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The effect of Intensive Care Unit-specific Virtual Reality (ICU-VR) to improve psychological well-being in ICU survivors: study protocol for a multicentre, randomised controlled trial - the HORIZON-IC study

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Keywords:	Adult intensive & critical care < ANAESTHETICS, INTENSIVE & CRITICAL CARE, Adult intensive & critical care < INTENSIVE & CRITICAL CARE

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1 The effect of Intensive Care Unit-specific Virtual Reality (ICU-VR) to 2 improve psychological well-being in ICU survivors: study protocol for a 3 multicentre, randomised controlled trial - the HORIZON-IC study

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ABSTRACT

Introduction A substantial proportion of Intensive Care Unit (ICU) survivors develops psychological impairments after ICU treatment, part of the Post-Intensive Care Syndrome (PICS), resulting in a decreased quality of life. Recent data suggest that ICU-specific Virtual Reality (ICU-VR) is feasible and safe, improves satisfaction with ICU aftercare, and might improve psychological sequelae. In the present trial, we firstly aim to determine whether ICU-VR is effective in mitigating posttraumatic stress disorder (PTSD)-related symptoms and secondly aim to determine the optimal timing for initiation with ICU-VR.

Methods and analysis This multicentre, randomized controlled trial will be conducted in nine hospitals in the Netherlands. Between December 2021 and October 2022, we aim to include 300 patients who have been admitted to the ICU ≥72 hours and were mechanically ventilated ≥24 hours. Patients will be followed for 12 consecutive months. Patients will be randomized in a 1:1:1 ratio to either the early ICU-VR group, the late ICU-VR group, or the usual care group. Patients in the early ICU-VR group will receive ICU-VR within two weeks after ICU discharge. All patients will receive usual care, including a mandatory ICU follow-up clinic visit three months after ICU discharge, during which patients in the late ICU-VR group will receive ICU-VR. The primary objective is to assess the effect of ICU-VR on PTSD-related symptoms. Secondary objectives are to determine optimal timing for initiation with ICU-VR, to assess the effects of ICU-VR on anxiety- and depression-related symptoms and health-related quality of life, and to assess patient satisfaction with ICU aftercare and their perspectives on ICU-VR.

Ethics and dissemination The Medical Ethics Committee United (MEC-U), Nieuwegein, the Netherlands, approved this study, and local approval was obtained from each participating centre

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(NL78555.100.21). Our findings will be disseminated by presentation of the results at (inter)national conferences and publication in scientific, peer-reviewed journals.

Trial registration number This trial has been prospectively registered on the Netherlands Trial Register (TrialRegister.nl, NL9812, registered October 21, 2021).

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53 **Strengths and limitations of this study**

54 • A randomised controlled trial examining the effect of Intensive Care Unit-specific Virtual Reality
55 (ICU-VR) on psychological well-being and health-related quality of life after ICU treatment.

56 • ICU-VR is easy applicable and safe and enables patients to be auditorily and visually exposed to
57 the ICU environment traumatizing them while receiving treatment-related information. However, the
58 optimal timing of ICU-VR after critical illness is unknown.

59 • Follow-up until 12 months after ICU discharge enables us to study long-term effects.

60 • Blinding of patients or investigators is not possible due to the nature of the intervention.

61 • ICU-VR content is hospital-specific to expose patients to the actual ICU environment, but it limits
62 the possibility of easily implementing the intervention in other hospitals.

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INTRODUCTION

Because of improved survival after Intensive Care unit (ICU) treatment, a new challenge arises.[1,2]. A substantial proportion of ICU survivors suffer from psychological impairments, such as post-traumatic stress disorder (PTSD), anxiety, and depression.[3,4,5] Along with cognitive and psychical impairments, these sequelae are referred to as the Post-Intensive Care Syndrome (PICS). PICS is common, can last for years after ICU discharge, and has a profound impact on daily functioning and quality of life.[6,7,8]

Prevention and treatment of PICS has been recognized as a fundamental part of ICU care by the critical care community and recently it was demonstrated that the psychological component of PICS is the most important determinant of a decreased health related quality of life (HRQoL) and impede a patients ability to rehabilitate.[9,10,11] Although several interventions have been explored, such as keeping ICU diaries, organizing ICU follow-up clinics, and offering psychosocial support, studies on their effectiveness in terms of psychological distress or quality of life have yielded unsatisfactory and ambiguous results.[10,12-17] As such, evidence based interventions to improve psychological recovery and health-related quality of life (HRQoL) are lacking.

Post-ICU psychological impairments may be caused by amnesia during the early period of critical illness in combination with sensory overload and sensory deprivation. Amnesia can lead to loss of factual recall of their ICU stay and patients can instead create delusional and frightening memories.[18] Moreover, the typical ICU-environment is characterized by unpatterned exposure and frequent sensory input such as light, noise, and tracheal tube aspiration. The exposure to these extremes initiates the development of PTSD and anxiety.[19] We hypothesized that exposure to the factual ICU environment, and additionally

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receiving ICU-related treatment information could enhance ICU treatment understanding, decrease delusional memories, and may reduce psychological impairments.[20 21]

Virtual Reality (VR) allows users to fully immerse within a computer-generated three-dimensional environment. In psychiatry, exposure therapy using VR has been proven effective for the treatment of PTSD and anxiety and thereby it addresses limitations of imaginal exposure.[22-26] Also, VR can effectively and easily be used to deliver information to patients. VR could thus be a valuable adjunct to safely inform and expose post-ICU patients to the environment traumatizing them and could enhance psychological recovery.[27 28] In the current study, our primary aim is to assess the effect of ICU-VR on PTSD-related symptoms. Secondly, we want to determine optimal timing for initiation with ICU-VR, to assess the effects of ICU-VR on anxiety- and depression-related symptoms, and to assess patient satisfaction with ICU aftercare and their perspectives on ICU-VR.

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3 94 **METHODS AND ANALYSIS**
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6 95 **Study design and setting**
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9 96 A multicentre, randomized controlled trial will be conducted in mixed medical-surgical ICUs of eight
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12 97 hospitals in the Netherlands; Erasmus Medical Centre (university hospital), Franciscus Gasthuis &
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15 98 Vlietland hospital, Maasstad hospital, Ikazia hospital, IJsseland hospital, Groene Hart hospital, Van
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18 99 Weel-Bethesda hospital, Haaglanden Medical Centre, and the Albert Schweitzer hospital. The Medical
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21 100 Ethics Committee United (MEC-U), Nieuwegein, the Netherlands, approved this study
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24 101 (NL78555.100.21, approved October 25, 2021), and local approval was obtained from the institutional
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27 102 ethic review boards of each participating hospital. Inclusion will be conducted from December 2021 to
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30 103 October 2022, and patients will be followed for 12 months after ICU discharge. Any modifications to the
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33 104 study protocol, which may affect the conduct of the study or patient safety, including changes of the
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36 105 study objectives, study design, study population, sample size, study procedures or significant
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39 106 administrative aspects, will be sent for approval to the MEC-U and the institutional ethic review boards.
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42 107 Health authorities will be informed in accordance with local regulations.
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45 108 **Study participants**
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48 109 We aim to include at least 300 patients. Patients admitted to the ICU for ≥72 hours, during which
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51 110 mechanically ventilated ≥24 hours, older than 17 years of age, and able to understand the Dutch
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54 111 language are eligible for inclusion. Patients admitted to the ICU with primary neurological impairment or
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57 112 with a life expectancy <48 hours or receiving palliative care, with documented active, established
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60 113 psychiatric disorders, a decreased cognitive function during inclusion (a telephone interview for cognitive

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status (TICS) score ≤26), with an active delirium during inclusion, or without a formal home address will be excluded.

Randomization and masking

Patients will be randomized in a 1:1:1 ratio to either the early ICU-VR group, the late ICU-VR group, or the usual care group. Randomization will be according to a 1:1:1 ratio, stratified for study site, using a centralized internet-based randomization procedure (Castor EDC, Amsterdam, The Netherlands). Due to the nature of the intervention, blinding of patients is not possible. Randomization allocation will be coded in analysis with "0" and "1", and the analysist will as such be unaware of the randomization allocation.

Intervention

ICU-VR is based on an uniform script that is designed by an interdisciplinary team and based on the several focus group meetings of this team. The content of the script is extensively described elsewhere and the content can be found in **Supplementary Data File 1**.[27 28] We also designed a movie directors script to produce uniform ICU-VR movie in each participating centre.[27 28] The ICU-VR was produced for each centre so it was hospital specific and so that patients were immersed into the environment that they were treated in. ICU-VR was designed with the aim to deliver relevant and truthful information regarding ICU stay and ICU treatment. The point of view for the camera is the field of vision of the mock patient lying in an ICU bed. ICU-VR will be watched using head-mounted display VR (Pico G2 VR All-In-One Headset) and a headset.

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133 **Study procedures**

134 An oversight of the study procedures is presented in **Figure 1**. Patients who are eligible for inclusion will
135 be approached by an investigator of the research team or by a dedicated research nurse within 7 days
136 after ICU discharge. A translation of the information for patients and the informed consent form can be
137 found in **Supplementary Data File 2**.

138 Once informed consent is obtained, the TICS will be used to screen patient cognitive status. Patients
139 will receive the first set of questionnaires (T0) directly after inclusion, consisting of a self-composed
140 questionnaire regarding demographics and their history of mental health, the Impact of Event Scale-
141 Revised (IES-R), the Hospital Anxiety and Depression Scale (HADS), the European Quality of life 5
142 dimensions (EQ-5D), and the short-form 36 (SF-36) (**Table 1**). Patients are asked to fill in the HADS,
143 EQ-5D and SF-36 both prospectively and retrospectively in order to obtain a measure of patient anxiety
144 and depression levels and quality of life both at that moment and prior to the most recent ICU admission.

145 Patients randomized to the early ICU-VR group will receive ICU-VR between day 8 and day 15 after
146 ICU discharge for a maximum of three times, unless the patient is discharged sooner. The number of
147 times ICU-VR is offered and accepted will be logged. Three months after ICU discharge, all patients will
148 visit the post-ICU follow-up clinic of the concurrent hospital. During this ICU follow-up visit, patients have
149 a consult with a dedicated ICU nurse and an intensivist. Patients randomized to the late ICU-VR group
150 will receive ICU-VR once during their concurrent post-ICU follow-up clinic visit.

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All patients will receive follow-up questionnaires at 1 month (T1), 3 months (T2), 6 months (T3), and 12 months (T4) after ICU discharge (**Table 1**).

Table 1. Questionnaires per follow-up time point.

Questionnaire:	**T0.** Inclusion	**T1.** 1 month after ICU discharge	**T2.** 3 months after ICU discharge	**T3.** 6 months after ICU discharge	**T4.** 12 months after ICU discharge
Demographics	X	X	X	X	X
Work resumption & financial decline		X	X	X	X
History of mental illness	X				
IES-R (Post-Traumatic Stress Disorder)	X	X	X	X	X
HADS (Anxiety and Depression)	X (retro- & prospectively)	X	X	X	X
SF-36 Quality of Life	X (retro- & prospectively)	X	X	X	X
EQ-5D Quality of life	X (retro- & prospectively)	X	X	X	X
Satisfaction with ICU care				X	
Perspectives on ICU-VR		X		X (late ICU-VR)	

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	(early ICU-VR)			
Visit to healthcare professionals	X	X	X	X

Abbreviations: EQ-5D, 5-level European Quality of life questionnaire; HADS, hospital anxiety and depression scale; ICU, intensive care unit; ICU, intensive care unit; ICU-VR, intensive care unit-specific virtual reality; IES-R, impact of event scale-revised; SF-36; short-form 36.

153

154 **Outcomes and measurements**

155 The primary outcome is the effect of ICU-VR on the severity of PTSD-related symptoms at six months
156 after ICU discharge.

157 The severity of PTSD-related symptoms will be expressed as the sum score of the IES-R and an IES-R
158 sum score ≥ 24 will be considered as clinically relevant PTSD.[29] The IES-R comprises 22 items,
159 assessing subjective distress caused by traumatic events, and has been used commonly in survivors of
160 critical illness.[30-32] The IES-R yields a total score (ranging from 0 to 88; higher scores indicate more
161 severe symptoms) and subscale scores can be calculated for symptoms of intrusion, avoidance, and
162 hyper arousal.

163 Secondary outcomes are the effects of ICU-VR on the severity and prevalence of PTSD-, anxiety-, and
164 depression-related symptoms and on HRQoL at each follow-up endpoint and on their courses
165 throughout follow-up, the patient satisfaction with ICU aftercare and patient perspectives on ICU-VR.

166 The severity of anxiety- and depression-related symptoms will be expressed as the HADS anxiety and
167 depression scores, and a HADS anxiety or depression score ≥8 will be considered as clinically relevant

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168 anxiety and depression, respectively. The HADS comprises of 14 items and is commonly used to
169 determine the levels of anxiety and depression. Seven of the items relate to anxiety and seven relate to
170 depression.[33-37]

171 HRQoL will be expressed as the overall HRQoL, which implies the time trade-of (TTO) score of the 5-
172 level EQ-5D, and the mental HRQoL, which implies the mental component score of the SF-36. The EQ-
173 5D measures HRQoL in five dimensions, i.e., mobility, self-care, usual activities, pain/discomfort, and
174 anxiety/depression.[38] By giving a certain weight to each answer option, the country-specific TTO score
175 can be calculated, ranging from -0.446 (worst quality of life) to 1.000 (best quality of life).[39] Also, patients
176 score their subjective health state on a visual analogue scale (EQ-VAS), ranging from 0 (worst health
177 imaginable) to 100 (best health imaginable). The SF-36 consists of 36 items, from which 8 scaled scores
178 can be calculated. These scores are the weighted sums of the questions in their section. Each scale is
179 directly transformed to a scale ranging from 0 to 100 on the assumption that each question carries an
180 equal weight. The 8 sections are vitality, physical functioning, bodily pain, general health perception,
181 physical role functioning, emotional role functioning, social role functioning and mental health.[40 41] In
182 addition, a mental- and physical component scale, the MSC-36 and PCS-36, respectively, can be
183 calculated as a reflection of physical and mental health.[40-42]

184 Patient satisfaction with ICU aftercare will be assessed using a novel questionnaire, based on the
185 Patient Satisfaction Questionnaire and Family Satisfaction with ICU Care tools, altered to the needs of
186 this study.[43 44] Additional novel items were added to evaluate patient perspectives on the ICU-VR
187 intervention.

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We will additionally explore feasibility and safety outcomes, and explore the cost-benefit ratio of ICU-VR. Feasibility will be expressed as the number of sessions patients in the early ICU-VR group will receive. Safety will be expressed as the number of ICU-VR sessions requiring interruption or termination due to side effects. For the cost-benefit ratio, costs will be expressed as employments costs of ICU nurses offering the intervention and the employment and organizational costs of the ICU follow-up clinic and benefits will be expressed as the gain in quality adjusted life years (QALYs) determined as the EQ-5D TTO score.

Demographics, such as age, gender, body weight, length, pre-existing comorbidities, previous ICU admissions, and ICU readmissions, treatment-related characteristics, such as type of admission, ICU- and hospital length of stay, mechanical ventilation-related characteristics, episodes of sedative coma and delirium during ICU treatment, use of renal replacement therapy, infections and illness severity scores during ICU treatment, and 3-, 6-, and 12-month mortality will be assessed using electronic patient records. Additionally, patients will be asked about their educational level, employment status prior to and after ICU treatment, financial decrease after ICU treatment, consultations with healthcare professionals, and their history of mental health in follow-up questionnaires.

Data management

Data will be uploaded, stored, and maintained using the electronic data capture (EDC) system of Castor (Castor EDC, www.castoredc.com, Amsterdam, the Netherlands). The study team will be responsible for data entry and quality control activities. Data will be checked by at least two persons from the study team and will be stored for at least 15 years on either the Castor EDC server or as a hardcopy in the

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208 ICU of the participating hospitals. Questionnaires will be sent digitally using Castor EDC or via hardcopy
209 via postal mail whenever requested.
210 To maintain anonymity, data will be coded with a number and this number will be the only reference to
211 patient identification. The principal investigator is the only one in possession of the translation key,
212 making it impossible to link data to the patient.

213 **Sample size calculation**

214 Based on two previous studies yielding an ICU-VR Cohen's *d* effect estimate of 0.56 (late intervention)
215 to 0.88 (early intervention), the power calculation of the current study is based on a Cohen's d of 0.56.[27]
216 [45] We performed a G*Power analysis based on the Wilcoxon Mann Whitney test, with no expectation
217 about the underlying distribution of the outcome (parental distribution: "min ARE"). Using a two-sided
218 alpha of 0.05, a power of 0.80, and a 1:1 allocation ratio, this resulted in a required sample size per
219 group of 60 patients.[46] We will use this required sample size for all three groups, resulting in a total
220 sample size of 180 patients. We anticipated a loss to follow-up rate of 40% for which we will anticipate
221 in the current trial. We therefore aim to include a total of (3 * 60 / 0.60 =) 300 patients, with 100 patients
222 per group.

223 **Statistical analysis**

224 All continuous data will be presented as medians (95% range). Categorical variables will be presented
225 as absolute and relative frequency. Baseline demographics, treatment-related characteristics, and
226 patient perspectives on ICU-VR will be summarized using descriptive statistics. Outcomes of mixed
227 effects linear and logistic regression models will be presented as the coefficient of the model, which

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implies the estimated mean difference between groups, including its 95% confidence interval, as the log of coefficient of the model, i.e., the odds ratio, including its 95% confidence interval, respectively.

To analyze the effect of ICU-VR on the severity of PTSD-, anxiety-, and depression related symptoms, on HRQoL, and on the prevalence of clinically relevant PTSD, anxiety, and depression at each follow-up time-point, we will use mixed effects linear (for continuous outcomes) or logistic (for categorical outcomes) regression models. In these, the outcome at each follow-up time-point will serve as dependent variable, the randomization group, the retrospectively assessed pre-existent score/prevalence of the outcome of interest, and a random intercept and/or slope for each study site will be used. The effect of ICU-VR on the course of 1) the severity of PTSD, anxiety-, and depression-related symptoms, 2) HRQoL, and 3) the prevalence of clinically relevant PTSD, anxiety, and depression throughout follow-up, will be analyzed using mixed effects linear (for continuous outcomes) and logistic (for categorical outcomes) regression models, in which the outcome/prevalence of interest of all follow-up time-points will be used as dependent variable, the randomization allocation, time, the retrospectively assessed pre-existent score/prevalence of interest will serve as independent variables, and a random intercept and/or slope for each study site will be used.

To determine when ICU-VR is most effective, i.e. early vs late, differences in psychological distress and HRQoL between the early ICU-VR group and late ICU-VR groups at 6 and 12 months will be assessed. We will analyze these using mixed effects linear and logistic regression models. In these models, the score/prevalence of interest at either 6 months or 12 months after ICU discharge will be used as dependent variable, the randomization allocation, the retrospectively assessed pre-existent

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score/prevalence of the outcome of interest, and, if applicable will serve as independent variables, and a random intercept and/or slope for each study site will be used. Differences in the course of the severity and prevalence of psychological distress and HRQoL between 6 and 12 months, will be assessed using mixed effects linear and logistic regression models, in which the outcomes at 6 and 12 months will simultaneously be used as dependent variable, and time after discharge in months, randomization allocation (early ICU-VR / late ICU-VR), the interaction between randomization and time (randomization * time), the pre-existent score of the outcome of interest will serve as independent variables, and a random intercept and/or slope for each patient and each study site will be used.

We will analyze differences in the subscales of the SF-36, patient resumption to work, experienced financial decline and consultation with healthcare professionals using the abovementioned manners.

The main analysis will be an intention-to-treat analysis, in which all included patients will be included. Secondly, we will perform a per-protocol analysis, in which patients are included if 1) they are randomized to the control group, 2) they are randomized to the early ICU-VR group and received ICU-VR three times in the hospital ward, and 3) they are randomized in the late ICU-VR group and received ICU-VR once during the ICU follow-up clinic visit. Thereafter, we will conduct a complete case analysis, in which all patients who have completed all assessment are included.

We will conduct the sub analyses in 1) patients who have been mechanically ventilated ≥ 72 hours, 2) patients who have been mechanically ventilated > 7 days , 3) patients who have been treated in the ICU for > 7 days, 4) patients who have been treated in the ICU for > 14 days, 5) patients who had a delirium,

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6 268 combined), 7) sepsis patients, to compare these results with our previously conducted pilot study
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10 269 If the loss to follow-up at six months after ICU discharge will be higher than anticipated, we will impute
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13 270 missing data using both the last observation carried forward method and multiple imputation according
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16 271 to the Markov-chain Monte-Carlo.[47]
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19 272 All data will be gathered using Castor EDC (Castor EDC, Amsterdam, the Netherlands). All analyses
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22 273 will be performed using SPSS (IBM SPSS Statistics for Windows, Version 27.0; IBM Corporation,
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25 274 Armonk, New York) and R for Statistics (R Foundation for Statistical Computing, Vienna, Austria, 2015).
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28 275 A p-value of ≤0.05 will be considered statistically significant.
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32 276 **Ethics and dissemination**
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35 277 This study will be conducted in accordance with the principles of the declaration of Helsinki (version
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38 278 October 2013; www.wma.net) and in accordance with the Medical Research involving human subjects
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41 279 act (WMO) and other guidelines, regulations, and acts. We received approval from the Medical
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44 280 Research Ethics Committees United (MEC-U, Nieuwegein) and local approval has been obtained from
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47 281 the institutional ethic review boards of each participating hospital. If deviation from the protocol is
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50 282 necessary, it will not be implemented without the prior review and approval of the MEC-U and each
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53 283 participating hospital's institutional ethic review board. Signed informed consent will be obtained from
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56 284 all patients prior to any study procedure. Previous research demonstrated that (ICU-)VR is safe, feasible,
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59 285 and well accepted.[26-28 48] Informed-consent forms will be kept in a locked cabinet in a limited-access
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room in the ICU of the participating study sites. Data will be archived for 15 years. The handling of personal data complies with the Dutch Law. On completion of the study, its findings will be published in peer-reviewed journals and presented at the national and internationals scientific conferences to publicize the research to healthcare professionals, health services authorities, and the public. A summary of results will be made available to the study patients if requested.

Patient and public involvement statement

Former ICU patients were involved in the development of the ICU-VR intervention. Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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294 ## Figures

295 **Figure 1. Flow-diagram of the study.**

296 ICU, Intensive Care Unit; ICU-LOS, ICU length of stay; ICU-VR, ICU-specific Virtual Reality;

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297 ## Declarations

298 **Authors' contributions**

299 J.V., J.v.B., E.W., M.v.M., D.G., and M.v.G. conceived the study and initiated the study design. M.v.G.
300 is the coordinating investigator and grant holder. D.G. is the principal investigator. T.K. provided
301 statistical expertise in the clinical trial design, and J.V. and T.K. wrote the statistical analysis plan. M.v.M.
302 provided expertise in the field of psychology, and J.V. and M.v.M. determined what questionnaires are
303 used. J.v.B., E.W., A.S., J.L., J.E., A.R., A.D., and S.A. are the local principal investigators at each study
304 site. All authors contributed to the refinement of the study protocol and approved the study protocol. J.V.
305 and A.J. wrote the first draft of the manuscript, J.v.B., E.W., T.K., E.K., M.v.M., D.G., M.v.G. helped to
306 further draft the manuscript. J.V. and A.J. will be responsible for data collection. All authors approved
307 the final version of the manuscript.

308 **Funding statement**

309 This study was supported by DSW (for the HORIZON-IC project; no grant number available), Stichting
310 Theia (grant number: 2020286), Stichting SGS (grant number: 2020355), and BeterKeten (for the
311 HORIZON-IC project; no grant number available). The funding sources had no role in the design of the
312 study and collection, analysis, and interpretation of data nor in writing the manuscript.

313 **Competing interests statement**

314 The authors declare that they have no conflicting or competing interests to disclose.

315 **Data Sharing statement**

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316 The de-identified individual clinical trial patient-level data will be shared as supplementary material when

317 publishing about the findings of the study.

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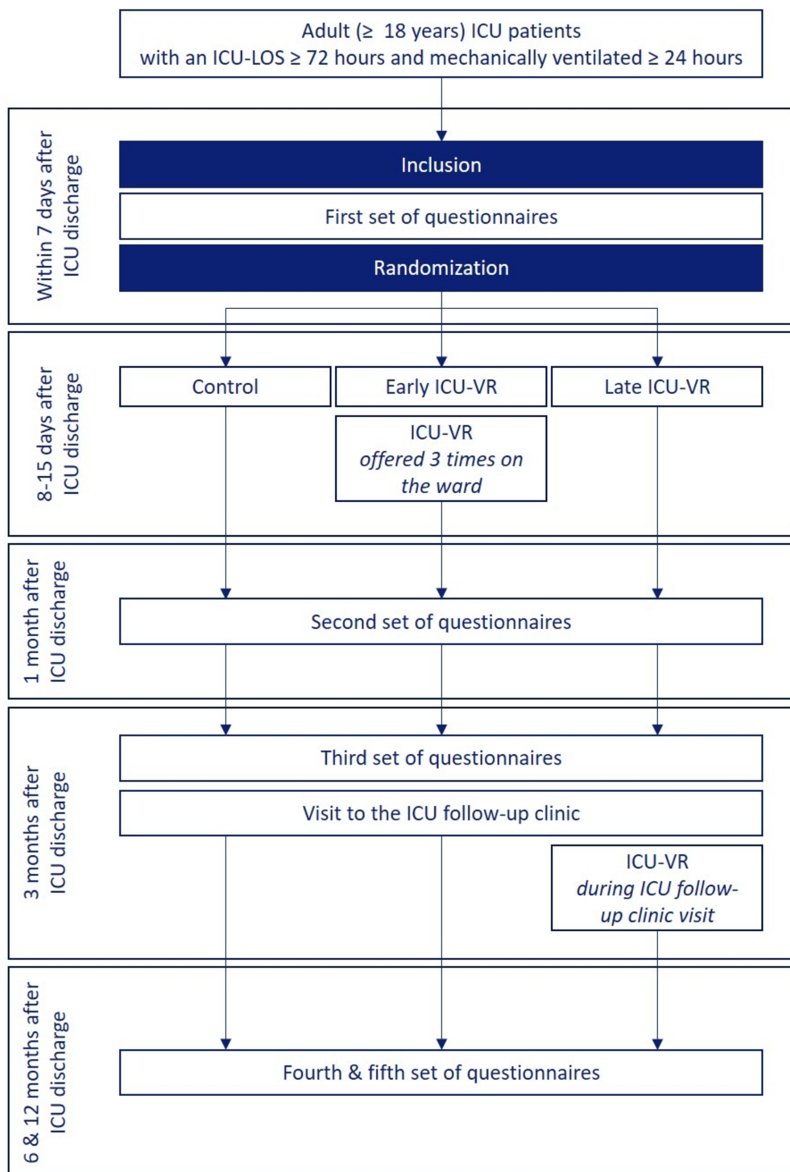

Figure 1. Flow-diagram of the study.
ICU, Intensive Care Unit; ICU-LOS, ICU length of stay; ICU-VR, ICU-specific Virtual Reality.

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Supplementary File 1.

Translation of the video script of ICU-VR

Supplement to:

Johan H. Vlake, Jasper van Bommel, Evert-Jan Wils, Tim I.M. Korevaar, Eva Klijn, Anna F.C. Schut, Jan H. Elderman, Joost A.M. Labout, Adrienne Raben, Annemieke Dijkstra, Stefanja Achterberg, Amber L. Jurriens, Margo M.M.C. van Mol, Diederik Gommers, Michel E. van Genderen.

The effect of Intensive Care Unit-specific Virtual Reality (ICU-VR) to improve psychological well-being in ICU survivors: study protocol for a multicentre, randomised controlled trial - the HORIZON-IC study

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Scene 1. Introduction by an ICU physician and a nurse and tour around the ICU guided by a voice-over.

Setting: The ICU physician and nurse are placed in front of the ICU.

ICU physician: Hello, welcome to this virtual environment. My name is **'name physician'**, one of the physicians in this ICU.

ICU nurse: Hello, I am **'name nurse'**, one of the nurses in this ICU.

ICU physician: You were recently treated in the ICU. In this virtual environment, we provide you with explanations about the ICU and about the treatment you received here.

ICU nurse: Together, we will join you during this virtual reality experience. Therefore, we will first lay you down on an ICU bed, and then bring you to your ICU room.

Setting: The patient will be virtually installed on an ICU bed during a fade in-fade out.

ICU nurse: We will now bring you to your ICU room.

Setting: The ICU physician and ICU nurse will bring the patient to one of the ICU rooms while walking over the intensive care department.

Voice-over: Intensive care means intensive and special care for critically ill patients, where the most important vital functions, such as the respiratory rate, oxygen saturation and heart rate, can be monitored and supported, if needed. Therefore, this department is different from other departments. If you look around, you'll see the intensive care department. The intensive care department consists of several one-patient ICU rooms and a post for nurses located in the middle of the department. In an ICU room, circumstances and materials are available to offer critically ill patients the optimal treatment. Moreover, the chances of hospital acquired infections and medication failures are minimal, and a quiet environment is provided. At the nurse post, nurses are present throughout the day, as are monitors. As such, nurses can monitor you 24 hours per day. Nurses can also monitor patients physically through the windows of the room, which allows nurses to be able to continuously keep an eye on you.

Setting: The patient arrives at the ICU room, and the ICU physician and ICU nurse place the patient on the bed in the ICU room.

ICU physician: We are now entering an ICU room. Here, you'll receive an explanation about intensive care treatment. We will first explain the devices in the room, which are placed next to you. We will now leave the room and will come back after the explanation.

Setting: The ICU physician and ICU nurse will leave the room.

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Scene 2. Explanation of all devices and noises in an ICU room.

Voice-over: There are several devices next to you, such as a monitor, medication pumps and a mechanical ventilator; look around you. To adequately monitor you, we want to know immediately when something is changing. For instance when your blood pressure is low, or when you're out of medication. Each device has its own functions and alarm noise to warn ICU nurses and physicians. As a result, you often hear alarm noises in your ICU room. Besides using monitors, you are monitored also in other manners. We will now explain the functions of each device to you.

Setting: The surveillance monitor is outlined.

Voice-over: When you look to your left, you'll see the surveillance monitor.

Setting: A white arrow appears that points from the surveillance monitor to an explanation window in front of the patient, where the surveillance monitor is animated.

Voice-over: When you look forward again, we will explain the function of the surveillance monitor. The surveillance monitor monitors heart rate, blood pressure, respiratory rate, and oxygen saturation. If, for instance, your blood pressure is too low, the following alarm signal is produced to warn the ICU nurse.
<ALARM SIGNAL SURVEILLANCE MONITOR>

Setting: The explanation window disappears. The medication pumps are outlined.

Voice-over: If you look to your right, you'll see the medication pumps.

Setting: A white arrow appears that points from the medication pumps to an explanation window in front of the patient, where the medication pumps are animated.

Voice-over: These pumps are used to give medication. When you hear the following sound,

<ALARM SIGNAL MEDICATION PUMPS>

the nurse is warned that your medication is almost empty.

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Scene 3. Explanation about mechanical ventilation, intubation, and tracheal tube suction.

Setting: The explanation about the mechanical ventilator disappears, and an animation appears in the explanation window explaining intubation and mechanical ventilation.

Voice-over: Because you were critically ill, we decided to support your breathing. This was done to maintain the appropriate amount of oxygen in your body. To support your breathing, we inserted a tracheal tube. This tube is placed through your mouth into your trachea. To make sure this procedure is carried out optimally and because this procedure is often uncomfortable, you were sedated during the insertion of the tube. At the end of the tube, there is a small air balloon, which is filled with air. This balloon prevents the leakage of oxygen and the contents of the stomach from entering the lungs. Due to the placement of the tube between the vocal cords, patients cannot talk when they are intubated. When the lungs have sufficiently recovered, the tracheal tube can be removed. The tracheal tube is frequently cleaned by suctioning the tube. The nurse will slide a suctioning tube in the tube. Hereby, mucus will be removed, and infections will be prevented. Sometimes, it will be enough to do this once, but this has to be repeated often.

Setting: The explanation window disappears. The mechanical ventilator is outlined.

Voice-over: If you look to your left, you'll see the mechanical ventilator.

Voice-over: When you look in front of you, we will give you a further explanation about the mechanical ventilator. The mechanical ventilator supports your breathing. If you heard the following sound,
<ALARM SIGNAL MECHANICAL VENTILATOR>
the nurse was warned.

Setting: The animation of the mechanical ventilator disappears, and the explanation about prone positioning is animated in the explanation window.

Voice-over: As a consequence of several diseases, including coronavirus, the alveoli and pulmonary vessels can partially close, resulting in the body being unable to absorb sufficient oxygen. There are relatively more alveoli in the back of the lungs. In the occasion mechanical ventilation in a normal position is no longer effective, it can be decided to ventilate patients in the prone position or laying on their stomach. The alveoli and pulmonary vessels in the back of the lungs are thereby better ventilated, hopefully resulting in better absorption of oxygen.
Often, there is an immediate improvement in the mechanical ventilation conditions after prone positioning. To prevent pressure marks on the face, the eyes are protected and the head is placed in a position to the side. Over time, the positive effect of this prone position diminishes, and the patient is again placed on their back. Therefore, it is often decided to ventilate in prone positioning for several hours and thereafter again on the back for several hours. Because prone positioning can be uncomfortable, patients are sedated.

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Scene 4. Explanation about central/peripheral lines, intravenous drips and the gastric tube,

Setting: The explanation window disappears, and the ICU physician and nurse enter the room.

ICU physician: The different devices, the mechanical ventilator and the alarm signals have just been explained to you. Now, you will receive an explanation concerning the drips, infusions and gastric tube.

Setting: The ICU physician and nurse leave the room.

Voice-over: IV drips and lines are necessary not only to administer medication and fluids but also to continuously monitor the blood pressure.

Setting: The explanation window appears, and the function of a peripheral drip is explained using an animation.

Voice-over: This is an 'ordinary' IV drip, also called a peripheral IV drip. This is usually inserted into a vessel in the forearm, but sometimes, it is placed in the foot. The nurse can administer medication or fluid through this drip. Because these peripheral vessels are thin, not every medication can be administered through the veins.

Setting: Explanation of a central line is explained using an animation.

Voice-over: Here, you see a central line. This is a think IV drip that is inserted into a large blood vessel, often in the neck or groin. The insertion of such a line will be performed in a sterile manner; therefore, a blue cloth is stretched over your head. Working in a sterile field minimises the risk of infection. The main reason to insert a central line is to administer medications that cannot be administered through ordinary IV drips. Nutrition can also be directly administered to the blood stream through a central line.

Setting: Explanation of an arterial line is explained using an animation.

Voice-over: This is an arterial line. This is an IV drip that is placed directly into an artery, so blood pressure can continuously be monitored. It is also used to take blood samples. Without such a line, blood samples may have to be taken too often.

Setting: Explanation about a gastric tube is given using an animation.

Voice-over: A gastric tube is a tube that is placed through the nose or mouth through the oesophagus into the stomach. The tube is usually to administer tube feedings. It can also be used to administer medications.

Setting: The tracheotomy procedure is explained using an animation.

Voice-over: When patients are mechanically ventilated for a prolonged period of time, they sometimes receive a tracheotomy. During a tracheotomy procedure, a tube (also known as a cannula) is placed in the trachea through the neck. This cannula replaces the ventilation tube, which is inserted through the mouth. There are several reasons to perform a tracheotomy, but the most important one is long-term mechanical ventilation. The patient must be slowly and gradually weaned off mechanical ventilation. Tracheotomy placement is often conducted in the ICU. The cannula is inserted just above the sternum through an incision

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in the trachea. The end of the tube can be inflated to prevent air leakage. Because the air flows through the cannula to the lungs and no air passes the vocal cords, patients initially cannot speak when they have a tracheotomy. However, the tracheal cannula can be closed using a speaking valve, whereby the end of the cannula is deflated; as a result, air will flow through the vocal cords making it possible to speak. The tracheostomy will be removed when a patient has sufficient strength to breath on their own and can cough up sputum properly.

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Scene 5. Explanation about the treatment team and ICU workflow.

Setting: The explanation window disappears, and an ICU physician, nurse and resident enter the ICU room.

Voice-over: In the ICU, you are treated 24 hours per day by a treatment team. Therefore, there are many people working in the ICU.
The medical treatment team that is primarily responsible for your treatment includes the ICU physician, the ICU resident and the ICU nurse.

ICU physician: My fellow ICU physicians and I, the intensivists, are specialised in the treatment of critically ill patients. Every morning, afternoon and evening, there is a meeting with the treatment team taking care of you to discuss how you are doing. This will take place in your room.

Resident Hello, my name is **'name resident'**, and I am the resident, a doctor in training to become a medical specialist. My fellow residents and I are responsible for the daily medical care, in which we are always supervised by the intensivists.

ICU nurse: My fellow ICU nurses and I will look after you, monitor you continuously and are trained to operate the devices for your treatment. You will be taken care of by the same nurse every shift.

Setting: The treatment team leaves the room.

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Scene 6. Explanation about isolation and personal protection measures.

Voice-over: During your stay in the ICU, you are treated in isolation. Isolation measures are aimed at preventing the spread of microorganisms, such as coronavirus. These measures are in addition to the basic hygiene measures. We will now show you how this was done.

Setting: The treatment team returns to the room with isolation measures.

Voice-over: The treatment team has applied isolation measures when entering the room by wearing personal protective equipment. Before entering the room, the team was therefore wearing: Non-sterile gloves, a mouth-nose mask, an isolation apron with long sleeves, safety glasses, a hair cap.
Prior to leaving the room, the personal protective equipment is removed and hands are disinfected.

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Scene 7. Outro

Setting: The explanation window disappears and the ICU physician and nurse re-enter the room.

ICU physician: We hope you now have a better understanding of the treatment you received in the ICU. This is the end of this video, you can remove the VR glasses.

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Supplementary File 2.

Translation of the information for participants and informed consent form.

Supplement to:

Johan H. Vlake, Jasper van Bommel, Evert-Jan Wils, Tim I.M. Korevaar, Eva Klijn, Anna F.C. Schut, Jan H. Elderman, Joost A.M. Labout, Adrienne Raben, Annemieke Dijkstra, Stefanja Achterberg, Amber L. Jurriens, Margo M.M.C. van Mol, Diederik Gommers, Michel E. van Genderen.

The effect of Intensive Care Unit-specific Virtual Reality (ICU-VR) to improve psychological well-being in ICU survivors: study protocol for a multicentre, randomised controlled trial - the HORIZON-IC study

For peer review only

Horizon IC
expertise door samenwerking

Participants information for participation in medical scientific research

The effect of Intensive Care-specific Virtual Reality (ICU-VR) on psychological complaints after Intensive Care treatment.

Introduction

Dear Sir / Madam,

Using this letter, we would like to inquire whether you would be interested to participate in medical research. Participation is on voluntary basis. You are receiving this letter because you have been treated in the intensive care unit for more than three days and were mechanically ventilated.

In this letter, we will inform you about the nature of the study, what participation means, and what the benefits and disadvantages are of participation. Would you like to carefully read the entire letter prior to deciding whether you want to participate? If you are willing to participate, you can fill in and sign the form that you can find in Appendix B. You are given 1 to 4 days to consider your participation; we will ask you to make a decision about participation no later than seven days after your discharge from the intensive care unit.

Ask your questions

You can make your decision using the information you will find in this information letter. In addition, we recommend you to:

- Ask questions to the investigator who has provided you with this information.
- Talk about participation in this study with your partner, family or friends.
- Ask questions to the independent expert, [redacted] (Appendix A)
- Read the information provided on www.rijksoverheid.nl/mensenonderzoek.

1. General information

This study was initiated by the Franciscus Gasthuis & Vlietland and Erasmus MC. We will refer to the Franciscus Gasthuis & Vlietland and the Erasmus MC as the 'sponsor'. Investigators, which can be personified by doctors, nurses and student investigators, conduct the study in several hospitals. Hospitals participating in this study include the Erasmus MC, Franciscus Gasthuis & Vlietland, Ikazia hospital, and Maasstad hospital in Rotterdam, the IJsselland hospital in Capelle aan den IJssel, the Van Weel-Bethesda Hospital in Dirksland, the Groene Hart Hospital in Gouda, the Haaglanden Medical Centre in The Hague and the Albert Schweitzer hospital in Dordrecht.

A total of 300 participants are needed for this study. The United Medical Ethics Committee (MEC-U) in Nieuwegein, a medical ethical review committee, has approved this study.

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2. What is the aim of the study?

In this study, we investigate whether an Intensive Care-specific Virtual Reality intervention, ICU-VR, can effectively reduce psychological impairments in patients who have been treated in an intensive care unit. Additionally, we study whether ICU-VR improves quality of life.

For this we compare three groups of patients;
1) patients not receiving ICU-VR,
2) patients receiving ICU-VR three times in the first two weeks after ICU discharge and
3) patients who receive ICU-VR during an ICU follow-up visit three months after discharge from the intensive care unit.

ICU-VR is an information film about the intensive care unit that can be watched using virtual reality. This film is implemented in the SyncVR Relax & Distract application. This application is approved for use in patients to help reduce stress and anxiety. Virtual reality, or VR, means virtual reality or apparent reality. The ICU-VR film lasts approximately 12 minutes. During the ICU-VR film, you will be virtually brought back to the intensive care unit and you will receive explanation about various aspects of the intensive care unit environment and treatment. During this explanation, you will be virtually laid down in an intensive care bed. You can always interrupt the ICU-VR film. In the latter case, you may decide to continue watching ICU-VR later on, or to not continue watching ICU-VR.

3. What is the background of the study?

In the Netherlands, approximately 90,000 adult patients are annually treated in an intensive care unit due to a critical illness. The chances of surviving life-threatening conditions such as cardiac arrest, trauma or sepsis have greatly improved over the past twenty years. In recent years, it has become increasingly apparent that surviving an acute and life-threatening critical illness can have long-term consequences on quality of life.

Many patients experience an intensive care unit treatment as stressful due to the different experiences and emotions they have during the intensive care unit stay. Think of moments of shortness of breath, having pain, feelings of powerlessness and fear of dying. Former intensive care unit patients therefore have an increased risk of developing psychological impairments, such as post-traumatic stress disorder (PTSD), anxiety, or depression. About 1 out of 5 former intensive care unit patients develop symptoms that are suitable with PTSD in the first year after discharge from the intensive care unit and 1 out of 3 develop symptoms of depression or symptoms that are suitable with an anxiety disorder. Although symptoms of PTSD, anxiety disorders and depression are most common in the first months after discharge, these can also last for years after discharge from the intensive care unit.

Recent studies show that treatment with Virtual Reality (VR) is beneficial for non-ICU patients with various psychological problems such as anxiety, PTSD and depression. We have previously shown that the use of Intensive Care-specific Virtual Reality is safe in intensive care unit patients. Additionally, ICU-VR appears to have a positive effect on the psychological recovery of patients treated for sepsis in the intensive care unit. In this study, we aim to investigate the effect of ICU-VR again in a larger group, to be sure whether ICU-VR can help to reduce psychological impairments and improve quality of life.

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4. How is the study progressing?

How long does the study take?

Are you participating in this study? Participation will last until twelve months after your discharge from the intensive care unit.

Step 1: Are you eligible to participate?

We first want to know if you are eligible to participate.

All patients who have been treated in the intensive care unit for at least three days and who have been mechanically ventilated at least 24 hours, are eligible to participate in this study. However, it is important that you are clear in mind and can make a well-considered decision. In addition, you must have enough understanding of the Dutch language to understand ICU-VR and to complete the questionnaires.

Step 2. Informed Consent

Within the first week after you are discharged from the intensive care unit, a doctor, nurse or investigator has given information about the study. You have also received this information letter. We ask you to carefully and thoroughly read this letter, and consider participation.

You will be given one to four days for your consideration. Here after, the doctor, nurse or investigator will visit you again. You will then have the opportunity to ask questions about the study. If you want to participate in the study, you, together with the doctor, investigator or nurse, will sign the consent form on the last page of this letter. By signing the informed consent form, you indicate that you have received sufficient information about the study, that you have had the opportunity to ask questions about the study, and that you want to participate in this study on that basis. After that, a short check-up will be carried out to determine whether you are clear in mind.

Step 3. Questionnaire and randomization

Once you have signed the consent form, you will receive the first questionnaire. First, we want to investigate how your psychological state and quality of life were before you were admitted to hospital. Secondly, we want to investigate your current psychological state and quality of life. It takes approximately 40 minutes to complete this questionnaire.

In addition, participants in this study will be randomly assigned to **three groups.** This randomization, comparable with a lottery, decides to which group you are assigned and will be conducted after having singed the informed consent form. The investigator or doctor **does not have any influence** on the outcome of the randomization. You therefore do not know in advance which group you will end up in, and you are not allowed to indicate a preference for this.

The three groups are as follows:

1) The control group. Participants in this group **will not receive ICU-VR.** You will receive the same care as if you did not participate in this study, but are additionally asked to fill out questionnaires.
2) The **early ICU-VR** group. Participants in this group will receive ICU-VR for **a maximum of three times**, between 8 and 15 days after your discharge from the intensive care unit, if you are still in the hospital ward. When you are discharged from the hospital, you will no longer be offered ICU-VR.

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3) The **late ICU-VR** group. Participants in this group will receive **ICU-VR during a visit to our intensive care unit follow-up clinic**, where you will be invited three months after your discharge from the intensive care unit.

Step 4. Intensive Care Unit-specific Virtual Reality

Participants in the early or late ICU-VR group will receive ICU-VR at least once. As previously described, ICU-VR is a 12-minute informational film about the Intensive Care Unit. To view ICU-VR, we use our Virtual Reality glasses. **Image 1** shows what these glasses look like (left), and how the VR glasses are used (right). You will also be explained how to use the VR glasses and how to behave in the virtual environment when you receive ICU-VR.

Image 1. On the left you see the VR glasses that will be used during this study. You put the glasses over your eyes, as shown on the right. The VR glasses use light that is harmless to your eyes. You can keep your glasses on while using the VR glasses.

Step 5: Intensive care unit follow-up clinic

Three months after your discharge from the intensive care unit, we will invite you to visit our intensive care unit follow-up clinic. During this visit, you and an ICU nurse and/or doctor will review your stay in the intensive care unit. They will see if you need help from other healthcare providers, such as a physiotherapist or psychologist, and you can ask questions about your intensive care unit stay. Prior to this visit you will be asked to complete questionnaires, which will be sent to you by e-mail or postal mail.

Step 6: Questionnaires

All participants will be asked to complete questionnaires on 5 time points during the study. You will receive the first questionnaire immediately after signing the consent form, as described in 'Step 2'. In addition, you will be asked to complete questionnaires 1 month, 3 months (before the visit to the aftercare outpatient clinic), 6 months and 12 months after your discharge from the intensive care unit. The length of the questionnaires varies per follow-up time point. Completing the questionnaires will take approximately 30 to 45 minutes per questionnaire.

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5. What commitments do you make when participating?

We would like this study to be conducted as intended. Therefore, we ask you to honour the following commitments:

- If you are in a group receiving ICU-VR, you are willing to watch ICU-VR and you will try to watch the entire film. Of course, you can stop if you want to, for example if it gets too intense or you have nausea symptoms.
- During this study, you will not also participate in other medical scientific research without discussing this with the investigator. He/she can determine whether or not you can simultaneously participate in the other study.
- You visit the intensive care unit follow-up clinic when you are invited. If you are unable to attend on the proposed date, please try to find another date for this appointment.
- You complete the questionnaires at the requested time points. The investigator will also send you reminders. If you are unable to complete the questionnaires yourself, ask a family member/friend/girlfriend to help you with this.
- You contact the investigator in these situations:
  - You will be re-admitted to the hospital or the intensive care unit.
  - You no longer wish to participate in the study.
  - Your contact details, such as your telephone number, address or e-mail address, change.

6. What side effects, adverse effects or inconveniences may you experience?

We have shown in previous studies that the use of ICU-VR for patients is safe. There were no serious or long-lasting side effects. However, virtual reality can cause short-term complaints that resemble motion sickness. Think of nausea or dizziness, both during the film and just after the film. These complaints are usually mild in nature, last a few minutes and go away on their own. If the complaints persist for longer, you can contact someone from the study team. Their contact details are listed in **Appendix A.**

7. What are the advantages and disadvantages of participating in the study?

Participating in the study may have advantages and disadvantages. We list them below. Consider these when considering participation, and talk about them with others.

A possible advantage of participating in this study is that it may lead to a better psychological recovery and a better quality of life after your intensive care unit stay. However, this is **not certain and is being investigated in this study.** In addition, this only applies to patients who have been randomized to the early or late ICU-VR group and who have received ICU-VR.

A disadvantage is that it takes time to complete the questionnaires. In addition, you must adhere to the commitments as discussed in section 5. Also, if you are randomized to the early or late ICU-VR group, you may experience side effects as described in section 6.

Don't want to participate?

You are the one to decide whether or not you want to participate. Do you not want to participate? This is no problem, and nothing will change with regard to how you are treated.

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8. When will the study end?

The investigator will let you know if there is new information about the study that is important for you as participant. The investigator will then ask you whether you want to continue your participation.

In these situations, the study will stop for you:

- You completed the last questionnaire 12 months after you were discharged from the intensive care unit.
- You decide that you no longer wished to participate. You can always terminate your participation. We ask you to immediately inform the investigator if you wish to no longer participate. You don't have to give a reason why you wish to no longer participate. Discontinuation of your participation will never have consequences for your treatment.
- The investigator thinks it's better for you to stop.
- One of the following authorities decides that the study should be terminated:
  - The sponsor,
  - the government, or
  - the medical ethics committee that assesses the research.

What happens if you stop the study?

The investigators may use your data which is collected until the moment you decide to discontinue your participation. If you want, data that is collected from you can be deleted. You can request this by the investigator.

The entire study will be ended if all participants have completed their last questionnaire.

9. What happens after the study?

Within twelve months after you completed the last questionnaire, the investigator will contact you to ask if you would like to be informed about the most important findings of the study.

10. What do we do with your data?

Are you participating in the research? Then you also give permission to collect, use and store your data.

What data do we keep?

We keep this data:

- your name
- your gender
- your (e-mail) address
- your date of birth
- information about your treatment in the intensive care unit
- data that we collect during the research, such as the outcomes of the questionnaires

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Why do we collect, use and store your data?

We collect, use and store your data to answer the questions of this study. And to be able to publish the results.

How do we protect your privacy?

To protect your privacy, a code will be assigned to all your data. This code will be the only identifier for your data. The key, which makes it possible to link the code with you, will be stored in a safe place in the intensive care unit where you were treated. When we process your data, we will only use this code. In reports or publications about the study, we will ensure no participants can be identified based on the data provided.

Who has access to your data?

There are persons can be given permission to access the data without codes. These are persons who monitor whether the study is conducted properly and reliably, and according to all regulations.

Persons who will be given permission are:

- A monitor who is an employee of the Erasmus MC
- National supervisory authorities.

These persons will treat you data confidentially. By consenting to participate in this study, you also give permission that your data can be monitored by these.

How long do we keep your data?

We store your data for 15 years in the hospital where you were treated, or in a secured online database.

Can you withdraw your consent to the use of your data?

You can always withdraw your consent for the use of you data. However, if you withdraw your consent, and the investigators have already collected data for the study, the investigator is allowed to use the data collected until the consent was withdrawn.

Would you like to know more about your privacy?

- Do you want to know more about your rights with regard to the use of your data? You can take a look at www.autoriteitpersoonsgegevens.nl.
- Do you have any questions about your right? Or do you have complaints about the use of your data? You may contact the person who is responsible to the collection of your data. For this study, this will be the principle investigator, of whom the contact details can be found in **Appendix A of this letter**.
- If you have complaints about the use of your data, we would recommend to first discuss these with the investigators of the study. You can also contact the Data Protection Officer of the hospital where you relative was treated. Their contact details are stated below. You can also file a complaint by the Authority of Personal Data.

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Where can you find more information about the study?

On the website www.trialregister.nl you will find more information about the study. After the study, the website may display a summary of the findings of this survey. You can find the study by searching for 'ICU-VR for patients in the ICU' (number: NL78555.100.078)

11. Will you be financially compensated when you participate in the study?

Participation in this study is free of charge. You will neither receive any compensation for participation in this study, also no travel or expense reimbursement.

12. Are you insured during the study?

You are not extra insured for this research, because participating in the research has no additional risks. Therefore, the investigators do not need to purchase additional insurance from the United Medical Ethics Committee, the medical ethics review committee that approved this study.

13. Do we inform your GP?

As participation to this study is not expected to have any negative consequences for your health, or the health of your family members/relatives, we will not inform you general practitioner about your participation in this study. You are however free to tell your general practitioner yourself, and he/she can contact the study team for questions.

14. Do you have questions?

Questions about the study can be asked to the study team. The contact details of the study team are stated in **Appendix A**. Would you like to be advised by someone who is not involved in the study team? You can then contact dr. [redacted], his contact details are in **Appendix A.** He is an independent expert of the study, and has thereby the knowledge to answer your questions and give you advice, but is not involved in the study.

Do you have a complaint? Then discuss this with the investigator or the doctor who is treating you. Do you prefer to talk to somebody else? You may contact the complaints officer or complaints committee of your hospital, or the Authority of Personal Data. **Appendix A** shows where you can find them.

15. How do you give consent for the study?

You should first think about participating in this study. Therefore, you should tell the investigator whether you have understood the provided information and whether or not you would like to participate. If you want to participate, you will be asked to fill out and sign the informed consent form on the last page of this letter. Both you as the investigator will receive a copy of the signed version of the informed consent form.

Thank you for your time.

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16. Attachments to this information

A. Contact Details

B. Consent Form

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Appendix A: Contact Details

Research team:

[redacted], executive investigator, first contact person

Mail: [redacted]

Telephone: [redacted]

Accessibility: Working days between 09.00 and 18.00

[redacted], coordinating investigator

Mail: [redacted]

Telephone: [redacted]

Accessibility: Working days between 09.00 and 18.00

[redacted], principal investigator

Mail: [redacted]

Telephone:

Intensive Care: [redacted]

Hospital: 010 704 07 04

Accessibility: Working days between 09.00 and 18.00

Independent physician:

[redacted]

Mail: [redacted]

Telephone:

Intensive Care: [redacted]

Hospital: [redacted]

Accessibility: Working days between 09.00 and 18.00

Complaints:

Do you have a complaint? Then discuss this with the researcher or the doctor who is treating you. Would you rather not? Then go to the complaints officer or complaints committee of your hospital ([redacted]). You can submit your complaint digitally ([redacted]), by mail ([redacted]), by post ([redacted]) or by telephone ([redacted]).

Erasmus MC Data Protection Officer:

Mail: [redacted]

Phone number: [redacted]

For more information about your rights, please contact Hans Vlake. He is responsible for the processing of your personal data.

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Appendix B. Informed Consent Form

Related to to: 'The effect of Intensive Care-specific Virtual Reality (ICU-VR) on psychological complaints after Intensive Care treatment.'

- I have read the information letter. I have been given the opportunity to ask additional questions, and my questions are answered sufficiently. I have had enough time to consider participation.
- I know that participation is on a voluntary basis. I also know that I can always decide to not participate or to stop participation. I do not have to give any reason if I decide not to participate or to stop participation.
- I give consent to the investigators to collect and use my data. The investigators will only collect and use data to answer the research question of the study.
- I am aware that there are persons who can be granted permission to access my data to monitor the study. I give consent to these persons to access my data.
- I give permission to collect, store and use my data to answer the research question: **☐YES / ☐ NO**
- I give permission to contact me after this study to ask if I am interested to participate in another, related study: **☐YES / ☐ NO**
- I want to participate in this research.

My name is (participant): ………………………………

Signature: …………………… Date : __ / __ / __

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I declare that I have fully informed this subject about the said study.

If new insights will be obtained about the study, which could influence the participant's decision to participate in the current study, I will timely inform the participant.

Name of investigator (or its representative):………………………………

Signature:…………………… Date: __ / __ / __

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The participant will receive a complete copy of the information letter, including a (copy of the) signed version of the informed consent form.

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Supplementary File 3.

SPIRIT Checklist

Supplement to:

Johan H. Vlake, Jasper van Bommel, Evert-Jan Wils, Tim I.M. Korevaar, Eva Klijn, Anna F.C. Schut, Jan H. Elderman, Joost A.M. Labout, Adrienne Raben, Annemieke Dijkstra, Stefanja Achterberg, Amber L. Jurriens, Margo M.M.C. van Mol, Diederik Gommers, Michel E. van Genderen.

The effect of Intensive Care Unit-specific Virtual Reality (ICU-VR) to improve psychological well-being in ICU survivors: study protocol for a multicentre, randomised controlled trial - the HORIZON-IC study

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	4-13
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	15
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 15
	5b	Name and contact information for the trial sponsor	1, 15
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	15
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	10, 15

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Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4, 5
	6b	Explanation for choice of comparators	4, 5, 6, 7
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	1, 6

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6, 10
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6-10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8-10
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7

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Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9-11
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7

Methods: Assignment of interventions (for controlled trials)

Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8-10
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	N/A

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Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	9
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11-12
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11-12
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11-12
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	N/A
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	12-13
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	12-13

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Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	10
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	15
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	12-13
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	15
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary File 2
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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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

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Manuscripts

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

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31 ## ABSTRACT

32 **Introduction** A substantial proportion of Intensive Care Unit (ICU) survivors develop psychological
33 impairments after ICU treatment, part of the Post-Intensive Care Syndrome (PICS), resulting in a
34 decreased quality of life. Recent data suggest that an ICU-specific Virtual Reality intervention for post-
35 ICU patients (ICU-VR) is feasible and safe, improves satisfaction with ICU aftercare, and might improve
36 psychological sequelae. In the present trial, we firstly aim to determine whether ICU-VR is effective in
37 mitigating post-traumatic stress disorder (PTSD)-related symptoms and secondly to determine the
38 optimal timing for initiation with ICU-VR.

39 **Methods and analysis** This international multicentre, randomized controlled trial will be conducted in
40 ten hospitals. Between December 2021 and April 2023, we aim to include 300 patients who have been
41 admitted to the ICU ≥72 hours and were mechanically ventilated ≥24 hours. Patients will be followed for
42 12 consecutive months. Patients will be randomized in a 1:1:1 ratio to the early ICU-VR group, the late
43 ICU-VR group, or the usual care group. All patients will receive usual care, including a mandatory ICU
44 follow-up clinic visit three months after ICU discharge. Patients in the early ICU-VR group will receive
45 ICU-VR within two weeks after ICU discharge. Patients in the late VR group will receive ICU-VR during
46 the post-ICU follow-up visit. The primary objective is to assess the effect of ICU-VR on PTSD-related
47 symptoms. Secondary objectives are to determine optimal timing for ICU-VR, to assess the effects on
48 anxiety- and depression-related symptoms and health-related quality of life, and to assess patient
49 satisfaction with ICU aftercare and perspectives on ICU-VR.

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50 **Ethics and dissemination** The Medical Ethics Committee United (MEC-U), Nieuwegein, the
51 Netherlands, approved this study and local approval was obtained from each participating centre
52 (NL78555.100.21). Our findings will be disseminated by presentation of the results at (inter)national
53 conferences and publication in scientific, peer-reviewed journals.

54 **Trial registration number** This trial has been prospectively registered on the Netherlands Trial
55 Register (TrialRegister.nl, NL9812, registered October 21, 2021).

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56 **Strengths and limitations of this study**

57 • A randomised controlled trial examining the effect of Intensive Care Unit-specific Virtual Reality
58 (ICU-VR) on psychological well-being and health-related quality of life after ICU treatment.

59 • ICU-VR is easy applicable and safe and enables patients to be auditorily and visually exposed to
60 the ICU environment traumatizing them while receiving treatment-related information. However, the
61 optimal timing of ICU-VR after critical illness is unknown.

62 • Follow-up until 12 months after ICU discharge enables us to study long-term effects.

63 • Blinding of patients or investigators is not possible due to the nature of the intervention.

64 • ICU-VR content is hospital-specific to expose patients to the actual ICU environment, but it limits
65 the possibility of easily implementing the intervention in other hospitals.

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INTRODUCTION

Because of improved survival after Intensive Care unit (ICU) treatment, a new challenge arises.[1 2] A substantial proportion of ICU survivors suffer from psychological impairments, such as post-traumatic stress disorder (PTSD), anxiety, and depression.[3 4 5] Along with cognitive and physical impairments, these sequelae are referred to as the Post-Intensive Care Syndrome (PICS). PICS is common, can last for years after ICU discharge, and has a profound impact on daily functioning and quality of life.[6 7 8]

Prevention and treatment of PICS has been recognized as a fundamental part of ICU care by the critical care community and recently it was demonstrated that the psychological component of PICS is the most important determinant of a decreased health related quality of life (HRQoL) and impede a patients ability to rehabilitate.[9 10 11] Although several interventions have been explored, such as keeping ICU diaries, organizing ICU follow-up clinics, and offering psychosocial support, studies on their effectiveness in terms of psychological distress or quality of life have yielded unsatisfactory and ambiguous results.[10 12-17] As such, evidence based interventions to improve psychological recovery and health-related quality of life (HRQoL) are lacking.

Post-ICU psychological impairments may be caused by amnesia during the early period of critical illness in combination with sensory overload and sensory deprivation. Amnesia can lead to loss of factual recall of their ICU stay and patients can instead create delusional and frightening memories.[18] Moreover, the typical ICU-environment is characterized by unpatterned exposure and frequent sensory input such as light, noise, and tracheal tube aspiration. The exposure to these extremes initiates the development of PTSD and anxiety.[19] We hypothesized that exposure to the factual ICU environment, and additionally

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86 receiving ICU-related treatment information, could enhance ICU treatment understanding and
87 subsequently could decrease delusional memories and psychological impairments.[20 21]

88 Virtual Reality (VR) allows users to fully immerse within a computer-generated three-dimensional
89 environment. In psychiatry, exposure therapy using VR has been proven effective for the treatment of
90 PTSD and anxiety and thereby it addresses limitations of imaginal exposure.[22-26] Also, VR can effectively
91 and easily be used to deliver structured and uniform information to patients. VR could thus be a valuable
92 adjunct to safely inform and expose post-ICU patients to the environment traumatizing them and could
93 enhance psychological recovery.[27 28] In the current study our primary aim is to assess the effect of an
94 ICU-specific Virtual Reality intervention for post-ICU patients (ICU-VR) on PTSD-related symptoms.
95 Secondly, we want to determine optimal timing for initiation with ICU-VR, to assess the effects of ICU-
96 VR on anxiety- and depression-related symptoms, and to assess patient satisfaction with ICU aftercare
97 and their perspectives on ICU-VR.

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METHODS AND ANALYSIS

Study design and setting

A multicentre, randomized controlled trial will be conducted in ICUs of ten hospitals in the Netherlands (Erasmus Medical Centre (university hospital), Franciscus Gasthuis & Vlietland hospital, Maasstad hospital, Ikazia hospital, IJsseland hospital, Groene Hart hospital, Van Weel-Bethesda hospital, Haaglanden Medical Centre, and the Albert Schweitzer hospital) and Belgium (Cliniques universitaires de Bruxelles - Hôpital Erasme, Bruxelles) (**Table 1**). The Medical Ethics Committee United (MEC-U), Nieuwegein, the Netherlands, approved this study (NL78555.100.21, approved October 25, 2021), and local approval was obtained from the institutional ethic review boards of each participating hospital. Inclusion will be conducted from December 2021 to October 2022, and patients will be followed for 12 months after ICU discharge. Any modifications to the study protocol, which may affect the conduct of the study or patient safety, including changes of the study objectives, study design, study population, sample size, study procedures or significant administrative aspects, will be sent for approval to the MEC-U and the institutional ethic review boards. Health authorities will be informed in accordance with local regulations.

Table 1. ICU-related characteristics of study site.

Study Site	Type of hospital	Type of ICU	No. Of ICU beds
Erasmus Medical Centre, Rotterdam, the Netherlands	Academic hospital	Mixed medical, surgical and cardiac ICU	56
Franciscus Gasthuis & Vlietland, Rotterdam, the Netherlands	Community, teaching hospital	Mixed medical and surgical ICU	19

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Maasstad hospital, Rotterdam, the Netherlands	Community, teaching hospital	Mixed medical and surgical ICU with an burn expertise centre	25
Ikazia hospital, Rotterdam, the Netherlands	Community hospital	Mixed medical and surgical ICU	12
IJsselland hospital, Capelle a/d Ijssel, the Netherlands	Community hospital	Mixed medical and surgical ICU	8
Groene Hart hospital, Gouda, the Netherlands	Community, teaching hospital	Mixed medical and surgical ICU	12
Van Weel-Bethesda hospital, Dirksland, the Netherlands	Community hospital	Mixed medical and surgical ICU	6
Haaglanden Medical Centre, The Hague, the Netherlands	Community, teaching hospital	Mixed medical and surgical ICU	22
Albert Schweitzer hospital, Dordrecht, the Netherlands	Community, teaching hospital	Mixed medical and surgical ICU	16
Cliniques universitaires de Bruxelles - Hôpital Erasme, Bruxelles, Belgium	Academic hospital	Mixed medical and surgical ICU	36

113

114 **Study participants**

115 We aim to include at least 300 patients. Patients admitted to the ICU for ≥72 hours, during which
116 mechanically ventilated ≥24 hours, older than 17 years of age, and able to understand the Dutch
117 language are eligible for inclusion. Patients admitted to the ICU with primary neurological impairment or
118 with a life expectancy <48 hours or receiving palliative care, with documented active, established
119 psychiatric disorders, a decreased cognitive function during inclusion (a telephone interview for cognitive

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status (TICS) score ≤27), with a new or active delirium during inclusion (defined as mentioning of a delirium in the daily status report of the treating physician or new administration of haloperidol), or without a formal home address will be excluded. 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.

Randomization and masking

Patients will be randomized in a 1:1:1 ratio to either the early ICU-VR group, the late ICU-VR group, or the usual care group. Randomization will be according to a 1:1:1 ratio, stratified for study site, using a centralized internet-based randomization procedure (Castor EDC, Amsterdam, The Netherlands). Due to the nature of the intervention, blinding of patients is not possible. Randomization allocation will be coded in analysis with "0" and "1", and the analysist will as such be unaware of the randomization allocation.

Intervention

The Intensive Care Unit-specific Virtual Reality intervention for post-ICU patients (ICU-VR) is based on an uniform script that is designed by an interdisciplinary team and based on the several focus group meetings of this team. The content of the script is extensively described elsewhere and the content can be found in **Supplementary Data File 1**.[27 28] We also have written a movie directors script to produce an uniform ICU-VR film in each participating centre.[27 28] The ICU-VR film was produced for each centre, i.e. hospital specific, to optimize immersiveness and to deliver relevant and truthful information regarding ICU stay and ICU treatment.[28 29] The point of view for the camera is the field of vision of the mock patient

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lying in an ICU bed. ICU-VR will be watched using head-mounted display VR (Pico G2 VR All-In-One Headset) and a headset.

Study procedures

An oversight of the study procedures is presented in **Figure 1**. Patients who are eligible for inclusion will be approached by an investigator of the research team or by a dedicated research nurse within 7 days after ICU discharge. A translation of the information for patients and the informed consent form can be found in **Supplementary Data File 2**.

After obtaining informed-consent and the TICS assessment, patients will receive the first set of questionnaires (T0), consisting of a self-composed questionnaire regarding demographics and their history of mental health, the Impact of Event Scale-Revised (IES-R), the Hospital Anxiety and Depression Scale (HADS), the European Quality of life 5 dimensions (EQ-5D), and the short-form 36 (SF-36) (**Table 2**). Patients are asked to fill in the HADS, EQ-5D, and SF-36 questionnaire both retrospectively and prospectively to obtain a baseline and over time measure of patient anxiety and depression levels and quality of life.

Patients randomized to the early ICU-VR group will receive ICU-VR between day 8 and day 15 after ICU discharge for a maximum of three times, unless the patient is discharged from the hospital ward sooner. The number of times ICU-VR is offered and accepted will be logged. Between three and six months after ICU discharge, all patients will visit the post-ICU follow-up clinic of the concurrent hospital. During this post-ICU follow-up visit, patients have a consult with a dedicated ICU nurse and an

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159 intensivist. Patients randomized to the late ICU-VR group will receive ICU-VR once during their
160 concurrent post-ICU follow-up clinic visit.

161 All patients will receive follow-up questionnaires at 1 month (T1), 3 months (T2), 6 months (T3), and 12
162 months (T4) after ICU discharge (**Table 2**).

163 **Outcomes and measurements**

164 The primary outcome is the effect of ICU-VR on the severity of PTSD-related symptoms at six months
165 after ICU discharge.

166 The severity of PTSD-related symptoms will be expressed as the sum score of the IES-R and an IES-R
167 sum score ≥ 24 will be considered as clinically relevant PTSD.[30] The IES-R comprises 22 items,
168 assessing subjective distress caused by traumatic events, and has been used commonly in survivors of
169 critical illness.[31-33] The IES-R yields a total score (ranging from 0 to 88; higher scores indicate more
170 severe symptoms) and subscale scores can be calculated for symptoms of intrusion, avoidance, and
171 hyper arousal.

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Table 2. Questionnaires per follow-up time point.

Questionnaire:	**T0.** Inclusion	**T1.** 1 month after ICU discharge	**T2.** 3 months after ICU discharge	**T3.** 6 months after ICU discharge	**T4.** 12 months after ICU discharge
Demographics	X	X	X	X	X
Work resumption & financial decline		X	X	X	X
History of mental illness	X				
IES-R (Post-Traumatic Stress Disorder)	X	X	X	X	X
HADS (Anxiety and Depression)	X (retro- & prospectively)	X	X	X	X
SF-36 Quality of Life	X (retro- & prospectively)	X	X	X	X
EQ-5D Quality of life	X (retro- & prospectively)	X	X	X	X
Satisfaction with ICU care				X	
Perspectives on ICU-VR		X (early ICU-VR)		X (late ICU-VR)	
Visit to healthcare professionals		X	X	X	X

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Abbreviations: EQ-5D, 5-level European Quality of life questionnaire; HADS, hospital anxiety and depression scale; ICU, intensive care unit; ICU, intensive care unit; ICU-VR, intensive care unit-specific virtual reality; IES-R, impact of event scale-revised; SF-36; short-form 36.

Secondary outcomes are the effects of ICU-VR on the severity and prevalence of PTSD-, anxiety-, and depression-related symptoms and on HRQoL throughout follow-up, the patient satisfaction with ICU aftercare and patient perspectives on ICU-VR.

The severity of anxiety- and depression-related symptoms will be expressed as the HADS anxiety and depression scores, and a HADS anxiety or depression score ≥8 will be considered as clinically relevant anxiety and depression, respectively. The HADS comprises of 14 items and is commonly used to determine the levels of anxiety and depression. Seven of the items relate to anxiety and seven relate to depression.[34-38]

HRQoL will be expressed as the overall HRQoL, which implies the time trade-of (TTO) score of the 5-level EQ-5D, and the mental HRQoL, which implies the mental component score of the SF-36. The EQ-5D measures HRQoL in five dimensions, i.e., mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.[39] By giving a certain weight to each answer option, the country-specific TTO score can be calculated, ranging from -0.446 (worst quality of life) to 1.000 (best quality of life).[40] Also, patients score their subjective health state on a visual analogue scale (EQ-VAS), ranging from 0 (worst health imaginable) to 100 (best health imaginable). The SF-36 consists of 36 items, from which 8 scaled scores can be calculated. These scores are the weighted sums of the questions in their section. Each scale is directly transformed to a scale ranging from 0 to 100 on the assumption that each question carries an

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3 190 equal weight. The 8 sections are vitality, physical functioning, bodily pain, general health perception,
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6 191 physical role functioning, emotional role functioning, social role functioning and mental health.[41 42] In
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9 192 addition, a mental- and physical component scale, the MSC-36 and PCS-36, respectively, can be
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12 193 calculated as a reflection of physical and mental health.[41-43]
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15 194 Patient satisfaction with ICU aftercare will be assessed using a novel questionnaire, based on the
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18 195 Patient Satisfaction Questionnaire and Family Satisfaction with ICU Care tools, altered to the needs of
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21 196 this study.[44 45] Additional novel items were added to evaluate patient perspectives on the ICU-VR
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24 197 intervention.
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27 198 We also explore feasibility and safety outcomes, and the cost-benefit ratio of ICU-VR. Feasibility will be
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30 199 expressed as the number of sessions patients in the early ICU-VR group will receive. Safety will be
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33 200 expressed as the number of ICU-VR sessions requiring interruption or termination due to side effects in
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36 201 terms of cybersickness, mainly experienced as nausea.[27 28] For the cost-benefit ratio, costs will be
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39 202 expressed as, among others, development costs for ICU-VR, employments costs of ICU nurses offering
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42 203 the intervention and the employment and organizational costs of the ICU follow-up clinic and benefits
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45 204 will be expressed as the gain in quality adjusted life years (QALYs) determined as the EQ-5D TTO
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48 205 score.
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51 206 Demographics, such as age, gender, body weight, length, pre-existing comorbidities, previous ICU
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54 207 admissions, and ICU readmissions, treatment-related characteristics, such as type of admission, ICU-
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57 208 and hospital length of stay, mechanical ventilation-related characteristics, episodes of sedative coma
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60 209 and delirium during ICU treatment, assessed using the Richmond Agitation Sedation Scale (RASS) and

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210 the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) scale, respectively, use of
211 renal replacement therapy, infections and illness severity scores during ICU treatment, and 3-, 6-, and
212 12-month mortality will be assessed using electronic patient records.[46 47] Additionally, patients will be
213 asked about their educational level, employment status prior to and after ICU treatment, financial
214 decrease after ICU treatment, consultations with healthcare professionals, and their history of mental
215 health in follow-up questionnaires.

216 **Data management**

217 Data will be uploaded, stored, and maintained using the electronic data capture (EDC) system of Castor
218 (Castor EDC, www.castoredc.com, Amsterdam, the Netherlands). The study team will be responsible
219 for data entry and quality control activities. Data will be checked by at least two persons from the study
220 team and will be stored for at least 15 years on either the Castor EDC server or as a hardcopy in the
221 ICU of the participating hospitals. Questionnaires will be sent digitally using Castor EDC or via hardcopy
222 via postal mail whenever requested.

223 To maintain anonymity, data will be coded with a number and this number will be the only reference to
224 patient identification. The principal investigator is the only one in possession of the translation key,
225 making it impossible to link data to the patient.

226 **Sample size calculation**

227 Based on two previous studies yielding an ICU-VR Cohen's *d* effect estimate of 0.56 (late intervention)
228 to 0.88 (early intervention), the power calculation of the current study is based on a Cohen's d of 0.56.[27]
229 [48] We performed a G*Power analysis based on the Wilcoxon Mann Whitney test, with no expectation

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230 about the underlying distribution of the outcome (parental distribution: “min ARE”). Using a two-sided
231 alpha of 0.05, a power of 0.80, and a 1:1 allocation ratio, this resulted in a required sample size per
232 group of 60 patients.[49] We will use this required sample size for all three groups resulting in a total
233 sample size of 180 patients. We anticipated a loss to follow-up rate of 40% for which we will anticipate
234 in the current trial. We therefore aim to include a total of (3 * 60 / 0.60 =) 300 patients, with 100 patients
235 per group.

236 **Statistical analysis**

237 All continuous data will be presented as medians (95% range). Categorical variables will be presented
238 as absolute and relative frequency. Baseline demographics, treatment-related characteristics, and
239 patient perspectives on ICU-VR will be summarized using descriptive statistics. Outcomes of mixed
240 effects linear and logistic regression models will be presented as the coefficient of the model, which
241 implies the estimated mean difference between groups, including its 95% confidence interval, as the log
242 of coefficient of the model, i.e., the odds ratio, including its 95% confidence interval, respectively.

243 To analyze the effect of ICU-VR on the severity of PTSD-, anxiety-, and depression related symptoms,
244 on HRQoL, and on the prevalence of clinically relevant PTSD, anxiety, and depression at each follow-
245 up time-point, we will use mixed effects linear (for continuous outcomes) or logistic (for categorical
246 outcomes) regression models. In these, the outcome at each follow-up time-point will serve as
247 dependent variable, the randomization group, the retrospectively assessed pre-existent
248 score/prevalence of the outcome of interest, and a random intercept and/or slope for each study site will
249 be used. The effect of ICU-VR on the course of 1) the severity of PTSD, anxiety-, and depression-related

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symptoms, 2) HRQoL, and 3) the prevalence of clinically relevant PTSD, anxiety, and depression throughout follow-up, will be analyzed using mixed effects linear (for continuous outcomes) and logistic (for categorical outcomes) regression models, in which the outcome/prevalence of interest of all follow-up time-points will be used as dependent variable, the randomization allocation, time, the retrospectively assessed pre-existent score/prevalence of interest will serve as independent variables, and a random intercept and/or slope for each study site will be used.

To determine when ICU-VR is most effective, i.e. early vs late, differences in psychological distress and HRQoL between the early ICU-VR group and late ICU-VR groups at 6 and 12 months will be assessed. We will analyze these using mixed effects linear and logistic regression models. In these models, the score/prevalence of interest at either 6 months or 12 months after ICU discharge will be used as dependent variable, the randomization allocation, the retrospectively assessed pre-existent score/prevalence of the outcome of interest, and, if applicable will serve as independent variables, and a random intercept and/or slope for each study site will be used. Differences in the course of the severity and prevalence of psychological distress and HRQoL between 6 and 12 months, will be assessed using mixed effects linear and logistic regression models, in which the outcomes at 6 and 12 months will simultaneously be used as dependent variable, and time after discharge in months, randomization allocation (early ICU-VR / late ICU-VR), the interaction between randomization and time (randomization * time), the pre-existent score of the outcome of interest will serve as independent variables, and a random intercept and/or slope for each patient and each study site will be used.

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3 269 We will analyze differences in the subscales of the SF-36, patient resumption to work, experienced
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6 270 financial decline and consultation with healthcare professionals using the abovementioned manners.
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10 271 The main analysis will be an intention-to-treat analysis, in which all included patients will be included.
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13 272 Secondly, we will perform a per-protocol analysis, in which patients are included if 1) they are
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16 273 randomized to the control group, 2) they are randomized to the early ICU-VR group and received ICU-
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19 274 VR three times in the hospital ward, and 3) they are randomized in the late ICU-VR group and received
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22 275 ICU-VR once during the ICU follow-up clinic visit. Thereafter, we will conduct a complete case analysis,
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25 276 in which all patients who have completed all assessment are included.
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27 277 We will conduct the sub analyses in 1) patients who have been mechanically ventilated ≥ 72 hours, 2)
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30 278 patients who have been mechanically ventilated > 7 days , 3) patients who have been treated in the ICU
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33 279 for > 7 days, 4) patients who have been treated in the ICU for > 14 days, 5) patients who had a delirium,
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36 280 as documented in the health care record, 6) per study site (study sites with <10 inclusions will be
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39 281 combined), 7) sepsis patients, to compare these results with our previously conducted pilot study
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42 282 If the loss to follow-up at six months after ICU discharge will be higher than anticipated, we will impute
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45 283 missing data using both the last observation carried forward method and multiple imputation according
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48 284 to the Markov-chain Monte-Carlo.[50]
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51 285 All data will be gathered using Castor EDC (Castor EDC, Amsterdam, the Netherlands). All analyses
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54 286 will be performed using SPSS (IBM SPSS Statistics for Windows, Version 27.0; IBM Corporation,
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57 287 Armonk, New York) and R for Statistics (R Foundation for Statistical Computing, Vienna, Austria, 2015).
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60 288 A p-value of ≤0.05 will be considered statistically significant.

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289 **Ethics and dissemination**

290 This study will be conducted in accordance with the principles of the declaration of Helsinki (version
291 October 2013; www.wma.net) and in accordance with the Medical Research involving human subjects
292 act (WMO) and other guidelines, regulations, and acts. We received approval from the Medical
293 Research Ethics Committees United (MEC-U, Nieuwegein) and local approval has been obtained from
294 the institutional ethic review boards of each participating hospital. If deviation from the protocol is
295 necessary, it will not be implemented without the prior review and approval of the MEC-U and each
296 participating hospital's institutional ethic review board. Signed informed consent will be obtained from
297 all patients prior to any study procedure. Previous research demonstrated that (ICU-)VR is safe, feasible,
298 and well accepted.[26-28 51] Informed-consent forms will be kept in a locked cabinet in a limited-access
299 room in the ICU of the participating study sites. Data will be archived for 15 years. The handling of
300 personal data complies with the Dutch Law. On completion of the study, its findings will be published in
301 peer-reviewed journals and presented at the national and internationals scientific conferences to
302 publicize the research to healthcare professionals, health services authorities, and the public. A
303 summary of results will be made available to the study patients if requested.

304 **Patient and public involvement statement**

305 Former ICU patients were involved in the development of the ICU-VR intervention. Patients and/or the
306 public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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307 **Figures**

308 **Figure 1. Flow-diagram of the study.**

309 ICU, Intensive Care Unit; ICU-LOS, ICU length of stay; ICU-VR, ICU-specific Virtual Reality;

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Declarations

311
Authors' contributions

312 J.V., J.v.B., E.W., M.v.M., D.G., and M.v.G. conceived the study and initiated the study design. M.v.G.
313 is the coordinating investigator and grant holder. D.G. is the principal investigator. T.K. provided
314 statistical expertise in the clinical trial design, and J.V. and T.K. wrote the statistical analysis plan. M.v.M.
315 provided expertise in the field of psychology, and J.V. and M.v.M. determined what questionnaires are
316 used. J.v.B., E.W., F.T., A.S., J.L., J.E., A.R., A.D., and S.A. are the local principal investigators at each
317 study site. All authors contributed to the refinement of the study protocol and approved the study
318 protocol. J.V. and A.J. wrote the first draft of the manuscript, J.v.B., E.W., T.K., E.K., M.v.M., D.G.,
319 M.v.G. helped to further draft the manuscript. J.V. and A.J. will be responsible for data collection. All
320 authors approved the final version of the manuscript.

321
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323 Theia (grant number: 2020286), Stichting SGS (grant number: 2020355), and BeterKeten (for the
324 HORIZON-IC project; no grant number available). The funding sources had no role in the design of the
325 study and collection, analysis, and interpretation of data nor in writing the manuscript.

326
Competing interests statement

327 DG has received speaker fees and travel expenses from Dräger, GE Healthcare (medical advisory board
328 2009–12), Maquet, and Novalung (medical advisory board 2015–18). TK has received speaker fees

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329 from Quidel, IBSA, Merck, Berlin Chemie, and Goodlife Healthcare. All other authors declare no

330 competing interests.

331 **Data Sharing statement**

332 The de-identified individual clinical trial patient-level data will be shared as supplementary material when

333 publishing about the findings of the study.

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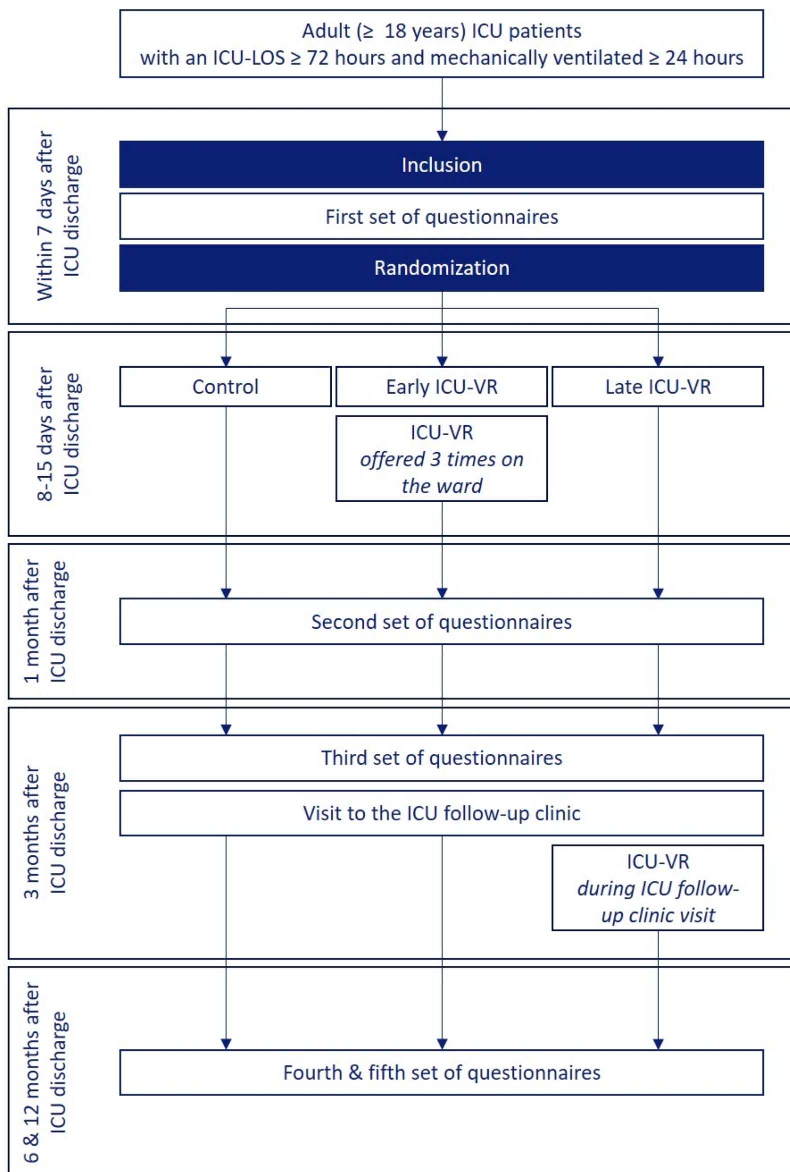

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Figure 1. Flow-diagram of the study.
ICU, Intensive Care Unit; ICU-LOS, ICU length of stay; ICU-VR, ICU-specific Virtual Reality.

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Supplementary File 1.

Translation of the video script of ICU-VR

Supplement to:

Johan H. Vlake, Jasper van Bommel, Evert-Jan Wils, Tim I.M. Korevaar, Eva Klijn, Anna F.C. Schut, Jan H. Elderman, Joost A.M. Labout, Adrienne Raben, Annemieke Dijkstra, Stefanja Achterberg, Amber L. Jurriens, Margo M.M.C. van Mol, Diederik Gommers, Michel E. van Genderen.

The effect of Intensive Care Unit-specific Virtual Reality (ICU-VR) to improve psychological well-being in ICU survivors: study protocol for a multicentre, randomised controlled trial - the HORIZON-IC study

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Scene 1. Introduction by an ICU physician and a nurse and tour around the ICU guided by a voice-over.

Setting: The ICU physician and nurse are placed in front of the ICU.

ICU physician: Hello, welcome to this virtual environment. My name is **'name physician'**, one of the physicians in this ICU.

ICU nurse: Hello, I am **'name nurse'**, one of the nurses in this ICU.

ICU physician: You were recently treated in the ICU. In this virtual environment, we provide you with explanations about the ICU and about the treatment you received here.

ICU nurse: Together, we will join you during this virtual reality experience. Therefore, we will first lay you down on an ICU bed, and then bring you to your ICU room.

Setting: The patient will be virtually installed on an ICU bed during a fade in-fade out.

ICU nurse: We will now bring you to your ICU room.

Setting: The ICU physician and ICU nurse will bring the patient to one of the ICU rooms while walking over the intensive care department.

Voice-over: Intensive care means intensive and special care for critically ill patients, where the most important vital functions, such as the respiratory rate, oxygen saturation and heart rate, can be monitored and supported, if needed. Therefore, this department is different from other departments. If you look around, you'll see the intensive care department. The intensive care department consists of several one-patient ICU rooms and a post for nurses located in the middle of the department. In an ICU room, circumstances and materials are available to offer critically ill patients the optimal treatment. Moreover, the chances of hospital acquired infections and medication failures are minimal, and a quiet environment is provided. At the nurse post, nurses are present throughout the day, as are monitors. As such, nurses can monitor you 24 hours per day. Nurses can also monitor patients physically through the windows of the room, which allows nurses to be able to continuously keep an eye on you.

Setting: The patient arrives at the ICU room, and the ICU physician and ICU nurse place the patient on the bed in the ICU room.

ICU physician: We are now entering an ICU room. Here, you'll receive an explanation about intensive care treatment. We will first explain the devices in the room, which are placed next to you. We will now leave the room and will come back after the explanation.

Setting: The ICU physician and ICU nurse will leave the room.

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Scene 2. Explanation of all devices and noises in an ICU room.

Voice-over: There are several devices next to you, such as a monitor, medication pumps and a mechanical ventilator; look around you. To adequately monitor you, we want to know immediately when something is changing. For instance when your blood pressure is low, or when you're out of medication. Each device has its own functions and alarm noise to warn ICU nurses and physicians. As a result, you often hear alarm noises in your ICU room. Besides using monitors, you are monitored also in other manners. We will now explain the functions of each device to you.

Setting: The surveillance monitor is outlined.

Voice-over: When you look to your left, you'll see the surveillance monitor.

Setting: A white arrow appears that points from the surveillance monitor to an explanation window in front of the patient, where the surveillance monitor is animated.

Voice-over: When you look forward again, we will explain the function of the surveillance monitor. The surveillance monitor monitors heart rate, blood pressure, respiratory rate, and oxygen saturation. If, for instance, your blood pressure is too low, the following alarm signal is produced to warn the ICU nurse.
<ALARM SIGNAL SURVEILLANCE MONITOR>

Setting: The explanation window disappears. The medication pumps are outlined.

Voice-over: If you look to your right, you'll see the medication pumps.

Setting: A white arrow appears that points from the medication pumps to an explanation window in front of the patient, where the medication pumps are animated.

Voice-over: These pumps are used to give medication. When you hear the following sound,

<ALARM SIGNAL MEDICATION PUMPS>

the nurse is warned that your medication is almost empty.

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Scene 3. Explanation about mechanical ventilation, intubation, and tracheal tube suction.

Setting: The explanation about the mechanical ventilator disappears, and an animation appears in the explanation window explaining intubation and mechanical ventilation.

Voice-over: Because you were critically ill, we decided to support your breathing. This was done to maintain the appropriate amount of oxygen in your body. To support your breathing, we inserted a tracheal tube. This tube is placed through your mouth into your trachea. To make sure this procedure is carried out optimally and because this procedure is often uncomfortable, you were sedated during the insertion of the tube. At the end of the tube, there is a small air balloon, which is filled with air. This balloon prevents the leakage of oxygen and the contents of the stomach from entering the lungs. Due to the placement of the tube between the vocal cords, patients cannot talk when they are intubated. When the lungs have sufficiently recovered, the tracheal tube can be removed. The tracheal tube is frequently cleaned by suctioning the tube. The nurse will slide a suctioning tube in the tube. Hereby, mucus will be removed, and infections will be prevented. Sometimes, it will be enough to do this once, but this has to be repeated often.

Setting: The explanation window disappears. The mechanical ventilator is outlined.

Voice-over: If you look to your left, you'll see the mechanical ventilator.

Voice-over: When you look in front of you, we will give you a further explanation about the mechanical ventilator. The mechanical ventilator supports your breathing. If you heard the following sound,
<ALARM SIGNAL MECHANICAL VENTILATOR>
the nurse was warned.

Setting: The animation of the mechanical ventilator disappears, and the explanation about prone positioning is animated in the explanation window.

Voice-over: As a consequence of several diseases, including coronavirus, the alveoli and pulmonary vessels can partially close, resulting in the body being unable to absorb sufficient oxygen. There are relatively more alveoli in the back of the lungs. In the occasion mechanical ventilation in a normal position is no longer effective, it can be decided to ventilate patients in the prone position or laying on their stomach. The alveoli and pulmonary vessels in the back of the lungs are thereby better ventilated, hopefully resulting in better absorption of oxygen.
Often, there is an immediate improvement in the mechanical ventilation conditions after prone positioning. To prevent pressure marks on the face, the eyes are protected and the head is placed in a position to the side. Over time, the positive effect of this prone position diminishes, and the patient is again placed on their back. Therefore, it is often decided to ventilate in prone positioning for several hours and thereafter again on the back for several hours. Because prone positioning can be uncomfortable, patients are sedated.

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Scene 4. Explanation about central/peripheral lines, intravenous drips and the gastric tube,

Setting: The explanation window disappears, and the ICU physician and nurse enter the room.

ICU physician: The different devices, the mechanical ventilator and the alarm signals have just been explained to you. Now, you will receive an explanation concerning the drips, infusions and gastric tube.

Setting: The ICU physician and nurse leave the room.

Voice-over: IV drips and lines are necessary not only to administer medication and fluids but also to continuously monitor the blood pressure.

Setting: The explanation window appears, and the function of a peripheral drip is explained using an animation.

Voice-over: This is an 'ordinary' IV drip, also called a peripheral IV drip. This is usually inserted into a vessel in the forearm, but sometimes, it is placed in the foot. The nurse can administer medication or fluid through this drip. Because these peripheral vessels are thin, not every medication can be administered through the veins.

Setting: Explanation of a central line is explained using an animation.

Voice-over: Here, you see a central line. This is a think IV drip that is inserted into a large blood vessel, often in the neck or groin. The insertion of such a line will be performed in a sterile manner; therefore, a blue cloth is stretched over your head. Working in a sterile field minimises the risk of infection. The main reason to insert a central line is to administer medications that cannot be administered through ordinary IV drips. Nutrition can also be directly administered to the blood stream through a central line.

Setting: Explanation of an arterial line is explained using an animation.

Voice-over: This is an arterial line. This is an IV drip that is placed directly into an artery, so blood pressure can continuously be monitored. It is also used to take blood samples. Without such a line, blood samples may have to be taken too often.

Setting: Explanation about a gastric tube is given using an animation.

Voice-over: A gastric tube is a tube that is placed through the nose or mouth through the oesophagus into the stomach. The tube is usually to administer tube feedings. It can also be used to administer medications.

Setting: The tracheotomy procedure is explained using an animation.

Voice-over: When patients are mechanically ventilated for a prolonged period of time, they sometimes receive a tracheotomy. During a tracheotomy procedure, a tube (also known as a cannula) is placed in the trachea through the neck. This cannula replaces the ventilation tube, which is inserted through the mouth. There are several reasons to perform a tracheotomy, but the most important one is long-term mechanical ventilation. The patient must be slowly and gradually weaned off mechanical ventilation. Tracheotomy placement is often conducted in the ICU. The cannula is inserted just above the sternum through an incision

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in the trachea. The end of the tube can be inflated to prevent air leakage. Because the air flows through the cannula to the lungs and no air passes the vocal cords, patients initially cannot speak when they have a tracheotomy. However, the tracheal cannula can be closed using a speaking valve, whereby the end of the cannula is deflated; as a result, air will flow through the vocal cords making it possible to speak. The tracheostomy will be removed when a patient has sufficient strength to breath on their own and can cough up sputum properly.

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Scene 5. Explanation about the treatment team and ICU workflow.

Setting: The explanation window disappears, and an ICU physician, nurse and resident enter the ICU room.

Voice-over: In the ICU, you are treated 24 hours per day by a treatment team. Therefore, there are many people working in the ICU.
The medical treatment team that is primarily responsible for your treatment includes the ICU physician, the ICU resident and the ICU nurse.

ICU physician: My fellow ICU physicians and I, the intensivists, are specialised in the treatment of critically ill patients. Every morning, afternoon and evening, there is a meeting with the treatment team taking care of you to discuss how you are doing. This will take place in your room.

Resident Hello, my name is **'name resident'**, and I am the resident, a doctor in training to become a medical specialist. My fellow residents and I are responsible for the daily medical care, in which we are always supervised by the intensivists.

ICU nurse: My fellow ICU nurses and I will look after you, monitor you continuously and are trained to operate the devices for your treatment. You will be taken care of by the same nurse every shift.

Setting: The treatment team leaves the room.

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Scene 6. Explanation about isolation and personal protection measures.

Voice-over: During your stay in the ICU, you are treated in isolation. Isolation measures are aimed at preventing the spread of microorganisms, such as coronavirus. These measures are in addition to the basic hygiene measures. We will now show you how this was done.

Setting: The treatment team returns to the room with isolation measures.

Voice-over: The treatment team has applied isolation measures when entering the room by wearing personal protective equipment. Before entering the room, the team was therefore wearing: Non-sterile gloves, a mouth-nose mask, an isolation apron with long sleeves, safety glasses, a hair cap.
Prior to leaving the room, the personal protective equipment is removed and hands are disinfected.

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Scene 7. Outro

Setting: The explanation window disappears and the ICU physician and nurse re-enter the room.

ICU physician: We hope you now have a better understanding of the treatment you received in the ICU. This is the end of this video, you can remove the VR glasses.

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Supplementary File 2.

Translation of the information for participants and informed consent form.

Supplement to:

Johan H. Vlake, Jasper van Bommel, Evert-Jan Wils, Tim I.M. Korevaar, Eva Klijn, Anna F.C. Schut, Jan H. Elderman, Joost A.M. Labout, Adrienne Raben, Annemieke Dijkstra, Stefanja Achterberg, Amber L. Jurriens, Margo M.M.C. van Mol, Diederik Gommers, Michel E. van Genderen.

The effect of Intensive Care Unit-specific Virtual Reality (ICU-VR) to improve psychological well-being in ICU survivors: study protocol for a multicentre, randomised controlled trial - the HORIZON-IC study

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Participants information for participation in medical scientific research

The effect of Intensive Care-specific Virtual Reality (ICU-VR) on psychological complaints after Intensive Care treatment.

Introduction

Dear Sir / Madam,

Using this letter, we would like to inquire whether you would be interested to participate in medical research. Participation is on voluntary basis. You are receiving this letter because you have been treated in the intensive care unit for more than three days and were mechanically ventilated.

In this letter, we will inform you about the nature of the study, what participation means, and what the benefits and disadvantages are of participation. Would you like to carefully read the entire letter prior to deciding whether you want to participate? If you are willing to participate, you can fill in and sign the form that you can find in Appendix B. You are given 1 to 4 days to consider your participation; we will ask you to make a decision about participation no later than seven days after your discharge from the intensive care unit.

Ask your questions

You can make your decision using the information you will find in this information letter. In addition, we recommend you to:

- Ask questions to the investigator who has provided you with this information.
- Talk about participation in this study with your partner, family or friends.
- Ask questions to the independent expert, [redacted] (Appendix A)
- Read the information provided on www.rijksoverheid.nl/mensenonderzoek.

1. General information

This study was initiated by the Franciscus Gasthuis & Vlietland and Erasmus MC. We will refer to the Franciscus Gasthuis & Vlietland and the Erasmus MC as the 'sponsor'. Investigators, which can be personified by doctors, nurses and student investigators, conduct the study in several hospitals. Hospitals participating in this study include the Erasmus MC, Franciscus Gasthuis & Vlietland, Ikazia hospital, and Maasstad hospital in Rotterdam, the IJsselland hospital in Capelle aan den IJssel, the Van Weel-Bethesda Hospital in Dirksland, the Groene Hart Hospital in Gouda, the Haaglanden Medical Centre in The Hague and the Albert Schweitzer hospital in Dordrecht.

A total of 300 participants are needed for this study. The United Medical Ethics Committee (MEC-U) in Nieuwegein, a medical ethical review committee, has approved this study.

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2. What is the aim of the study?

In this study, we investigate whether an Intensive Care-specific Virtual Reality intervention, ICU-VR, can effectively reduce psychological impairments in patients who have been treated in an intensive care unit. Additionally, we study whether ICU-VR improves quality of life.

For this we compare three groups of patients;
1) patients not receiving ICU-VR,
2) patients receiving ICU-VR three times in the first two weeks after ICU discharge and
3) patients who receive ICU-VR during an ICU follow-up visit three months after discharge from the intensive care unit.

ICU-VR is an information film about the intensive care unit that can be watched using virtual reality. This film is implemented in the SyncVR Relax & Distract application. This application is approved for use in patients to help reduce stress and anxiety. Virtual reality, or VR, means virtual reality or apparent reality. The ICU-VR film lasts approximately 12 minutes. During the ICU-VR film, you will be virtually brought back to the intensive care unit and you will receive explanation about various aspects of the intensive care unit environment and treatment. During this explanation, you will be virtually laid down in an intensive care bed. You can always interrupt the ICU-VR film. In the latter case, you may decide to continue watching ICU-VR later on, or to not continue watching ICU-VR.

3. What is the background of the study?

In the Netherlands, approximately 90,000 adult patients are annually treated in an intensive care unit due to a critical illness. The chances of surviving life-threatening conditions such as cardiac arrest, trauma or sepsis have greatly improved over the past twenty years. In recent years, it has become increasingly apparent that surviving an acute and life-threatening critical illness can have long-term consequences on quality of life.

Many patients experience an intensive care unit treatment as stressful due to the different experiences and emotions they have during the intensive care unit stay. Think of moments of shortness of breath, having pain, feelings of powerlessness and fear of dying. Former intensive care unit patients therefore have an increased risk of developing psychological impairments, such as post-traumatic stress disorder (PTSD), anxiety, or depression. About 1 out of 5 former intensive care unit patients develop symptoms that are suitable with PTSD in the first year after discharge from the intensive care unit and 1 out of 3 develop symptoms of depression or symptoms that are suitable with an anxiety disorder. Although symptoms of PTSD, anxiety disorders and depression are most common in the first months after discharge, these can also last for years after discharge from the intensive care unit.

Recent studies show that treatment with Virtual Reality (VR) is beneficial for non-ICU patients with various psychological problems such as anxiety, PTSD and depression. We have previously shown that the use of Intensive Care-specific Virtual Reality is safe in intensive care unit patients. Additionally, ICU-VR appears to have a positive effect on the psychological recovery of patients treated for sepsis in the intensive care unit. In this study, we aim to investigate the effect of ICU-VR again in a larger group, to be sure whether ICU-VR can help to reduce psychological impairments and improve quality of life.

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4. How is the study progressing?

How long does the study take?

Are you participating in this study? Participation will last until twelve months after your discharge from the intensive care unit.

Step 1: Are you eligible to participate?

We first want to know if you are eligible to participate.

All patients who have been treated in the intensive care unit for at least three days and who have been mechanically ventilated at least 24 hours, are eligible to participate in this study. However, it is important that you are clear in mind and can make a well-considered decision. In addition, you must have enough understanding of the Dutch language to understand ICU-VR and to complete the questionnaires.

Step 2. Informed Consent

Within the first week after you are discharged from the intensive care unit, a doctor, nurse or investigator has given information about the study. You have also received this information letter. We ask you to carefully and thoroughly read this letter, and consider participation.

You will be given one to four days for your consideration. Here after, the doctor, nurse or investigator will visit you again. You will then have the opportunity to ask questions about the study. If you want to participate in the study, you, together with the doctor, investigator or nurse, will sign the consent form on the last page of this letter. By signing the informed consent form, you indicate that you have received sufficient information about the study, that you have had the opportunity to ask questions about the study, and that you want to participate in this study on that basis. After that, a short check-up will be carried out to determine whether you are clear in mind.

Step 3. Questionnaire and randomization

Once you have signed the consent form, you will receive the first questionnaire. First, we want to investigate how your psychological state and quality of life were before you were admitted to hospital. Secondly, we want to investigate your current psychological state and quality of life. It takes approximately 40 minutes to complete this questionnaire.

In addition, participants in this study will be randomly assigned to **three groups.** This randomization, comparable with a lottery, decides to which group you are assigned and will be conducted after having singed the informed consent form. The investigator or doctor **does not have any influence** on the outcome of the randomization. You therefore do not know in advance which group you will end up in, and you are not allowed to indicate a preference for this.

The three groups are as follows:

1) The control group. Participants in this group **will not receive ICU-VR.** You will receive the same care as if you did not participate in this study, but are additionally asked to fill out questionnaires.
2) The **early ICU-VR** group. Participants in this group will receive ICU-VR for **a maximum of three times**, between 8 and 15 days after your discharge from the intensive care unit, if you are still in the hospital ward. When you are discharged from the hospital, you will no longer be offered ICU-VR.

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3) The **late ICU-VR** group. Participants in this group will receive **ICU-VR during a visit to our intensive care unit follow-up clinic**, where you will be invited three months after your discharge from the intensive care unit.

Step 4. Intensive Care Unit-specific Virtual Reality

Participants in the early or late ICU-VR group will receive ICU-VR at least once. As previously described, ICU-VR is a 12-minute informational film about the Intensive Care Unit. To view ICU-VR, we use our Virtual Reality glasses. **Image 1** shows what these glasses look like (left), and how the VR glasses are used (right). You will also be explained how to use the VR glasses and how to behave in the virtual environment when you receive ICU-VR.

Image 1. On the left you see the VR glasses that will be used during this study. You put the glasses over your eyes, as shown on the right. The VR glasses use light that is harmless to your eyes. You can keep your glasses on while using the VR glasses.

Step 5: Intensive care unit follow-up clinic

Three months after your discharge from the intensive care unit, we will invite you to visit our intensive care unit follow-up clinic. During this visit, you and an ICU nurse and/or doctor will review your stay in the intensive care unit. They will see if you need help from other healthcare providers, such as a physiotherapist or psychologist, and you can ask questions about your intensive care unit stay. Prior to this visit you will be asked to complete questionnaires, which will be sent to you by e-mail or postal mail.

Step 6: Questionnaires

All participants will be asked to complete questionnaires on 5 time points during the study. You will receive the first questionnaire immediately after signing the consent form, as described in 'Step 2'. In addition, you will be asked to complete questionnaires 1 month, 3 months (before the visit to the aftercare outpatient clinic), 6 months and 12 months after your discharge from the intensive care unit. The length of the questionnaires varies per follow-up time point. Completing the questionnaires will take approximately 30 to 45 minutes per questionnaire.

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5. What commitments do you make when participating?

We would like this study to be conducted as intended. Therefore, we ask you to honour the following commitments:

- If you are in a group receiving ICU-VR, you are willing to watch ICU-VR and you will try to watch the entire film. Of course, you can stop if you want to, for example if it gets too intense or you have nausea symptoms.
- During this study, you will not also participate in other medical scientific research without discussing this with the investigator. He/she can determine whether or not you can simultaneously participate in the other study.
- You visit the intensive care unit follow-up clinic when you are invited. If you are unable to attend on the proposed date, please try to find another date for this appointment.
- You complete the questionnaires at the requested time points. The investigator will also send you reminders. If you are unable to complete the questionnaires yourself, ask a family member/friend/girlfriend to help you with this.
- You contact the investigator in these situations:
  - You will be re-admitted to the hospital or the intensive care unit.
  - You no longer wish to participate in the study.
  - Your contact details, such as your telephone number, address or e-mail address, change.

6. What side effects, adverse effects or inconveniences may you experience?

We have shown in previous studies that the use of ICU-VR for patients is safe. There were no serious or long-lasting side effects. However, virtual reality can cause short-term complaints that resemble motion sickness. Think of nausea or dizziness, both during the film and just after the film. These complaints are usually mild in nature, last a few minutes and go away on their own. If the complaints persist for longer, you can contact someone from the study team. Their contact details are listed in **Appendix A.**

7. What are the advantages and disadvantages of participating in the study?

Participating in the study may have advantages and disadvantages. We list them below. Consider these when considering participation, and talk about them with others.

A possible advantage of participating in this study is that it may lead to a better psychological recovery and a better quality of life after your intensive care unit stay. However, this is **not certain and is being investigated in this study.** In addition, this only applies to patients who have been randomized to the early or late ICU-VR group and who have received ICU-VR.

A disadvantage is that it takes time to complete the questionnaires. In addition, you must adhere to the commitments as discussed in section 5. Also, if you are randomized to the early or late ICU-VR group, you may experience side effects as described in section 6.

Don't want to participate?

You are the one to decide whether or not you want to participate. Do you not want to participate? This is no problem, and nothing will change with regard to how you are treated.

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8. When will the study end?

The investigator will let you know if there is new information about the study that is important for you as participant. The investigator will then ask you whether you want to continue your participation.

In these situations, the study will stop for you:

- You completed the last questionnaire 12 months after you were discharged from the intensive care unit.
- You decide that you no longer wished to participate. You can always terminate your participation. We ask you to immediately inform the investigator if you wish to no longer participate. You don't have to give a reason why you wish to no longer participate. Discontinuation of your participation will never have consequences for your treatment.
- The investigator thinks it's better for you to stop.
- One of the following authorities decides that the study should be terminated:
  - The sponsor,
  - the government, or
  - the medical ethics committee that assesses the research.

What happens if you stop the study?

The investigators may use your data which is collected until the moment you decide to discontinue your participation. If you want, data that is collected from you can be deleted. You can request this by the investigator.

The entire study will be ended if all participants have completed their last questionnaire.

9. What happens after the study?

Within twelve months after you completed the last questionnaire, the investigator will contact you to ask if you would like to be informed about the most important findings of the study.

10. What do we do with your data?

Are you participating in the research? Then you also give permission to collect, use and store your data.

What data do we keep?

We keep this data:

- your name
- your gender
- your (e-mail) address
- your date of birth
- information about your treatment in the intensive care unit
- data that we collect during the research, such as the outcomes of the questionnaires

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Why do we collect, use and store your data?

We collect, use and store your data to answer the questions of this study. And to be able to publish the results.

How do we protect your privacy?

To protect your privacy, a code will be assigned to all your data. This code will be the only identifier for your data. The key, which makes it possible to link the code with you, will be stored in a safe place in the intensive care unit where you were treated. When we process your data, we will only use this code. In reports or publications about the study, we will ensure no participants can be identified based on the data provided.

Who has access to your data?

There are persons can be given permission to access the data without codes. These are persons who monitor whether the study is conducted properly and reliably, and according to all regulations.

Persons who will be given permission are:

- A monitor who is an employee of the Erasmus MC
- National supervisory authorities.

These persons will treat you data confidentially. By consenting to participate in this study, you also give permission that your data can be monitored by these.

How long do we keep your data?

We store your data for 15 years in the hospital where you were treated, or in a secured online database.

Can you withdraw your consent to the use of your data?

You can always withdraw your consent for the use of you data. However, if you withdraw your consent, and the investigators have already collected data for the study, the investigator is allowed to use the data collected until the consent was withdrawn.

Would you like to know more about your privacy?

- Do you want to know more about your rights with regard to the use of your data? You can take a look at www.autoriteitpersoonsgegevens.nl.
- Do you have any questions about your right? Or do you have complaints about the use of your data? You may contact the person who is responsible to the collection of your data. For this study, this will be the principle investigator, of whom the contact details can be found in **Appendix A of this letter**.
- If you have complaints about the use of your data, we would recommend to first discuss these with the investigators of the study. You can also contact the Data Protection Officer of the hospital where you relative was treated. Their contact details are stated below. You can also file a complaint by the Authority of Personal Data.

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Where can you find more information about the study?

On the website www.trialregister.nl you will find more information about the study. After the study, the website may display a summary of the findings of this survey. You can find the study by searching for 'ICU-VR for patients in the ICU' (number: NL78555.100.078)

11. Will you be financially compensated when you participate in the study?

Participation in this study is free of charge. You will neither receive any compensation for participation in this study, also no travel or expense reimbursement.

12. Are you insured during the study?

You are not extra insured for this research, because participating in the research has no additional risks. Therefore, the investigators do not need to purchase additional insurance from the United Medical Ethics Committee, the medical ethics review committee that approved this study.

13. Do we inform your GP?

As participation to this study is not expected to have any negative consequences for your health, or the health of your family members/relatives, we will not inform you general practitioner about your participation in this study. You are however free to tell your general practitioner yourself, and he/she can contact the study team for questions.

14. Do you have questions?

Questions about the study can be asked to the study team. The contact details of the study team are stated in **Appendix A**. Would you like to be advised by someone who is not involved in the study team? You can then contact dr. [redacted], his contact details are in **Appendix A.** He is an independent expert of the study, and has thereby the knowledge to answer your questions and give you advice, but is not involved in the study.

Do you have a complaint? Then discuss this with the investigator or the doctor who is treating you. Do you prefer to talk to somebody else? You may contact the complaints officer or complaints committee of your hospital, or the Authority of Personal Data. **Appendix A** shows where you can find them.

15. How do you give consent for the study?

You should first think about participating in this study. Therefore, you should tell the investigator whether you have understood the provided information and whether or not you would like to participate. If you want to participate, you will be asked to fill out and sign the informed consent form on the last page of this letter. Both you as the investigator will receive a copy of the signed version of the informed consent form.

Thank you for your time.

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16. Attachments to this information

A. Contact Details

B. Consent Form

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Appendix A: Contact Details

Research team:

[redacted], executive investigator, first contact person

Mail: [redacted]

Telephone: [redacted]

Accessibility: Working days between 09.00 and 18.00

[redacted], coordinating investigator

Mail: [redacted]

Telephone: [redacted]

Accessibility: Working days between 09.00 and 18.00

[redacted], principal investigator

Mail: [redacted]

Telephone:

Intensive Care: [redacted]

Hospital: 010 704 07 04

Accessibility: Working days between 09.00 and 18.00

Independent physician:

[redacted]

Mail: [redacted]

Telephone:

Intensive Care: [redacted]

Hospital: [redacted]

Accessibility: Working days between 09.00 and 18.00

Complaints:

Do you have a complaint? Then discuss this with the researcher or the doctor who is treating you. Would you rather not? Then go to the complaints officer or complaints committee of your hospital ([redacted]). You can submit your complaint digitally ([redacted]), by mail ([redacted]), by post ([redacted]) or by telephone ([redacted]).

Erasmus MC Data Protection Officer:

Mail: [redacted]

Phone number: [redacted]

For more information about your rights, please contact Hans Vlake. He is responsible for the processing of your personal data.

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Appendix B. Informed Consent Form

Related to to: 'The effect of Intensive Care-specific Virtual Reality (ICU-VR) on psychological complaints after Intensive Care treatment.'

- I have read the information letter. I have been given the opportunity to ask additional questions, and my questions are answered sufficiently. I have had enough time to consider participation.
- I know that participation is on a voluntary basis. I also know that I can always decide to not participate or to stop participation. I do not have to give any reason if I decide not to participate or to stop participation.
- I give consent to the investigators to collect and use my data. The investigators will only collect and use data to answer the research question of the study.
- I am aware that there are persons who can be granted permission to access my data to monitor the study. I give consent to these persons to access my data.
- I give permission to collect, store and use my data to answer the research question: **☐YES / ☐ NO**
- I give permission to contact me after this study to ask if I am interested to participate in another, related study: **☐YES / ☐ NO**
- I want to participate in this research.

My name is (participant): ……………………………….

Signature: ……………………… Date : __ / __ / __

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I declare that I have fully informed this subject about the said study.

If new insights will be obtained about the study, which could influence the participant's decision to participate in the current study, I will timely inform the participant.

Name of investigator (or its representative):……………………………….

Signature:……………………… Date: __ / __ / __

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The participant will receive a complete copy of the information letter, including a (copy of the) signed version of the informed consent form.

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Supplementary File 3.

SPIRIT Checklist

Supplement to:

Johan H. Vlake, Jasper van Bommel, Evert-Jan Wils, Tim I.M. Korevaar, Eva Klijn, Anna F.C. Schut, Jan H. Elderman, Joost A.M. Labout, Adrienne Raben, Annemieke Dijkstra, Stefanja Achterberg, Amber L. Jurriens, Margo M.M.C. van Mol, Diederik Gommers, Michel E. van Genderen.

The effect of Intensive Care Unit-specific Virtual Reality (ICU-VR) to improve psychological well-being in ICU survivors: study protocol for a multicentre, randomised controlled trial - the HORIZON-IC study

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	4-13
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	15
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 15
	5b	Name and contact information for the trial sponsor	1, 15
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	15
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	10, 15

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Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4, 5
	6b	Explanation for choice of comparators	4, 5, 6, 7
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	1, 6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6, 10
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6-10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8-10
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7

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Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9-11
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8-10
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	N/A

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Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	9
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11-12
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11-12
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11-12
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	N/A
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	12-13
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	12-13

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Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	10
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	15
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	12-13
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	15
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary File 2
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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