Author’s response to reviews

Title: A pragmatic pilot randomized trial to investigate the effectiveness of Behavioural Activation group therapy in reducing depressive symptoms and improving quality of life in patients with depression: The BRAVE pilot trial protocol

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Author’s response to reviews: see over
Dear Dr. Lancaster,

June 27, 2015

We would like to thank you and the reviewers for taking the time to carefully review our manuscript entitled “A pragmatic pilot randomized trial to investigate the effectiveness of BehaviouRal ActiVation group therapy in reducing dEpressive symptoms and improving quality of life in patients with depression: The BRAVE pilot trial protocol” (MS:1553760329157748). We have made thorough revisions to the manuscript in accordance with the constructive feedback provided during the peer review process. We have also added an author (Brittany B. Dennis, author 5) for her extensive writing and methodological contributions during our revision of the trial protocol. We feel the manuscript in its revised form will be of high interest for the journal readers. We detail below our response to the reviewers’ comments:

Reviewer 1 Comment 1: Major compulsory revision - Quantitative study design - Methods/Design - "For this pilot study we will adopt the following principles simulating naturalistic real life clinical setting to test the study question based on the pragmatic design":

1. No restrictive criteria will be used. Adults with major depressive disorders will be asked to participate in the study. This suggests that the groups will be mixed appreciating the different types of depression. Would the impact of type of depression within the group and the individual be assessed, apart from the Beck Depression Inventory and quality of life? This is not reflected in analyses

Author Response to Reviewer 1 Comment 1: We thank the reviewer for taking the time to carefully evaluate the manuscript. The reviewer brings forward an important point requiring clarification. Our decision to include all types of major depression into the trial was selected in order to enhance the generalizability of the trial findings. Regardless of the large case mix in types of depression, the randomization process will eliminate prognostic imbalance between arms. We will not be assessing types of depression or depressive symptoms using tools other than the BDI. The BDI will measure depression severity among participants. A defining characteristic of pragmatic trials includes the use of simple easy to administer case report forms and psychometric tools. To ensure the feasibility of our baseline assessment instruments we have elected to include one validated tool to assess for depression severity. This is clarified on page 23 (paragraph 1) of the manuscript.
Reviewer 1 Comment 2: The intervention will be an add-on to usual care - What does the "usual care" entail? Should this not rather be "standard care"

Author Response to Reviewer 1 Comment 2: While we acknowledge studies often provide “standard of care,” as the comparator arm, we are reluctant to use this term when defining our own comparator. Contention exists in the medical community over use of the term “standard of care,” which stems largely from the lack of consensus as to 1) what constitutes appropriate use of the term, 2) what expertise is required to declare an intervention the standard of care, and 3) what level of evidence is adequate to support or refute a therapy as the standard. In fact, researchers suggest the term not be adopted for any intervention unless confirmatory randomized controlled trials or meta-analyses exist to support this declaration. Recognizing there is limited evidence to suggest what is provided to patients in our comparator arm fulfills the criteria for “standard of care,” we’ve elected to use the term “usual care” to describe the intervention provided for the comparator arm of this trial. This has been clarified on page 8 (paragraph 1) of the manuscript.

Reviewer 2 Comment 1: A well written proposal on intervention that is much needed in this population. I agree that a feasibility study is a responsible starting point since there is limited evidence on the effectiveness of this intervention in a group setting. The idea to implement this in a group setting would be especially helpful in environments with limited resources.

Author Response to Reviewer 2 Comment 1: We appreciate the positive feedback and agree that this manuscript offers an important contribution to the psychiatry literature, particularly the need for high-quality evidence evaluating group-based interventions for patients with major depressive disorder.

Reviewer 2 Comment 2: - I am unable to see the tables or figures in the submitted document. These would add great value to the protocol and should kindly be added.

Author Response to Reviewer 2 Comment 2: We apologize if these figures were not easy to view in the previous manuscript. The figures have been included as additional attachments with the submission (the journal does not allow embedded figures into the manuscript). Please see attached figured with the main manuscript pdf.

Reviewer 2 Comment 3: Discretionary revision - A brief description of the data collection tools used would be helpful. The mood scale is named but I am not clear in the QoL questionnaire used or if this be addressed in the qualitative component in the study. Some additional information on why these were decided on will strengthen the protocol, e.g. reliability and validity. Information on the structure of these tools would also be helpful (e.g. Likert scales) to understand the data analysis better.

Author Response to Reviewer 2 Comment 3: The reviewer brings forward an excellent point. We have revised the manuscript to include a rationale for inclusion of these instruments. A defining characteristic of pragmatic trials includes the use of simple easy to administer case report forms and psychometric tools. To ensure the feasibility of our baseline assessment instruments we have elected to include as few psychometric tools as
possible. We have chosen the BDI for two purposes. Firstly, the BDI-II will measure depression severity among participants.¹ The BDI-II identifies prognostically relevant depressive symptoms, such that it strongly predicts a variety of patient important outcomes for populations suffering with depressive disorders.³ Secondly, the BDI was chosen as a safety measure for the trial. The main concern for this type of study is the presence of suicidal risk in the intervention and control groups. Suicide risk is increased in depressive disorders and a specific question in the depression symptoms score using BDI-II is dedicated to suicidal ideas. Therefore monitoring this specific question is important during the study. For this reason, the BDI-II questionnaires will be completed at the clinic and the answers checked by the clinician while the participants are in the program. The BDI-II includes 21 items measured on a scale of 0-3, with higher scores indicating a higher depressive symptom severity.⁴ The BDI-II score is analyzed using four categories of depressive symptom severity.⁴ The reasons behind our decision to use the BDI have been carefully described on pages 25 (paragraph 1) and 23 (paragraph 1) of the manuscript.


Reviewer 2 Comment 4: - Short background on the Out of the Blues program would help the reader to understand where it was developed, by who and what the content was based on. An outline of the program is given but the background would help to position this intervention in the field of available interventions.

Author Response to Reviewer 2 Comment 4: The background of the Out of the Blues program is currently being described in another manuscript detailing the qualitative study used to assess the acceptance of the intervention among clinicians and patients. This study is now cited in the revised manuscript (page 8 paragraph 2).

Reviewer 2 Comment 5: - It is stated that previous studies focused on mild to moderate depression where this study focuses on moderate to severe/major depressive disorders. This might effect the results obtained if compared with previous studies. Just consider this during interpretation.

Author Response to Reviewer 2 Comment 5: We appreciate this feedback and will consider this during our interpretation of the results.

Reviewer 2 Comment 6: 18 weeks should be sufficient for a feasibility study but be mindful that more time might be required to determine effectiveness. Consideration can be given to a longer follow up time in a full scale study if the pilot indicates that this is feasible.

Author Response to Reviewer 2 Comment 6: The reviewer brings forward an
important point. We have noted this in our discussion section of the protocol. Please refer to page 29 (paragraph 1) of the manuscript.

Reviewer 2 Comment 7: I agree that consideration should be given to how data will be analysed if participants miss sessions since they will not have the benefit of the full intervention.

Author Response to Reviewer 2 Comment 7: We have considered the possibility of using various imputation methods including: 1) multiple imputation, and 2) sensitivity analysis using different imputations (sample mean, highest value, positive/negative) to determine overall impact on primary and secondary outcomes.

Reviewer 2 Comment 8: The statistical analysis included is accurate and I agree that due to the nature of this study and sample size these should only be seen as exploratory.

Author Response to Reviewer 2 Comment 8: We agree with the reviewer’s comment.

Reviewer 3 Comment 1: Discretionary Revision - The study question is identifiable. It is somewhat lengthy, albeit with the necessary detail. The question is located after the section entitled ‘The Choice of Comparators for the Pilot Trial’. If placed before the question, this information may better situate the study.

Author Response to Reviewer 3 Comment 1: We thank the reviewer for their thorough appraisal of the manuscript. We agree with the reviewer that the research question would be better situated above the section entitled “The Choice of Comparators for the Pilot Trial.” Please refer to page 6 of the revised manuscript.

Reviewer 3 Comment 2: Replace ‘improve’ to decrease’ or a synonym for depressive symptoms.

Author Response to Reviewer 3 Comment 2: We have revised the manuscript to address this change. Please refer to page 6 (paragraph 3).

Reviewer 3 Comment 3: Discretionary Revision - The Pilot Study Primary Objectives contains detail about the pilot study and links to primary objectives by adapting the framework by Thabane et al. This adaptation is more of an application than an adaption of objectives. If presented as a set of principles, it will be of greater use as a heuristic device to other researchers.

Author Response to Reviewer 3 Comment 3: While we thank the reviewer for this suggestion, we have formatted the manuscript to fit the recommended pilot study objectives proposed by Thabane et. al. We followed the suggested presentation of pilot and feasibility studies proposed and would prefer to leave the manuscript in its current form and simply use the objectives proposed in the original guidance by Thabane et. al. Additionally, Dr. Thabane is also a senior author on this project and approves our application of the criteria proposed in the previous work.
Reviewer 3 Comment 4: A core point to manage vis-à-vis the study design is defining what exactly usual care refers to. This study needs to be theoretically (and methodology) valuable to researchers, clinicians, policy makers and/or educators. So to present terms of usual care using nebulous descriptors is not useful. For example, the authors talk of usual care and include ‘occupational therapy’ – and in doing so reduces an entire profession’s practice range to one strategy of care. While the use of ‘usual care’ may be acceptable in e.g., drug trials, for this study, the challenge is to go beyond an inherent medical orientation (bias?). This means that authors need to position depression as both a group/socially situated illness and a personal health issue, to solidly theorise depression as a disability – perhaps even within frameworks like the International Classification of Functioning. If this is managed well, then the study will be able align its focus on group interventions, resource constraints and efficacy in a theoretically richer – and more pragmatically meaningful way.

Author Response to Reviewer 3 Comment 4: We acknowledge the reviewer important point, and agree that depression is a complex syndrome with many different interventions and strategies are required to address its impact. The description of depression in context of disability is however beyond the scope of this protocol. We have revised the manuscript to ensure a more explicit description of our “usual care” therapies, please see page 9.

Reviewer 3 Comment 5: A key question for the authors to respond to as they work through their pilot study is: Can a method essentially imagined for the individual be validly applied at a group (or, importantly, a population) level?

Author response to reviewer 3 Comment 5: This is an excellent point and important to consider from the viewpoint of both the patient and healthcare system. This intervention is designed to be provided at the group level. Few previous studies have investigated the use of behavioral activation for individuals as well as groups, both forms showed promising results albeit with methodological limitations. We plan to use group format (Page 4 of the manuscript details group-based involved needed for this intervention) as we outlined the advantage of group therapy on page 4. Additionally, we have performed a qualitative study, which actually details patient and clinicians perspectives of the applicability of this intervention. In this work patients were very responsive to the group-based treatment used for BA. Both the patient and clinician groups endorsed the development of social skills, team-building, accountability, and shared experiences as benefits of a group-based BA approach. Social skill building was a major challenge identified in the patient focus group, and one that patients felt would be effectively addressed through the Out of the Blues Program. This patient went so far to liken the social skills aspect of the program to a necessity. This work is currently prepared for submission to Pilot and Feasibility Studies. We intend to also discuss this in the results paper for the BA feasibility trial. However for the purpose of the protocol we will not be discussing the implications of group-based therapy, we will only be discussing the trial methodology.
Reviewer 3 Comment 6: The control group is uncritically framed as a support group. Support groups may in and of themselves manage depression. See, for example: Pfeiffer, P.N., Heisler, M., Piette, J.D. Rogers, M.A.M. & Valenstein, M. (2011). Efficacy of peer support interventions for depression: a meta-analysis. General Hospital Psychiatry. 33(1), 29-36. The researchers have controlled for the key health care worker (nurse) and for the activity (topic selection and an open discussion). However, that the even unstructured peer support is therapeutic in and of itself is a valid threat to the core study design and must be managed – at least at the point of data analysis.

Author Response to Reviewer 3 Comment 6: The control group is receiving an enriched “standard of care” whereby patients enter an additional support group. We acknowledge support groups have an efficacy for improving quality of life, and that the implications of an active control arm require consideration in the discussion of the results. We have revised the manuscripts discussion to reflect the implications of using active control interventions. Please refer to page 9 (paragraph 1) of the manuscript. We thank the reviewer for providing reference to this important study.

Reviewer 3 Comment 7: The principles of the pilot pragmatic trial are well described for simulating real life settings – and is an excellent review of allowing context to interdigitate with methodology. Real-life clinical settings, and how this determines such research, is worth exploiting and connecting to the subject matter as a conceptual/theoretical framework for this study.

Author Response to Reviewer 3 Comment 7: We agree with the reviewer and acknowledge the important of effectiveness research, whereby pragmatic trial design allows us to maximise the safety of participants included in the trials while also balancing the applicability of the findings. Until we have completed our pilot study (both the qualitative assessment and randomised trial), we will refrain from making any assumptions about how the clinical setting, patient profile, or social context can affect the patient’s treatment course. The purpose of this study is to provide readers with a detailed outline of the study methods used for the pilot randomized controlled trial. A discussion of the influence of real-life clinical setting will be better suited for the discussion section of the pilot trial findings paper.

Reviewer 3 Comment 8: What is highly contestable is that the nature of what constitutes therapeutic practice and – more importantly - the social, political, cultural understanding depression as a pathology, is totally ignored/masked and is what will present as a core threat to the study.

Author Response to Reviewer 3 Comment 8: We acknowledge the reviewers suggestions that the concepts of treatment as well as the definitions of “standard care” can vary greatly between cultures, health care systems, and even among psychiatrists within the same community. We will direct the reviewer to our comment to reviewer 1 comment 2. We have revised the manuscript to directly discuss what we determined is the “usual care.” However, the issues of the transferability of definitions for therapeutic practice are important and these implications will be discussed in the findings of the pilot
trial paper. In addition the social, political and cultural understanding of depression as a psychiatric disorder/pathological state is beyond the scope of this manuscript. We whole heartedly agree with the reviewer that depression is a complex phenomenon and the simplified yet pragmatic approach that is taken by the classification systems and treatment approaches does not incorporated the sophisticated nature of depression, nonetheless we can use what has been harmonized internationally as acceptable definition of depression in this trial.

**Reviewer 3 Comment 9:** Beck Depression Inventory should be specified in full (BDI-II) throughout the protocol.

**Author Response to Reviewer 3 Comment 9:** This has been addressed.

**Reviewer 3 Comment 10:** PRECIS criteria need explaining/reviewing – consider the journal’s readership.

**Author Response to Reviewer 3 Comment 10:** We have revised the manuscript to address this. Please refer to page 13 (paragraph 2) of the manuscript.

**Reviewer 3 Comment 11:** That the experimental structure of the study depends on person and context sensitive variables must be addressed, if not in the data collection – at least within the analytical framework. A critical orientation that acknowledges people’s complexities is necessary to address external and/or ecological validity. For example, how the BDI-II addresses cultural issues are not alluded to at all. This implies the danger of piloting a ‘once-size’ fits all approach while (ironically) valuing individual needs.

**Author Response to Reviewer 3 Comment 11:** We acknowledge there is also inter-individual variability which may impact the application of different psychometric tools, especially cultural variation. However, we are hesitant to believe there will be dramatic cross-cultural differences between the cohort of participants recruited in the Hamilton area. In addition The BDI was not tested to assess cultural variation in response to questions about depressive symptoms within the same country/language (all of the proposed patients to be included in this trial will be English Speaking), however it has validated to assess symptoms of depression in many languages and cultures including Persian (Ghassemzadeh, Habibollah, et al. "Psychometric properties of a Persian-language version of the Beck Depression Inventory-Second edition: BDI-II-PERSIAN." Depression and anxiety 21.4 (2005): 185-192), Arabic (Al-Musawi, Nu'man M. "Psychometric properties of the Beck Depression Inventory-II with university students in Bahrain." Journal of Personality Assessment 77.3 (2001): 568-579.), Chinese (Chang, Hsiaowen. "Dimensions of the Chinese Beck Depression Inventory-II in a University Sample." Individual Differences Research 3.3 (2005)) and Japanese (Kojima, Masayo, et al. "Cross-cultural validation of the Beck Depression Inventory-II in Japan." Psychiatry research 110.3 (2002): 291-299) among others.

**Reviewer 3 Comment 12:** Reference to the BDI-II as assessing change in mood seems to minimise its diagnostic potential and relevance for the proposed study.
Author Response to Reviewer 3 Comment 12: To enhance our confidence in the estimates obtained from our study we wish to only employ tools that have been validated for the assessment of a given disorder or symptoms resulting from a disorder within our population of interest. We are using the BDI-II in the context of measuring depressive symptoms in patients diagnosed with depression.

Reviewer 3 Comment 13: It is only in the section entitled eligibility criteria under the qualitative data analysis that the reader discovers that English is a criterion for inclusion/exclusion. This needs declaring much earlier. Hence, the suggestion is to be have an explicitly stated section, upfront under methods/design (perhaps where paragraph 2 positions the study principles). If this is unsuitable then all participant inclusion/exclusion criteria needs a complete section of its own.

Author Response to Reviewer 3 Comment 13: This has been addressed, please refer to page 13 (paragraph 1) of the manuscript where we moved the eligibility criteria to the methods and design section, right after the objectives of the study.

Reviewer 3 Comment 14: The effective use and management of language/communication is vital in such a study. If English is being used as an exclusion criteria then issues of external validity must be addressed especially when one considers a context (Hamilton?) that is (pragmatically) multilingual in nature. Importantly, English speakers are not mono-cultural. So, even while language may be perceived as practical research problem that needs resolving in relation to the restrictions of English-speaking researchers/staff/therapists, clinical cultural competence is of prime concern.

Author Response to Reviewer 3 Comment 14: We acknowledge that placing a language restriction on the eligibility criteria may impact the generalizability of the findings. However, while Hamilton may be pragmatically multi-lingual by nature, the delivery of services in this area (as well as the majority of Canada notwithstanding Quebec and New Brunswick) are delivered in English or with the use of a translator. In this study we aimed to demonstrate the effectiveness of this intervention under optimal conditions. We have included an additional discussion of the limitations and reasons guiding our decision to use this criteria in the eligibility criteria section of the manuscript. Please refer to page 13 (paragraph 1).

Reviewer 3 Comment 15: If verbal communication is the main medium of the methodology under study, why is English literacy an exclusion? Self- administered forms can be completed with the help of research assistants/facilitators. The concern here is that literacy is a proxy for socio-economic class.

Author Response to Reviewer 3 Comment 15: Please see response to comment 14.

Reviewer 3 Comment 16: Researchers may argue that such a study has practical limitations and is limited by e.g., econometric and temporal constraints. What they need to do, is then ask how useful or how (politically, culturally) pragmatic is such a study for real world practitioners?
Author Response to Reviewer 3 Comment 16: We acknowledge the reviewers point, however this is beyond the scope of the presented study. We aim to only provide a protocol detailing the methodology of our randomized trial. The real setting for such a discussion will be in the primary findings paper, where limitations of the trial will evaluated through out the discussion section.

Reviewer 3 Comment 17: The use of some strategies like researcher 2 to note body language and so on is not well justified and appears to overlap with a discourse analysis or clinical method – not a research strategy per se for this this study. If such strategies are to be used, then it certainly needs a great deal more systematic design - regarding data collection, analysis, interpretation, etc.

Author Response to Reviewer 3 Comment 17: We have clarified that this information is not being collected for the purpose of a discourse analysis. Please refer to page 15 (paragraph 2) of the manuscript. Since we are administering a new intervention it is important we record all aspect of face-to-face contact, including during the qualitative sessions. We did not wish to suggest we will be performing a discourse analysis.

Reviewer 3 Comment 18: Details like how transcription will be done, how data will be cleaned, scanned and represented should be considered. Indeed, the section called ‘qualitative data analysis’ contains a very broad allusion to the process of data analysis.

Author Response to Reviewer 3 Comment 18: Reviewer 3 brings forward an important limitation of the current qualitative section, and the need for a clearer discussion of our planned analysis for the qualitative study. We have revised the discussion of the data within the qualitative data section. Please refer to page 17 (paragraph 1) of the manuscript.

Reviewer 3 Comment 19: Grounded theory is referred to and used relative to general, qualitative data collection and analysis methods. While details are provided, the necessary level of rigour in data collection, analysis and representation needs elevating to a more acceptable standard. For example, that the question guide will evolve throughout the study is acceptable but lacks credibility and trustworthiness – both criteria for how qualitative data may be collected/analysed. Consider using qualitative data analysis texts like the following to inform the ways in which reliability/validity can be managed in this study: Miles MH, A; Saldana, J Qualitative Data Analysis: A Methods Sourcebook (3rd Edition) Los Angeles: Sage Publishing; 2014

Author Response to Reviewer 3 Comment 19: We have revised our section to further detail the methods of our qualitative study. We again would like to note that the detailed methods including the development of the interview guide, as well as changes, criteria used to inform the questioning are extensively described in the primary qualitative paper currently under preparation. We feel the detailed methods reviewer 3 wishes for us to include are better suited in the findings paper, whereby we detail the evolution of the interview guide, as well as the patient and health system important factors influencing
these changes should only be discussed after the initial piloting has taken place. However, please refer to page 17 (paragraph 1) for the revised description of the qualitative study methods.

**Reviewer 3 Comment 20:** Do a grammar check. See e.g., study question for a missing article/‘a’ before the term ‘support group’; cantered for centred, line 6 under BA antidepressant should be in plural, etc. Terms like ‘depressive disorders in patients with depression’, ‘patient-important’ and ‘missingness’ need clarity.

**Author Response to Reviewer 3 Comment 20:** The protocol has been extensively revised to ensure 1) there are no typographical errors, and 2) the proper terms are better described. Please see page 6 (paragraph 2), page 20 (primary outcome number 3), page 23 (paragraph 1), page 24 (paragraph 1). We have provided a detailed description and reference to the DSM-IV for a discussion of depressive disorders.

**Reviewer 3 Comment 20:** The tables need to be set/aligned to text. Columns labelled intervention and control in Table 1 are empty – which implies it is both a recording form and an explanatory table. This will need tidying up or clearer positioning as a tool/table to augment the text.

**Author Response to Reviewer 3 Comment 20:** The table has been revised according to the journal style.

We thank the reviewers and editor for their constructive evaluation. We hope we have clarified any of the issues the reviewers have brought forward.

Sincerely,

Additional References