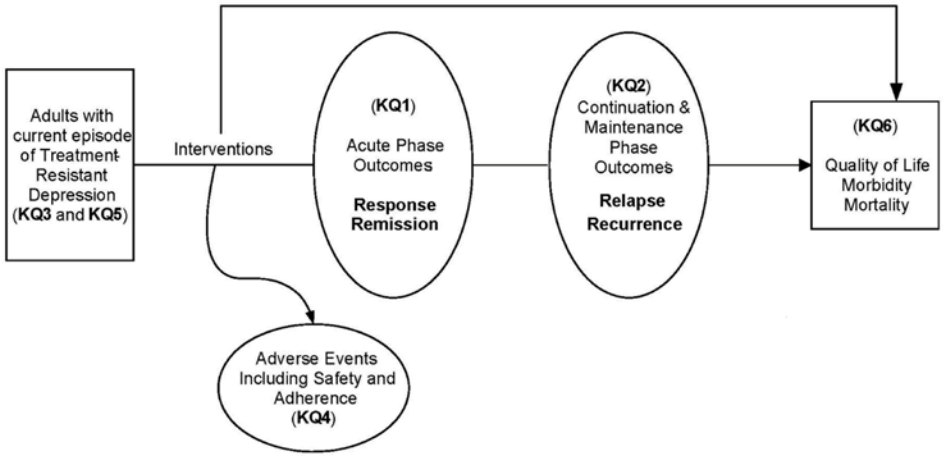
Notes. Given the varying definitions of TRD, the EPC will attempt to determine how these definitions affect these comparative results. In studies where the TRD definition is unclear (e.g., the number of failed adequate trials is not clarified, or the timing of the failed trials is not specified), the EPC will attempt to be inclusive of quality evidence while being clear about the potential variance of the definitions. The EPC will consider looking at methodological differences of the non-pharmacologic interventions (e.g., intensity, frequency, duration, etc.). When comparative studies are lacking, the EPC will consider reviewing data for each non-

pharmacologic intervention from the best available studies. New treatments without a current evidence that require further research, such as Magnetic Seizure Therapy or Deep Brain Stimulation, will be identified but not reviewed.

III. Analytic Framework

Based on the key questions, we developed an analytic framework to guide the systematic review (Exhibit 3-1). Specifically, the first two key questions pertain to the efficacy and effectiveness of obtaining (KQ1) and maintaining (KQ2) response and remission using these non-pharmocologic treatments – where KQ1 addresses the acute phase and KQ2 the continuation or maintenance phase. KQ3 addresses response and remission for psychiatric subtypes of treatment-resistant depression (e.g., coexisting anxiety), and KQ5 focuses on the specific subgroups (e.g., the elderly). KQ4 focuses on safety issues (adverse effects, adherence) with each of the interventions. Finally, KQ6 looks at how these interventions affect other health outcomes, such as quality of life.

Exhibit 3-1. Analytic Framework for the Non-pharmacologic Treatment of Treatment-resistant Depression Comparative Effectiveness Review



Many factors have been shown in the literature to influence both the use and quality of tests. While the patient is ultimately the one to make the decision about whether to receive the non-pharmacologic treatment, this decision is directly impacted by a discussion with the health care provider about benefits and harms of each treatment for one's particular case. Our analytic framework addresses the non-pharmacologic options available to clinicians for treating their patients with treatment-resistant depression.

IV. Methods

A. Criteria for Inclusion/Exclusion of Studies in the Review

Exhibit 4-1 presents the inclusion/exclusion criteria we will use during abstract and full test review.

Exhibit 4-1. Inclusion/Exclusion Criteria for the Systematic Review

Category	Criteria	
	Inclusion	**Exclusion**
Study population	Humans, all races, ethnicities, cultural groups, adults Patients with treatment-resistant depression (defined as two or more failed trials of a biologic intervention) in their acute or continuation phase	Studies which include children or adolescents Studies which include patients with treatable depression or healthy volunteers
Study outcomes*	KQ 1,3, and 5: Remission Response KQ2: Relapse Recurrence As measured by validated instruments KQ 4: Safety, adverse effects, and adherence KQ 6: Quality of Life and other health related outcomes	Costs Intermediate Biochemical Outcomes
Study geography	All developed countries: United States, Canada, United Kingdom, Europe, Australia, China, Japan	All other countries
Time period	1/1/1980–6/1/2009	Prior to 1/1/1980
Settings	Mental Health Inpatient, Mental Health Outpatient, Primary Care Outpatient	
Interventions	ECT VNS rTMS Demonstrated effective psychotherapies Pharmacologic (KQ1 only)	Deep Brain Stimulation Magnetic Seizure Therapy Phototherapy Alternative Medicine
Publication language	English	All other languages

Category	Criteria	
	Inclusion	**Exclusion**
Admissible evidence (study design and other criteria)	Original research studies that provide sufficient detail regarding methods and results to enable use and adjustment of the data and results; relevant outcomes must be able to be abstracted from data presented in the papers (includes Systematic Reviews and Meta-analyses) Eligible study designs include: Randomized controlled trials (RCTs) for all KQs Nonrandomized controlled trials, observational studies (comparing one treatment with another): prospective and retrospective cohort studies for KQ 3 through KQ6 All treatment and followup durations and all sample sizes will be accepted	Studies of poor quality[1] Single case reports or small case series Editorials, letters, non-systematic literature reviews

B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions.

We will systematically search, review, and analyze the scientific evidence for each key question and any subsidiary questions. The steps that we will take to accomplish the literature review are described below.

To identify articles relevant to each key question, we began with a focused MEDLINE search on depression crossed with the various non-pharmacologic interventions, using a variety of terms, MeSH and major headings, limited to English and human-only studies. We also searched other databases (The Cochrane Library, the Cochrane Central Trials Registry, and PsycInfo).

Our initial searches yielded 1,993 citations across databases. We will review our search strategy with the TEP and supplement it as needed according to their recommendations. In addition, to attempt to avoid retrieval bias, we will manually search the reference lists of landmark studies and background articles on this topic to look for any relevant citations that might have been missed by electronic searches. We will also conduct an updated literature search (in MEDLINE, the Cochrane Library, the Cochrane Central Trials Registry, PsycInfo) before completing the final draft of the report. Any literature suggested by peer reviewers or from the public will be investigated and if appropriate incorporated into the final review.

[1] Studies deemed "poor quality" will have to be appraised formally and rated with the template developed by EPC.

We do not anticipate incorporating gray literature in any of the searches.

C. Data Abstraction and Data Management

We will review all titles and abstracts identified through searches against our inclusion/exclusion criteria, using the SRS 4.0 Mobius Analytics software. Each abstract will be independently reviewed by two members of the team. When differences between the reviewers arise, we will include studies for full-text review. For studies without adequate information to make the determination, we will again review the full text. All results will be tracked in an EndNote database.

We will retrieve the full text of all titles included during abstract review. Each full-text article will be independently reviewed by two members of the team for inclusion or exclusion based on the eligibility criteria described above. If both reviewers agree that a study does not meet the eligibility criteria, the study will be excluded. If the reviewers disagree, conflicts will be resolved by discussion and consensus or by consulting a third, independent party. As above, all results will be tracked in an EndNote database including, where applicable, the reason a study did not satisfy eligibility criteria so that we can later compile a listing of excluded articles and reasons for such exclusions.

We will design data collection forms that include questions on identifying information for the article, study design, methods, and results. Trained abstractors will extract the relevant data from each included article into preformatted tables. Data abstractions will be reviewed for accuracy by a second member of the team.

D. Assessment of Methodological Quality of Individual Studies

To assess the quality (internal validity) of studies, we will use predefined criteria based on those developed by the US Preventive Services Task Force (ratings: good, fair, poor) and the National Health Service Centre for Reviews and Dissemination. In general terms, a "good" study has the least bias and results are considered to be valid. A "fair" study is susceptible to some bias but probably not sufficient to invalidate its results. A "poor" rating indicates significant bias (e.g., stemming from serious errors in design or analysis) that may invalidate the study's results. To assess the quality of observational studies, we will use criteria outlined by Deeks and colleagues.[3]

Two independent reviewers will assign quality ratings to each study. Disagreements will be resolved by discussion and consensus or by consulting a third, independent party.

E. Data Synthesis

We anticipate that the data found from the literature review will be synthesized qualitatively. However, if we find a sufficient number (three or more) of similar studies of factors influencing the use of non-pharmacological treatments, we will consider quantitative analysis (meta-analysis) of data from those studies. We will also review the evidence to asses whether indirect comparisons can be made.

For each of these comparisons, we will first stratify by whether the data assess the effects of a single treatment intervention (e.g., after medication failure, switching to ECT vs. continuing medications) or of a treatment combination (e.g., after medication failure, adding ECT to medications vs. continuing medications). Following this stratification, we will compare specific types of interventions. These comparisons will be of two forms: head-to-head trials (e.g., ECT vs. RTMS, which provides a direct comparison) or trials with an active intervention vs. control (e.g., VNS vs. placebo, which may allow indirect comparisons of effect sizes). In comparing these outcomes, we will pay careful attention to the role of depressive severity.

F. Grading the Evidence for Each Key Question

We will rate the strength of evidence based on the standard methods of the EPCs, which use a revised version of the approach devised by the GRADE working group.[4] Developed to grade the quality of evidence and the strength of recommendations, this approach incorporates the following elements: study design, study quality, consistency, directness, presence of imprecise or sparse data, high probability of publication bias, and magnitude of the effect. We use four grades: high, moderate, low, and insufficient.

V. References

1. Kessler RC, Berglund P, Demler O, et al, for the National Comorbidity Survey Replication Group. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *JAMA* 2003;289:3095-105.
2. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry* 2006;163:1905-17.
3. Deeks JJ, Dinnes J, D'Amico R, et al, for the International Stroke Trial Collaborative Group and the European Carotid Surgery Trial Collaborative Group. Evaluating non-randomised intervention studies. *Health Technol Assess* 2003;7: iii-x, 1-173.
4. Atkins D, Eccles M, Flottorp S, et al, for the GRADE Working Group. Systems for grading the quality of evidence and the strength of recommendations I: critical appraisal of existing approaches. *BMC Health Serv Res* 2004;4:38.

VI. Definition of Terms – if applicable

Cognitive Behavioral Therapy (CBT): form of psychotherapy; when used with depressed patients the focus is on restructuring negative thought patterns and learning to interpret their environment in a less biased way.

Electroconvulsive Therapy (ECT): electric current is passed through the brain to produce a convulsion; requires general anesthetic and muscle relaxants.

Interpersonal Therapy (IPT): short-term supportive psychotherapy focusing on the connection between interactions between people and the development of a person's psychiatric symptoms

Treatment-Resistant Depression: two or more failed adequate trials of a biologic (medication or device) intervention(s). The word "adequate" is to indicate a trial that employs at least a minimal clinically-relevant dose and duration of treatment.

Repetitive Transcranial Magnetic Therapy (rTMS): focal magnetic stimulation through the scalp to produce a seizure, does not require anesthesia.

Vagus Nerve Stimulation (VNS): surgically placed electrodes around the left vagus nerve to provide stimulation, requires anesthesia.

VII. Summary of Protocol Amendments

This is a revised protocol to account for the addition of subquestion KQ1a. See notes under the key question for the rationale. Previous language of “evidence-based psychotherapy” is also changed to “demonstrated effective psychotherapy” to avoid a priori categorization and use factual rather than presumptive language.

NOTE: The following protocol elements are standard procedures for all protocols.

VIII. Review of Key Questions

For Comparative Effectiveness reviews (CERs) the key questions were posted for public comment and finalized after review of the comments. For other systematic reviews,
key questions submitted by partners are reviewed and refined as needed by the EPC and the Technical Expert Panel (TEP) to assure that the questions are specific and explicit about what information is being reviewed.

IX. Technical Expert Panel (TEP)

A TEP panel is selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design and/or methodological approaches do not necessarily represent the views of individual technical and content experts. The TEP provides information to the EPC to identify literature search strategies, review the draft report and recommend approaches to specific issues as requested by the EPC. The TEP does not do analysis of any kind nor contribute to the writing of the report.

X. Peer Review (*Standard Language*)

Approximately five experts in the field will be asked to peer review the draft report and provide comments. The peer reviewer may represent stakeholder groups such as professional or advocacy organizations with knowledge of the topic. On some specific reports such as reports requested by the Office of Medical Applications of Research, National Institutes of Health there may be other rules that apply regarding participation in the peer review process. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will, for CERs and Technical briefs, be published three months after the publication of the Evidence report.

It is our policy not to release the names of the Peer reviewers or TEP panel members until the report is published so that they can maintain their objectivity during the review process.

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