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

<table>
<thead>
<tr>
<th>TITLE (PROVISIONAL)</th>
<th>The Tulsa 1000: A naturalistic study protocol for multi-level assessment and outcome prediction in a large psychiatric sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUTHORS</td>
<td>Victor, Teresa; Khalsa, Sahib; Simmons, W; Feinstein, Justin; Savitz, Jonathan; Aupperle, Robin; Yeh, Hung-wen; Bodurka, Jerzy; Paulus, Martin</td>
</tr>
</tbody>
</table>

VERSION 1 – REVIEW

| REVIEWER             | Urben Sébastien  
Child and Adolescent Psychiatry, University Hospital of Lausanne (CHUV), Switzerland |
| REVIEW RETURNED      | 13-Apr-2017 |

| GENERAL COMMENTS     | The manuscript described an interesting study, well-designed and which has the potential to lead to new and relevant findings. However, before I could recommend the manuscript for publication, some concerns should be addressed. 

Abstract  
Instead of giving the duration of the assessment, the authors should describe the type of assessment, which seems more informative. Either to have an ethics and dissemination section in the abstract, the reader is perhaps more interested to have information about the expected outcome of the project. 

Introduction  
More information and justification of the chosen pathologies should be provided. 
Page 3 GDP should be written in all letters  
Page 4. The first paragraph is difficult to read for a naïve reader. This should perhaps come later after having presented the whole RDoC domains. At the end of the introduction for example.  
At the end of the introduction, a figure and a more integrative view of the articulation between the various domains or units of analyses assessed should help the reader to better understand the rationale of the study.  
Page 11. The link between the aims and the description of various interesting concepts (microbiome, etc) presented in the introduction should be clarified. 

Method  
Participants.  
More information are needed. Which treatment they will have, etc? The exclusion criteria should be described here.  
Why having so many information about pre-processing and analyses steps of the IMRI and EEG data? |
Exclusion criteria should be in participants section.
End of page 26 as well as the page 27 and 28 are rather uninformative and should not be reported in such a manuscript. By contrast, readers are more interested to have information about the expected outcomes, the way the results of the project could help to enhance treatment, etc.

**VERSION 1 – AUTHOR RESPONSE**

Reviewer comments:

1. We have indicated the specific types of assessment to be obtained over the course of 1 year in the abstract on page 2 instead of focusing on the duration of the assessment.

2. We have kept the ethics and dissemination section of the abstract as indicated in the instructions to the authors. However, if this section is no longer required, we would be happy to remove it from the abstract. We have highlighted the information on the expected outcomes of the project.

3. We have added more information and justification for the chosen pathologies in the introduction on page 3.

4. We have indicated GDP as gross domestic product on page 3.

5. We have expanded the introductory paragraph to better introduce the proposed research to naïve readers and provide clarification of the rationale for choosing the pathologies and the importance of emphasizing the global burden of disease and need for efficacious treatment interventions using the RDoC initiative framework that is described in more detail in the paragraphs that follow.

6. Throughout the introduction we have modified and more succinctly described the rationale of the study and the measures used to address the study aims and concepts in a more integrative manner. We have prepared a modified figure that describes the study in a more visually-focused and clarified way to highlight the various portions of the study. A stronger link between the aims and measures to be obtained in alignment with the RDoC domains has been provided in the study design section on pages 13-14.

7. As noted in the editorial comments, we have moved the exclusion criteria to the participants section. In the participants section, we have not described any specific treatments for this naturalistic study. Instead, we will track participation and adherence to their treatment of choice over the course of the year through medication and treatment compliance questionnaires.

8. We have removed or moved to the supplemental materials the detailed information provided for the pre-processing and analysis steps of the fMRI and EEG data.

9. We understood the information included on pages 27-30 to be required information in the instructions to authors. We would be happy to remove any information as advised by the editorial staff and appreciate the comment. We agree that readers will be more interested in the expected outcomes of the research and have included this section at the end of the manuscript.

Thank you again for your insightful comments and suggestions to improve our manuscript submission.
VERSION 2 – REVIEW

REVIEWER
Sébastien Urben
Head of Research Unit, Department of Child and Adolescent Psychiatry, University Hospital of Lausanne, Switzerland

REVIEW RETURNED
15-Aug-2017

GENERAL COMMENTS
The authors addressed many of my previous concerns and did a great job in this revised manuscript.

However, some minor concerns should be addressed to strengthen the manuscript.

First, the rationale for choosing these psychiatric disorders should be strengthened.
Why the authors did not include conduct disorders or psychotic disorders, for instance? Are there any theoretical model helping to understand why the authors focus on these psychiatric disorders?

When describing in details the analytic units, the authors have either to report details for each psychiatric disorders they included in their study, or to report only global justification for psychiatric disorders in general. For instance, details in immunophenotyping is given only for MDD and not the other psychiatric disorders.

Are some exclusion criteria only transient excluding criteria? or are they all definite exclusion criteria?

The expected outcomes is very interesting and should be described in more details, to enhance the description of the usefulness of this study.

VERSION 2 – AUTHOR RESPONSE

Response to reviewer comments:

1. There are several positive and negative valence domains that theoretically extend across the populations included in the present study – i.e., reward dysfunction in depression and anxiety (usually dampened) as well as substance abuse, and eating disorders (enhanced or dysfunctional). While there is some literature to suggest these constructs may be relevant for other disorders, i.e., psychotic disorders, OCD, conduct disorders, etc. – the case is less compelling, with perhaps other domains playing primarily roles (sensory discrimination; habit learning; etc.) that were not the focus of the Tulsa 1000 study.

While the large sample allows us to examine domains across diagnostic categories, being too expansive would have drastically reduced the number per category. As an example, by adding psychotic disorders, we then would have had to drop down to perhaps 150 per group; if we included obsessive-compulsive disorders, maybe to 75 per group. Thus, to be able to powerfully investigate effects within the diagnostic categories, we chose to focus on the 3 we felt the domains proposed would be the most powerful predictors.
2. We have included additional specific scientific examples of the relationship between the analytic units of measurement and the diagnostic groups where appropriate for the microbiome, stem cells, genetic/epigenetic and immunophenotyping units of measurement in the introduction on pages 6-8. As well, we have included additional references to Table 3 on page 15 that cover an expanded review of the immune-related measures for depression, eating disorders and addiction disorders.

3. Some of the exclusion criteria are transient. For example, if a participant tested positive for substance use during a follow-up visit, became pregnant, or developed a psychotic disorder over the course of the study, he or she would be permitted to continue participating in the study provided the investigators agree that it will not significantly affect the person’s ability to participate. We have clarified this point on page 10.

4. We have enhanced the expected outcomes section to better describe the usefulness of this study on page 24.

Thank you again for your insightful comments and suggestions to improve our manuscript submission.

**VERSION 3 – REVIEW**

<table>
<thead>
<tr>
<th>REVIEWER</th>
<th>Sebastien Urben</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>University Hospital of Lausanne (CHUV), Switzerland</td>
</tr>
<tr>
<td>REVIEW RETURNED</td>
<td>10-Oct-2017</td>
</tr>
</tbody>
</table>

**GENERAL COMMENTS**

I have only two small points that authors should address. The two last limitations should be more explicitly described. As at current state it did not refer really to limitations. Are the exclusion criteria 4 and 7 transient? As authors aimed to include individuals with SUD and MDD, these criteria will be overrepresented in these samples and will exclude a large part of the population.
Response to reviewer comments:

1. We have expanded upon the last two limitations in the strengths and limitations section of the manuscript on page 3. While a longitudinal observational study is not a strong limitation, it does present some unique challenges, including a large number of participants to yield statistically significant results and the risk of higher attrition rates over the course of the study compared to a longitudinal study. Also, the study will recruit a representative sample of individuals from a Midwestern community in Tulsa, Oklahoma, however the results may not be generalizable to individuals with mood, substance use or eating disorders in other regions of the U.S. or worldwide due to factors such as access to and quality of healthcare or demographic, social or cultural differences.

2. We have clarified the exclusion criteria 4 and 7 on page 11. A positive test for drugs of abuse during a follow-up session will not exclude a participant. However, a participant may be excluded from the study during a follow-up session for the development of suicidal ideation with clear intent or plan if the study physician determines that participation will interfere with the individual’s treatment or negatively affect the outcome of the underlying disorder.