Author’s response to reviews

Title: Exploring the Determinants of Suicidal Behavior: Conventional and Emergent Risk (DISCOVER): A feasibility study

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

March 12th, 2015

We would like to thank the reviewers for taking the time to carefully review our manuscript entitled *Exploring the Determinants of Suicide: Conventional and Emergent Risk (DISCOVER): A feasibility study* (MS: 1282488266146788) and the helpful suggestions the reviewers made. We believe the comments and suggestions have strengthened and clarified the manuscript. We have made thorough revisions to the manuscript with an emphasis on providing appropriate changes in accordance with the constructive feedback. We feel the manuscript in its revised form will be of high interest to the audience of Pilot and Feasibility Studies. We summarize our response to the reviewers below.

**Reviewer 1 Summary:**

The authors provide a considered summary of the advantages and disadvantages of alternate study designs. The case-control nature of this study is the gold-standard favoured by epidemiologists. This study has a particularly efficient design because it has two control groups.

The study group’s ability to recruit more than their intended sample sizes, in both cases and controls, and in the proportion providing blood and urine samples is encouraging and bodes well for recruitment success of the larger, future study. I am heartened that participants have been so keen to help in this study, and they are commended for this.

Also, given that this study is physically invasive due to blood and urine samples being taken from patients, on top of the psychological impact of answering questions, a pilot of such studies, ironing out any methodological or practical difficulties is beneficial to the wellbeing of the increased number of patients due to take part in the larger second study planned following this pilot study.

This is a successful pilot/feasibility study because the authors have made appropriate amendments to the study design before embarking on their larger study. This sample size is large enough to make decisions on methodology but not onerously so.

It would be useful to publish what the authors have learnt about doing such a study because if people in other geographical areas wish to repeat the study they can do with these lessons in mind.

Generalizability of results: This study was done in a mid-size Canadian city. Obviously the cases are a specific subgroup of the psychiatric population, who have been an inpatient for an extended period, and these are people who have not (yet) died by suicide. The generalizability of methods and findings should bear in mind these facts.

Overall, I would say this was a professionally planned and well-executed study, with valuable results, particularly in terms of learning/improving methodologies which can be directly
implemented in the next stage of their study. Most of my comments seek only a little more clarification on definitions and methods.

I wish the authors well with their larger study and await their results with interest.

**Authors’ Response:**

We are sincerely thankful to the reviewer’s comments and the positive remarks on the study design and implementation. Like the reviewer we are heartened by the generosity of the participants and their keen investment in this research. This is truly an altruistic participation to which we are most grateful.

**Reviewer 1 Minor Essential Revisions:**

Reviewer 1 Comment 1: Given that the study data is of episodes of suicide attempts which did not directly result in death and it does not include data on completed suicides, I would suggest changing the title from ‘Exploring the Determinants of Suicide …’, to ‘Exploring the Determinants of Suicidal Behaviour …’.

**Author Response to Reviewer 1 Comment 1:** We have revised the title of the manuscript to, “Exploring the Determinants of Suicidal Behavior: Conventional and Emergent Risk (DISCOVER): A feasibility study.”

Reviewer 1 Comment 2: Cases were inpatients with a recent suicide attempt. Suicide and self-harm literature differentiates risk factors between completed suicides, parasuicides, attempted suicides, non-suicidal self-injury and self-harm. In the second paragraph of the Background section ‘suicidal behaviour’ is defined as behaviour where the person did not die but had intended to. However, in the Results section, paragraph two, the cases are defined as those who had made a serious suicide attempt. However, this ‘serious’ qualifier was not mentioned in the Methods section. Could the authors provide their definition of a ‘serious’ suicide attempt?

**Author Response to Reviewer 1 Comment 2:** We have clarified this definition in the methods section of our manuscript (Page 4 paragraph 1).

Reviewer 1 Comment 3: Using this definition, how did the researchers code and make case determination decisions where the patient said they were ambivalent about dying, or were not sure at the time of the act whether they actually wanted to die or not? I work with UK self-harm data, and this occurs in quite a high proportion of cases. Could the authors clarify that they excluded people who self-harm, but whose intent was not to die by suicide?

**Author Response to Reviewer 1 Comment 3:** We thank the reviewer for highlighting this issue. We only defined and included cases as patients who responded yes to intent to die. We did not include ambivalent patients as SA cases. We have clarified this on page 4 paragraph 1 of the manuscript.

**Reviewer 1 Discretionary Revisions:**

Reviewer 1 Comment 4: As the authors state, many studies have published on conventional risk factors associated with suicidal behaviour. They also say, Background section,
paragraph 3, “however, novel risk factors are less investigated”. Is this phrase meaningful? Are they not called novel because they are less investigated/evidenced? I would consider changing the word ‘novel’ to ‘other’ in this sentence.

Author Response to Reviewer 1 Comment 4: We have modified this sentence accordingly. Please see page 1 paragraph 3 of the manuscript.

Reviewer 1 Comment 5: Background section, paragraph 3, “Understanding both the inherent and modifiable risk factors of SB will assist in the prevention of SB and completed suicide as well”. Does this not contradict their earlier statement in this paragraph that “SB is not a spectrum of severity phenomenon with suicide ideas… but likely to be better characterized as discrete categories with different risk factors for each category”?

Author Response to Reviewer 1 Comment 5: We wish to clarify that in our discussion about the inherent and modifiable risk factors as well as discrete categorization of SB with different risk factors we intended to include prevention of suicidal behavior in general including completed suicide. We have clarified that our intentions are to understand and prevent all types of suicidal behavior.

Reviewer 1 Comment 6: Were any service users/patients consulted in the design of the pilot study? If so, could the authors mention this in the paper. Also, how did the patients provide feedback during/after the pilot study? Was this verbally/in writing/face-to-face/anonymously etc?

Author Response to Reviewer 1 Comment 6: This is an excellent question from the review and will consider service users/patients feedback in our future studies. For this study however there was no consultation with patients during the design of study. We did solicit healthcare providers feedback including front line staff working with emergency psychiatric services during the protocol development and obtained nurses’ feedback during the study conduct through weekly study meetings on the processes, case report forms, as well as time it took to recruit and interview patients. Specific attention was paid to any feedback on patients’ comments during the interview, particularly whether patient found them long, tiring, and whether any questions were difficult to understand. Revisions were made to our questionnaires based on this feedback. For example we changed the wording on one of our questionnaires from rather much to often. This clarification has been addressed on page 6 paragraph 2 of the manuscript.

Reviewer 1 Comment 7: How did the research team know which patients did not have past suicide attempts? Had they approached medical staff and asked them to identify appropriate candidates, or was there a medical database they utilized?

Author Response to Reviewer 1 Comment 7: For the inpatient recruitment, the researchers approached the clinical staff and asked about suitable participants based on the study inclusion criteria. Clinical staff identified suitable patients after obtaining verbal consent from patients to be approached by research staff. Research staff would then provide information about the study to potential participants and go over the inclusion and exclusion criteria, if potential participants fulfilled the study criteria they will be asked to sign an informed consent form and start the study procedures. In the consent form, the participants also consent for access to their medical record. A second check of past suicidal behaviour will then be done. In few instances the medical notes
reported a past history of suicidal behaviour, and in this case the participant would be excluded as a control. We have kept the data from this group of participants as “cases past” with the participants permission and these are the cases we mentioned as per comment 15 below. We wanted to see how different current risk factors are for recent or past history of suicide attempt even in a small subset of participants.

For community recruitment, the researchers put out advertisements in hospitals and community requesting volunteers to participate in study. Upon obtaining consent, researcher would take a history of SA and mental health from community participants. All participants were subject to screening and diagnostic interviewing for psychiatric disorders using the MINI. Medical history was also obtained from all patients, including history of attending clinical services, current medications. The medical charts of included participants attending medical or surgical services we also checked for confirmation of diagnoses and history. This clarification is included on page 5 paragraph 1 and 2 of the manuscript.

**Reviewer 1 Comment 8:** Control group 2 is a sample of patients from a general medical outpatient/community sample. Could the authors clarify in the paper whether individuals in this group were screened to exclude those with previous mental health issues or who had made previous suicide attempts?

**Author Response to Reviewer 1 Comment 8:** Please refer to comment 7 for description of recruitment. We excluded participants from this group if they reported previous history of suicide attempt but did not excluded them if they had previous history of mental illness. All participants were screened for psychiatric disorders using the MINI.

**Reviewer 1 Comment 9:** It looks like the comparison statistics in Table 1 measures statistically significant differences between all 3 groups at once (though I could have misunderstood). Could additional statistics highlight where eg statistical differences exist between 2 of the groups but not the third?

**Author Response to Reviewer 1 Comment 9:** While we used analysis of variance (ANOVA) to present the preliminary pilot findings, we acknowledge the limitations of this analysis and intend to use more advanced statistical methods in the main investigation. We maintain the focus of this manuscript is on feasibility and not the statistical analyses. We only wished to provide preliminary evidence for trends.

**Reviewer 1 Comment 10:** Ethical issues; the paper states that the study was passed by two research ethics boards but maybe a little more detail could be written on this about what needed to be considered. Eg Were the patients told they could choose to leave the study at any point? Were interviews stopped if the patient became distressed? Was there a time-frame for disposal of blood and urine samples and were there any other ethical issues around the collection of blood and urine samples?

**Author Response to Reviewer 1 Comment 10:** The study conduct is in compliance with our intuitional standards in accordance with the standard consenting procedures and ethical practices outlined in the Declaration of Helsinki. We used to have two ethics boards one for St. Joseph’s Healthcare services and one for Hamilton Health Sciences and McMaster University services, all of which are healthcare and academic services in our city of Hamilton. As of
January 1st 2013, a joint ethics board was formed called the Hamilton Integrated Research Ethics Board (HiREB). The studies that were previously approved by one REB had to be approved by the other prior to the two boards joining, since then we have to submit the annual renewal report for the study to the new HiREB.

During the consenting process patients were informed of the study purpose, procedures, potential benefits, possible harms, as well as their ability to withdraw from the study at any time. They are also informed that the participation is voluntary and will not impact their healthcare that they would usually receive. Participants were also required to consent to the collection and storage of biological material (blood and urine samples) that will be used for the purpose of the study and stored for 20 years. The participants also informed that regardless of reason, interviews would be stopped at any time patients wished to stop, withdraw or wanted to continue at another time or only wished to provide part of the study data. This has been clarified on page 6 paragraph 3 of the manuscript.

Reviewer 1 Comment 11: There are quite a few variables which the authors collected data on, but did not show the results of, eg psychopathology/psychiatric diagnoses, previous suicidal behaviour, social support, impulsivity, current medication, ethnicity, religion. Is this due to low numbers and therefore insufficient statistical power or potential identifiability of cases/controls, or were the results non-significant, or perhaps there are there other reasons?

Author Response to Reviewer 1 Comment 11: The reviewer is accurate, there were too few patients reporting in many of these variables. In addition, this was not the primary focus of this feasibility work, we intended to evaluate the feasibility and process of collecting these measures, not their results.

Reviewer 1 Comment 12: In Figure 2, who are the ‘other’ excluded category?

Author Response to Reviewer 1 Comment 12: Reasons for exclusion combined within the “other,” category as provided by potential participants were: not interested, deterred by blood or fasting, deterred by subject of study, deterred by questionnaire completion, deterred by follow-ups, too busy/time commitment, concerned about effect on mental health, wanted to consult doctor first, interviewer not a psychologist, not recommended by nurse/not approachable, language barrier, changed mind, family issues, disinterested in research, bad experience with research, suspicious, concerned about confidentiality, and does not specify why declined participation. Due to the small number of participants among these categories we combined them into a single “other” category. We have appended our figure to include a description of the categories combined to form “other.”

Reviewer 1 Comment 13: Exclusion criteria include ‘inability to provide informed consent’. Does this automatically exclude those with a formal admission to a psychiatric ward (this is what UK patients are termed as if they have been admitted to a psychiatric ward against their wishes) so that only informal admission patients (ie where the patient agreed to be admitted) would be approached for informed consent? This may have repercussions over the generalizability of findings, because it may exclude the more severely ill patients.
Author Response to Reviewer 1 Comment 13: We thank the reviewer for bringing this important point forward. The admission criteria and the use of mental health act differ between Canada and the UK. Patients approached could be voluntary (informal) or admitted under a form using the mental health act (formal). The Mental Health Act (MHA) in our jurisdiction does not automatically consider patients that were admitted informally to lack the capacity to provide consent. In our system patients can be admitted formally and still be considered competent to consent to treatment. Therefore the patients included in this study contained a mixture of both informal and formal admissions however all patients are deemed competent to consent to treatment. Patients who are considered incompetent to consent to treatment are assessed using the MHA in a different process than the one used for informal admission criteria and would have substitute decision maker to make decisions on their behalf. We did not approach patients who were deemed incompetent to consent. People who are assessed using MHA considered incompetent to consent are usually patients with confusion, significant cognitive or intellectual impairment, severe acute psychotic symptoms impairing judgment and therefore considered unable to make informed decisions. Patients who were severely ill at the time of admission but considered competent to consent to treatment were approached at a later time when their clinical team believed that they have improved, compete to consent and agreed to talk to research staff. This has been clarified on page 6 paragraph 4 of the manuscript.

Reviewer 1 Comment 14: Do the researchers have any follow-up data on whether any study patients engaged in suicidal behaviour after the interview period?

Author Response to Reviewer 1 Comment 14: We are planning on following up with the study participants on yearly basis up to 5 years to identify participants engaging in suicidal behavior. These data are not yet available.

Reviewer 1 Comment 15: Who were the 34 individuals who had a past history of suicide attempts but who were not included in the pilot study data analyses? Were these people who were thought to qualify to be in the case group or control groups but who were disqualified from being in one of the groups at a later stage?

Author Response to Reviewer 1 Comment 15: Yes the reviewer is correct. This group of participants were recruited as controls who were then clarified to have a past history of suicide attempts and rarely recruited as cases but clarification of date of suicide attempt fell longer then the study inclusion criteria of one month. However these patients were keen on participating and therefore we decided to keep their data in the study. We have also changed the duration of suicide attempts inclusion criteria for the full study based on what we have learned form the pilot, this is described in our lessons learned section.

Reviewer 1 Comment 16: Care must be taken when looking for associations between biological markers/genetics and behaviour. Even if there is a predisposition, it does not make it inevitable. Whilst there may be biomarker influences on psychopathology, this does not necessarily mean the biomarkers are direct influences on a person’s likelihood to try to kill themselves. Association does not necessarily mean causality.

Author Response to Reviewer 1 Comment 16: We agree with the reviewer that cross sectional associations does not infer causality.
Reviewer 1 Comment 17: What are we supposed to do with the knowledge that specific genes are associated with a higher likelihood of suicidal behaviour? Are we supposed to test psychiatric patients for presence of such genes? Is it good for a person to know this about themselves, especially if they may get into the mindset of inevitability. Would health insurance companies start testing for such genes? Would it make some couples think twice before having children together if they are both carriers of the gene(s)? Is it any advantage to know that a person may not have a higher genetic predisposition to suicide, if they do have other modifiable risk factors? Would it make them less likely to try and change their lives, as they think they won’t feel suicidal without the genetic predisposition? Conversely, would someone labelled as having a predisposition to suicidal behaviour feel less inclined to make modifications to factors they can change because they feel they are in a higher risk group anyway? Also, it is very difficult to separate out the nature/nurture debate, if most people are brought up by biological family members.

Author Response to Reviewer 1 Comment 17: We agree with the reviewer that the clinical utility of genetic variants in complex disorders is still up for debate, the reviewer is making very sound arguments for and against the knowledge of having a genetic predisposition with which we concur. We do hope that the identification of genetic risk factors will help people make informed decisions about their health, risk for disease or certain behaviours and future plans. We agree that having genetic predisposition does not mean the person will definitely develop the disorder as we know there are multiple factors involved in the development of common disorders and behaviors including suicidal behavior. However this knowledge may lead to earlier identification of vulnerable individuals, intense clinical monitoring, modification of modifiable risk factors and eventually stratified medical care approach. These ideas may seem premature in psychiatry but genetic gains in other fields of medicine may make one more optimistic and if anything, the identification of biological markers may help to reduce the stigma associated with suicide. We agree that there is a concern about insurability and decisions to be made about paternity/maternity when it comes to knowing about a genetic risk variant, however this is no so different than having any genetic disorder including Huntington disease, familial Alzheimer disease or certain types of breast cancer where genetic counseling is a commonplace. We do not anticipate any immediate action to be taken to screen every psychiatric patient for these genetic variants however it could be a stepping-stone towards stratified treatments for complex disorders as we understand that the same treatments cannot be applied for everyone.

Reviewer 1 Comment 18: What were the reasons for behind the 10% who did not provide blood/urine samples? Were these people who had not fasted, or who could not attend on a particular day?

Author Response to Reviewer 1 Comment 18: There were few reasons patients did not provide blood/urine samples, including that people did not return to the appointment to provide samples, they did not have the time to come back, they were discharged from hospital before providing the samples, or we were unable to obtain blood after trying. This has been clarified on page 8 paragraph 4 of the manuscript.

Reviewer 1 Comment 19: Presumably, the point of identifying associations between suicidal behaviour, exercise and diet is to encourage patients to modify their behaviour. So, could getting patients to exercise more and eat more vegetables and nuts make people less likely
to engage in suicidal behaviours? Maybe the authors could add in a little detail on what biological processes link diet, exercise and improved psychopathology.

Author Response to Reviewer 1 Comment 19: Many studies have sought to evaluate the links between diet and suicidal behavior. Increased suicide rates in people with low cholesterol or after lowering cholesterol through diet have been reported 1-6. Interestingly, low cholesterol levels were also seen in violent crimes.7 In addition, studies of eicosapentaenoic acid (EPA) report a significant association between low EPA and SB 8. EPA is a polyunsaturated fatty acid found in fish oil. Japanese studies reported lower risk of suicide in individuals consuming fish regularly.9 Other dietary factors may also have a significant contribution to SB. In this study, such dietary factors will be explored using standardized diet questionnaires. To our knowledge few studies have sought to determine the impact of exercise on suicidal behavior, showing a direct link between exercise and suicide risk.10 However this investigation was limited by its small and non-generalizable patient population consisting of American veterans.10 Acknowledging what has been done thus far, we sought to evaluate the feasibility of collecting this information from a large patient population. We have included a discussion of this on page 1 paragraph 3 of the manuscript.

Reviewer 1 Comment 20: One of the surprising results (for me) is the high percentage (24%) of the community sample (control group two) which had a family history of suicidal behaviour. The fact that 24% of second control group had a family history of suicidal behaviour proves to show just how far reaching this issue is, and the number of people potentially affected by other people’s suicidal behaviour. Did any of their results surprise the authors?

Author Response to Reviewer 1 Comment 20: We agree with the reviewer that this rate did catch our attention. To see the number of community samples with a family history of suicidal behavior confirms that the problem is far more prevalent than we know. We believe it is more common than reported and we are only exposed to the selected number of cases in hospitals, where majority of suicidal behavior occurs in community.

Reviewer 1 Comment 21: Future directions: Is the larger study occurring in the same geographical location as the pilot, but with later years and larger sample sizes?

Author Response to Reviewer 1 Comment 21: Yes, the larger study is still taking place in The Greater Hamilton Area, Ontario, Canada, where our psych services cater to large geographic area of 3 million people in southern ON. We are open for collaborations with other sites if opportunities do arise.

Reviewer 2 Minor Essential Revisions

Reviewer 2 Comment 1: Abstract: the results pertaining to hospitalization period and time since suicide attempt (i.e., more than 1 month) are not presented in the Results section of the manuscript. These results are also discussed in the Discussion (page 10; a comment on time since suicide attempt and modifying inclusion criterion). Can you please add these findings to the Results section?

Author Response to Reviewer 2 to Comment 1: Thank you for pointing this out, it seems confusing how we reported the duration and would like to clarify here: Some participants
were admitted to hospital with a suicide beyond the 30-day parameter, however our inclusion criteria specified participants suicide attempt needed to be in the last 30-days. Since these patients were keen on participating we decided to keep their data in the study. We have changed the duration of suicide attempts inclusion criteria for the full study, this is described in our lessons learned section. We did not wish to present the results of these patients with the larger sample collected for this study since they did not technically meet our inclusion criteria.

Reviewer Comment 2: Page 8, last paragraph of results: If I'm interpreting this correctly, these are results that link to the objective of obtaining preliminary evidence on emergent risk factors. If this is correct, when I review Figure 1 (risk factors model), I don't readily see where food group consumption fits in. Could this be clarified? 3. Grammatical notes: Page 3, third line: "The objectives of this study were" (not 'are'). Page 4, line 9: "Exclusion criteria included the" (not 'include ability').

Author Response to Reviewer 2 to Comment 2: We have now included the link between environmental factors such as diet and exercise into the revised Figure 1. These factors are directly linked to mediating factors which alter biology such as the lowering of cholesterol.

Reviewer 2 Comment 3: On page 2, objective 4 (preliminary evidence on emergent risk factors), it's not clear to me how this addresses feasibility for the main study. Could this possibly be clarified?

Author Response to Reviewer 2 to Comment 3: We wanted to show some preliminary trends of the association between emergent risk factors and suicidal behaviour, providing rationale for our investigation of these risk factors in the larger study.

Reviewer 2 Comment 4: On page 3, one of the study inclusion criteria was ability to follow study procedures. Could you clarify how this was determined a priori?

Author Response to Reviewer 2 to Comment 4: Please refer to Reviewer 1 Comment 7 for a description of the recruitment process and comment 13 for a description of competency assessment. The clinical staff determined competency to consent as determined by the mental health act. the research staff after meeting with the patient then determined if they were able to follow study procedures during the first meeting between the research assistant and the patient as part of the process of obtaining informed consent. The research assistant approached patients to explain the study objectives and procedures as well as ask for their consent. If patients did not understand the study procedures, or did not wish to follow them they were not consented.

Reviewer 2 Comment 5: Results: Is it possible to better link the results to the domains introduced in the methods section (page 3) as a way to link this through?

Author Response to Reviewer 2 to Comment 5: We have modified the manuscript to include subject headings that follow the domains introduced in the Methods section. Please refer to page 8 of the manuscript.

Reviewer 2 Comment 6: Page 9, Discussion: The last para introduces the time commitment related to the questionnaires. This finding isn't presented in the results but could go in the Feasibility Results section on page 7
Author Response to Reviewer 2 to Comment 6: This has been added on the last paragraph of page 8 of the manuscript.

Reviewer 2 Comment 7: Page 10: Consider combining the two stand alone sentences into a paragraph on study measures ("We learned that.." and "The Social Support Questionnaire...")

Author Response to Reviewer 2 to Comment 7: We have revised the manuscript to combine these sentences. Please refer to page 11 paragraph 2 of the manuscript.

We sincerely thank the reviewers for providing excellent and constructive feedback. We hope we have addressed all of their concerns.

Sincerely,

References