Author’s response to reviews

Title: An intensive multimodal group programme for patients with psychotic disorders at risk of rehospitalization: a controlled intervention study

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Version: 1 Date: 11 Jul 2019

Author’s response to reviews:

To the editors of BMC Psychiatry

Dordrecht, July 11th, 2019

Dear dr. Harris,

We thank you for offering us the opportunity to submit a revised version of our manuscript entitled “An intensive multimodal group programme for patients with psychotic disorders at risk of rehospitalization: a controlled intervention study” (BPSY-D-19-00382) . All authors agree with its revision and resubmission to BMC Psychiatry.
Please find below the reviewers’ comments and our replies (italics), including the changes made to the manuscript, which have been highlighted yellow in the manuscript file. We would like to draw your special attention to comment 1.7 and our response, in which we explain why and how we modified the manuscript with regard to the secondary outcome measure of mental healthcare costs.

On behalf of all authors,

Yours sincerely,

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Reviewer 1:

1.1 This paper appears to be generally well-written apart from the results section which could be improved. The first major issue with this paper is that while the authors report unadjusted mean values for LOS or costs, for adjusted values they report a beta coefficient, standard error and p-value. This does not make it clear for readers how they should interpret these adjusted differences. The authors should present the adjusted differences in the natural unit e.g. length of stay in number of days/night and costs in euros. It would really help the clarify the results of the analyses if all of these differences were presented in a table. This would enable readers to better assess some of the conclusions being made.

Reply: We agree with the reviewer that results of the analyses reported in natural units will be more understandable for readers. So, we entered Table 2 (p 15, line 367) entitled “Hospitalization days and total mental healthcare costs (summary of outcomes and sensitivity analyses)” displaying the estimated means in natural units along with the B-coefficients, standard errors, and p-values.

Moreover, we added a line referring to this table (p 8, line 192): “Table 2 summarizes the outcomes and sensitivity analyses.”
1.2 The second major issue is the "outlier" in the control group with an inpatient stay of more than 300 days. Was this duration of stay double-checked to ensure it was not a data entry error? The authors conclude that essentially it did not make a difference when this person was excluded, however before excluding them the difference in length of stay and mental healthcare costs were significant and following exclusion the differences were not statistically significant, so is this fair to say?

Reply: We can assure the reviewer that the exceptional length of stay was double checked. The reported p-values refer to the Wald-test which is known to be conservative. Based on the regression coefficients and the estimated means (see Table 2) we concluded that the outlier did not make an important difference in the primary outcome. We also refer the reviewer to our reply to comment 1.7 with regard to costs.

1.3 Related to the comment above, if the authors presented the differences in natural units then regardless of statistical significance, readers could assess for themselves whether there was a meaningful difference. For example a difference in length of stay of 0.5 days may be statistically significant but not significant in real-world terms. Please can the authors present the adjusted mean differences between treatment groups including and excluding this individual - it is unclear if the second sensitivity analysis reported excluded only this person or this person and the people who were in hospital at the start of the study.

Reply: We added differences in natural units in the table. To clarify the difference in the sensitivity analyses we rephrased the text as follows (p 8, lines 213 and 216): “Otherwise, when we excluded the outlier …”

1.4 There is no indication of whether this was a pilot or feasibility study, and if it is not to be interpreted as such then whether it was powered to detect a difference in the primary outcome measure as the sample size is small.

Reply: Actually, it was a pilot study. We added this to the text (p 5, line 116): “This pilot study had a quasi-experimental controlled study design.”

The paper presents the outcomes of the very first FACT Plus groups in Rotterdam. When planning the study we assumed 75 patients in both groups would be sufficient. However, we did not reach these numbers within a reasonable time period and we had to finish the study with the numbers as presented in the manuscript.

We acknowledge that the sample size was small. In response to this comment and also to comment 2.10 addressing the same issue, we added a line to the strengths and limitations paragraph (p 10, line 255-257): “Despite this, the number of patients enrolled in this pilot study remained rather small and a larger sample size would be required for more definitive answers.”
1.5 Background - page 3, it is unclear what the authors mean by "Its interventions included adherence treatment…", should this read "treatment adherence"?

Reply: To clarify this we changed the formulation as follows (p 3, line 67-69): “Its interventions included psycho-education focussing on the importance of antipsychotic drug adherence and family treatment.”

1.6 Background - the authors report the results from previous studies for both intention-to-treat and "completer" analyses. The authors should acknowledge why the completer analyses may yield different results than ITT (i.e. biases) and why these should therefore be interpreted with caution.

Reply: We acknowledge the importance of the difference between completer analysis and ITT analysis. That is why we stated that the completer analysis of the German study showed a different result than the ITT analysis (p 3, lines 70-71). We added the following line to emphasize the importance of careful interpretation of the German study results (p 3, lines 71-73): “This important difference between completer analysis and intention-to-treat-analysis may be due to biases, e.g. selective drop out, so this result should be interpreted with caution.”

1.7 Methods - the authors include the cost of FACT Plus in their analysis of healthcare costs however they do not report what the cost of FACT Plus was or how it was calculated. The description of the intervention, especially the co-prepared lunch, seems like it would be complex to measure the resources involved. The details of the costs/costing approach should be included.

Methods - one of the secondary outcomes was "mental healthcare costs", please specify which services were included in this category.

Reply: Reviewing the data and calculations regarding the mental healthcare costs, we discovered that in the originally submitted manuscript we only reported the costs of inpatient care in both groups, leaving out the other components of mental healthcare costs, such as outpatient care and additional costs for lunches and materials. It was probably due to a misunderstanding between the authors and the data analyst who supported the data collection with regard to costs. We would like to emphasize, however, that the main conclusions of our study did not essentially change after correction of these data.

In answer to the reviewer’s comment: pretty much all costs of FACT Plus itself as well as outpatient care as usual in the control group consist of the expended staff time. This is a consequence of the complex Dutch system of pricing and invoicing mental healthcare to the insurance companies, in which the costs are calculated based on exact registration of all minutes directly and indirectly expended on the patient.
We therefore collected the data regarding costs from the electronic patient registration system of the Parnassia Psychiatric Institute, in which all costs are registered at an individual level. Moreover, we collected the additional costs for the program, e.g. lunches and materials.

To explain the components of the mental healthcare costs we added a line (p 5, lines 128-131): “Mental healthcare costs consisted of actual costs for outpatient care, including the expended staff time for the group sessions in the intervention group, inpatient care, and additional costs for the programme, such as lunches and materials in the intervention group.”

We slightly changed the following sentence to clarify the methods of data collection with regard to costs (p 7, lines 170-171): “The hospitalization data and total mental healthcare costs of each group were collected from the electronic patient registration system of the Parnassia Psychiatric Institute.”

With regard to the additional costs we added the following statement (p 8, lines 201-203): “The additional costs for the FACT Plus program for lunches and materials added €135 on average to the total per patient, which is a very small proportion of the mean total costs of €21,098 per patient in the intervention group.”

Finally, we modified the following sections of the article regarding mental health costs, with use of the correct figures:

P 2, lines 41-42: “Mean total mental healthcare costs per patient were €21,098 in the intervention group versus €25,054 in the control group, a difference of about €4,000 per patient (16%).”

P 2, lines 46-47: “This result was accompanied by a limited reduction in mental healthcare costs.”
“.. the mean total mental healthcare costs per patient were €21,098 in the intervention group (including the costs of FACT Plus) versus €25,054 in the control group, a difference of about €4,000 per patient (16%). In a regression analysis this difference in costs was not statistically significant (B=-.196, SE=.207, p=.172).”

P 9, sensitivity analyses, rewritten the entire paragraph (lines 207-218): “Despite fulfilling all the inclusion criteria, five patients in the control group turned out on the first day of the chosen observation to have been hospitalized. During the follow-up period, another patient in the control group was hospitalized for more than 300 days (outlier). After exclusion of the patients who were in hospital at the start of the observation period, sensitivity analyses regarding the number of hospitalization days showed that the difference in LOS between the two groups was somewhat smaller (B=-.554, SE=.492, p=.13). Otherwise, when we excluded the outlier, again the difference in LOS (B=-.614, SE=.489, p=.10) changed only slightly.

With regard to costs, the exclusion of the patients hospitalized at baseline, the model showed a difference in costs in favour of the control group (B=.237, SE=.206, p=.125). Otherwise, when we excluded the outlier, there was a small difference in costs in favour of the intervention group (B=-.026, SE=.197, p=.448).”

P 9, line 224-225: “.. we observed a limited saving of about €4,000 per patient with regard to the total of mental healthcare costs in the intervention group compared to the control group.”

P 10, line 260: “with regard to LOS”

P 10, lines 261-262: “However, the outcomes with regard to costs were considerably attenuated in the sensitivity analyse.”

P 10, line 273: “.. accompanied by a limited reduction ..”

1.8 Discussion - the authors note that there was a difference in the number of compulsory admissions - some discussion of what may lead to these types of admission would be helpful, for example are they an indication of illness severity or of engagement with healthcare professionals.

Reply: We agree that the topic of compulsory admissions is of importance. Therefore we added a line to the text (p 9, lines 235-236) along with an extra literature reference (no. 15): “.. a subcategory of admissions which indicates high illness severity and low treatment adherence [14,15].”
1.9 Discussion - the authors describe their reasoning for treatment allocation by north/south geography. Could there be some other differences in characteristics between the groups that may be related to the outcomes explored which haven't been adjusted for, for example socioeconomic status, or different care pathways in the localities?

Reply: Criteria for inclusion in FACT care and the organization of FACT care were exactly the same for both parts of the city. We have no reasons to assume differences in socioeconomic status or other factors between both sides of the city.

Reviewer 2:

An intensive multimodal group programme for patients with psychotic disorders at risk of rehospitalisation: a controlled intervention study. The study was aimed to compare the length of stay (LOS), healthcare costs compulsory admissions between intervention and control groups. Intervention group consisted of participants who received intensive multimodal group programme (FACT & FACT Plus). Control group received care as usual (FACT). The results showed that the psychiatric LOS and mental healthcare costs were notable lower in the intervention group compared to the control group.

The specific comments are presented below:

2.1 INTRODUCTION The introduction section is clearly written and the cited articles are up-to-date.

Reply: We thank the reviewer for this kind remark.

2.2 METHODS Intervention/Care as usual: The intervention procedure is described on in the text. It would be easier for reader if the core points of the FACT and FACT Plus programmes are described in Table or Figure format.

Reply: We added Figure 1 presenting the core points of FACT Plus and FACT (p 4, line 105): “(see also Figure 1)” and caption (p 14, line 360): “Figure 1: Core points of FACT Plus and FACT” and submitted it along with the revised manuscript in a separate file.
2.3 At the beginning of the page 5 the authors noted that "… the mean number of patients is 200 …". Does this mean the annual number of patients?

Reply: As FACT patients tend to stay in treatment for several years, the population served by a FACT team is relatively stable. The number of 200 patients refers to the average number of patients per team at any point in time. Annually, the estimated turnover is between 10 and 15% of the total.

2.4 How many patients refused to participate to the study? Did this rate differ between those allocated to the intervention and control groups?

Reply: We counted 15 patients who refused to participate in FACT Plus (intervention group). The control group was selected from the patients in the FACT teams in the south part of the city, based on the same inclusion and exclusion criteria. The data of these patients with regard to hospitalizations and costs were anonymously collected from the electronic patient files. The control group formed as such a carefully anonymized group of reference patients. See also our response to comment 2.7.

2.5 Participants: Table 1 shows the baseline characteristics of the study groups. The results of the statistical significance tests need to be added to that table.

Reply: Following the STROBE-guidelines, in line with the CONSORT-statement, we only report N and percentages in table 1. "Inferential measures such as standard errors and confidence intervals should not be used to describe the variability of characteristics, and significance tests should be avoided in descriptive tables." See: Vandenbroucke JP, von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, et al. (2007) Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): Explanation and Elaboration. PLoS Med 4(10): e297. https://doi.org/10.1371/journal.pmed.0040297

We hope that the reviewer agrees with our choice not to present statistical significance tests in the table.

2.6 Describe also what the "history of addiction" means.

Reply: To clarify this we changed “history of addiction” to “Dx of addiction (except nicotine)” in Table 1 (starting at p 14, line 363), meaning any current addiction or substance misuse (alcohol, cannabis, cocaine, amphetamine, etc.).
2.7 Ethical issues and data processing: From my point of view, it is rather unusual practise that the patients in the control did not need to sign the informed consent form prior entering to the study. Please, explain this practise in more detailed manner. The patients in the control group, however, allowed the use of their data based on the care as usual (regular FACT):

Reply: See also our response to comment 2.4. The control group formed as such a carefully anonymized group of reference patients. The data regarding the prospectively identified control patients was retrospectively collected from the electronic patient files. If carefully conducted and anonymized, Dutch legislation allows electronic patient file research without informed consent, in specified circumstances pertaining feasibility. When doing so, it is very important that patients are not subjected to any assessment or study intervention, which was the case in our study. Therefore, the medical ethics committee explicitly waived the obligation of informed consent in this case.

2.9 RESULTS All results in the result section are presented only in the text. It would be more reader-friendly if those are reported in table.

Reply: We thank the reviewer for this comment. We entered Table 2 (starting at p 15, line 367) entitled “Hospitalization days and total mental healthcare costs (summary of outcomes and sensitivity analyses)” displaying the estimated means in natural units along with the B-coefficients, standard errors, and p-values.

Moreover, we added a line referring to this table (p 8, line 192): “Table 2 summarizes the outcomes and sensitivity analyses.”

2.10 DISCUSSION The discussion section is clearly written. Small number of cases in the study groups needs to be discussed as a limitation of the study.

Reply: We acknowledge that the sample size is small. In response to this comment and also to comment 1.4 addressing the same issue, we added a line to the strengths and limitations paragraph (p 10, line 255-257): “Despite this, the number of patients enrolled in this pilot study remained rather small and a larger sample size would be required for more definitive answers.”