PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	SafeSpace: What is the feasibility and acceptability of a co-designed virtual reality intervention, incorporating compassionate mind training, to support people undergoing cancer treatment in a clinical setting?
AUTHORS	O'Gara, Geraldine; Murray, Lisa; Georgopoulou, Sofia; Anstiss, Tim; Macquarrie, Andrew; Wheatstone, Pete; Bellman, Barbie; Gilbert, Paul; Steed, Anthony; Wiseman, Theresa

VERSION 1 – REVIEW

REVIEWER	Stefan Nilsson University of Gothenburg, Institute of Health and Care Sciences
REVIEW RETURNED	19-Dec-2020

GENERAL COMMENTS	Thank you for this interesting study. I think that the results contribute to knowledge about VR, but I have some comments. There are a lot of statistics, but I lack a power calculation. How should this statistics be interpreted? "…nearly two-thirds of participants completing three sessions, meeting the defined end-point". 35 % of the participants did not completed the intervention, and in 12 (24 %) sessions were experienced with a problem. Still the conclusion is that the group was satisfied. Please, describe the theoretical arguments for the criteria for cut-off (e.g., >60%). None of the participants chose the forest the last session. The results remind me of a previous study that used trees. One of the participants described the environment as "gloomy as it reminded her of a scary movie she had watched recently ("The Blair Witch Project")" in: Does Audiovisual Stimulation With Music and Nature Sights (MuViCure) Reduce Pain and Discomfort During Placement of a Femoral Nerve Block?" Maybe it is worth a note that the forest was not that popular. Only 11 participants chose to participate in the qualitative interviews. Was this group representative for the whole group, or was it a selection bias?

REVIEWER	Lauren Rynar Rush University, Psychology
REVIEW RETURNED	09-Apr-2021

GENERAL COMMENTS	Overall, this represents an interesting and unique intervention. Virtual Reality equipment and interventions may be particularly useful in cancer populations, given apparent ease of use in multiple treatment/care settings. However, I have several major questions and concerns, which put into question whether the conclusions can

	be justified by the results: 1. The research question is not clearly defined. It is not clear throughout the paper why CFT/CMT was chosen as a treatment modality to be delivered with VR, nor how these interventions relate to the unique distress experienced by cancer patients. Why CMT? Why would CMT be enhanced when delivered via VR? Is CMT difficult or costly to deliver otherwise? In what ways are these two tools complementary, or even related? 2. While the small sample size is mentioned briefly in the conclusions and limitations, I think it needs to be addressed more substantially. I would think this study would be significantly underpowered given the huge number of variables (demographic, psychological, and physiological) and the small sample size that was made even smaller due to attrition. This may have been addressed by doing less in a single study, e.g., less components, less variables of interest, or by recruiting a larger sample size. This needs to be addressed and the results accepted with caution. 3. After reading the paper more than once, I'm still not entirely clear what the intervention entails. It may be useful to include a table or image that clearly outlines the content of each VR/CMT session given neither are widely utilized interventions. 4. I have some concerns about the study population. While the authors do acknowledge a convenience sample, there seem to be substantial differences across participants, which are not controlled for or addressed in a meaningful way. There is a large body of literature on differences in cancer-related distress across both disease sites and across the cancer continuum. I would wonder about any notable differences in baseline characteristics or response to intervention in the study population, though I realize this would make the study even further under-powered. It's also interesting that the mean time since diagnosis is over 3 years, but that 80% of participants were still in treatment. That makes for an unusual population, which is not addressed anywhere in the paper. 5. The rate of attrition in the study was very high, particularly when considering the small sample size and small number of sessions. This is concerning for several aspects of the intervention and the ability to replicate the study with a larger sample. Additional comments/revisions: 1. Background paragraph 1: unpleasant treatments don't lead to non-adherence, people lead to non-adherence. Reword. 2. Background paragraph 2: Start with defining VR. What is it? What's the technology? What does it/can it include? What is the mechanism of action? 3. Background paragraph 2: reword sentence 1, "technologies designed to deliver supportive interventions" 4. Background paragraph 2: "other studies reported positive results as a distraction technique". Not clear what you are referring to here. Is it VR that's used as a means of distraction? 5. Background paragraph 3: please better describe CMT. How many sessions? Is it manualized? Are there particular therapeutic tools, approaches, or goals? 6. Background last paragraph: "application of VR within cancer is accepted". You say above results are equivocal. 7. Background: please make a case for why you chose CMT as an adjunct to VR. What is the relationship here? Why CMT in general, as opposed to other psychotherapeutic interventions that incorporate relaxation?

	8. Methods paragraph 1: first sentence is not a full sentence. Review/revise. 9. Methods: consider a table or flowchart on the process of EBCD or how you reached conclusions on intervention design, acceptability, and feasibility. 10. Instruments: please justify the use of a non-validated, adapted version of the WEMWBS. In what way is it different than the original tool? 11. Procedure: why is VR contra-indicated for persons with known psychological disorders? How did you screen out for this? 12. Procedure: It's not clear who participated in the workshops and different phases of development. Was it the same or different people? You also do not include any demographic or disease-related information about those individuals. 13. Results: may want to consider presenting the results of phase 1 in the results section, e.g., a table of themes that emerged or summary of the EBCD process. 14. Results: difficult to follow throughout. Review for run-on sentences or results that are repetitive to what is presented in the tables. 15. Results paragraph 1: check for missing words and grammar. 16. Descriptive Statistics, psychological measures: second paragraph is hard to follow. Reword. 17. Not sure how necessary it is to include the quotes from the post-intervention interviews. Scope of the article is already extensive. 18. Discussion paragraph 1: Makes it sound like the current study results indicated VR+CMT was effective regardless of age, background, or gender like the other referenced studies. 19. Discussion paragraph 3: Not sure what "presence" refers to. Unfortunately, considering these major and minor questions collectively, I cannot recommend acceptance to BMJ at this time. I might consider abbreviating the article to focus only on one component, e.g., development of the intervention submitted as a program review paper. I would be happy to review a subsequent version should the authors be given the opportunity to revise. Thank you for the opportunity to review.

VERSION 1 – AUTHOR RESPONSE

Response Reviewer #1:

1. There are a lot of statistics, but I lack a power calculation. How should these statistics be interpreted? "…nearly two-thirds of participants completing three sessions, meeting the defined end-point". 35 % of the participants did not completed the intervention, and in 12 (24 %) sessions were experienced with a problem. Still the conclusion is that the group was satisfied. Please, describe the theoretical arguments for the criteria for cut-off (e.g., >60%).

   Thank you for highlighting this. We have clarified the sample size on page 13 under the heading Descriptive Statistics. We have also clarified the cut-off criteria (>60%) on page 12, last paragraph, under heading 'Acceptability/feasibility data.' Apologies for the omission of this important information in the previous submission.

2. None of the participants chose the forest the last session. The results remind me of a previous study that used trees. One of the participants described the environment as "gloomy as it reminded her of a scary movie she had watched recently ("The Blair Witch Project")" in: Does Audiovisual Stimulation With Music and Nature Sights (MuViCure) Reduce Pain and Discomfort During Placement of a Femoral Nerve Block?" Maybe it is worth a note that the forest was not that popular.

Thank you for highlighting this, it is an important and relevant point. We have added this to the discussion on page 17 and referenced appropriately.

3. Only 11 participants chose to participate in the qualitative interviews. Was this group representative for the whole group, or was it a selection bias?

   Thank you for highlighting this. We have clarified this on page 14 under the sub-heading 'Qualitative findings.' Table 4 has also been created for within the text and inserted on page 14/15 to highlight demographic information of the participants.

Response reviewer #2:

a. The research question is not clearly defined. It is not clear throughout the paper why CFT/CMT was chosen as a treatment modality to be delivered with VR, nor how these interventions relate to the unique distress experienced by cancer patients. Why CMT? Why would CMT be enhanced when delivered via VR? Is CMT difficult or costly to deliver otherwise? In what ways are these two tools complementary, or even related?

Thank you. The research question has now been further clarified on page 6, 2nd paragraph, and by the insertion of the aim on the same page. Apologies for previous omission.

We have clarified the choice of the use of CMT on page 5 under the sub-heading 'Compassion Focussed Therapy' in which we highlight its potential for use in multiple environments including at home. We have also highlighted the potential benefits of CMT over other interventions such as CBT on page 5/6.

We acknowledge that the application of CMT through VR is unexplored but have highlighted that VR is low cost and has previously been accepted in the clinical environment as a distraction tool, lending itself to an acceptable form of delivery for CMT.

b. While the small sample size is mentioned briefly in the conclusions and limitations, I think it needs to be addressed more substantially. I would think this study would be significantly underpowered given the huge number of variables (demographic, psychological, and physiological) and the small sample size that was made even smaller due to attrition. This may have been addressed by doing less in a single study, e.g., less components, less variables of interest, or by recruiting a larger sample size. This needs to be addressed and the results accepted with caution.

Thank you for highlighting this, as did Reviewer #1. We appreciate this is an important point and reiterate that we have clarified the sample size on page 13 under the heading 'Descriptive Statistics'. Furthermore, we have highlighted the study as underpowered in the Discussion section, page 18, last paragraph, and recommended caution with results in Discussion section, paragraph 2, page 17. Reasons for attrition are highlighted in table 4 on page 12 and noted as providing intelligence for any future pilot or larger study in the Discussion section, last paragraph, page 18.

c. After reading the paper more than once, I'm still not entirely clear what the intervention entails. It may be useful to include a table or image that clearly outlines the content of each VR/CMT session given neither are widely utilized interventions.

Thank you for highlighting this lack of clarity regarding what the intervention entails. To address this, we have included a descriptive table as suggested, table 1, page 10. Further detail about the intervention is now included at the top page 10.

d. I have some concerns about the study population. While the authors do acknowledge a convenience sample, there seem to be substantial differences across participants, which are

not controlled for or addressed in a meaningful way. There is a large body of literature on differences in cancer-related distress across both disease sites and across the cancer continuum. I would wonder about any notable differences in baseline characteristics or response to intervention in the study population, though I realize this would make the study even further under-powered.

Thank you for highlighting this. We have clarified this in the Discussion section, page 18, last paragraph by adding the following sentence: 'The small sample did not allow for adjustment of confounding variables in the quantitative analysis so that any notable differences in baseline characteristics or response to the intervention in the study population could be identified.'

It's also interesting that the mean time since diagnosis is over 3 years, but that 80% of participants were still in treatment. That makes for an unusual population, which is not addressed anywhere in the paper.

Thank you for highlighting this unusual aspect of the convenience sample which we had omitted to comment on, apologies for this. This and potential implications have been highlighted in the Discussion Section, last paragraph on page 17.

e. The rate of attrition in the study was very high, particularly when considering the small sample size and small number of sessions. This is concerning for several aspects of the intervention and the ability to replicate the study with a larger sample.

Thank you, we acknowledge that the sample size is small, and the pragmatic reasons for this on page 13 under the heading 'Descriptive Statistics.' We further acknowledge the high attrition rate in the Discussion Section, last paragraph, page 18. The various reasons for attrition are highlighted in table 4 on page 12 and noted, and as an acceptability/feasibility study, providing intelligence for any future pilot or larger study in the Discussion section, last paragraph, page 18. We apologise for not previously highlighting these important points.

Additional comments/revisions:
Background:

1. Background paragraph 1: unpleasant treatments don't lead to non-adherence, people lead to non-adherence. Reword.

Thank you, this has been reworded.

2. Background paragraph 2: Start with defining VR. What is it? What's the technology? What does it/can it include? What is the mechanism of action?

Thank you, we acknowledge that there was a lack of background information regarding VR in the manuscript background, mainly due to the brevity required by the word count. This has been expanded as suggested on page 5, paragraph 2, 'Background/subheading Virtual Reality'.

3. Background paragraph 2: reword sentence 1, "technologies designed to deliver supportive interventions".

Thank you, this has been amended to 'Healthcare has seen a growth in technologies such as VR to provide support.'

4. Background paragraph 2: "other studies reported positive results as a distraction technique". Not clear what you are referring to here. Is it VR that's used as a means of distraction?

Thank you, and apologies for confusion. This has been amended to 'Other studies using VR reported positive results as a distraction technique during chemotherapy administration.'

5. Background paragraph 3: please better describe CMT. How many sessions? Is it manualized? Are there particular therapeutic tools, approaches, or goals?

Thank you. CMT has been further clarified by adding: '…which was originally developed for people who find self-warmth and self-acceptance difficult. It teaches the skill and practice of training the mind, by inviting people to develop their own images of warmth through practices such as slow and deeper breathing, compassionate voice tones, imagery, and facial expressions, and helps people develop self-compassion. CMT can be delivered on a one to one or group basis.'

And…

'CMT can be self-administered and once learned, can be recalled in multiple environments including at home.'

Apologies for the omission of this information in the previous submission.

6. Background last paragraph: "application of VR within cancer is accepted". You say above results are equivocal.

Thank you and apologies for confusion. This has been amended to 'Whilst effectiveness is equivocal, the application of VR within cancer as a distraction technique is accepted.'

7. Background: please make a case for why you chose CMT as an adjunct to VR. What is the relationship here? Why CMT in general, as opposed to other psychotherapeutic interventions that incorporate relaxation?

Thank you. We hope we have addressed this in the following section on page 5/6: '…CMT, which was originally developed for people who find self-warmth and self-acceptance difficult. It teaches the skill and practice of training the mind, by inviting people to develop their own images of warmth through practices such as slow and deeper breathing, compassionate voice tones, imagery, and facial expressions, and helps people develop self-compassion. CMT can be delivered on a one to one or group basis. Studies examining other psychological interventions such as Cognitive Behavioural Therapy in a cancer population have shown favourable effects, however, this requires specialist training, supervision and certification needs, and appropriate training can be complex and costly. CMT can be self-administered and once learned, can be recalled in multiple environments including at home. CFT and CMT have been shown to reduce suffering and improve QoL in a range of health problems such as anxiety/depression, eating disorders, phobias and pain management and are becoming more mainstream and acceptable.'

Further, we have clarified the use of VR within the following sentence:

'Whilst effectiveness is equivocal, the application of VR within cancer as a distraction technique is accepted. However, its use to deliver psychological therapies, such as CMT, remains unexplored. Little is known about how these treatment approaches might be combined, whether there is any synergistic effect, and if such an intervention is acceptable and feasible in the clinical environment.'

Methods:

8. Methods paragraph 1: first sentence is not a full sentence. Review/revise.

Thank you. This has been revised to: 'This was a two-phased study using mixed-methods and an experience-based co-design (EBCD) approach.'

9. Methods: consider a table or flowchart on the process of EBCD or how you reached conclusions on intervention design, acceptability, and feasibility.

Thank you, and apologies for omission of this important information. Please see a flowchart on our process to the intervention using an EBCD approach in Supplementary file flowchart 1.

Instruments:

10. Instruments: please justify the use of a non-validated, adapted version of the WEMWBS. In what way is it different than the original tool?

Thank you, and apologies for lack of clarity in the original manuscript. This has now been clarified on page 7, in paragraph under heading 'Instruments for psychological assessment', sub-heading 'WEMWBS' as follows: 'The WEMWBS asks participants to describe their experience over the last two weeks. The adapted version asks the participant to describe how they are feeling immediately after the intervention.'

Procedure:

11. Procedure: why is VR contra-indicated for persons with known psychological disorders? How did you screen out for this?

Thank you, and apologies for omission of this important information. This has been clarified in the manuscript on page 8 as follows: 'Exclusion criteria were people: 1) considered too unwell; 2) in who use of VR is not recommended e.g. registered blind, motion sickness, seizure disorder, or known psychiatric conditions, such as schizophrenia or personality disorder. Exclusion criteria were assessed by medical records, self-report and in consultation with clinical staff.' Appropriate references are given.

12. Procedure: It's not clear who participated in the workshops and different phases of development. Was it the same or different people? You also do not include any demographic or disease-related information about those individuals.

Thank you, this has been clarified as follows on page 6/7 under the heading 'Sample': 'A convenience sample was used to recruit participants to both phases of the study. Two separate groups of participants were recruited to either phase; phase 1 participants were no longer in treatment or follow-up; phase 2 participants were either receiving treatment or were in treatment follow-up.'

This has been further clarified under the heading 'Procedure' at the bottom page 8/top of page 9: 'Procedure included two phases with two different groups of participants; phase 1 aimed to inform development of the intervention through a series of workshops with patients with previous experience of cancer and treatment. Phase 2 involved the application and evaluation of the intervention in the clinical setting with patients currently in treatment or follow-up, to assess acceptability and feasibility through intervention uptake and user experience.' Demographic data for phase 1 participants is included in supplementary table 1. Disease related information for participants in phase 2 is included in table 3 on page 12.

Results:

13. Results: may want to consider presenting the results of phase 1 in the results section, e.g., a table of themes that emerged or summary of the EBCD process.

Thank you, the heading 'Results' has been moved to page 9, before 'Phase 1 – Intervention development' heading, to clarify that phase 1 is part of the overall study results. We have rephrased the words 'key features' to 'themes' on page 9 in 'Findings' for clarity and apologise for confusion.

14. Results: difficult to follow throughout. Review for run-on sentences or results that are repetitive to what is presented in the tables.

Thank you. This has been clarified within the text on page 12, Acceptability and Feasability data paragraph 2. Further clarified on page 14, Psychological Measures paragraph 2.

15. Results paragraph 1: check for missing words and grammar.

Thank you. This has been reworded on page 11 to: 'Summary measures for participant characteristics, VR use data variables and questionnaire scores were presented as means and

standard deviations for continuous (approximate), normally distributed variables and frequencies. Categorical variables were reported as percentages.'

16. Descriptive Statistics, psychological measures: second paragraph is hard to follow. Reword.

Thank you. This has been reworded on page 14, paragraph 2 to: 'There was a statistically significant reduction in stress levels as measured by the DASS21 from baseline to post-session 3 ($z= -2.138^{b}$, $p = 0.03$). While there was a positive and beneficial trend from baseline to post-session 3 (VR3) in most of the sub scores, none reached statistical significance.'

17. Not sure how necessary it is to include the quotes from the post-intervention interviews. Scope of the article is already extensive.

Thank you. Whilst we strongly agree that the scope of the article is extensive, we feel it is important to include the quotes from our qualitative work as this demonstrates the patient experience which is important within our mixed-methods approach. The qualitative findings complement the quantitative data, providing a better insight into the patient experience, and we feel that inclusion of this is important within the acceptability/feasibility context. We have kept quotes to a minimum as much as possible.

Discussion:

18. Discussion paragraph 1: Makes it sound like the current study results indicated VR+CMT was effective regardless of age, background, or gender like the other referenced studies.

Thank you, we have clarified on page 17, paragraph 1 as follows: 'This is consistent with wider literature in which new technologies were also found to be favourable, in their case regardless of age, background or gender.'

We have also added the following line at the end of the same paragraph for further clarity: 'Whilst a positive trend was observed in some psychological domains, the overall effectiveness of the intervention remains unclear.'

19. Discussion paragraph 3: Not sure what "presence" refers to.

Thank you, and apologies for lack of clarity on this. We have added the following to aid clarity: 'Presence' has been defined as the "sense of being there", or as the "feeling of being in a world that exists outside the self"… and referenced appropriately.

The word count is 5227. We appreciate that is in excess of the guidelines but became necessary in order to incorporate all the recommended reviewers' revisions. We also feel that the qualitative findings component of the study has added to the overall word count excess, but that the reporting of this is important, and necessary within the mixed-method approach to reflect patient experience.

VERSION 2 – REVIEW

REVIEWER	Stefan Nilsson University of Gothenburg, Institute of Health and Care Sciences
REVIEW RETURNED	17-Jun-2021

GENERAL COMMENTS	Thanks for this revised version of the manuscript. The authors have revised the manuscript in an appropriate manner. However, I lack a more detailed description of the analyses, in accordance to mixed methods. I also would like to get a theoretical description of how the methods were mixed in accordance with the

	appropriate method literature.

REVIEWER	Lauren Rynar Rush University, Psychology
REVIEW RETURNED	29-Jun-2021

GENERAL COMMENTS	The revision addresses several of my concerns, most notably simplifies, clarifies, and better defines terms. I have a much better understanding of VR, CMT, combination of the two, and application to a cancer population. Shifting to an acceptability/feasibility study makes sense given the sample size and study design. I continue to have concerns about the small sample size, high rate of attrition (though addressed/justified in this version), and the unusual nature of the sample in terms of cancer treatment timeline. I also have concerns about differences between the group in Phase 1 (post-treatment) and the group in Phase 2 (in treatment), as the likely physical and emotional differences between these groups could not be controlled for given the small sample size. Nonetheless, this is somewhat addressed in the limitations section of the discussion. In this new version, the study offers some novel interventions and approaches that would be worthwhile for the cancer community to review and hopefully replicate in a way that addresses some of the more significant limitations. Thank you for the opportunity to review.

VERSION 2 – AUTHOR RESPONSE

Response Reviewer #1:
The authors have revised the manuscript in an appropriate manner.

However, I lack a more detailed description of the analyses, in accordance to mixed methods. I also would like to get a theoretical description of how the methods were mixed in accordance with the appropriate method literature.

Thank you for highlighting this. We have clarified the use of mixed-methods in the Abstract on page 4. We have also highlighted in the methods section, page 6, that mixed-methods were used in phase 2 of the study, and that data were triangulated to add credibility and strengthen the acceptability and feasibility findings. We have included a supporting reference and added a supplementary flowchart 2 to visually show how data was triangulated. We have also clarified in the Discussion Section, page 18, paragraph 3. Furthermore, we have included supplementary table 7 to demonstrate data synthesis.

Response Reviewer #2:

The revision addresses several of my concerns, most notably simplifies, clarifies, and better defines terms. I have a much better understanding of VR, CMT, combination of the two, and application to a cancer population. Shifting to an acceptability/feasibility study makes sense given the sample size and study design. I continue to have concerns about the small sample size, high rate of attrition (though addressed/justified in this version), and the unusual nature of the sample in terms of cancer treatment timeline. I also have concerns about differences between the group in Phase 1 (post-treatment) and the group in Phase 2 (in treatment), as the likely physical and emotional differences between these groups could not be controlled for given the small sample size. Nonetheless, this is somewhat addressed in the limitations section of the discussion. In this new version, the study offers some novel interventions and approaches that would be worthwhile for the cancer community to

review and hopefully replicate in a way that addresses some of the more significant limitations. Thank you for the opportunity to review.

Thank you for your considered and constructive response post major revisions. We acknowledge and share your concerns regarding the small sample size and rate of attrition, which was unavoidable despite our best efforts. In addition, as a feasibility study in a real-world setting, we hope that this project highlights potential challenges for a larger study or implementation of such interventions in clinical practice.

The word count is 5279. We appreciate that is in excess of the guidelines but became necessary in order to incorporate all the previously recommended reviewers' revisions. We also feel that the qualitative findings component of the study has added to the overall word count excess, but that the reporting of this is important, and necessary within the mixed-method approach to reflect patient experience.

VERSION 3 – REVIEW

REVIEWER	Stefan Nilsson University of Gothenburg, Institute of Health and Care Sciences
REVIEW RETURNED	23-Sep-2021

GENERAL COMMENTS	The authors have revised the manuscript in accordance with the reviewer's comments.