PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Protocol for a systematic review and meta-analysis of the placebo response in treatment-resistant depression: Comparison of multiple treatment modalities
AUTHORS	Jones, Brett; Weissman, Cory; Razza, Lais; Husain, Muhammad; Brunoni, Andre R.; Daskalakis, Zafiris

VERSION 1 – REVIEW

REVIEWER	jan spijker Pro Persona Mental Healthcare/Radboud University Nijmegen, the Netherlands
REVIEW RETURNED	24-Jul-2020

GENERAL COMMENTS	Protocol for a systematic review and meta-analysis of the placebo response in treatment-resistant depression: comparison of multiple treatment modalities. This is an interesting protocol for the above-mentioned review and meta-analysis. I have only a few questions Pp 7: 53 2 separate treatments: the authors mean treatments with antidepressive medication. Because I understand that they do not include other treatments in the definition of TRD Pp 8: 12: explain why it is important to characterize and understand the placebo response in TRD Pp 8: 37 to characterize the placebo … what is meant by to characterize? Maybe better to assess? Pp 9: 39/40 how will failed psychotherapy or brain stimulation will be included in TRD staging? Pp 10: 10 unless 15% or less.. Why not exclude bipolar depression totally? Pp 11: 49 why include portuges language only next to English? Pp 14: 5 how will qualitative data be analysed? Pp 14: 10 which treatment modalities will be included: medication, psychotherapy, neurostimulation, any others?

REVIEWER	DAVID FOGELSON David Geffen School of Medicine at UCLA And The Semel Institute for Neuroscience and Human Behavior at UCLA
REVIEW RETURNED	06-Sep-2020

GENERAL COMMENTS	The six questions I have answered "no" all pivot on the same flaw in this protocol design which is the definition of treatment resistant depression (TRD). The authors state, "TRD will be defined as a failure to respond to at least 2 interventions of adequate dose or

	duration." As I have stated in my letter to the editor of JAMA Psychiatry, reference in attached file list, defining treatment resistance as the failure of two treatment modalities, medication or psychotherapy, is reasonable, but fails to acknowledge that not all "depressions" are the same. Some patients will present with Major Depressive Disorder without comorbidity and others will have a co-morbid personality disorder/a history of childhood adversity (some form of abuse or neglect). Patients with such comorbidity may have a different response to placebo than those patients without such comorbidity. Patients with comorbidity may be more likely to fall in the TRD category. I believe it would be helpful to stratify index subjects by comorbidity if such data is available. Other comorbidity variables that might aid in stratification of index subjects would be a family history of Bipolar Disorder or Psychosis, number of past depressive episodes, past episodes of psychotic depression, onset of Major Depressive Disorder before the age of 18, and past suicide attempts. While the authors state that psychiatric comorbidity will be included, see line 3, page 10, they do not specify how this will be operationalized. See attached reference, Perugi 2019, for a discussion of some of these variables. I think they should operationalize what they mean by comorbidity. Do they mean all comorbid psychiatric disorders? Do they mean temporal symptoms, severity of symptoms, anxiety symptoms? Do they mean childhood adversity? Are they including personality disorders? Are they including a history of suicide attempts? Are they including family history of psychiatric disorders? Search strategy: consider using a search term such as Major Depressive Disorder and comorbidity and treatment outcome" Getting back to the definition of TRD, the article by Hagg, 2020, argues that failure of two antidepressant trials may be the best definition of TRD. In the proposed study a patient would be classified as having TRD if they failed one antidepressant trial and one other treatment modality, including a second trial of antidepressants. It may be best to do two analyses: one where the definition must be failure of two medication trials and the other some stratification by total number of treatment failures of all modalities. TRD is likely to be very different in someone who has failed many treatment trials or trials of different modalities than someone who has only failed two medication trials. see ref. by Hagg 2020 attached.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Jan Spijker
Institution and Country: Pro Persona Mental Healthcare/Radboud University Nijmegen, the Netherlands

Comments to the Author: Protocol for a systematic review and meta-analysis of the placebo response in treatment-resistant depression: comparison of multiple treatment modalities. This is an interesting protocol for the above-mentioned review and meta-analysis. I have only a few questions.

Response: We would like to thank Dr Spijker for his thoughtful and thorough review of this protocol.

Comments to the Author: Pp 7: 53 2 separate treatments: the authors mean treatments with antidepressive medication. Because I understand that they do not include other treatments in the definition of TRD

Response: Thank you very much for noting this. We agree the most often TRD is defined as 2 failed anti-depressant trials; however, as noted on page 9 line 40 we will include failed psychotherapy trials and brain stimulation in the TRD staging. For additional clarity, we have amended this section to include other failed psychotropic agents such as atypical anti-psychotics in the staging.

Comments to the Author: Pp 8: 12: explain why it is important to characterize and understand the placebo response in TRD

Response: Thank you very much for this comment. We have expanded this section of the introduction to include why it is important to characterize and understand the placebo response in TRD.

Comments to the Author: Pp 8: 37 to characterize the placebo … what is meant by to characterize? Maybe better to assess?

Response: Thank you very much for this comment. We have chosen to use the word characterize as our objective is to assess the nature of the placebo response i.e. 'what is the placebo response' and the features of it 'what contributes to the placebo response.' We would be open to using the word assess and would defer that decision to the editors.

Comments to the Author: Pp 9: 39/40 how will failed psychotherapy or brain stimulation will be included in TRD staging?

Response: Thank you for making this comment. If a study includes a failed psychotherapy or brain-stimulation trials as one of the 2 failed 'anti-depressant trials', we will include it in our analysis.

Comments to the Author: Pp 10: 10 unless 15% or less.. Why not exclude bipolar depression totally?

Response: Thank you for making this comment. This is based upon our knowledge of the literature as well as previous work in treatment resistant depression. There are a number of studies, most often small pilot studies, that include a small number of participants with bipolar depression. We included these studies so not to bias the exclusion of smaller studies. We chose 15% as a cut-off so not to over include bipolar depression. Overall these patients will represent a small number of patients in the overall analysis; however, we can include this as a variable to control for.

Comments to the Author: Pp 11: 49 why include portuges language only next to English?

Response: Thank you very much for this comment. The spoken languages of our collaborators are English and Portuguese. All other languages will be included; however, attempts will have to be made at translation.

Comments to the Author: Pp 14: 5 how will qualitative data be analysed?

Response: Thank you to the reviewer for this comment. What was meant by this state is that data from studies such as data regarding sham procedures, clinical outcome, clinical characteristics will be extracted to ensure that studies that are included in each aggregate meta-analysis are sufficiently homogenous. We will update the manuscript accordingly.

Comments to the Author: Pp 14: 10 which treatment modalities will be included: medication, psychotherapy, neurostimulation, any others?

Response: Thank you for this comment. The 3 main modalities that will be included are indeed medication, psychotherapy, and neurostimulation. During the pairwise meta-analysis, we will further split these modalities to ensure adequate similarity among studies. Proposed splitting of modalities includes invasive brain-stimulation, non-invasive brain-stimulation, oral medications, parental medications, and psychotherapy. We have amended this section to reflect this comment.

Reviewer: 2
Reviewer Name: DAVID FOGELSON
Institution and Country: David Geffen School of Medicine at UCLA
And The Semel Institute for Neuroscience
and Human Behavior at UCLA

We would like to thank Dr Fogelson for taking the time to review our article and providing his thoughtful comments.

Comments to the Author: The six questions I have answered "no" all pivot on the same flaw in this protocol design which is the definition of treatment resistant depression (TRD). The authors state, "TRD will be defined as a failure to respond to at least 2 interventions of adequate dose or duration." As I have stated in my letter to the editor of JAMA Psychiatry, reference in attached file list, defining treatment resistance as the failure of two treatment modalities, medication or psychotherapy, is reasonable, but fails to acknowledge that not all "depressions" are the same. Some patients will present with Major Depressive Disorder without comorbidity and others will have a co-morbid personality disorder/a history of childhood adversity (some form of abuse or neglect). Patients with such comorbidity may have a different response to placebo than those patients without such comorbidity. Patients with comorbidity may be more likely to fall in the TRD category. I believe it would be helpful to stratify index subjects by comorbidity if such data is available. Other comorbidity variables that might aid in stratification of index subjects would be a family history of Bipolar Disorder or Psychosis, number of past depressive episodes, past episodes of psychotic depression, onset of Major Depressive Disorder before the age of 18, and past suicide attempts. While the authors state that psychiatric comorbidity will be included, see line 3, page 10, they do not specify how this will be operationalized. See attached reference, Perugi 2019, for a discussion of some of these variables. I think they should operationalize what they mean by comorbidity. Do they mean all comorbid psychiatric disorders? Do they mean temporal symptoms, severity of symptoms, anxiety symptoms? Do they mean childhood adversity? Are they including personality disorders? Are they including a history of suicide attempts? Are they including family history of psychiatric disorders?

Response: Thank you very much for this insightful comment. We agree with Dr Fogelson around the limitations of the current definition of TRD and that it fails to acknowledge that not all “depressions are the same.” Though we recognize the current limitations with the definition of TRD, we are utilizing a definition of TRD that is consistent with the most common consensus of TRD (McAllister-Williams et al. 2020) so to maintain consistency with the literature. We are also limited in how we can operationalize psychiatric co-morbidity into the analysis given the likely heterogeneity of how the original studies include comorbidity and report it. We intend to address comorbidity in our analysis by including multiple variables in our meta-regression when available. These include variables such as number of depressive episodes, age of onset, number of failed trials (page 14 line 42 to Page 15 line 15). We will also include studies that had diagnostic psychiatric comorbidity, so long as MDD was the primary treatment target of the study, for example MDD with GAD or MDD with personality disorder (page 10 line 21). We have amended this section to make it clearer to the reader as to what is intended by psychiatric comorbidity (page 10 line 21). We will include a categorical variable of psychiatric comorbidity, present or not, to control for this (page 15 line 12). Though Dr Fogelson asserts excellent points around other factors that would contribute to TRD and also placebo response, we are limited in what we can include in the analysis to what is reported in the original studies. To remedy this, we propose including a discussion around the flaws of the current definition of TRD and the limitations it poses in the discussion of the final meta-analysis based upon what was made available once the data is extracted. A proposition for future studies in TRD to include expanded reporting on these variables would be made.

Comments to the Author: Search strategy: consider using a search term such as Major Depressive Disorder and comorbidity and treatment outcome".

Repsonse: Thank you for this comment. Our search strategy includes the terms ‘Major Depress*’ and ‘treatment’. We re-ran the search adding the search terms outcome and comorbidity which significantly limited the results. By not including the term ‘comorbidity’ it allows for results that do not include this word and does not exclude results that have it. We are confident that our search term as well as reviewing relevant references will obtain the appropriate references.

Comments to the Author: Getting back to the definition of TRD, the article by Hagg, 2020, argues that failure of two antidepressant trials may be the best definition of TRD. In the proposed study a patient would be classified as having TRD if they failed one antidepressant trial and one other treatment modality, including a second trial of antidepressants. It may be best to do two analyses: one where the definition must be failure of two medication trials and the other some stratification by total number of treatment failures of all modalities. TRD is likely to be very different in someone who has failed many treatment trials or trials of different modalities than someone who has only failed two medication trials. see ref. by Hagg 2020 attached.

Response: Thank you very much for this comment. We agree with Dr Fogelson’s hypothesis that response may be different in someone who has failed many treatment trials than someone who has failed on 2 medication trials. Where available, we will be extracting the number of failed trials and all modalities from the included studies and include this as a variable in the meta-regression. (page 15 line 6).

Thank you again to both reviewers for taking the time to review our article. We hope that our revised paper addresses each of their concerns.

VERSION 2 – REVIEW

REVIEWER	David L. Fogelson Department of Psychiatry and Biobehavioral Sciences, Semel Institute for Neuroscience and Human Behavior, The David Geffen School of Medicine at the University of California, Los Angeles, USA
REVIEW RETURNED	13-Dec-2020

GENERAL COMMENTS	Good job revising the protocol. Look forward to reading the results.

REVIEWER	Jan Spijker Pro Persona Mental Health, the Netherlands
REVIEW RETURNED	16-Dec-2020

GENERAL COMMENTS	the authors answered my questions very adequately. So, I sugest to accept the paper for publication