PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Study protocol for a single-blind, randomized controlled, non-inferiority trial of Internet-based versus face-to-face cognitive behaviour therapy for obsessive-compulsive disorder
AUTHORS	Rück, Christian; Lundström, Lina; Flygare, Oskar; Enander, Jesper; Bottai, Matteo; Mataix-Cols, David; Andersson, Erik

VERSION 1 – REVIEW

REVIEWER	Jamie Feusner UCLA Semel Institute for Neuroscience and Human Behavior; Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA, USA
REVIEW RETURNED	16-Apr-2018

GENERAL COMMENTS	The authors describe a study protocol for a non-inferiority trial of two types of internet CBT to treat OCD (therapist-guided or non-therapist-guided) compared with standard face-to-face CBT, a gold standard treatment. This is a carefully-designed study and the description of the protocol is clear and well-written. It appears likely that the study will be able to determine if either therapist-guided or unguided iCBT is not inferior to face-to-face CBT. There are some additional points that would strengthen the manuscript, for the authors to address: • The section “Cost-effectiveness analysis” is somewhat vague. Given that it is written in general terms, is the plan to solely conduct an estimate of the costs of therapist vs. unguided iCBT vs. guided iCBT treatment for OCD, in general, in Sweden? Or, will specific costs estimates be calculated for patients with the same characteristics as those in this study (e.g. OCD severity/YBOCS scores, level of depression, employment status, etc.)? • Is there a limit on the # of emails and responses that a patient can send and/or the therapist can receive in the therapist guided iCBT arm? I could imagine scenarios in which a patient sends multiple emails every day. Although in situations where the patient was asking for reassurance the therapist would likely not reply to all emails (and explain why). However, other scenarios are theoretically possible (especially since they are not excluding those with personality disorders). If there are limits, the authors should provide details; if not, they should explain how # of emails and/or therapist time involvement with emails factor into their calculation of the costs and cost effectiveness of different treatment modalities. • It is a nice feature of the study that they will include self- and clinic-referred patients, to help determine if iCBT is effective for patients from more real world situations. However, it is a stretch to say they are “real patients” both because they still had to meet multiple inclusion/exclusion criteria and it is a clinical trial setting. The

	authors should consider not using that term but instead that they were clinic-referred. In the Article Summary they mention that this design will help generalize results to more typical OCD cases but it would be more precise to say self- or clinic-referred cases here, for the same reason. (It is noted that the authors mention in this section a limitation of generalizability to those who don't meet inclusion/exclusion criteria.) • What is the specific protocol if subjects express suicidal ideation for each of the treatment arms? The authors mentioned suicidality will be handled, "according to standardized clinical routines and reported to the PI within 24 hours," but more details would be useful here, particularly for the subjects getting non face to face treatment. • Regarding the "Analysis of predictors and moderators" section, the authors may consider a cross-validation procedure to reduce the chances of overfitting, such as leave-k-out cross-validation or k-fold cross-validation. • What was the rationale for choosing the 3-month follow up as the primary endpoint? • What was the rationale for choosing a non-inferiority margin of 3 points? The two references cited in that section of the statistical analysis section each used a margin of 5 points. • The authors mention a limitation in the Article Summary regarding generalizability. However, additional limitations should be spelled out in the main manuscript. • In the SPIRIT checklist, while most of the items appear to have been addressed in the manuscript, there are a few that were not. Some of these that would be useful for the authors to include are item 18b, "Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols." Regarding the second part of this, the authors mention that the assumption that data are missing at random will be tested, but additional details how this would be done would be informative. Also, the authors should address item 23, "Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor."

VERSION 1 – AUTHOR RESPONSE

ICBT vs F2F protocol - response to reviewer comments

We address the reviewer comments below:

1. *The section "Cost-effectiveness analysis" is somewhat vague. Given that it is written in general terms, is the plan to solely conduct an estimate of the costs of therapist vs. unguided iCBT vs. guided iCBT treatment for OCD, in general, in Sweden? Or, will specific costs estimates be calculated for patients with the same characteristics as those in this study (e.g. OCD severity/YBOCS scores, level of depression, employment status, etc.)*

   Response: We plan to carry out a single cost-effectiveness analysis of face-to-face CBT vs. unguided iCBT vs. guided iCBT treatment for OCD patients. We have not planned additional subgroup analyses. However, we may consider post-hoc analyses if we feel that these will be reasonably well powered and meaningful. The trial was designed to maximise the chances of the results being as generalizable as possible. However, despite the best of our efforts to recruit both clinic and self-referred

individuals, it will be difficult to confidently claim that our results will be representative of the entire population of OCD patients in Sweden. This is a problem for all clinical trials.

2. *Is there a limit on the # of emails and responses that a patient can send and/or the therapist can receive in the therapist guided iCBT arm? I could imagine scenarios in which a patient sends multiple emails every day. Although in situations where the patient was asking for reassurance the therapist would likely not reply to all emails (and explain why). However, other scenarios are theoretically possible (especially since they are not excluding those with personality disorders). If there are limits, the authors should provide details; if not, they should explain how # of emails and/or therapist time involvement with emails factor into their calculation of the costs and cost effectiveness of different treatment modalities.*

   Response: We have clarified the response pattern of therapists in the "Interventions" section (page 6) and specified treatment costs for both face-to-face treatment and iCBT in the cost-effectiveness section (page 9).

3. *It is a nice feature of the study that they will include self- and clinic-referred patients, to help determine if iCBT is effective for patients from more real world situations. However, it is a stretch to say they are "real patients" both because they still had to meet multiple inclusion/exclusion criteria and it is a clinical trial setting. The authors should consider not using that term but instead that they were clinic-referred. In the Article Summary they mention that this design will help generalize results to more typical OCD cases but it would be more precise to say self- or clinic-referred cases here, for the same reason. (It is noted that the authors mention in this section a limitation of generalizability to those who don't meet inclusion/exclusion criteria.)*

   Response: We agree that the term clinic-referred is a more accurate description and have changed the wording throughout the manuscript.

4. *What is the specific protocol if subjects express suicidal ideation for each of the treatment arms? The authors mentioned suicidality will be handled, "according to standardized clinical routines and reported to the PI within 24 hours," but more details would be useful here, particularly for the subjects getting non face to face treatment.*

   Response: We agree that this section needed more details and have extended the description of suicide risk assessments (page 8).

5. *Regarding the "Analysis of predictors and moderators" section, the authors may consider a cross-validation procedure to reduce the chances of overfitting, such as leave-k-out cross-validation or k-fold cross-validation.*

   Reponse: We thank the reviewer for pointing this out and have now changed the section on page 9 to read as follows: "We will analyse predictors and moderators of response and remission status at 3- and 12-month follow-up using repeated k-fold cross validation with 10 folds and 20 repeats to reduce the risk of model instability.

We then average model performance over the repeats using area under the receiver operating characteristic curve (AUC) of sensitivity and specificity to distinguish between responders/remitters and non-responders/non-remitters."

6. *What was the rationale for choosing the 3-month follow up as the primary endpoint?*

Response: Scientifically it is more interesting to see results on a longer time-frame but since we have an experimental treatment arm, with unclear efficacy (unguided ICBT), it would be ethically unfeasible to wait with cross-over until 12-months and therefore we decided to have the 3-months follow-up as the primary endpoint.

7. *What was the rationale for choosing a non-inferiority margin of 3 points? The two references cited in that section of the statistical analysis section each used a margin of 5 points.*

Response: A unique feature of this trial is the high frequency of outcome measurement. As a result, our power to detect even small differences between groups is superior to previous non-inferiority trials. This will provide a more stringent non-inferiority test than ever before, which we think is important. We reasoned that the previously used margin of 5 points may result in uncertainty amongst clinicians about the true non-inferiority of the experimental treatments. A margin of 3 points will reassure them and the patients (should our hypotheses be confirmed).

8. *The authors mention a limitation in the Article Summary regarding generalizability. However, additional limitations should be spelled out in the main manuscript.*

Response: We now list limitations in the main manuscript (page 9).

9. *In the SPIRIT checklist, while most of the items appear to have been addressed in the manuscript, there are a few that were not. Some of these that would be useful for the authors to include are item 18b, "Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols." Regarding the second part of this, the authors mention that the assumption that data are missing at random will be tested, but additional details how this would be done would be informative. Also, the authors should address item 23, "Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor."*

Response (item 18b): We thank the reviewer for spotting this. We had overlooked this item and have therefore added the following text to the measurements section (page 7): "In order to increase participant retention at follow-up assessments, participants will be notified via text message 48 hours prior to an appointment. Should a participant not attend a follow-up session, a psychiatrist will contact participants via telephone to perform the assessments."

Response (item 23): We have now edited the section “Ethics and dissemination” to present the monitoring process in more detail (page 10).

VERSION 2 – REVIEW

REVIEWER	Jamie Feusner UCLA Semel Institute for Neuroscience and Human Behavior; Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA, USA
REVIEW RETURNED	14-Jun-2018

GENERAL COMMENTS	The authors have responded to all questions and comments adequately.