PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Dismantling, personalizing and optimizing internet cognitive-behavioral therapy for depression: A study protocol for individual participant data component network meta-analysis
AUTHORS	Furukawa, Toshi; Karyotaki, Eirini; Suganuma, Aya; Pompoli, Alessandro; Ostinelli, Edoardo; Cipriani, Andrea; Cuijpers, Pim; Efthimiou, Orestis

VERSION 1 – REVIEW

REVIEWER	Matthew Sunderland UNSW Sydney, Australia.
REVIEW RETURNED	14-Sep-2018

GENERAL COMMENTS	Review: bmjopen-2018-026137 The current manuscript provides a study protocol for a individual participant data component network meta-analysis to determine the efficacy of individual components of Internet-delivered cognitive-behavioral therapy for the treatment of adult depression. The protocol is well written and clearly describes enough information regarding the planned study. The study will make use of a novel design both in terms of meta-analytic techniques and in the application of iCBT to dismantle the therapeutic components of treatment. I do not have many comments about the protocol and list relatively minor points below. 1. I did not get a good sense of how the individual participant data will be harmonized (or equated) with respect to different depression scales and the prognostic factors/moderators. For example, how will the differential severity or differential item functioning associated with different depression scales across studies be accounted for when running combined analyses? Perhaps some kind of scale linking (using item response theory or similar) based on a set of anchor items is required? How will some of the prognostic factors or effect modifiers be harmonized (for example employment, education) given there tends to be slight differences in how these are assessed across studies? 2. What are the proposed dates of the study? Minor corrections: 1. Abstract: there is a typo in the PROPSERO registration number.

REVIEWER	Tobias Krieger University of Bern, Switzerland
REVIEW RETURNED	18-Sep-2018

GENERAL COMMENTS	The authors present a well-written study protocol on an important and very interesting topic. The manuscript is written straightforwardly and in a very clear language which enables replication. Furthermore, the study is timely and the results of the study will advance the field.

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	As a consequence, I have only some minor points that I think could be addressed in a revised version. In my opinion, the title of the manuscript should be changed slightly, since the title in its present form suggests something that may only be a consequence of the results of the present study and not a result per se. P6: It would be good to explain to the unfamiliar reader what „ecological bias“ means. P12: It is not clear yet, what will be the procedure will be if the authors of the original studies did not report a threshold or a definition for completion? Relatedly, it seems important to me that the authors include a statement on adherence to an intervention and how "completion" and "adherence“ could differ and how their results should then be interpreted adequately. Table 2: A note below Table 2 that abbreviations are explained in Table 1 would be helpful. Limitations: Some components may only be of incremental value if they are combined with other components; furthermore, the incremental value of a specific component may depend on the order of the components. These are questions that are not addressed by the present study. Therefore, these factors could be addressed in a discussion or added to the limitations of the present study.

REVIEWER	Probst, Thomas Danube University Krems
REVIEW RETURNED	24-Sep-2018

GENERAL COMMENTS	This is an interesting meta-analysis and I only have some minor comments. 1. References A. The authors should address adding vs. dismantling studies in the introduction and cite the following publication, it should also be noted that differences between treatment components are unlikely to detect and require large sample sizes https://www.ncbi.nlm.nih.gov/pubmed/23688145 B. The following reference could be cited in the introduction regarding treatment-patient matching in depression https://www.ncbi.nlm.nih.gov/pubmed/29494258 C. The following reference (PRISMA-P) must be cited according to the BMJ Open guidelines https://www.ncbi.nlm.nih.gov/pubmed/19621072 D. Attempts to tailor iCBT to patients should be mentioned, e. g. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3352859/ E. The reference Roemer 2008 in Table 1 is not listed in the References 2. Methods

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	A. It is written in the text that telephone and face-to-face sessions will be excluded. However, in Table 1 face-to-face sessions (ff) are included (if initial contact) as are telephone (he). It should be clarified in the text that adding telephone or initial face-to-face sessions to iCBT was possible. B. The same sentence was used for the inclusion and exclusion criterion: "depression comorbid with another mental disorder" (p.7, line 44/45 vs.47/48). This is irritating. Maybe it is better to say to exclude studies on other mental disorders with depression as comorbidity? C. P. 6, line 23/24: "The control condition needs to be a psychological one". However, in Table 1 you include waiting-list (no treatment) or "conventional drug treatment". Please specify. D. In Table 1, it was irritating that psychoeducation, placebo, and TAU were in the waiting list box as psychoeducation appeared later in the PE box, TAU in the dt box, and placebo in the pl box. Maybe there is a way to make this easier to understand? E. I did not find the abbreviation IPD explained in the text. F. p. 12, lines 38-45. First you describe that for more than one depression outcome measure the primary outcome measure of the study will be used, but in the next sentence you state that for more than one depression outcome measure a composite score will be calculated. Which option is the correct one? Or will you only calculate the composite score if a study has more than one "primary" depression outcome measure? G. I missed an explicit description of missing data imputation H. p. 16, formula: "j" is not explained in the text or I missed it I. It would be good to provide a rational for the 80% cut-off for drop-outs on p. 12 (line 52) and the 50% cut-off on p. 18 (line 9) - why are there two cut-offs? J. P. 17, line 16/17. "probability of dropping out" - does this mean drop-out from treatment or drop-out from assessment as specifed on p. 12 (lines 47-55) K. I would advice to use iCBT instead of CBT throughout the text.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Reviewer Name: Matthew Sunderland

Institution and Country: UNSW Sydney, Australia.

Please state any competing interests or state 'None declared': None declared.

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Please leave your comments for the authors below

Review: bmjopen-2018-026137

The current manuscript provides a study protocol for a individual participant data component network meta-analysis to determine the efficacy of individual components of Internet-delivered cognitive-behavioral therapy for the treatment of adult depression. The protocol is well written and clearly describes enough information regarding the planned study. The study will make use of a novel design both in terms of meta-analytic techniques and in the application of iCBT to dismantle the therapeutic components of treatment. I do not have many comments about the protocol and list relatively minor points below.

RESPONSE:

We appreciate the reviewer's positive comments.

1. I did not get a good sense of how the individual participant data will be harmonized (or equated) with respect to different depression scales and the prognostic factors/moderators. For example, how will the differential severity or differential item functioning associated with different depression scales across studies be accounted for when running combined analyses? Perhaps some kind of scale linking (using item response theory or similar) based on a set of anchor items is required? How will some of the prognostic factors or effect modifiers be harmonized (for example employment, education) given there tends to be slight differences in how these are assessed across studies?

RESPONSE:

We thank the reviewer for these insightful comments. We have added details how to harmonize various studies using different scales as follows.

> (Page 13, para 2) If the studies use different outcome measures, they will be converted into the most commonly used scale using the established conversion algorithms [24 25]. If this approach cannot cover a substantial proportion of the obtained data, scale scores will be standardized (transformed into z-scores) to create a common metric for depression severity [26-28].
>
> (Page 14, para3) It can be expected that different studies use different scales or different categorizations to measure the same or similar constructs. Some measures (e.g. social adjustment, baseline anxiety) may be standardized to arrive at a common metric; others may need be dichotomized (e.g. employment status, marital status) to harmonize the covariates in the analyses.

2. What are the proposed dates of the study?

RESPONSE:

We have started study identification and plan to complete the analyses by summer 2019 and to submit the paper by end 2019.

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Minor corrections:

1. **Abstract: there is a typo in the PROPSERO registration number.**

RESPONSE:

Thank you. Corrected.

Reviewer: 2

Reviewer Name: Tobias Krieger

Institution and Country: University of Bern, Switzerland

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

The authors present a well-written study protocol on an important and very interesting topic. The manuscript is written straightforwardly and in a very clear language which enables replication. Furthermore, the study is timely and the results of the study will advance the field.

RESPONSE:

We thank the reviewer for the positive comments.

As a consequence, I have only some minor points that I think could be addressed in a revised version.

In my opinion, the title of the manuscript should be changed slightly, since the title in its present form suggests something that may only be a consequence of the results of the present study and not a result per se.

RESPONSE:

We appreciate the opportunity to clarify this point. The results of this IPD component NMA will include incremental efficacy estimates for various components of iCBT and identification of the effect modifiers and prognostic factors for these estimates. Dismantling iCBT achieves the former, and personalizing/optimizing iCBT signifies the latter. We therefore believe that the title expresses the process of the study itself and would like to keep it as is. However, if the editor judges otherwise, we would like to follow their advice.

P6: It would be good to explain to the unfamiliar reader what „ecological bias" means.

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RESPONSE:

As suggested, we have added: (Page 5, para 3)

> due to the risk of ecological bias which occurs when the association at the group level does not reflect the underlying association at the individual level [8 9].

P12: It is not clear yet, what will be the procedure will be if the authors of the original studies did not report a threshold or a definition for completion? Relatedly, it seems important to me that the authors include a statement on adherence to an intervention and how "completion" and "adherence" could differ and how their results should then be interpreted adequately.

RESPONSE:

We agree with the reviewer that the term "adherence" may be ambiguous. We therefore avoided its use and always discussed "completion." Even then, we again agree with the reviewer that the original studies may not report their threshold or definition of completion. In the meta-analysis we are often limited by this lack of clarity of the original studies. However, in the context of pooling relative risk of completion, this is less of a problem so long as the same definition is applied to the intervention and the control arms (as would be expected in a randomized trial). We therefore wrote in the Methods section: (Page 13, para 4)

> (3) Dropouts from the treatment, defined as completing less than 80% of the contents of the program. If the original authors used a different threshold/definition for "completion" of the program, we will use their definition.

By contrast, in a sensitivity analysis where we need be sure that the majority of the participants have completed the program, we explicitly wrote: (Page 18, para 4)

> (iv)We will run a sensitivity analysis by limiting to studies where at least 60% of the participants have completed at least 80% of the program in order to exclude the influence of trials where the completion rate may have been particularly low due to some external circumstances that are not inherent to the components themselves.

and will only include such studies which used this definition.

Table 2: A note below Table 2 that abbreviations are explained in Table 1 would be helpful.

RESPONSE:

Thank you very much for this helpful suggestion. We added a footnote.

Limitations: Some components may only be of incremental value if they are combined with other components; furthermore, the incremental value of a specific component may depend on the order of the components. These are questions that are not addressed by the present study.

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Therefore, these factors could be addressed in a discussion or added to the limitations of the present study.

RESPONSE:

We completely agree with the reviewer's comments. We therefore added in the Methods section: (Page 17, para 1)

> Limitations of the proposed statistical model
>
> The basic model assumes additivity of components and does not take account of possible interactions among components, i.e. when some components may be particularly effective or ineffective in combination with some other components. The dataset will likely lack statistical power to test for such interactions. However, for components that are well represented in the network (i.e. those which have been studied in many trials involving many participants), we will run exploratory analyses of some representative interactions.
>
> The proposed model cannot discern the effect of the ordering of the components – but we expect that we will not have enough relevant data from the studies to explore this effect. If enough data become available, we will modify our model to explore the ordering effect among the most well-represented components of the network.

Reviewer: 3

Reviewer Name: Thomas Probst

Institution and Country: Danube University Krems

Please state any competing interests or state 'None declared': None

Please leave your comments for the authors below

This is an interesting meta-analysis and I only have some minor comments.

RESPONSE:

We thank the reviewer for the positive comments and also for the very careful reading of our manuscript.

1. References

A. The authors should address adding vs. dismantling studies in the introduction and cite the following publication, it should also be noted that differences between treatment components are unlikely to detect and require large sample sizes

https://www.ncbi.nlm.nih.gov/pubmed/23688145

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RESPONSE:

We cited Bell et al's and Ahn et al's reviews of component studies when we noted "The complexity of psychotherapeutic interventions … adds much uncertainty to their analyses and interpretations." (Page 5, para 3) Furthermore we added "Detection of differences among treatments and treatment components would require extremely large samples" after noting "identification of specificity in psychotherapy has proved extremely difficult." (Page 5, para 3)

B. The following reference could be cited in the introduction regarding treatment-patient matching in depression

https://www.ncbi.nlm.nih.gov/pubmed/29494258

RESPONSE:

We cited this study as an example to examine treatment-patient matching at the level of meta-analysis when we wrote: (Page 5, para 3)

> Individual data, either at the level of a trial or of a meta-analysis, are necessary to examine effect modification by individual characteristics.

C. The following reference (PRISMA-P) must be cited according to the BMJ Open guidelines

https://www.ncbi.nlm.nih.gov/pubmed/19621072

RESPONSE:

Done.

D. Attempts to tailor iCBT to patients should be mentioned, e. g.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3352859/

RESPONSE:

We cited this study as an example to examine treatment-patient matching at the level of an individual trial when we wrote: (Page 5, para 3)

> Individual data, either at the level of a trial or of a meta-analysis, are necessary to examine effect modification by individual characteristics.

E. The reference Roemer 2008 in Table 1 is not listed in the References

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RESPONSE:

We thank the reviewer for the careful reading. We added the reference.

2. Methods

A. It is written in the text that telephone and face-to-face sessions will be excluded. However, in Table 1 face-to-face sessions (ff) are included (if initial contact) as are telephone (he). It should be clarified in the text that adding telephone or initial face-to-face sessions to iCBT was possible.

RESPONSE:

We appreciate the reviewer's suggestions. We added the following explanation where we explained the eligibility criteria: (Page 7, para 1)

> Encouragement to proceed with iCBT by telephone or face-to-face contact limited to an initial evaluation or orientation session will be allowed and considered to be a component of iCBT program.

B. The same sentence was used for the inclusion and exclusion criterion: "depression comorbid with another mental disorder" (p.7, line 44/45 vs.47/48). This is irritating. Maybe it is better to say to exclude studies on other mental disorders with depression as comorbidity?

RESPONSE:

We appreciate the opportunity to clarify this point. As the relevant sentences concern the eligibility criteria and need be as explicit as possible to avoid misunderstanding among the co-authors as well as between the authors and the readers, we prefer to leave them as is, even when there is some degree of redundancy.

C. P. 6, line 23/24: "The control condition needs to be a psychological one". However, in Table 1 you include waiting-list (no treatment) or "conventional drug treatment". Please specify.

RESPONSE:

We thank the reviewer for these insightful comments. We have included the control conditions so long as they would contribute to the component NMA. We therefore judged that it would be necessary and helpful to spell out the included and excluded control conditions, with reasons here. We therefore added: (Page 7, para 2)

> The control conditions of interest will include the waiting list control, no treatment control, attention/psychological placebo control and treatment as usual. Different studies call different

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conditions as treatment as usual [21]. In this cNMA study, treatment as usual must include pharmacotherapy: watchful waiting or follow-up by community nurses will be classified as attention/psychological placebo even when it is "treatment as usual" in some settings. Pill placebo control will not be included in the present network as it is not decomposable into the components of our interest.

D. In Table 1, it was irritating that psychoeducation, placebo, and TAU were in the waiting list box as psychoeducation appeared later in the PE box, TAU in the dt box, and placebo in the pl box. Maybe there is a way to make this easier to understand?

RESPONSE:

We have distinguished an intervention which would be called "psychoeducation" and an intervention component of "psychoeducation" by denoting the former with capital letters and the latter with italicized small letters. The same applies to APP and *pl*, or TAU and *dt*.

E. I did not find the abbreviation IPD explained in the text.

RESPONSE:

We spelled out IPD at its first occurrence in the text. (Page 5, para 4)

F. p. 12, lines 38-45. First you describe that for more than one depression outcome measure the primary outcome measure of the study will be used, but in the next sentence you state that for more than one depression outcome measure a composite score will be calculated. Which option is the correct one? Or will you only calculate the composite score if a study has more than one "primary" depression outcome measure?

RESPONSE:

We appreciate the reviewer's careful reading. It was our choice of the term "composite variable" that created this confusion. We therefore rewrote the relevant sentence as: (Page 13, para 2)

scale scores will be standardized (transformed into z-scores) to create a common metric for depression severity

G. I missed an explicit description of missing data imputation

RESPONSE:

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We apologize for the lack of clarity on how we will impute missing covariate data. We now have added this text after explanation of the model. (Page 16, para1)

> In order to include in our analysis patients with missing values for one or more of the covariates (both prognostic factors and effect modifiers) we will use a study-specific imputation scheme. E.g. if for patient i in study j there is no information regarding age, we will stochastically impute it by drawing from a study-specific distribution, i.e. $age_{ij} \sim N(\overline{age_j}, s^2_{age,j})$. Here $\overline{age_j}$ denotes the mean age of patients in this study and $s^2_{age,j}$ the corresponding variance.

With regard to the missing outcomes, we discussed this issue in the sensitivity analyses section:

> Our main analyses regarding depression severity will only use information from patients for whom the outcome was reported. This corresponds to a 'missing completely at random (MCAR)' assumption [56]. In this sensitivity analysis we will explore a 'missing not at random' scenario, where we will assume that the probability of dropping out from assessment is affected by the (unobserved) depression severity.

H. p. 16, formula: "j" is not explained in the text or I missed it

RESPONSE:

We very much appreciate the reviewer's careful reading of our manuscript. There was a typo; apologies for this. This variable j denotes the study. We have now corrected the text a few lines above the formula. (Page 15, last para)

I. It would be good to provide a rational for the 80% cut-off for drop-outs on p. 12 (line 52) and the 50% cut-off on p. 18 (line 9) - why are there two cut-offs?

RESPONSE:

We again appreciate the reviewer's careful reading. We decided to use the 80% cutoff to denote "completion" of the program throughout: many iCBT programs have 3-5 components and by requiring 80% we reasoned that participants would have missed less than one component. We changed the threshold of the proportion of such completers to 60% in the sensitivity analysis: by requiring at least 60% of the participants finishing at least 80% of the program, we figured half or more of the program will be covered.

J. P. 17, line 16/17. "probability of dropping out" - does this mean drop-out from treatment or drop-out from assessment as specifed on p. 12 (lines 47-55)

RESPONSE:

It means "dropout from assessment" and we added this explanation by writing: (Page 18, para 5)

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In this sensitivity analysis we will explore a 'missing not at random' scenario, where we will assume that the probability of dropping out from assessment is affected by the (unobserved) depression severity.

K. I would advice to use iCBT instead of CBT throughout the text.

RESPONSE:

We used iCBT where it referred to internet CBT. We used CBT where we discussed CBT in general. There were several instances where we changed CBT into iCBT following the reviewer's advice.

VERSION 2 – REVIEW

REVIEWER	Tobias Krieger University of Bern, Switzerland
REVIEW RETURNED	13-Nov-2018

GENERAL COMMENTS	In my opinion, the authors did a very thorough and very good job revising the first submission of the present manuscript. They addressed all of the points I raised adequately. It still is my personal opinion that the title could be changed slightly so that it reflects more the anticipated study results of the present study protocol. However, as the authors, I would like to leave the decision of whether the present title is suitable to the editor's discretion and I could accept the authors' opinion.

REVIEWER	Thomas Probst Danube University Krems, Austria
REVIEW RETURNED	06-Nov-2018

GENERAL COMMENTS	Dear authors, thank you for addressing all the comments of the reviewers adequately.

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