PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The effect of Intensive Care Unit-specific Virtual Reality (ICU-VR) to improve psychological well-being in ICU survivors: study protocol for an international, multicentre, randomised controlled trial - the HORIZON-IC study
AUTHORS	Van Genderen, Michel; Vlake, Johan; van Bommel, Jasper; Wils, Evert-Jan; Korevaar, Tim; Taccone, Fabio; Schut, Anna; Elderman, Jan; Labout, Joost; Raben, Adrienne; Dijkstra, Annemieke; Achterberg, Sefanja; Jurriens, Amber; Van Mol, Margo; Gommers, Diederik

VERSION 1 – REVIEW

REVIEWER	Wacker, David Department of Internal Medicine, University of Minnesota Medical School, Division of Pulmonary, Allergy, Critical Care and Sleep Medicine
REVIEW RETURNED	25-Apr-2022

GENERAL COMMENTS	Thank you for the opportunity to review this manuscript. In it, the authors present a relevant and well-thought-out study to utilize the emerging technology of virtual reality (VR) to address the important problem of post-ICU cognitive syndrome, for which few effective therapies currently exist. Overall the protocol presented is thorough, well-reasoned, and all relevant portions of the SPIRIT checklist are addressed. The methodology including patient inclusion and recruitment, intervention, measurements and outcomes, and analysis plan all seem sound. I only have minor suggestions: 1. The authors refer to the use of VR in their study as “ICU-VR”, but it seems that participants only undergo VR after their ICU course has concluded. A more accurate term for this then may be “post ICU-VR” or “ICU survivor-VR” to differentiate from other studies in which patients undergo VR while still in the ICU. 2. It would be helpful to the reader to have more information about the participating sites listed in the Study design and setting section. For example, are these academic or community sites? How large are the ICUs? Are they general ICUs or specialty ICUs (e.g. medical, surgical, cardiac, etc.)? 3. In the Study Procedures section, the authors state that the telephone interview for cognitive status (TICS) will be performed after informed consent is obtained (line 138); however the TICS appears to be part of the inclusion/exclusion criteria. Is it the author’s intention to consent subjects prior to completion of inclusion/exclusion screening? While some protocols require this, it is not the convention, and more explanation should be provided

	about this process. 4. In line 146, the authors refer to the subject's discharge. From the context it seems they are referring to hospital discharge (as opposed to ICU discharge) but it would be more clear if this were directly stated. 5. In their discussion of the cost-benefit analysis in the Outcomes and Measurements section (lines 191-194), the authors do not include the costs of the VR equipment or production of the VR content in their analysis. This should be commented on further; are these costs simply negligible relative to the other costs the authors list?

REVIEWER	Bounes, Fanny Département d'Anesthésie et de Réanimation, Centre Hospitalier et Universitaire de Toulouse
REVIEW RETURNED	08-May-2022

GENERAL COMMENTS	The authors propose the writing of a research protocol that is clear to understand and quite complete. Nevertheless I have two very minor points to clarify please. 1.Can you detail the possible adverse effects related to the technique. 2. Can you specify which scale you use for the evaluation of delirium. Thank you very much.

VERSION 1 – AUTHOR RESPONSE

RESPONSES TO THE REVIEWERS:
Response to Reviewer 1
Dr. David Wacker, Department of Internal Medicine, University of Minnesota Medical School

Comments to the Author:
Thank you for the opportunity to review this manuscript. In it, the authors present a relevant and well-thought-out study to utilize the emerging technology of virtual reality (VR) to address the important problem of post-ICU cognitive syndrome, for which few effective therapies currently exist. Overall the protocol presented is thorough, well-reasoned, and all relevant portions of the SPIRIT checklist are addressed. The methodology including patient inclusion and recruitment, intervention, measurements and outcomes, and analysis plan all seem sound. I only have minor suggestions:

Response:
We would like to thank dr. David Wacker for reviewing our manuscript and for his valuable comments. Based on your comments, we revised our manuscript and truly believe that addressing these comments further improved the quality of the manuscript. The point-to-point responses to your comments can be found below.

1. The authors refer to the use of VR in their study as "ICU-VR", but it seems that participants only undergo VR after their ICU course has concluded. A more accurate term for this then may be "post ICU-VR" or "ICU survivor-VR" to differentiate from other studies in which patients undergo VR while still in the ICU.

Response:
We truly grasp your comment. Because we have chosen this terminology in our previous publications (Vlake et al. Front Med. 2021;5(7):629086; Vlake et al. Trials. 2021;22(1):328; Vlake et al. Crit Care Explor. 2021;3(5):e0388; Vlake et al. Crit Care Explor. 2021;3(9):e0538; Vlake et al. BMJ Open. 2021;11(9):e049704; Vlake et al. J Med Internet Res. 2022;24(1):e32368), we continued this terminology in the current paper. We however agree that we should better emphasize that ICU-VR is indeed used after ICU. To better clarify we added post-ICU patients as following to the manuscript:
"… that an ICU-specific Virtual Reality intervention for post-ICU patients (ICU-VR) is feasible …" (Abstract, page 3, line 34-35)
"… to assess the effect of an ICU-specific Virtual Reality intervention for post-ICU patients (ICU-VR) on …" (Introduction, page 7, lines 93-94)
"The ICU-specific Virtual Reality intervention for post-ICU patients (ICU-VR) is based on…" (Methods and analysis, Intervention, page 10, line 133)

2. It would be helpful to the reader to have more information about the participating sites listed in the Study design and setting section. For example, are these academic or community sites? How large are the ICUs? Are they general ICUs or specialty ICUs (e.g. medical, surgical, cardiac, etc.)?

Response:
We agree that we should have added this information. We therefore added the following information to the new Table 1 (Methods and Analysis, Study design and setting, page 8-9, lines 113).

3. In the Study Procedures section, the authors state that the telephone interview for cognitive status (TICS) will be performed after informed consent is obtained (line 138); however the TICS appears to be part of the inclusion/exclusion criteria. Is it the author's intention to consent subjects prior to completion of inclusion/exclusion screening? While some protocols require this, it is not the convention, and more explanation should be provided about this process.

Response:
We agree that we should clarify. A cognitive functioning is assessed using the TICS questionnaire, as part of a study-related procedure. Therefore we cannot perform the TICS without prior patient consent and perform TICS directly after informed consent. Patients with a TICS < 27 are excluded and will not be randomized.
We now describe this process more thoroughly in the subheading ´Study participants´:
"Because the TICS is part of the study procedures, this will be assessed after inclusion and written informed-consent. Patients with a TICS score ≤27 will be excluded after inclusion." (Methods and Analysis, Study participants, page 10, lines 122-124)
"After obtaining informed-consent and the TICS assessment, patients will receive…" (Methods, Study procedures, page 11, line 147)

4. In line 146, the authors refer to the subject's discharge. From the context it seems they are referring to hospital discharge (as opposed to ICU discharge) but it would be more clear if this were directly stated.

Response:
We agree and changed accordingly:
"…, unless the patient is discharged from the hospital ward sooner." (Methods and Analysis, Study procedures, Page 11, line 155-156)

5. In their discussion of the cost-benefit analysis in the Outcomes and Measurements section (lines 191-194), the authors do not include the costs of the VR equipment or production of the VR content in their analysis. This should be commented on further; are these costs simply negligible relative to the

other costs the authors list?

Response:
We apologize for this untidiness. To explain, we will determine which costs are made at the end of the study and include those in the exploration of the cost-benefit ratio. We now describe this more clearly:
"…costs will be expressed as, among others, development costs for ICU-VR, employments costs of ICU nurses offering the intervention and the employment and organizational costs of the ICU follow-up clinic …" (Methods and analysis, Outcomes and measurements, page 15, lines 201-203)

Response to Reviewer 2:
Dr. Fanny Bounes, Département d'Anesthésie et de Réanimation, Centre Hospitalier et Universitaire de Toulouse

Comments to the Author:
The authors propose the writing of a research protocol that is clear to understand and quite complete. Nevertheless I have two very minor points to clarify please.
1.Can you detail the possible adverse effects related to the technique.

Response:
Dear Dr. Fanny Bounes, many thanks for taking the time to review our manuscript and for your valuable comments. We agree that some additional information about the adverse events of VR might benefit the reader. We therefore added the following to the manuscript:
"… due to side effects in terms of cybersickness, mainly experienced as nausea.27 28" (Methods and Analysis, Outcomes and measurements, page 15, lines 200-201)

2. Can you specify which scale you use for the evaluation of delirium.

Response:
We agree that we should clarify. Based on our previous studies, we continued the same definition for scoring new or active delirium. We defined this is as the mentioning of a delirium in the daily status report or as the new administration of haloperidol. We changed accordingly:
"… (defined as mentioning of a delirium in the daily status report of the treating physician or new administration of haloperidol),…." (Methods and analysis, Study participants, page 10, lines 120-121)

We also added the following to the Methods and analysis, Outcomes and measurements subheading:
"… episodes of sedative coma and delirium during ICU treatment, assessed using the Richmond Agitation Sedation Scale (RASS) and the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) scale, respectively …" (Methods and analysis, Outcomes and measurements, page 15-16, lines 208-210)

VERSION 2 – REVIEW

REVIEWER	Wacker, David Department of Internal Medicine, University of Minnesota Medical School, Division of Pulmonary, Allergy, Critical Care and Sleep Medicine
REVIEW RETURNED	27-Jun-2022

GENERAL COMMENTS	I thank the authors for addressing my concerns. I believe the manuscript is now ready for publication and I wish the authors good luck for completion of the study.