Author’s response to reviews

Title: Testing decision-making competency of schizophrenia participants in clinical trials. A meta-analysis and meta-regression

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Author’s response to reviews:

Dear Dr. Markus Boeckle, Dr. Amri Sabharwal, and Dr. Jared Van Snellenberg,

Thank you so much for evaluating our manuscript and for your professional observations!

As we are convinced that the requested modifications significantly improve our manuscript, we tried to do our best to follow the recommendations.

Specific answers to each enquiry are presented below:

Markus Boeckle, MMag. Dr. (Reviewer 1):

The introduction is focusing directly on schizophrenic patients without giving general information about decision making capacity in healthy people. Based on this one could follow how these compare to patients with schizophrenia and some background why this is different in these patients. Thus, I suggest that the authors should only turn to specific test and moral conclusions after setting the field in a more general way.

Answer: we have expanded the literature review by adding a few paragraphs, including: “Schizophrenia patients, as a group, are considered less able to give a proper consent for either a medical procedure, or for their inclusion in a clinical trial, because they tend to have a decreased capacity to understand, retain and process relevant information [1]. However, various studies suggested that many patients with this disease, even in the acute phases, have intellectual properties similar to the ones found in the general population. Moreover, once the treatment begins, many deficits are significantly diminished; therefore, some authors consider mandatory, that the decision making capacity analysis should be thorough, mandatory and done multiple times during the course of the treatment [2]. As a means, Jeste found that between 10 and 52% of
schizophrenia patients do not have insight [3]. The absence of decision-making capacity (DMC) is more important in hospitalized patients [3], if they are in a psychotic state, or if they have a decreased educational level [4].”’, or Some studies suggest that various factors such as age, gender or inpatient status could alter DMC [24, 10, 22].

Additionally, all results on meta-regression are non-significant but are interpreted in the discussion as if they have found significant differences.

Answer: we emphasised the lack of statistical significance of the meta-regression analysis. See below specific comments

Additionally the comparisons between 2 outside and 11 studies within the US across all subscaled does not provide an unbiased sample for meta-analysis.

Answer: we have detailed the issue below, and included potential geographical bias as a limit of the study

Detailed comments:

Page 2

Background: This does not provide information about the background but is presenting the research questions only. Please rephrase in order to represent the background of the research questions.

Answer: Done. We added a brief background information: The process of assessing the decision-making capacity of potential subjects before their inclusion in clinical research is a legal requirement and a moral obligation, as it is essential for respecting their right to self-determination. This issue is especially important in psychiatry patients (such as those diagnosed with schizophrenia).

Materials and Methods: This represents the literature review but not the meta-analysis, please rephrase.

Answer: Done. We used the words: “systematically reviewed”

Page 3:

After conclusion insert space.

Answer: done.

Rephrase first sentence in order to state first facts and then contrast them to your ethical predicament.
Answer: Done. The phrase now states: “Schizophrenia patients should be considered as competent unless very severe changes are identified during the clinical examination, even if they have a significantly decreased decision-making competence compared to non-mentally-ill controls.”

Line 31. Decreased the difference between schizophrenia patients and healthy controls in what dimension?

Answer: we rephrased into: “Using enhanced informed consent techniques significantly decreased the difference between schizophrenia patients and non-mentally-ill controls in all dimensions and should be employed whenever the investigators want to include more severe patients in their clinical trials,

Page 5

Line 21 and subsequent occurrences. Add a space between word and citation.

Answer: corrected

Page 6

Line 19. Please give short definitions of positive and negative symptoms for the general reader.

Answer: we added a short definition for positive and negative symptoms. The phrase now reads as: “Schizophrenia patients have quantitative and qualitative mental deficits, mainly classified in three main categories: cognitive, negative (associated with the disruption of normal behaviors and emotions) and positive (psychotic) symptoms. Their presence can potentially lead to an incorrect assessment of a request participate in a clinical trial”

Page 13.

Line 14. Conducting a meta-analysis based on three studies needs highly cautious interpretation.

Answer: we detailed this issue to the chapter in the limits of the study: “Moreover, only three studies included data about enhanced ways of informing potential subjects. Even if the number was small, the results reached statistical significance in most scales, suggesting that they did profoundly improve the DMC.”

Line 31. The overall relates to the three studies or all 13 studies in your sample. Please be more precise.

Answer: We compared the result obtained on the standard versus enhanced informed consent forms, by using the Z-test. We detailed its use in the materials and methods section (“For comparison of the effect size between two groups, we used the Z test method.”), and to streamlined the sentences regarding the comparisons for each subscale
Line 45. Same as above. But also in all following last paragraph within a sub-scale it is not clear what the results relate to, the full sample or a partial sample.

Answer: Done (see the previous observation)

Page 15.

You always included the 13 studies except in the sub-scale "expressing a choice" please write that in the general information above and do not reiterate in each sub-scale. Potentially indicate number of studies with N=13 or 10 in brackets.

Answer. We added the number of studies in Search synthesis (“. From the total number of 60 studies, we selected 13, which ultimately fulfilled the inclusion criteria, and were added to the meta-analysis (with the except of the “expressing a choice” subscale, where we there were only ten studies with relevant information”), and deleted the info from subscale analysis

Line 38. Eleven studies were performed in the US and two outside only. I would exclude this comparison from the main text and put it into a supplementary as this not representing an adequate comparison. Please consider this for the whole text.

Answer: The minimum number of studies to be included in a meta-analysis is 2. Of course, with the increase in the number of studies, the error estimation is smaller, but the results obtained from two studies are considered acceptable, as long as the statistical analysis is relevant, which was the case here (especially for reasoning subscale). See e.g. Advances in Meta-Analysis by Terri Piggot. We added the low number of studies outside US to the limits of the study, as: “Only two studies were performed outside US, potentially making the results geographically biased. Therefore, they be interpreted with caution in significantly different population groups. Also, the comparisons US-outside US should be regarded as potentially having poor error estimation”

Page 20.

Line 7. You discuss non-significant results in a way that suggests that your results are significant. Please interpret your results according to your findings.

Answer: we specified that our results failed to reach statistical significance (except for the reasoning subscale). However, the descriptive results showed a negative correlation between the percentage of men and subscale scores. There are other studies that showed the presence of this association, which we presented in the discussion section. To clarify however that our result were not statistically significant, we added some paragraphs, including: “The scores on every subscale decreased once the percentage of men in the schizophrenia group increased, but the result did fail to reach statistical significance (except for the reasoning subscale). This failure could be generated either by a low number of studies included in the analysis, or an actual absence of an association between gender and decision capacity. Some studies published in the scientific literature showed that women have a better social adaptability to the disease.”, and
“However, more studies are needed before we can definitely associate (or fail to associate) gender with decreased decision capacity in schizophrenia patients.”

Line 55. Same as above. Age is not significant in your analysis, still you discuss them in a way suggesting that there is a significant result without bringing your own results in relation to the findings of the other studies.

Answer: we minimized the argumentation regarding this issue, by rephrasing the paragraph into: “Various studies have suggested that age could alter decision-making capacity in schizophrenia patients (see e.g. [26]). Our study showed that there might be an age-related deterioration in various MacCAT-CR subscales, but we could not prove it with statistical significance. This failure could be generated either by a low number of studies included in the analysis, or an actual absence of an association between age and decision capacity.”

Page 22

Line 7. Is the number in brackets the number of studies? I thought you have 13 studies in the sample.

Answer: corrected

Amri Sabharwal (Reviewer 2): Abstract

* A brief overview of the existing literature about decision-making capacity in schizophrenia would be helpful in providing the reader some background on the need for such a study and the gap in literature that is being addressed.

Done: We added background information: “The process of assessing the decision-making capacity of potential subjects before their inclusion in clinical research is a legal requirement and a moral obligation, as it is essential for respecting their right to self-determination. This issue is especially important in psychiatry patients (such as those diagnosed with schizophrenia).”

* The first mention of MacCAT-CR should include the full form of the instrument.

Answer: done

* p-value for the understanding dimension is missing.

Answer: added p-value

Introduction

* The introduction, overall, needs a more thorough review of literature.
Answer: we have expanded the literature review by adding a few paragraphs, including: “Schizophrenia patients, as a group, are considered less able to give a proper consent for either a medical procedure, or for their inclusion in a clinical trial, because they tend to have a decreased capacity to understand, retain and process relevant information [1]. However, various studies suggested that many patients with this disease, even in the acute phases, have intellectual properties similar to the ones found in the general population. Moreover, once the treatment begins, many deficits are significantly diminished; therefore, some authors consider mandatory, that the decision making capacity analysis should be thorough, mandatory and done multiple times during the course of the treatment [2]. As a means, Jeste found that between 10 and 52% of schizophrenia patients do not have insight [3]. The absence of decision-making capacity (DMC) is more important in hospitalized patients [3], if they are in a psychotic state, or if they have a decreased educational level [4].”, or Some studies suggest that various factors such as age, gender or impatient status could alter DMC [24, 10, 22].

* No justification has been made in the introduction for the secondary objectives of the study. What are the existing findings regarding the association between enhanced informed consent and DMC in schizophrenia? Have other studies found an association between DMC and any of the demographic factors the authors are interested in?

Answer: to this, we answered in the extended literature analysis from the introduction section (see above), and some studies are analysed specifically in the discussion section.

* Also, why is it important to study the dimensions of MacCAT-CR separately? Have any other studies done that before? What have they found?

Answer: most studied analysed them separately, as each subscale is needed to be present to assess decision capacity, for signing the informed consent. See e.g. the classical article of Applebaum: Appelbaum, Paul S, and Loren H Roth. "Competency to Consent to Research: A Psychiatric Overview." Archives of General Psychiatry 39, no. 8 (1982): 951.

Methods & Results

* I’m not sure if the initials of specific authors are required in the methods. The sentences with author initials can be reworded.

Answer: we removed the initials

* Although not included as a specific aim of the study, it would be helpful to know if the MacCAT-CR scores in the selected studies show an association with positive, negative, or disorganized symptoms, as well as with any neuropsychological/cognitive measures and antipsychotic medication usage. It would be interesting to see if differences in DMC are related to cognitive functioning or severity of psychopathology.

Answer: relevant details, that we were able to properly reconstruct from most studies, were included in Table 1. However, to include all that is stated above would mean doing another,
Discussion

* Since one of the primary conclusions of the authors from their work is that despite the significant difference between patients and controls in the dimension scores of MacCAT-CR, individuals with schizophrenia can be considered as being capable of making informed decision in clinical trials, a more formal statistical analysis should be included in the methods/results sections. In the discussion, the authors merely show how the mean score for the patients can be seen as being above threshold on one of the dimensions.

Answer: the mean values for each subscale are presented in Table 2. The reasoning behind this conclusion is presented in the discussion section: “Therefore, to include subjects in clinical trials, the investigators must make a binary decision about the presence/absence of DMC. Some studies recommend various threshold values for some or all DMC parameters[25, 20]. For example, in the Clinical Antipsychotic Trials of Intervention Effectiveness – Schizophrenia (CATIE) study[26], the investigators established a threshold value of 15 for the understanding scale, a value that was proven to be a little too conservative[20]. Our study showed that there is a circa 4-point difference between schizophrenia and control subjects in the understanding scale. If we were to take into account the mean value for understanding (20.16, see Table 2) and add to this the average difference obtained in the meta-analysis (-4.43), we would see that the mean theorised value for the schizophrenia subjects [20.16-(4.43/2)=17.95] is well above this threshold. Similarly, the lower limit with a 95%CI (-5.76, corresponding to a lower limit for the schizophrenia group of 18.06) is well above the 15 points threshold. By also considering the results of Kim et al. [20], our analysis supports the idea that schizophrenia patients should be considered, per prima facie, as being able to make informed decisions regarding the participation to clinical trials. By assuming decision-making incapacity in these patients, we might discriminate them based on their disease; therefore, by trying to obey the bioethical principle of autonomy fully, we might breach the principle of justice”. To perform a more formal analysis of the level for each subscale that is needed to obtain decisional incompetence, we would have to perform a totally distinct meta-analysis, with other objectives, included studies, and so on, that is beyond the purpose of this article.

* As the authors note themselves, the number of studies included in the analyses is small. The authors argue that including more studies would make the results more heterogeneous, but I'm not sure if that justifies the small number - perhaps it is important to explain the heterogeneity in the findings.

Answer: this test is the most frequently used for assessing decision capacity for clinical trials in schizophrenia patients; by including studies done using other scales, we would significantly increase heterogeneity mainly based on the difference in the quantification of the dimensions of decisional capacity. We clarified this issue in the limits section by stating: “however, if we were to include studies in which decision-making capacity was evaluated using other scales, the
results would have been more heterogeneous, mainly due to the usage of distinct methodologies for assessing DMC”

* The manuscript would be much stronger if more effort was made to explicitly delineate the existing gap in literature and the important way in which this study fills that gap - it would help the reader to understand why this research is meaningful.

Answer: by answering to the above enquiries (especially by extending the Introduction and Discussions section), we believe to have clearly delineated the gap in literature and its practical importance.

Overall

* The manuscript would benefit from another round of editing for grammar and language.

Answer: we reviewed the grammar and language with the aid of a professional editing firm.