PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Virtual reality for relatives of ICU patients to improve psychological sequelae: study protocol for a multicentre, randomized controlled trial.
AUTHORS	Vlake, Johan; van Bommel, Jasper; Wils, Evert-Jan; Korevaar, Tim; Hellemons, Merel; Klijn, Eva; Schut, Anna; Labout, Joost; Van Bavel, Marten; Van Mol, Margo; Gommers, Diederik; Van Genderen, Michel

VERSION 1 – REVIEW

REVIEWER	Foxen-Craft, Emily University of Michigan
REVIEW RETURNED	12-Apr-2021

GENERAL COMMENTS	Thank you for the opportunity to review this protocol, Virtual reality for relatives of ICU patients to improve psychological sequelae: study protocol for a multicentre, randomized controlled trial. This protocol is aimed to examine the effectiveness of delivering information to family members of ICU patients through virtual reality, with the goal of reducing distress and adverse long term outcomes. In particular, the authors thoughtfully describe the stressors of being a relative of a patient in the ICU. The protocol is well written and designed, but a few minor concerns remain: • The main purpose of this study is to examine the relative effectiveness of delivering information through VR above and beyond standard information delivey. . Inferences from future results would be strengthened by describing the current standard of care to which VR is being compared. Authors should also better describe planned analyses to compare VR, home viewing, and standard care. • Authors should correct pronoun in page 8 line 60: “its relatives.” • There is a strong background in information delivery regarding procedures with VR and child life that may be useful to describe and reference. • A more thorough description of the content of the VR intervention would be helpful as well as content in the standard care.

REVIEWER	Mills, Erin Monash Health, Paediatric Emergency Department
REVIEW RETURNED	05-May-2021

GENERAL COMMENTS	Thank you for the opportunity to review your study protocol, which aims to provide an innovative, safe, relatively cheap and potentially replicable intervention to reduce the significant burden

	of PICS-F for relatives and close friends of patients with ICU admissions. I think your introduction would benefit of some reference to the incidence of PICS-F in these patient groups, and it would be interesting to know if the incidence is different in groups not allowed to physically visit ICUs due to the Covid-19 pandemic. I think the development of the VR program would benefit from consumer input - specifically asking what specific factors during a relative's ICU stay contribute to distress, and what information they would like to receive about the environment and procedures in the ICU. The consumer concerns could then be specifically addressed using the VR program. If you could clarify: are all eligible relatives and close friends invited to participate in the study? How are these people identified? Is there a maximum number of participants per patient? I have concerns around the clustering of data from multiple relatives for a single patient. It is not clear to me from the methods how this data will be managed if one relative fails to complete the study (there are many questionnaires to fill in over the 6 month period), or how individual risk factors for PICS-F such as age, gender, education, past mental health history will be addressed. I will leave this to expert statisticians for comment. There are some minor spelling mistakes and grammatical errors that would benefit from review prior to publication. Overall I feel that this is a worthwhile study and I look forward to reading the outcome.

VERSION 1 – AUTHOR RESPONSE

Response to Reviewer 1:
Dr. Emily Foxen-Craft, University of Michigan

Comments to the Author:
Thank you for the opportunity to review this protocol, Virtual reality for relatives of ICU patients to improve psychological sequelae: study protocol for a multicentre, randomized controlled trial. This protocol is aimed to examine the effectiveness of delivering information to family members of ICU patients through virtual reality, with the goal of reducing distress and adverse long term outcomes. In particular, the authors thoughtfully describe the stressors of being a relative of a patient in the ICU. The protocol is well written and designed, but a few minor concerns remain.

R: We thank the reviewer for its valuable comments.

• The main purpose of this study is to examine the relative effectiveness of delivering information through VR above and beyond standard information delivery. Inferences from future results would be strengthened by describing the current standard of care to which VR is being compared. Authors should also better describe planned analyses to compare VR, home viewing, and standard care.

R: We agree with the reviewer that we should better describe the current standard of care. We accordingly changed the manuscript:

“Standard care comprises either of 1) a family meeting with the treating ICU physician during the first week of ICU admission, and 2) bi-weekly meetings with the treating ICU physician when patients have a stay more than 14 days according to a hospital’s local protocol. Additionally, family will members will always be offered a digital/hardcopy ICU diary according to national guidelines.” (Methods, Interventions, page 7, lines 138-141)

“During ICU treatment, all relatives will receive standard care, which comprises either of 1) a family meeting with the treating ICU physician during the first week of ICU admission, and 2) bi-weekly meetings with the treating ICU physician when patients have a stay more than 14 days. Additionally, family will members will always be offered a digital/hardcopy ICU diary.” (Methods, Study procedures, page 8, lines 153-156)

To better describe how we analyze potential differences in effectiveness between VR, home viewing and standard care, we added the following:
“The main analyses will be conducted per protocol. In these, all patients who have received ICU-VR-F, either both in the hospital as at home or only at home, will be compared with those who did not, and patients of whom the relative has deceased during ICU treatment will be excluded. To determine whether there is a difference in effect between having watched ICU-VR-F the first time in the hospital and having watched the ICU-VR-F only at home, we will use a dummy variables (ICU-VR-F in the hospital and at home / ICU-VR-F only at home / no ICU-VR-F) instead of the randomization variables in the mixed effects regression models, and determine whether that dummy variable has a significant contribution to the model. We will additionally perform an analysis in which 1) patients who did not watch ICU-VR-F in the hospital will be excluded and 2) patients who watched ICU-VR in the hospital will be excluded to determine whether there is a difference in effect.” (Methods, Statistical analysis, page 12, lines 263-271)

• Authors should correct pronoun in page 8 line 60: “its relatives.”

R: We apologize for the untidiness and changed the pronoun:
“An Intensive Care Unit (ICU) admission is known to be a stressful experience for both patients and their relatives.” (Introduction, page 4, line 57)

• There is a strong background in information delivery regarding procedures with VR and child life that may be useful to describe and reference.

R: We agree and concordantly added the following to the introduction:
“Information provision using VR has shown to decrease preoperative anxiety in both adults and pediatric patients, to help women and their partner to feel better prepared for cesarean delivery, to successfully deliver healthcare related information to adults with intellectual disabilities, and to be an appropriate tool to deliver additional treatment-related information to increase patients’ satisfaction.[23-26]” (Introduction, page 5, lines 86-89)

• A more thorough description of the content of the VR intervention would be helpful as well as content in the standard care.

R: We agree with the reviewer that we should have better described this.
For the VR intervention we therefore added hyperlinks to the YouTube versions of the used ICU-VR-F films in the current study. We also added a translation of the video script. We have added the following to the Methods section:
“ The hospital specific ICU-VR-F from the Erasmus MC can be found here, from the Franciscus Gasthuis & Vlietland can be found here, and from the Ikazia hospital can be found here. The uniform video script can be found in the Supplementary Data.” (Methods, Intervention, page 7, lines 135-137)

Additionally, we better described what is meant with care as usual:
“Standard care comprises either of 1) a family meeting with the treating ICU physician during the first week of ICU admission, and 2) bi-weekly meetings with the treating ICU physician when patients have a stay more than 14 days according to a hospital’s local protocol. Additionally, family will members will always be offered a digital/hardcopy ICU diary according to national guidelines. ” (Methods, Intervention, page 7, lines 138-141)

Response to Reviewer 2:
Dr. Erin Mills, Monash Health, Monash University

Comments to the Author:
Thank you for the opportunity to review your study protocol, which aims to provide an innovative, safe, relatively cheap and potentially replicable intervention to reduce the significant burden of PICS-F for relatives and close friends of patients with ICU admissions.

R: We thank the reviewer for its valuable comments.

I think your introduction would benefit of some reference to the incidence of PICS-F in these patient groups, and it would be interesting to know if the incidence is different in groups not allowed to physically visit ICUs due to the Covid-19 pandemic.

R: We agree with the reviewer and concordantly added the following to the introduction:
“…; clinically relevant symptoms of PTSD occur in 21% of relatives of ICU patients, especially in relatives of adult patients, clinically relevant symptoms of anxiety occur in 40%, and clinically relevant symptoms of depression occur in 23%.[1-11]“ (Introduction, page 4, lines 60-62)

“Relatives of ICU COVID-19 patients are therefore confronted with the impracticableness of visiting their relative in the ICU or to receive good communication from the ICU staff, which may result in a higher psychological burden.[19 20]” (Introduction, page 4, lines 76-78)

I think the development of the VR program would benefit from consumer input - specifically asking what specific factors during a relative's ICU stay contribute to distress, and what information they would like to receive about the environment and procedures in the ICU. The consumer concerns could then be specifically addressed using the VR program.

R: We understand the comment of the reviewer and agree that input from relatives of ICU patients would be useful to further improve our intervention. In our composed questionnaire we therefore ask in the perspectives section about suggestions to improve the content of the VR module. As such family members contribute to future adaptations of the intervention for future studies. In this way the intervention will became more ‘patient (in this case relative)’ specific. We realize that we have not described this clear enough and therefore added a translation of both self-composed questionnaires (i.e., the perceived stress factors questionnaire and the perspectives on the ICU-VR-F intervention questionnaire) to the supplementary materials, and changed the following in the manuscript:
“Outcomes of these self-composed questionnaires will be used to determine different aspects of information that relatives were missing or were in need of in the current ICU-VR-F intervention. This data will be used to further improve the VR intervention and its content so it will better meet the needs of relatives. Translations of the self-composed questionnaires can be fund in the Supplementary Data.” (Methods, Outcomes and measurements, page 10, lines 208-212)

If you could clarify: are all eligible relatives and close friends invited to participate in the study? How are these people identified? Is there a maximum number of participants per patient?

R: In hindsight, we realize that we should have more thoroughly described this. We therefore added the following to the manuscript:
"Multiple relatives per patient can participate; the primary contact person of the ICU patient will be approached firstly and will be invited to share the study information with other relatives that could be interested. There is no maximum number of relatives per patients that can participate." (Methods, Study participants, page 6, lines 115-117)
"The primary contact person of the ICU patient will be approached by an investigator of the research team within 2 days after ICU admission and will be asked to share the study information with other relatives. In case that other relatives were interested in participation, their contact details were shared by the primary contact person with the investigator so informed consent could be obtained." (Methods, Study procedures, page 7, lines 143-147)

I have concerns around the clustering of data from multiple relatives for a single patient. It is not clear to me from the methods how this data will be managed if one relative fails to complete the study (there are many questionnaires to fill in over the 6 month period), or how individual risk factors for PICS-F such as age, gender, education, past mental health history will be addressed. I will leave this to expert statisticians for comment.

R: We discussed this matter with our statistician (T. Korevaar). With regard to the concerns about missing data in one of the relatives of a patient; we use mixed effects linear or logistic regression models. In these, all available data will be taken into account to determine the contribution of each independent variables to the model, and, as such, there will be accounted for missing data. With regard to the individual risk factors for PICS-F; as this is a randomized trial, it can be assumed that risk factors for PICS-F are well balanced between groups and should therefore not adjusted for. We will check whether this assumption is met and if there are any differences between groups with regard to these risk factors. We will adjust for them by adding them to the regression models as independent variables. However, the clustering of relatives does not affect this.

There are some minor spelling mistakes and grammatical errors that would benefit from review prior to publication.

R: We apologize for the untidiness and copy-edited the full manuscript.

Overall I feel that this is a worthwhile study and I look forward to reading the outcome.

R: Thank you once again.

VERSION 2 – REVIEW

REVIEWER	Foxen-Craft, Emily University of Michigan
REVIEW RETURNED	13-Aug-2021

GENERAL COMMENTS	I commend the authors on sufficiently addressing concerns of reviewers, especially to include videos of the educational material. I would recommend accepting pending minor grammatical revisions; specifically, I suggest the authors' change language

	throughout regarding "comparing participants" to "comparing responses/outcomes from participants" or some variation thereof.

REVIEWER	Mills, Erin Monash Health, Paediatric Emergency Department
REVIEW RETURNED	29-Jul-2021

GENERAL COMMENTS	Thank you for the opportunity to review this revised manuscript. The revisions you have made clarify the incidence of PICS-F, and highlight that it is a significant issue for relatives of ICU patients that has not been improved with any previously trialled practical and clinical meaningful interventions. Your significant revisions to the Methods and Analysis clarify my previous questions about identification and inclusion of study participants, as well as data management. There are a couple of minor grammatical errors remaining, and lines 149-152 are repeated again on lines 165-168 which requires minor editing. Overall I think this is an interesting and novel study that has potential to improve the experience for relatives of ICU patients. I look forward to reading the results.