PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Web-based Mindfulness and Skills Based Distress Reduction for Cancer Patients - Study Protocol of the Multicentre, Randomized, Controlled Confirmatory Intervention Trial Reduct
AUTHORS	Teufel, Martin; Bäuerle, Alexander; Martus, Peter; Erim, Yesim; Schug, Caterina; Heinen, Jana; Krakowczyk, Julia; Steinbach, Jasmin; Damerau, Mirjam; Bethge, Wolfgang; Dinkel, Andreas; Dries, Sebastian; Mehnert, Anja; Neumann, Anja; Schadendorf, Dirk; Tewes, Mitra; Wiltink, Jörg; Wünsch, Alexander; Zipfel, Stephan; Graf, Johanna

VERSION 1 – REVIEW

REVIEWER	Svetlak, Miroslav Masaryk University
REVIEW RETURNED	23-Nov-2021

GENERAL COMMENTS	Dear authors, thank you that I could read your study protocol. It is exciting to read the text of other researchers and validate my own research ideas and assumptions. Congratulations on creating your e-Health programme. I also appreciate that you introduce your ideas and plans forward. I believe that this is the right direction of the research and thank you for that. The study design, statistical methods and sample size assumption are appropriate. The motives for the study are clear and understandable from the introduction. I would recommend rewriting the part about intervention. I would recommend writing it as a story of the patient who enrolled on the program from the start to the end. It is difficult for me to imagine the structure of the program (when patients get reminders, emails when they start the program and if it is only 30 minute part every two weeks, or if there are any other parts). Study design Authors write: „ The medical data are taken from the patient's medical records at T0.“ Reviewer: I suggest specifying what kind of information will be collected. Are you going to collect information about the kind of chemo, reaction on it, the survival time, the amount of psychology consultation, the consumption of antidepressives or anxiolytics? Intervention Authors write: „Make It Training. The psycho-oncological Make It Training is a self-guided and patient-oriented e-mental health intervention for cancer patients to overcome distress and improve their well-being. Reviewer: I suggest specifying the program more concretely. The citation of their work (Bäuerle A, et al. BMJ Open

	2020;10:e036466. doi:10.1136/bmjopen-2019-036466) would be appropriate. The structure of the programme is described there in detail. Authors write: „Each Make It module is conceptualized to be completed over the course of one week; after one week, the next module is delivered and trained. At the end of the same paragraph, they write: „Eight optional modules, as well as one technical introduction module, complement the eight bi-weekly mandatory modules, each lasting about 30 minutes. Reviewer: Maybe I am inattentive but I am confused. Will patients get the program each week or every two weeks? Will they get the next part of the program even if they don't complete the previous parts? Reviewer: It is not clear to me, how you are going to measure the activity of patients within the two weeks after they watch the 30 minutes video? Maybe I am inattentive again but I am no able to find it in the text. Treatment as usual optimized It should be specified as much as possible. Authors write that: „These information sets will be based on CBT and contain written information about skills like reframing, activating resources, relaxation, distraction, or stress management. Reviewer: The TAU usually includes psychotherapy, relaxation and so on and it can vary among selected oncology centres. The content of TAU optimized is quite specific and is almost at the level of intervention. Skills like reframing, activation resources, relaxation, distraction and stress management are powerful and we do not know if psychoeducation is not enough for many patients. Moreover, the patients in the TAU arm will expect the next content of the programme which is another powerful variable. Authors also write:“ Every other week, a new set of non-interactive written information will briefly inform patients about the benefits of these skills during the course of the disease and motivate them to use these skills“. If I imagine, that the team of researchers write me that something could help me, I would definitely start to look for it on the internet or in books (the internet is full of mindfulness programs these days). I understand the ethical motives, however, from the point that authors want to verify the effectiveness of the specific program (Make it Training) which is composed of the various components of other approaches (MBSR, CBT, psycho-education, emotion regulation and stress management) I see the current TAU O as a huge source of variability in the results which could disappear the difference between observed groups. You will be able to say that your program is better than psychoeducation, but you will have no evidence if it is better than the current TAU in Germany (group and individual psychotherapy and so on). I do not know the universal solution, however, this RCT study should use only TAU. Kind explanation to the patients why they are in the control group and the promise that they will get the programme after months could be appropriate. Nevertheless, as a researcher in this field, I absolutely understand your decision with psychoeducation. Reminders I understand that reminders will be sent by email. Does it mean that I get an email to remind me to log in? I would invite a clear description of the process.

	I am missing the explanation of the analytical part of the patients´ behaviour in the text (I can see it below the table). I think that it could be a separate subchapter. I think that this analytical part is key and new. I think that is a direct objective observation of the behaviour. This is the main advantage of e-Health research. To be able to describe the relationship between adherence and the outcomes, this part should be specified as much as possible. The analytical part of the real behaviour in the programme should be specified to be able to assess the outcomes of the study in the future. Do you expect some specific outcomes? I suggest including it in the Other study goals as an exploration of possible relationships between the intervention and outcomes. It is a commitment of the publication of these unique results. It is the key question, what is enough, in which amount, in which time and which method are the best for our patients. One level is to verify existing methods but the other is (I think that it should be our mission) to find the new one, more effective than already existing. A dropout assessment Authors in their sooner published protocol of study (Bäuerle A, et al. BMJ Open 2020;10:e036466. doi:10.1136/bmjopen-2019-036466) wrote that: „Although a dropout rate of up to 50% for online interventions has been shown, we might expect an even higher rate of dropout given the physically vulnerable patient group that will form our sample and because the last measurement will occur 6 months after the intervention has ended. Assuming that some patients will not complete the first online assessment and thus not start Make It Training after recruitment we plan to recruit 500 patients at T0. Contrary to this, they write (subchapter Sample size calculation) that: „In this publication, a dropout rate of 25% was assumed for the planning of the study, but only a 5% dropout rate was observed at T1 (primary endpoint). In our project, we conservatively assume a dropout rate of 20%, which to us seems to be a realistic assumption for an e-mental health intervention. Why do the authors expect a different dropout rate in almost the same study design and selected patient populations? Participant eligibility and recruitment I understand the HADS ≥ 13 for at least one-week criterium and it would be appropriate in the study design with a highly homogenous group of patients (same chemo, same diagnosis, same stage of the treatment). On the other hand, because of it, you could loos information about the development of the observed variables. This criterion increases the probability that HADS will decrease. The role of the program can be treatment (HADS decreases) or prevention/protection (HADS does not increase under the program condition in comparison to a group of people with the same diagnosis, stage, chemo and so on without the intervention). Methods Used methods are appropriate. References I am missing this recent review which I find important for this topic. Matis J, Svetlak M, Slezackova A, Svoboda M, Šumec R Mindfulness-Based Programs for Patients With Cancer via eHealth and Mobile Health: Systematic Review and Synthesis of Quantitative Research J Med Internet Res 2020;22(11):e20709

REVIEWER	Nissen, Eva

	Aarhus University, Department of Psychology and Behavioral Sciences
REVIEW RETURNED	07-Feb-2022

GENERAL COMMENTS	Thank you for the opportunity to review this relevant study adding to the litterature within e-mental health Mindfulness-Based Interventions for the cancer population. It is a thoroughly described study with many stregths, that I am looking forward to read when completed. I do, however, have some concerns regarding the manuscript, that I believe should be clarified before publication. Please see below: Abstract: Please clarify that you are focusing on 'psychological distress'. Please elaborate the description of the intervention: please clarify duration of the intervention, how the intervention is delivered (e.g. web-based, video conference, in groups or individually), and if it is a fully automatized intervention or there is support. It appears a bit confusing that the hypothesis is stating "...reducing destress at T1 (primary endpoint)". Could this be changed to "...reducing distress immediately after the xx week intervention"? or something similar? Regarding statistics: please see comments to protocol text. Introduction: The argumentation about the relevancy of the study is centered around a heighthened level of distress among cancer patients in general. The present study, however, only includes patients in curative treatment domains, which is known to be a different situation than patients in life-sustaining or palliative care. Please clarify the argumentation about distress level with regards to cancer patients in curative treatment to reflect the study population properly. In the introduction, different empirical arguments for providing e-health psychological treatments for psychological distress is provided. It would, however, strengthen the argumentation with some theoretical arguments as well - why is mindfulness-based interventions in combination with cognitive behavioral therapy (CBT) beneficial for distressed cancer patients? Furthermore, an inclusion of other mindfulness-based interventions than Mindfulness-Based Stress Reduction (MBSR) would be necessary to get a sufficient overview of the field of this type of mental health interventions. Many other interventions have combined mindfulness-techniques with CBT before, for example Mindfulness-Based Cognitive Therapy (MBCT), also in e-mental health interventions. Not responding to this development within the field of mindfulness-based interventions is a serious inadequacy in describing the background of the present study. Consider reading a recent systematic review on this matter here: Matis J, Svetlak M, Slezackova A, Svoboda M, Šumec R. Mindfulness-Based Programs for Patients With Cancer via eHealth and Mobile Health: Systematic Review and Synthesis of Quantitative Research J Med Internet Res 2020;22(11):e20709. Methods: The argument for not including cancer patients aged >65 years is not clear. It is stated that "...a German survey analyzing the internet literacy of cancer patients determined that while no significant differences regarding gender or age were seen, most of the cancer patients were younger than 70 years old." If no significant differences were found regarding age, why use this as an exclusion criteria? If the concern is to have patients with a lack

	of internet literacy included in the study, consider using a questionnaire or single-item question to clarify this as inclusion criteria instead of age. Intervention: The description of the duration of the interventions is not quite clear. First it is stated that "Both interventions last four months.", but then that "Each Make It module is conceptualized to be completed over the course of one week..." and "Eight optional modules as well as one technical introduction module complement the eight bi-weekly mandatory modules, each lasting about 30 minutes." An overview of the specific module content would furthermore be relevant for clarity, possibly in combination with a clarification of the module structure. Please also clarify the content of the control condition: how is it planned to control for this various treatment? In the discussion it is mentioned that "...other patient groups could benefit from this approach as well...". Please elaborate if the treatment content in the Make It Training is generic or cancer specific. Statistical methods: Please consider using Mixed Linear Modelling (MLM) for analysis instead of ANCOVA. MLMs tollerates missing values without imputations, which should be preferred. I am not a statistician and therefore I lack the qualifications to thoroughly account for the differences between ANCOVAs and MLMs, but my impression is that MLM is considered a more contemporary state-of-the-art statistical approach for conducting analyses in randomized controlled intervention trials. Patient and public involvement: It is commendable that patients are consulted in the project work. It is, however, not clear whether patients have been involved in the formulation of the present study protocol ('research design'). Please clarify this matter, how patients' input will be implemented, how incongruency between researchers and patients is handeled, and hence how tokenistic involement is avoided.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Miroslav Svetlak, Masaryk University Comments to the Author:

Dear authors,
thank you that I could read your study protocol. It is exciting to read the text of other researchers and validate my own research ideas and assumptions. Congratulations on creating your e-Health programme. I also appreciate that you introduce your ideas and plans forward. I believe that this is the right direction of the research and thank you for that. The study design, statistical methods and sample size assumption are appropriate. The motives for the study are clear and understandable from the introduction.

Response: Dear Dr. Svetlak, thank you very much for your positive feedback and the validation of our idea in general and our study protocol.
Below we have prepared a point-by-point response letter. In the beginning, however, we would like to point out that this study is funded by the German Federal Ministry of Education and Research. The

funding approval was preceded by an international review process lasting approximately two years. Several international clinical- and statistical reviewers have assessed our project as eligible for funding in the present form. We implemented the comments from the international experts in the different review rounds regarding the intervention, the study design, and the overall trial. We receive funding explicitly for the described project and can therefore only make limited changes to the design and the manuscript, respectively.
In particular, we have attempted to incorporate any comments that improve the understanding and structure of the trial. Thank you for your support to improve the manuscript.

I would recommend rewriting the part about intervention. I would recommend writing it as a story of the patient who enrolled on the program from the start to the end. It is difficult for me to imagine the structure of the program (when patients get reminders, emails when they start the program and if it is only 30 minute part every two weeks, or if there are any other parts).

Response: Thank you for the feedback. We have tried to address your point with further additions. Furthermore, we have added screenshots (see supplementary material III) from the training and table 2 with a short overview of each module. However, currently, we are preparing a manuscript that thoroughly describes the intervention, framework as well as development process in more detail. Due to the word count of BMJ Open it is not possible to further elaborate the intervention in this study protocol. Hence, The present protocol primarily focuses on the study design.

Study design
Authors write: „ The medical data are taken from the patient's medical records at T0.“
Reviewer: I suggest specifying what kind of information will be collected. Are you going to collect information about the kind of chemo, reaction on it, the survival time, the amount of psychology consultation, the consumption of antidepressives or anxiolytics?

Response: Thank you for your feedback. We have added this information in the text and referred to the CRFs.

We added this sentence „The medical data (e.g. tumour entity, cancer treatment, tumour status, mental health diagnosis, previous mental health treatment, psychiatric medication; see supplementary material II for the complete case report forms) are taken from the patient's medical records at T0.”

Intervention
Authors write: „Make It Training. The psycho-oncological Make It Training is a self-guided and patient-oriented e-mental health intervention for cancer patients to overcome distress and improve their well-being.
Reviewer: I suggest specifying the program more concretely. The citation of their work (Bäuerle A, et al. BMJ Open 2020;10:e036466. doi:10.1136/bmjopen-2019-036466) would be appropriate. The structure of the programme is described there in detail.

Response: Thank you for the feedback. We have added the mentioned citation. However, the intervention in this trial has evolved significantly (content-wise and technically) and we have added 8 more modules. We have added this information when citing the reference. We have modified the intervention part and added screenshots and table 2 (overview of the modules), see also comment 1.

The following sentence was added to the manuscript. “In a previously published paper the previous version of the intervention is described.[31]”

Authors write: „Each Make It module is conceptualized to be completed over the course of one week; after one week, the next module is delivered and trained.
At the end of the same paragraph, they write: „Eight optional modules, as well as one technical introduction module, complement the eight bi-weekly mandatory modules, each lasting about 30 minutes. Reviewer: Maybe I am inattentive but I am confused. Will patients get the program each week or every two weeks? Will they get the next part of the program even if they don't complete the previous parts?

Response: We apologize for this inconvenience. We agree with you, that this part about the intervention is not clearly described. We have rewritten the part “experimental intervention”. We think it is now clear and understandable.
There are 16 modules in total. Every week a new module is available. See also comment 1 and 3. As you said, the next module of the program is provided, even if the participant did not entirely complete the previous module. This is a major difference compared to the previously published study protocol (https://pubmed.ncbi.nlm.nih.gov/32792437/). However, this change was mandatory for us, since the international experts recommend this. The change was made due to methodological as well as practical reasons If the next part of the program is only provided when the previous part has already been completed, the duration of the intervention could differ significantly between the participants.. In addition, a regulated time schedule of the trial would not be possible to plan. Therefore, the trial would not be feasible.

Reviewer: It is not clear to me, how you are going to measure the activity of patients within the two weeks after they watch the 30 minutes video? Maybe I am inattentive again but I am no able to find it in the text.

Response: Thanks for your question. Videos are parts of each module just like audio-guided mindfulness exercises, an individual skills box, and an interactive skills training. Furthermore, written information is provided. Therefore, it is not the videos that are 30 minutes long, but it takes about 30 minutes to complete the entire module (including e.g. videos).
Usage behaviour will be assessed by clickstream analyses. Clickstream files store all activity in the web-based program- including the pages (each module page) that have been visited, the length of time spent on each page accessed, and the order in which certain pages were accessed. Therefore, the backend of the system records the usage behaviour only during the use of the program. We also assess whether, when, and how often participants repeat modules while waiting for the next one. However, we also collect information via questionnaire on how the users use the content of the modules in their everyday lives after the intervention (see case report forms). Of course, these information are self-reported.

Treatment as usual optimized
It should be specified as much as possible. Authors write that: „These information sets will be based on CBT and contain written information about skills like reframing, activating resources, relaxation, distraction, or stress management.
Reviewer: The TAU usually includes psychotherapy, relaxation and so on and it can vary among selected oncology centres. The content of TAU optimized is quite specific and is almost at the level of intervention. Skills like reframing, activation resources, relaxation, distraction and stress management are powerful and we do not know if psychoeducation is not enough for many patients. Moreover, the patients in the TAU arm will expect the next content of the programme which is another powerful variable. Authors also write:“ Every other week, a new set of non-interactive written information will briefly inform patients about the benefits of these skills during the course of the disease and motivate them to use these skills“. If I imagine, that the team of researchers write me that something could help me, I would definitely start to look for it on the internet or in books (the internet is full of mindfulness programs these days). I understand the ethical motives, however, from the point that authors want to

verify the effectiveness of the specific program (Make it Training) which is composed of the various components of other approaches (MBSR, CBT, psycho-education, emotion regulation and stress management) I see the current TAU O as a huge source of variability in the results which could disappear the difference between observed groups.
You will be able to say that your program is better than psychoeducation, but you will have no evidence if it is better than the current TAU in Germany (group and individual psychotherapy and so on). I do not know the universal solution, however, this RCT study should use only TAU. Kind explanation to the patients why they are in the control group and the promise that they will get the programme after months could be appropriate. Nevertheless, as a researcher in this field, I absolutely understand your decision with psychoeducation.

Response: Thank you very much for this comment. We have specified the TAU-O in the manuscript (please see the control intervention section). Unfortunately, we are not able to change the control group, since we are funded for this specific trial. In fact, this trial already enrolled patients due to the very long review process for this manuscript (more than 5 months). We have submitted this study protocol on September 1st 2021 to BMJ Open. Due to the very strict timeline of the federal ministry for funded projects we were not able to wait for the peer-review process. Of course, we completely agree with your comment about the variability of this TAU-O and we believe that this is a discussion with many pros and cons. In the planning of this trial and after intense consultation with our patient council we decided to implement a TAU-O. At one point, we represent a different opinion. You write “You will be able to say that your program is better than psychoeducation, but you will have no evidence if it is better than the current TAU in Germany (group and individual psychotherapy and so on).”. Our TAU-O includes the German TAU AND additional psychoeducation via the web. In the manuscript, we write: This refers to (i) standard treatments in the German healthcare system, the patient can receive, (ii) the support to access those treatments. Patients receive all the information that is routinely provided as part of inpatient or outpatient treatment (e.g. “how to find psychotherapy”) In addition, the study team will help identify appropriate treatment options, if desired. (iii) TAU-O also included an active contingent, which will function as the ‘optimized’ part of the control intervention, explained below. Therefore, we will be able to show (hopefully) that our intervention is superior to an optimized version of the TAU in Germany.

Reminders
I understand that reminders will be sent by email. Does it mean that I get an email to remind me to log in? I would invite a clear description of the process.

Response: Thank you very much for this comment. We have rewritten the part about the reminders in a designated sub-chapter “Remindesr”.

I am missing the explanation of the analytical part of the patients´ behaviour in the text (I can see it below the table). I think that it could be a separate subchapter. I think that this analytical part is key and new. I think that is a direct objective observation of the behaviour. This is the main advantage of e-Health research. To be able to describe the relationship between adherence and the outcomes, this part should be specified as much as possible. The analytical part of the real behaviour in the programme should be specified to be able to assess the outcomes of the study in the future.
Do you expect some specific outcomes? I suggest including it in the Other study goals as an exploration of possible relationships between the intervention and outcomes. It is a commitment of the publication of these unique results. It is the key question, what is enough, in which amount, in which time and which method are the best for our patients. One level is to verify existing methods but the other is (I think that it should be our mission) to find the new one, more effective than already existing.

Response: Thank you for bringing this up. We agree with you, that this part is a very interesting addition to this trial and gives us a broad range of opportunities. We are interested in further debating on the matter in personal contact. Maybe there is a way to find a discussion on this type of research question.
We agree with you, that we missed this part in our objective section. We now have added this sentence to the “objective section”. “Furthermore, we will explore relations between the observed usage behaviour and other study outcomes.”
Thank you for this important aspect.

However, we think we already mentioned the part about the usage behaviour in our manuscript. Please see section “Outcomes” and under point (h) you will find “Time to dropout and usage behaviour”. In this section it is described in detail what information will be assessed regarding the usage behaviour. From our point of view this is described sufficiently, since this is not the main objective of our trial. However, we will address these important questions in future manuscripts regarding the results of the trial.

A dropout assessment
Authors in their sooner published protocol of study (Bäuerle A, et al. BMJ Open 2020;10:e036466. doi:10.1136/bmjopen-2019-036466) wrote that: „Although a dropout rate of up to 50% for online interventions has been shown, we might expect an even higher rate of dropout given the physically vulnerable patient group that will form our sample and because the last measurement will occur 6 months after the intervention has ended. Assuming that some patients will not complete the first online assessment and thus not start Make It Training after recruitment we plan to recruit 500 patients at T0.
Contrary to this, they write (subchapter Sample size calculation) that: „In this publication, a dropout rate of 25% was assumed for the planning of the study, but only a 5% dropout rate was observed at T1 (primary endpoint). In our project, we conservatively assume a dropout rate of 20%, which to us seems to be a realistic assumption for an e-mental health intervention.
Why do the authors expect a different dropout rate in almost the same study design and selected patient populations?

Response: We thank you for this comment. We very much appreciate that you have paid close attention to the manuscript and the predecessor studies. We would like to explain this divergence in the sample size calculation of these two study protocols. First, we are working with a very experienced statistician in the present study. Prof Martus (https://pubmed.ncbi.nlm.nih.gov/?term=Peter+Martus&sort=fauth) has great expertise in conducting clinical trials and planning as well as evaluating RCTs. Prof. Martus planned and calculated the sample size for this study. Furthermore, we would like to point out that the sample size calculation was assessed as appropriate by the international reviewer (including statisticians). All issues regarding the statistical analysis / sample size calculation were and will be discussed with our data safety and monitoring board. Our DSMB includes Prof. Nina Timmesfeld (https://pubmed.ncbi.nlm.nih.gov/?term=Nina+Timmesfeld). She is head of the Department of Medical Informatics, Biometry, and Epidemiology, Ruhr University, and has great expertise in clinical research. As expected, we had a much lower dropout rate in the MINDS study (Bäuerle A, et al. BMJ Open 2020;10:e036466. Doi:10.1136/bmjopen-2019-036466). This was an indicator that Prof. Martus used to calculate the current sample size. We are currently preparing the data of the MINDS study for publication. Further, in addition to many similarities between the two studies, there are some important differences. One is that the e-mental health intervention is now much more attractive to users. Thanks to the funding, we were able to have a graphic update done here.
And more importantly, every patient is seen at baseline diagnosis. The MINDS study was completely remote without face-to-face contact with the study team. Therefore, we expect to see a lower dropout

rate in the current trial. These are major differences to the MINDS study, which led to the differences in the sample size calculation.

Participant eligibility and recruitment
I understand the HADS ≥ 13 for at least one-week criterium and it would be appropriate in the study design with a highly homogenous group of patients (same chemo, same diagnosis, same stage of the treatment). On the other hand, because of it, you could loos information about the development of the observed variables. This criterion increases the probability that HADS will decrease. The role of the program can be treatment (HADS decreases) or prevention/protection (HADS does not increase under the program condition in comparison to a group of people with the same diagnosis, stage, chemo and so on without the intervention).

Response: Dear Dr. Svetlak, thank you very much for this important comment. We completely agree with you on this matter. In fact, this would be more patient-oriented. However, as I described previously we are not able to change this inclusion criterion due to the circumstances of a funded project. Unfortunately, because of one international reviewer, we needed to implement this inclusion criterion. In our opinion, it could be a really interesting research project in the future to assess the efficacy of a preventive e-mental health intervention for cancer patients.

Methods
Used methods are appropriate.

Response: Thank you for your positive feedback.

References
I am missing this recent review which I find important for this topic.
Matis J, Svetlak M, Slezackova A, Svoboda M, Šumec R Mindfulness-Based Programs for Patients With Cancer via eHealth and Mobile Health: Systematic Review and Synthesis of Quantitative Research J Med Internet Res 2020;22(11):e20709

Response: Thank you very much for this important input. We have implemented this important reference in our manuscript and added it to our reference list.

Matis and colleagues conclude in their systematic literature review that mindfulness-based eHealth interventions are feasible and effective in improving different outcomes in cancer patients [23]. Particularly in improving depression, anxiety, and post-traumatic growth.

Reviewer: 2
Dr. Eva Nissen, Aarhus University
Comments to the Author:
Thank you for the opportunity to review this relevant study adding to the litterature within e-mental health Mindfulness-Based Interventions for the cancer population. It is a thoroughly described study with many stregths, that I am looking forward to read when completed.
I do, however, have some concerns regarding the manuscript, that I believe should be clarified before publication. Please see below:

Response: Dear Dr. Nissen, thank you very much for your helpful and positive evaluation. We thank you for your time and engagement. We have tried to incorporate all of your recommendations in our revised manuscript. Below you will find a point-by-point response. Our study is funded by the German Federal Ministry of Education and Research after three rounds of a reviews conducted by international experts over almost two years. Therefore, we cannot address points related to the study design or the statistical analysis plan. However, we have attempted to address all of your points in our

response letter. In addition, we have made significant changes to our manuscript to make it clearer and more comprehensive. We think that the manuscript has improved in quality thans to your contribution.

Abstract: Please clarify that you are focusing on 'psychological distress'.

Response: Thank you for your comment. We have clarified this in the abstract by adding ‘psychological’ when mentioning distress.

Please elaborate the description of the intervention: please clarify duration of the intervention, how the intervention is delivered (e.g. web-based, video conference, in groups or individually), and if it is a fully automatized intervention or there is support.

Response: Thank you very much for this comment. We have clarified this in the abstract by adding the following sentences. “Make It Training is a self-guided and web-based psycho-oncological intervention, which includes elements of cognitive behavioural therapy, mindfulness-based stress reduction, and acceptance and commitment therapy. The training supports the patients over four months.”

It appears a bit confusing that the hypothesis is stating "...reducing destress at T1 (primary endpoint)". Could this be changed to "...reducing distress immediately after the xx week intervention"? or something similar?

Response: Thank you for bringing this up. We agree with you here. We have changed the sentence to “We expect the Make It Training to be superior to treatment as usual optimized (TAU-O) in terms of reducing psychological distress after completing the intervention (T1, primary endpoint).”

Regarding statistics: please see comments to protocol text.

Introduction: The argumentation about the relevancy of the study is centered around a heighthened level of distress among cancer patients in general. The present study, however, only includes patients in curative treatment domains, which is known to be a different situation than patients in life-sustaining or palliative care. Please clarify the argumentation about distress level with regards to cancer patients in curative treatment to reflect the study population properly.

Response: Thank you for your important comment. We have added further information regarding the distress of patients in curative treatment domains. However, we would like to point out that, there are no major differences in distress levels between curative and palliative care. Of course, the relevant topics and the stressors differ between the patients. We added the literature on this matter to the introduction. Briefly, we summarized this here.
Mehnert et al. 2017 (https://onlinelibrary.wiley.com/doi/10.1002/pon.4464), Table 1: Tumor stages I and II (which are, after all, more likely to be treated curatively) 52.2% and 48.2%, respectively, reported high levels of distress (DT cutoff ≥5).

The meta-analysis from Mitchell et al., published in Lancet Oncology concluded that the patients burden in palliative and non-palliative care is comparable.
Mitchell AJ, Chan M, Bhatti H, et al: Prevalence of depression, anxiety, and adjustment disorder in oncological, haematological, and palliative-care settings: A metaanalysis of 94 interview-based studies. Lancet Oncol 12:160-174, 2011

We have added the following sentences to our introduction to point out that patients in curative treatment domains also experience elevated distress.

The results from the study of Mehnert and colleagues reveal that 52.2% and 48.2% of patients with tumor stage one and two report elevated distress, respectively.[3] Indicating that, many patients in earlier tumor stages show high distress levels. The meta-analysis by Mitchell et al., published in Lancet Oncology concluded that the distress levels of patients in palliative and non-palliative care are comparable.[5] Concluding from these results, patients in palliative and non-palliative care are comparably burdened. However, the needs and demands are different between patients in palliative and non-palliative care.

In the introduction, different empirical arguments for providing e-health psychological treatments for psychological distress is provided. It would, however, strengthen the argumentation with some theoretical arguments as well - why is mindfulness-based interventions in combination with cognitive behavioral therapy (CBT) beneficial for distressed cancer patients? Furthermore, an inclusion of other mindfulness-based interventions than Mindfulness-Based Stress Reduction (MBSR) would be necessary to get a sufficient overview of the field of this type of mental health interventions. Many other interventions have combined mindfulness-techniques with CBT before, for example Mindfulness-Based Cognitive Therapy (MBCT), also in e-mental health interventions. Not responding to this development within the field of mindfulness-based interventions is a serious inadequacy in describing the background of the present study. Consider reading a recent systematic review on this matter here: Matis J, Svetlak M, Slezackova A, Svoboda M, Šumec R. Mindfulness-Based Programs for Patients With Cancer via eHealth and Mobile Health: Systematic Review and Synthesis of Quantitative Research J Med Internet Res 2020;22(11):e20709.

Response: Thank you for this important comment. We agree with you that our introduction needs more substantial background information on MBCT (why is MBCT beneficial?; previous studies addressing it). We have added the following paragraph to our introduction. We have also added the cited literature to our reference list.

Matis and colleagues conclude in their systematic literature review that mindfulness-based eHealth interventions are feasible and effective in improving different outcomes in cancer patients [23]. Particularly in improving depression, anxiety, and post-traumatic growth. Different e-mental health interventions combined CBT and mindfulness-techniques to support cancer patients. Internet mindfulness-based cognitive therapy (iMBCT) showed promising results in terms of psychological distress, depression and anxiety symptoms, and fear of cancer recurrence.[24]. One trial evaluating a therapist-assisted internet-based MBCT intervention for breast and prostate cancer survivors showed reduced depression and anxiety symptoms post intervention.[22] The effect sustained in anxiety, but not for depression.

Methods: The argument for not including cancer patients aged >65 years is not clear. It is stated that "...a German survey analyzing the internet literacy of cancer patients determined that while no significant differences regarding gender or age were seen, most of the cancer patients were younger than 70 years old." If no significant differences were found regarding age, why use this as an exclusion criteria? If the concern is to have patients with a lack of internet literacy included in the study, consider using a questionnaire or single-item question to clarify this as inclusion criteria instead of age.

Response: Thank you for your feedback. We completely agree with you that such an item would be a good addition. Unfortunately, we are not able to add this to our inclusion criteria, since the study design cannot be changed and is already in progress after evaluation by the international experts. However, we will keep this in mind for future projects. We pointed out, that most patients were younger than 70 years in this survey. Therefore, it is not possible to evaluate the difference in internet literacy between younger and older cancer patients. Since one of the reviewer comments was “The patient population must be critically reviewed, especially concerning the age of the patients and the respective access to online interventions.” we tried to address this matter by choosing this age range 18-65 years. In addition, a representative survey shows that daily Internet use decreases with age (D21-Digital-Index 2020/2021. Jährliches Lagebild zur Digitalen Gesellschaft. Initiative D21. https://initia-tived21.de/app/uploads/2021/02/d21-digital-index-2020_2021.pdf.).

We have added this sentence to make it clearer. “In addition, representative data on the daily Internet use of the German population shows that Internet use decreases with age.[30]”

Intervention: The description of the duration of the interventions is not quite clear. First it is stated that "Both interventions last four months.", but then that "Each Make It module is conceptualized to be completed over the course of one week..." and "Eight optional modules as well as one technical introduction module complement the eight bi-weekly mandatory modules, each lasting about 30 minutes."

Response: Thank you for bringing this up. We have clarified this in the “experimental intervention” section. Moreover, we have added a table to give an overview of the modules.

An overview of the specific module content would furthermore be relevant for clarity, possibly in combination with a clarification of the module structure.

Response: Thank you for your comment. We have added table 2 to the manuscript. Table 2 contains an overview of the 16 interventional modules.

Please also clarify the content of the control condition: how is it planned to control for this various treatment?

Response: Thank you for your important comment. We added information about the control condition in the section “Control intervention: Treatment as Usual optimized”. We now think TAU-O is described in sufficient detail. Of course, controlling for various treatments in the German health care system is complex. However, we can control for the data measured in the CRFs used in this study. Furthermore, we assess whether the patient is currently in psychotherapeutic care after each module. Of course, all data is self-reported.

In the discussion it is mentioned that "...other patient groups could benefit from this approach as well...". Please elaborate if the treatment content in the Make It Training is generic or cancer specific.

Response: Thank you for bringing this up. Indeed, this sentence is not clear. Of course, the intervention contains cancer-specific content. However, other patient groups could benefit from similar e-mental health interventions. Especially somatic ill patients with comorbid psychological distress. We specified this in the manuscript.
New sentence: Accordingly, other patient groups could benefit from similar e-mental health approaches as well.

Statistical methods: Please consider using Mixed Linear Modelling (MLM) for analysis instead of ANCOVA. MLMs tollerates missing values without imputations, which should be preferred. I am not a statistician and therefore I lack the qualifications to thoroughly account for the differences between ANCOVAs and MLMs, but my impression is that MLM is considered a more contemporary state-of-the-art statistical approach for conducting analyses in randomized controlled intervention trials.

Response: Thank you for your comment. As shown above, the study protocol is the protocol of an already peer-reviewed trial. We are specifically funded by the Ministry for the implementation of the project described here. During the evaluation rounds, a statistician also evaluated the project and gave it a positive assessment. Moreover, we are working with a very experienced statistician in the present study. Prof Martus (https://pubmed.ncbi.nlm.nih.gov/?term=Peter+Martus&sort=fauth) has great expertise in conducting clinical trials and planning as well as evaluating RCTs. Prof. Martus followed the state of the art guidelines for planning large multicenter RCTs when preparing the statistical analysis plan. More important is the fact, that we followed the recommendations of an international statistician, which reviewed our project plan, sample size calculation, and statistical analysis plan. Furthermore, we would like to point out that the sample size calculation was assessed as appropriate by the international reviewer (including statisticians). All issues regarding the statistical analysis / sample size calculation were and will be discussed with our data safety and monitoring board. Our DSMB includes Prof. Nina Timmesfeld (https://pubmed.ncbi.nlm.nih.gov/?term=Nina+Timmesfeld). She is head of the Department of Medical Informatics, Biometry and Epidemiology, Ruhr University and has great expertise in clinical research. Therefore, we are not able to change the statistical analysis plan.

Patient and public involvement: It is commendable that patients are consulted in the project work. It is, however, not clear whether patients have been involved in the formulation of the present study protocol ('research design'). Please clarify this matter, how patients' input will be implemented, how incongruency between researchers and patients is handeled, and hence how tokenistic involement is avoided.

Response: Thank you for your comment regarding this important topic. In fact, this trial is funded as part of the initiative „Förderung klinischer Studien mit hoher Relevanz für die Patientenversorgung (Promotion of clinical studies with high relevance for patient care)“. One of the main prerequisites is participation and the involvement of affected patients. The reviewers of the trial particularly emphasized good and intensive patient participation. We have uploaded the review reports and provided them to the Journal. Patient representatives were involved during the whole planning and application phases (in total over two years). At all stages, the patient representatives were informed. Decisions regarding study design (e.g. endpoints) were made in close exchange and after consultation. A participatory decision-making process was implemented and followed.

We have added this sentence: A participatory decision-making process between the patient council and the researcher was implemented and followed.

Furthermore, we are always in close contact with the patient representatives and work with them directly on different matters (e.g. recruitment, publications in different patient magazines). We understand the patient council as a major participant in our project.
We have changed “…patient council will be consulted regarding research design…” into “…patient council was consulted regarding research design…” because the planning phase has long since been completed. Patient involvement will be informed by the online resources of UK National Health Services (INVOLVE; http://www.invo.org.uk/). We have added this to our manuscript.

VERSION 2 – REVIEW

REVIEWER	Svetlak, Miroslav Masaryk University
REVIEW RETURNED	19-Mar-2022

GENERAL COMMENTS	Dear Colleagues, thank you for accepting my comments and thank you for your great job. I am looking forward to the results of your study. Good luck. Best regards, Mirek Svetlak

REVIEWER	Nissen, Eva Aarhus University, Department of Psychology and Behavioral Sciences
REVIEW RETURNED	23-Mar-2022

GENERAL COMMENTS	Dear authors, It is a pleasure to see how the manuscript has i been significantly improved and clarified. I understand that procedures cannot be changed due to prior registrations with the funding body and ethical comittees. I think you have clarified the argumentation for the different decisions made to an adequate extend. The elaborated description of the intervention is thorough and it appears very relevant for this population. In the background section, I do, however, still miss a theoretical argumentation for combining CBT, mindfulness, and acceptance and commitment therapy for treating psychological distress in cancer patients. I appologize if this request was not clear in the first review. What is mindfulness, CBT and ACT and why is a combination a possibly fruitful treatment for cancer patients with psychological distress? What are the proposed mechanisms you have combined in this treatment to make a better offer for the patients than already exist in the previously tested interventions? I do not think that the fact that previous studies are adressing these interventions in different combinations is a theoretical argumentation. When combining already existing treatment paradigms into a new combination, I think an argumentation for doing so is appropriate. The study protocol is overall thorough and well-described, and I belive that with this minor elaboration of the theoretical aspects it will be suitable for publication. Kind regards Eva Nissen

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Dr. Miroslav Svetlak, Masaryk University Comments to the Author:
Dear Colleagues,
thank you for accepting my comments and thank you for your great job. I am looking forward to the results of your study. Good luck.
Best regards, Mirek Svetlak

Response: Dear Mr. Svetlak, Thank you for your positive evaluation and supporting this study protocol with your valuable feedback.

Kind regards,
Alexander Bäuerle & Martin Teufel, on behalf of all co-authors

Reviewer: 2
Dr. Eva Nissen, Aarhus University
Comments to the Author:
Dear authors,

It is a pleasure to see how the manuscript has i been significantly improved and clarified.
I understand that procedures cannot be changed due to prior registrations with the funding body and ethical comittees. I think you have clarified the argumentation for the different decisions made to an adequate extend.
The elaborated description of the intervention is thorough and it appears very relevant for this population.

In the background section, I do, however, still miss a theoretical argumentation for combining CBT, mindfulness, and acceptance and commitment therapy for treating psychological distress in cancer patients. I appologize if this request was not clear in the first review. What is mindfulness, CBT and ACT and why is a combination a possibly fruitful treatment for cancer patients with psychological distress? What are the proposed mechanisms you have combined in this treatment to make a better offer for the patients than already exist in the previously tested interventions? I do not think that the fact that previous studies are adressing these interventions in different combinations is a theoretical argumentation. When combining already existing treatment paradigms into a new combination, I think an argumentation for doing so is appropriate.

The study protocol is overall thorough and well-described, and I belive that with this minor elaboration of the theoretical aspects it will be suitable for publication.

Kind regards
Eva Nissen