PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Examining the effectiveness of a web-based intervention for symptoms of depression and anxiety in college students: Study protocol of a randomised controlled trial.
AUTHORS	Karyotaki, Eirini; Klein, Anke; Riper, Heleen; Leonore de Wit, Leonore de Wit; Krijnen, Lisa; Bol, Eline; Bolinski, Felix; Burger, Simone; Ebert, David; Auerbach, Randy; Kessler, Ronald; Bruffaerts, Ronny; Batelaan, Neeltje; van der Heijde, Claudia; Vonk, Peter; Kleiboer, Annet; Wiers, Reinout; Cuijpers, Pim

VERSION 1 - REVIEW

REVIEWER	Neil Thomas Swinburne University of Technology, Australia
REVIEW RETURNED	24-Jan-2019

GENERAL COMMENTS	The protocol presents a well-designed trial of a therapist-assisted self-guided web-based program for anxiety and depression among college students. The protocol is methodologically sound and clearly written. It has been developed to be consistent with SPIRIT guidelines, and is consistent with good practice in the reporting of internet interventions. The protocol is also consistent with what is recorded on the Nederlands Trial Register. There are a just few details that require clarification: 1. In the “Support” part of the Intervention section (p7), it was not clear whether therapists delivered a maximum of one message for each completed module (in which they incorporated respones to any questions which were asked during that module), or whether therapists delivered one message per module plus additional messages to answer questions. It sounded likely to be an asynchronous model - please specify that all messages are asynchronous (rather than involving real-time chat) if this is the case. If therapist time is being recorded please note this. 2. Assessments section (p12): please provide details on how the follow-up assessments will be administered (e.g., online questionnaire vs telephone interview; how the person is being prompted to complete, e.g. email, vs scheduled contact; if

	automated, how completion is being monitored; what protocols are in place for following people up who do not complete measures or are not contactable on the first attempt) 3. Please clarify how data from the MINI will be used (which is being administered at T1 and T4). It was included as one of the three primary outcome measures, but no details are provided in the measure section or the statistical analysis plan of what will be used from the MINI in analysis of outcome (I imagine number with a current diagnosis, but of what (target disorders, any disorder, etc), how will this be analysed, etc). 4. If the MINI is being used for outcome data, I'd note that the MINI will be administered by telephone by Masters students trained for this purpose. These could feasibly be conducted blind to treatment allocation, so the statement "It is not possible to mask personnel … to the treatment allocation because of the nature of the intervention" (p. 14 line 25) is not strictly true. If the T4 assessment is being conducted blind please indicate this. If not due to practical constraints please add a clarification framing the reason for not blinding on p. 14 and/or note as a limitation (completing with knowledge of treatment condition will be a significant source of bias) on p. 17. 5. There is no mention of clinical significance in the analysis plan. If intending to report this (which would seem useful given the data being collected) please indicate how this will be conceptualised (e.g., below clinical/case threshold on measures at follow-up vs MCID in change scores; if a count of the number cases, whether this will be primarily considered by using GAD-7 or PHQ-9 thresholds, and/or MINI diagnoses) 6. The section on "Possible Harms" (p15) addresses how adverse events will be managed from an ethical point of view, but does not consider how potential adverse effects will be monitored and reported on in the results. Please clarify. It will depend on what is in place, but I expect that there will be some form of recording of when serious adverse events (e.g., death, hospital admission) occur: although the expected rate of these will be low in the population and unlikely related to the intervention, it would be transparent to be reporting these by group in the results. Deterioration rates are referred to for other studies, will these be reported on for this study by group, and if so how (e.g., number above a MCID threshold of change)? Do the authors plan to report the numbers of persons discontinuing or being withdrawn due to distress (and if there is any process for determining whether or not distress was related to intervention please specify here). Are there any other procedures for monitoring distress associated with the intervention in the intervention arm? 7. Related to this, by focusing on the ethical management, the first paragraph of the Possible Harms section reads as reassuring that the risks of harm are low. In doing so, I found it dismissive of the possibility that a psychological intervention might have adverse effects for some individuals worth measuring (e.g., distress). It is increasingly acknowledged that researchers and practitioners have tended to overlook and minimise the likelihood or importance of adverse effects of psychological and internet interventions. Hence, I would also suggest modifying the wording so it sounds

	less “reassuring” in tone, and more matter-of-fact (e.g., omitting “On the contrary”, and “moreover”). Typos: - p4 line 40, “student psychologists” sounds like trainee psychologists, but I think is intended to mean psychologists for students, suggest rephrasing (e.g., “psychologists offering services to students”) - p5 line 31, decimal point missing for second g statistic - p5 line 44, remove comma after “it include studies”

REVIEWER	Ulrike Schmidt Institute of Psychiatry, Psychology and Neuroscience. King's College London I am a developer of another student mental health online prevention/early intervention programme that is currently being tested.
REVIEW RETURNED	03-Feb-2019

GENERAL COMMENTS	Student mental health is an increasingly important area of investigation. As such the proposed study is very much to be welcomed. The proposed study compares a guided online CBT programme for treatment of depression and anxiety with treatment as usual in University students. A strength of the study is that student guides will be used to support the study, which is a model that may be applicable in multiple contexts. Other strengths include the length of the follow-up period and the fact that an attempt is made to assess academic outcomes. The paper is well written and clear and the study is overall well designed. I have a few small points: Introduction – the term ‘College student’ comes from the US system, for example in the UK College students are not the same as University students. I think it would be clearer to talk about University students throughout. Introduction, page 4 line 40 ‘student psychologist’ – this is ambiguous, it sounds like these might be psychologists in training, but I think what you mean here are ‘University counselling / student mental health staff ‘. Intro, line 40 to 46: What is the evidence for the following statement: “ In many Universities, student psychologists treat only study related problems……” Intro, line 53: “The question arises as to how we can provide treatment” – please rephrase, as it is not clear who ‘we’ refers to here. Introduction page 5: In your review of the literature on internet based interventions for students you quote a systematic review by Farrer and colleagues. You may also wish to include a more recent review on this topic by: : Harrer M, Adam SH, Baumeister H, Cuijpers P, Karyotaki E, Auerbach RP, Kessler RC, Bruffaerts R, Berking M, Ebert DD. Internet interventions for mental health in university students: A systematic review and meta-analysis. Int J Methods Psychiatr Res. 2018 Dec 26:e1759. doi: 10.1002/mpr.1759. [Epub ahead of print] PubMed PMID: 30585363.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Neil Thomas

Institution and Country: Swinburne University of Technology, Australia

Please state any competing interests or state ‘None declared’: None declared.

Please leave your comments for the authors below

The protocol presents a well-designed trial of a therapist-assisted self-guided web-based program for anxiety and depression among college students.

The protocol is methodologically sound and clearly written. It has been developed to be consistent with SPIRIT guidelines, and is consistent with good practice in the reporting of internet interventions. The protocol is also consistent with what is recorded on the Nederlands Trial Register.

There are a just few details that require clarification:

Question 1.

1. In the “Support” part of the Intervention section (p7), it was not clear whether therapists delivered a maximum of one message for each completed module (in which they incorporated respones to any questions which were asked during that module), or whether therapists delivered one message per module plus additional messages to answer questions. It sounded likely to be an asynchronous model - please specify that all messages are asynchronous (rather than involving real-time chat) if this is the case. If therapist time is being recorded please note this.

Answer 1.

Indeed e-coaches deliver asynchronous feedback. Moreover, e-coaches are instructed to send one message per completed session and additional messages to answer questions that participants might have. We have added the following clarifications to the manuscript:

Under Support:

“Research staff experienced in web-based interventions give the training. Coaches provide individual manualized asynchronous feedback via the messaging function of the intervention platform after the completion of each module. Moreover, coaches are available to answer additional messages about the treatment content in case they are contacted by the participants at any time point throughout the intervention.”

Question 2

2. Assessments section (p12): please provide details on how the follow-up assessments will be administered (e.g., online questionnaire vs telephone interview; how the person is being prompted to complete, e.g. email, vs scheduled contact; if automated, how completion is being monitored; what protocols are in place for following people up who do not complete measures or are not contactable on the first attempt)

Answer 2.

As requested, we have added further details under the assessment section:

In the RCT, participants will complete online self-report questionnaires (via the Qualtrics platform) and the MINI clinical diagnostic interview, which is administered via the telephone (further details are given under Primary and Secondary outcomes). In both the intervention and control condition, participants are followed up to 12 months post-randomisation. After eligibility screening (t0), measures are administered at baseline (t1), post-treatment - 7 weeks post-randomisation (t2), six months (t3) and twelve months post-randomisation (t4). Participants are invited to complete the assessments through emails. In case a participant is not contactable on the first attempt, the research team sends up to two reminder emails within two weeks. To booster study adherence, if a participant does not respond to reminders, the research team contacts the participant via telephone. Figure 1 shows the flowchart of participants' inclusion.

Question 3.

3. Please clarify how data from the MINI will be used (which is being administered at T1 and T4). It was included as one of the three primary outcome measures, but no details are provided in the measure section or the statistical analysis plan of what will be used from the MINI in analysis of outcome (I imagine number with a current diagnosis, but of what (target disorders, any disorder, etc), how will this be analysed, etc).

Answer 3.

The MINI will be used to estimate the number of participants with a current diagnosis of depression and anxiety disorders at the baseline and 12-month follow-up assessment. Moreover, at baseline, we use MINI to gather information on major comorbidities. We will use descriptive statistics to estimate the number of participants with a diagnosis of depression or anxiety disorders. Finally, at 12-month post-randomization we will examine the effects of the intervention on the current diagnosis of depression and anxiety disorders using a multilevel mixed effects logistic regression model.

We have added the following to the manuscript:

Under Primary Outcomes:

"The MINI is used to determine the number of participants with a current / lifetime diagnosis of Major Depressive Disorder, Panic Disorder, Agoraphobia, Social Phobia, Generalised Anxiety Disorder both at the baseline and 1-month follow-up. Moreover, during baseline the MINI will be used to estimate the number of participants with current / lifetime diagnosis of major comorbidities (Dysthymia, Suicidality, (hypo) Manic Episode, Obsessive Compulsive Disorder, Post-Traumatic Stress Disorder, Alcohol Dependence/ Abuse, Drug Dependence / Abuse, Psychotic Disorders, Anorexia Nervosa, and Bulimia Nervosa)."

Under statistical analysis:

"The results of the M.I.N.I interview will be summarised using descriptive statistics."

[…]

"Finally, at 12 months follow-up assessment, we will analyse the effects of the intervention on current diagnosis of depression and anxiety disorders, using the data from MINI. We will use a multilevel mixed effects logistic regression with a restricted maximum likelihood algorithm. The follow-up current diagnosis of depression or anxiety disorders will be used as a dependent variable and trial arm condition as independent while adjusting for baseline depression and anxiety severity."

Question 4.

4. If the MINI is being used for outcome data, I'd note that the MINI will be administered by telephone by Masters students trained for this purpose. These could feasibly be conducted blind to treatment

allocation, so the statement “It is not possible to mask personnel … to the treatment allocation because of the nature of the intervention” (p. 14 line 25) is not strictly true. If the T4 assessment is being conducted blind please indicate this. If not due to practical constraints please add a clarification framing the reason for not blinding on p. 14 and/or note as a limitation (completing with knowledge of treatment condition will be a significant source of bias) on p. 17.

Answer 4.

We thank the reviewer for this critical observation. Indeed, the MINI interview will be administered by interviewers who will be blind to the allocation assignment. We have added the following to our manuscript:

Randomization, blinding and treatment allocation:

“However, the MINI diagnostic interview will be performed by blind interviewers with no knowledge about the allocation assignment.”

Question 5.

5. There is no mention of clinical significance in the analysis plan. If intending to report this (which would seem useful given the data being collected) please indicate how this will be conceptualised (e.g., below clinical/case threshold on measures at follow-up vs MCID in change scores; if a count of the number cases, whether this will be primarily considered by using GAD-7 or PHQ-9 thresholds, and/or MINI diagnoses)

Answer 5.

We added the following under statistical analysis:

To measure clinical significance, we will calculate response and symptom deterioration rates according to Reliable Change Index56. The reliable change will be calculated using the pre-treatment standard deviation, and the test re-test reliability coefficient of PhQ-9 (0.76)29 and GAD-7 (0.83)37.

Question 6.

6. The section on “Possible Harms” (p15) addresses how adverse events will be managed from an ethical point of view, but does not consider how potential adverse effects will be monitored and reported on in the results. Please clarify. It will depend on what is in place, but I expect that there will be some form of recording of when serious adverse events (e.g., death, hospital admission) occur: although the expected rate of these will be low in the population and unlikely related to the intervention, it would be transparent to be reporting these by group in the results. Deterioration rates are referred to for other studies, will these be reported on for this study by group, and if so how (e.g., number above a MCID threshold of change)? Do the authors plan to report the numbers of persons discontinuing or being withdrawn due to distress (and if there is any process for determining whether or not distress was related to intervention please specify here). Are there any other procedures for monitoring distress associated with the intervention in the intervention arm?

Answer 6.

We thank the reviewer for emphasising the importance of being transparent regarding adverse events. We acknowledge that this is a critical issue in clinical trials, which is often underreported. In our trial, we will report possible adverse events (e.g., increase suicidal risk, hospital admission, clinically significant symptom deterioration, study and treatment dropout rates), thus we have clarified this in the revised version of our manuscript (see below “changes to the manuscript”). However, distress is not a well-defined concept, and it is often examined by depression and anxiety measures. In our trial, we do have such measures (PhQ-9 & GAD-7) as we specifically focus on depression and

anxiety. Moreover, as mentioned above we will measure clinically significant symptom deterioration, which should capture participants who get distressed at post-test.

Changes to the manuscript: we have added the following to the manuscript under possible harms:

Adverse events (e.g., increase suicidal risk, hospital admission, clinically significant symptom deterioration, study and treatment dropout rates) will be monitored and recorded throughout the trial. All adverse events will be reported per group in the outcomes of the present study.

Question 7.

7. Related to this, by focusing on the ethical management, the first paragraph of the Possible Harms section reads as reassuring that the risks of harm are low. In doing so, I found it dismissive of the possibility that a psychological intervention might have adverse effects for some individuals worth measuring (e.g., distress). It is increasingly acknowledged that researchers and practitioners have tended to overlook and minimise the likelihood or importance of adverse effects of psychological and internet interventions. Hence, I would also suggest modifying the wording so it sounds less "reassuring" in tone, and more matter-of-fact (e.g., omitting "On the contrary", and "moreover").

Answer 7.

We acknowledge that psychological intervention might result in adverse effects. However, according to our previous work, self-guided iCBT interventions result in lower symptom deterioration rates compared to controls (see reference below). Thus, we expect that the examined internet-based intervention will have minimal risks for the participants. However, we agree with the reviewer that we should modify the wording to sound less reassuring since "minimal risks" do not imply "no risks".

In the revised version of our manuscript, the paragraph "Possible harms" has been modified as follows:

"According to previous literature, internet-based interventions lead to lower symptom deterioration rates compared to controls. 57 58 Moreover, in this study participants are college students with mild to moderate symptoms of depression and/ or anxiety. This population has a high degree of functioning (e.g., attending university) and is unlikely to enter the general medical healthcare system. Nevertheless, psychological intervention might lead to unwanted outcomes. For instance, it is possible that the students experience suicidal ideation. If we detect a student who is at high suicidal risk, a specific protocol is followed: the e-coach calls the student to assess the risk by asking a series of questions. Afterwards, the e-coach contacts an experienced psychiatrist, who is involved in the study, to discuss the situation. If needed, the psychiatrist contacts the participant to advise him/ her to seek help from his/her General Practitioner (GP) or the student counselling services. The research team checks if the student sought help after a couple of days. Moreover, if the student permits us to use the contact details of his/ her GP, the research team notifies the GP to ensure that the student will get help timely.

Adverse events (e.g., increase suicidal risk, hospital admission, clinically significant symptom deterioration, study and treatment dropout rates) will be monitored and recorded throughout the trial. All adverse events will be reported per group in the outcomes of the present study."

Question 8.

Typos:

- p4 line 40, "student psychologists" sounds like trainee psychologists, but I think is intended to mean psychologists for students, suggest rephrasing (e.g., "psychologists offering services to students")

- p5 line 31, decimal point missing for second g statistic

- p5 line 44, remove comma after “it include studies”

Answer 8.

In the Netherlands psychologists offering services to students are called “studentenpsycholoog”, which literally means “student psychologists”. However, we acknowledge that this term is misleading in English. So, we have changed according to the suggestion of dr. Thomas. All typos have been corrected in the new version of the manuscript.

Reviewer: 2

Reviewer Name: Ulrike Schmidt

Institution and Country: Institute of Psychiatry, Psychology and Neuroscience. King's College London

Please state any competing interests or state ‘None declared’: I am a developer of another student mental health online prevention/early intervention programme that is currently being tested.

Please leave your comments for the authors below

Student mental health is an increasingly important area of investigation. As such the proposed study is very much to be welcomed. The proposed study compares a guided online CBT programme for treatment of depression and anxiety with treatment as usual in University students. A strength of the study is that student guides will be used to support the study, which is a model that may be applicable in multiple contexts. Other strengths include the length of the follow-up period and the fact that an attempt is made to assess academic outcomes. The paper is well written and clear and the study is overall well designed.

I have a few small points:

Question 9.

Introduction – the term ‘College student’ comes from the US system, for example in the UK College students are not the same as University students. I think it would be clearer to talk about University students throughout.

Answer 9

Indeed, college students are not the same as university students in many European countries. However, we would like to keep the term “college students” because in our trial we include all students who attend tertiary education regardless of whether they attend a university or a college. Thus, we believe that the term “college” is more inclusive compared to the term “university” as the later falsely implies that we are interested only in those students who attend a university.

Question 10.

Introduction, page 4 line 40 ‘student psychologist’ – this is ambiguous, it sounds like these might be psychologists in training, but I think what you mean here are ‘University counselling / student mental health staff ‘.

Answer 10.

As mentioned above, in the Netherlands psychologists offering services to students are called “studentenpsycholoog”, which literally means “student psychologists”. However, we acknowledge that this term is misleading in English. So, we have changed according to the suggestion of dr. Thomas.

Question 11.

Intro, line 40 to 46: What is the evidence for the following statement: “In many Universities, student psychologists treat only study related problems……”

Answer 11.

This statement is based on the current state of the art in Dutch universities and colleges. Moreover, our study is embedded within the WHO World Mental Health International College Student initiative (WMH-ICS). Based on this work, we know that this statement holds for many universities around the world. As a supportive reference for this statement, in the revised version of our manuscript, we refer to the paper that provides an overview of the WHO World Mental Health International College Student initiative.

Supportive reference:

“Cuijpers P, Auerbach RP, Benjet C, et al. The World Health Organization World Mental Health International College Student initiative: An overview. International journal of methods in psychiatric research 2019:e1761.”

Question 12.

Intro, line 53: “The question arises as to how we can provide treatment” – please rephrase, as it is not clear who ‘we’ refers to here.

Answer 12.

We have rephrased this sentence as follows:

The question arises as to how universities and colleges can provide treatment, which is effective, timely, available at low cost, accessible, and that overcomes worries about stigmatisation by maintaining students’ anonymity.

Question 13.

Introduction page 5: In your review of the literature on internet-based interventions for students you quote a systematic review by Farrer and colleagues. You may also wish to include a more recent review on this topic by: : Harrer M, Adam SH, Baumeister H, Cuijpers P, Karyotaki E, Auerbach RP, Kessler RC, Bruffaerts R, Berking M, Ebert DD. Internet interventions for mental health in university students: A systematic review and meta-analysis. Int J Methods Psychiatr Res. 2018 Dec 26:e1759. doi: 10.1002/mpr.1759. [Epub ahead of print] PubMed PMID: 30585363.

Answer 13.

We thank the reviewer for the suggestion to refer to our recently published paper. We hadn’t referred to this paper because it included a wide range of studies (e.g., studies targeted at both prevention and treatment, guided and unguided interventions were both included, etc.). However, we acknowledge that the conclusions of our study are pretty much the same as the findings of Farrer and colleagues’ study. Thus, we added our study as a reference in the same paragraph. We have added the following to the revised version of our manuscript:

“Nevertheless, up to now, there have been relatively few studies focusing on the effectiveness of web-based interventions in treating college students with depression and/or anxiety disorders. Systematic reviews of technology-based interventions for tertiary students with mental disorders have shown mixed evidence for the effectiveness of technology interventions targeting depression and/or anxiety

10 24. However, the focus of these reviews was broad; they included studies that employed either prevention or treatment interventions 24-28.”

VERSION 2 – REVIEW

REVIEWER	Neil Thomas Swinburne University of Technology, Australia
REVIEW RETURNED	21-Mar-2019

GENERAL COMMENTS	Thank you, all points have been addressed.