The purpose of this document is to provide guidance to members drafting insurance appeal letters. Alterations to this document reflect the views and opinions of the author and do not necessarily reflect the views of the Clinical TMS Society, its affiliates, or its employees.

Treatment Resistance Level and TMS Treatment

Response #1

Transcranial magnetic stimulation (TMS) is a United States Food and Drug Administration (FDA) cleared treatment for adult patients who have failed to reach remission with *one* or more antidepressants.[1] All TMS systems in the United States sold commercially have been cleared to be safe and efficacious in this patient population. Pivotal trials have also shown that patients do not need to have a high level of treatment resistance in order to benefit from TMS and, in fact, patients with a lower level of treatment resistance are more likely to respond to TMS.

Three triple blind pivotal trials have selected patients who failed to reach remission with a minimum of one or more antidepressants. Multiple failed medication trials and/or psychotherapy were not a part of the selection criteria. For example, the 2007 Neuronetics pivotal trial required patients to have failed one but not more than four antidepressants in the current episode of depression.[2]

In 2010, George et al. conducted a study in which patients with major depression were required, once again, to fail at least one but no more than four antidepressants in the current episode.[3] Patients who had not tolerated three or more antidepressants were also included. However, there was no requirement for augmentation medication trials, multiple failed antidepressant trials, nor psychotherapy trials.

The 2015 Brainsway pivotal trial had similar requirements: one to four failed antidepressants trials or inability to tolerate at least two antidepressant treatments in the current episode.[4]

In 2009, Lisanby et al. pooled data from a multi-site sham-controlled study and an open label extension trial in order to look for clinical predictors of outcome.[5] Univariate predictor analyses showed that a *lower* degree of prior treatment resistance in the current episode was the strongest predictor for positive response to acute treatment with TMS.

In summary, the [INSERT INSURANCE COMPANY NAME] policy of restricting coverage of TMS to depressed patients with a high level of treatment resistance is not consistent

with the selection criteria for these pivotal trials. In fact, patients who have failed fewer prior treatments are more likely to respond to TMS. We urge you to reconsider these restrictive requirements that prevent thousands of patients from receiving effective treatment.

References #1

1. Class II special controls guidance document: repetitive transcranial magnetic stimulation (rTMS) systems. Food and Drug Administration Center for Devices and Radiological Health. 2011.
2. O'Reardon, J. P., Solvason, H. B., Janicak, P. G., Sampson, S., Isenberg, K. E., Nahas, Z., ... & Demitrack, M. A. (2007). Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. *Biological psychiatry*, *62*(11), 1208-1216.
3. George, M. S., Lisanby, S. H., Avery, D., McDonald, W. M., Durkalski, V., Pavlicova, M., ... & Holtzheimer, P. E. (2010). Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. *Archives of general psychiatry*, *67*(5), 507-516.

4. Levkovitz, Y., Isserles, M., Padberg, F., Lisanby, S. H., Bystritsky, A., Xia, G., ... & Hafez, H. M. (2015). Efficacy and safety of deep transcranial magnetic stimulation for major depression: a prospective multicenter randomized controlled trial. *World Psychiatry*, *14*(1), 64-73.

5. Lisanby, S. H., Husain, M. M., Rosenquist, P. B., Maixner, D., Gutierrez, R., Krystal, A., ... & Canterbury, R. (2009). Daily left prefrontal repetitive transcranial magnetic stimulation in the acute treatment of major depression: clinical predictors of outcome in a multisite, randomized controlled clinical trial. *Neuropsychopharmacology*, *34*(2), 522.4

Response #2

Transcranial magnetic stimulation (TMS) is a United States Food and Drug Administration (FDA) cleared treatment for adult patients who have failed to reach remission with *one* or more antidepressants.[1] Pivotal trials that used various FDA-cleared devices have also shown that patients do not need to have a high level of treatment resistance in order to benefit from TMS.

Three major pivotal trials have selected patients who failed to reach remission with a minimum of one or more antidepressants. Multiple failed medication trials and/or psychotherapy were not a part of the selection criteria. The 2007 Neuronetics pivotal trial[2], the 2010 trial conducted by George et al.[3], and the 2015 Brainsway trial[4] all showed efficacy of TMS in patients who had failed at least one but no more than four antidepressants in the current episode.

In 2009, Lisanby et al.[5] pooled data from a sham-controlled study and open label trial in order to evaluate clinical predictors of outcomes for patients with depression who had received TMS. Analyses showed that a *lower* degree of prior treatment resistance in the current episode was the strongest predictor for positive response to acute treatment with TMS.

In summary, the [INSERT INSURANCE COMPANY NAME] policy that restricts coverage of TMS based on treatment resistance is inconsistent with the selection criteria for these pivotal trials. In fact, patients who have failed fewer prior treatments are more likely to respond to TMS. We urge you to reconsider these restrictive requirements that prevent thousands of patients from receiving effective treatment.

References #2

1. Class II special controls guidance document: repetitive transcranial magnetic stimulation (rTMS) systems. Food and Drug Administration Center for Devices and Radiological Health. 2011.
2. O'Reardon, J. P., Solvason, H. B., Janicak, P. G., Sampson, S., Isenberg, K. E., Nahas, Z., ... & Demitrack, M. A. (2007). Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. *Biological psychiatry*, *62*(11), 1208-1216.
3. George, M. S., Lisanby, S. H., Avery, D., McDonald, W. M., Durkalski, V., Pavlicova, M., ... & Holtzheimer, P. E. (2010). Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. *Archives of general psychiatry*, *67*(5), 507-516.
4. Levkovitz, Y., Isserles, M., Padberg, F., Lisanby, S. H., Bystritsky, A., Xia, G., ... & Hafez, H. M. (2015). Efficacy and safety of deep transcranial magnetic stimulation for major depression: a prospective multicenter randomized controlled trial. *World*

Psychiatry, *14*(1), 64-73.

5. Lisanby, S. H., Husain, M. M., Rosenquist, P. B., Maixner, D., Gutierrez, R., Krystal, A., ... & Canterbury, R. (2009). Daily left prefrontal repetitive transcranial magnetic stimulation in the acute treatment of major depression: clinical predictors of outcome in a multisite, randomized controlled clinical trial. *Neuropsychopharmacology*, *34*(2), 522.4