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Complete List of Authors:	Vlake, Johan; Erasmus Medical Center, Intensive Care; Franciscus Gasthuis en Vlietland, Intensive Care van Bommel, Jasper; Erasmus MC, Department of Intensive Care Wils, Evert-Jan; Franciscus Gasthuis en Vlietland, Intensive Care Korevaar, Tim; Erasmus Universiteit Rotterdam Hellemons, Merel; Erasmus Medical Center, Pulmonology Klijn, Eva; Erasmus MC, Department of Intensive Care Schut, Anna; Ikazia Hospital, Intensive Care Labout, Joost; Maasstad Hospital, Intensive Care Van Bavel, Marten; Erasmus MC, Department of Intensive Care Van Mol, Margo; Erasmus Universiteit Rotterdam, Intensive Care Adults Gommers, Diederik; Erasmus MC, Intensive Care Van Genderen, Michel; Erasmus MC, Department of Intensive Care
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Virtual reality for relatives of ICU patients to improve psychological sequelae: study protocol for a multicentre, randomized controlled trial.

Johan H. Vlake, BSc[1,2]; Jasper Van Bommel, MD, PhD[1]; Evert-Jan Wils, MD, PhD[2]; Tim I.M. Korevaar, MD, PhD[3,4]; Merel E. Hellemons, MD, PhD[5]; Eva Klijn, MD, PhD[1]; Anna F.C. Schut, MD, PhD[6]; Joost A.M. Labout, MD, PhD[7]; Marten P. van Bavel, BSc[1]; Margo M.C. van Mol, PhD[1]; Diederik Gommers, MD, PhD[1]; Michel E. van Genderen, MD, PhD[1,]

[1] Department of Intensive Care, Erasmus Medical Centre, Rotterdam, the Netherlands

[2] Department of Intensive Care, Franciscus Gasthuis & Vlietland, Rotterdam, the Netherlands

[3] Department of Internal Medicine, Erasmus Medical Centre, Rotterdam, the Netherlands

[4] Academic Centre for Thyroid Diseases, Erasmus Medical Centre, Rotterdam, the Netherlands

[5] Department of Pulmonology Medicine, Erasmus Medical Centre, Rotterdam, the Netherlands

[6] Department of Intensive Care, Ikazia Hospital, Rotterdam, the Netherlands

[7] Department of Intensive Care, Maasstad Hospital, Rotterdam, the Netherlands

Corresponding author:

Michel van Genderen

M.vanGenderen@erasmusmc.nl

Tel.: +31 10 704 0 704

ORCID: 0000-0001-5668-3435

Department of Intensive Care

Erasmus Medical Centre

Doctor Molewaterplein 40

3015 GD Rotterdam, the Netherlands

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ABSTRACT

Introduction Intensive Care Unit (ICU) admission of a relative might lead to psychological distress and complicated grief (post–intensive care syndrome–family; PICS-F). Evidence suggests that increased distress during ICU stay increases risk of PICS-F, resulting in difficulty returning to their normal lives after the ICU experience. Effective interventions to improve PICS-F are currently lacking. In the present trial, we hypothesized that information provision using Intensive Care Unit-specific Virtual Reality for Family members/relatives (ICU-VR-F) may improve understanding of ICU and subsequently improve psychological well-being and quality of life in relatives of patients admitted to the ICU.

Methods and analysis This multicentre, clustered randomized controlled trial will be conducted from January to December, 2021, in the mixed medical-surgical ICUs of four hospitals in Rotterdam, the Netherlands. We aim to include adult relatives of 160 ICU patients, with an expected ICU length-of-stay over 72 hours. Participants will be randomized clustered per patient in a 1:1 ratio to either the intervention or control group. Participants allocated to the intervention group will receive ICU-VR-F, an information module that can be watched in VR, while the control group will receive usual care. Initiation of ICU-VR-F will be during their hospital visit, unless participants cannot visit the hospital due to COVID-19 regulations, than VR can be watched digitally. The primary objective is the effect of ICU-VR-F on psychological well-being and quality of life up to 6 months after ICU discharge of the patient. The secondary outcome is the degree of understanding of ICU treatment and ICU modalities.

Ethics and dissemination The Medical Ethics Committee of the Erasmus Medical Centre, Rotterdam, the Netherlands, approved the study, and local approval was obtained from each

participating centre (NL73670.078.20). 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, NL9220, registered January 25, 2021).

Strengths and limitations of this study

- A randomized controlled trial examining the effect of an intensive care unit-specific virtual reality intervention for family members/relatives (ICU-VR-F) on psychological well-being and quality of life using an innovative and uniform modality.
- ICU-VR-F represents an easy applicable, safe, and immersive modality to improve communication through better information provision regarding treatment- and environment-related information about the ICU, enabling relatives to receive uniform and complete information.
- ICU-VR-F is an innovative method that is generalizable and makes information easy accessible and immersive.
- Blinding of patients or investigators is not possible due to the nature of the intervention.

INTRODUCTION

An Intensive Care Unit (ICU) admission is known to be a stressful experience for both the patient and its relatives. As a result, relatives of ICU patients are at risk of developing several psychological symptoms, such as symptoms of post-traumatic stress disorder (PTSD), anxiety, depression, and complicated grief in the unfortunate event of a patient dying during ICU treatment. These impairments are collectively referred to as the Post-Intensive Care Syndrome Family (PICS-F).[1-3]

PICS-F frequently results in loss of employment, financial burden, lifestyle interference, and a profound impact on quality of life.[4] These consequences often last a long time and already start during ICU stay of their kin.[5] Important risk factors for the development of PICS-F are the unexpectedness of critical illness, the dramatic nature of the relatives' experience leading to emotional upset, the level of communication of the ICU staff, and the use medical jargon, that frequently makes it hard for the relative to understand the treatment explanation.[6-11] As such, relatives may witness invasive treatments with unfamiliar medical procedures and devices in an environment they do not understand. Therefore, communication between ICU staff and families is essential in the care process, and good communication and information provision improves the relatives' understanding of ICU treatment, satisfaction, limit lawsuits, and is associated with lower prevalence of PTSD during the ICU stay.[12-14] As such, good information provision to relatives of ICU patients is essential in improving the relatives' comprehension of ICU procedures and ICU surrounding during the ICU stay.

During the COVID-19 pandemic, many hospitals worldwide disallowed visitors for all adult inpatients including all COVID-19 and non-COVID ICU patients. Relatives of ICU COVID-19 patients are therefore

confronted with the impracticableness of visiting their relative in the ICU or to receive good communication from the ICU staff. In the face of mounting the increase in PICS-F-related sequelae, several interventions, such as information brochures, family conferences, and educational programs for relatives, have been tested, but did not result in a clinically meaningful improvement in psychological well-being or quality of life.[15 16] The COVID-19 pandemic has resulted in the disruption of an integral aspect of care in most ICUs across the world and the importance of generalizable and on demand information has been addressed. To date, a clinically meaningful, simple and generalizable intervention remains unavailable.

Virtual Reality (VR) is a relatively new technique that allows the user to fully immerse within a virtual environment. As such, it allows relatives to experience what the patient is experiencing during ICU treatment, possibly leading to a better comprehension of ICU stay. VR has been demonstrated to be an appropriate tool to deliver additional information to increase patient satisfaction and reduce preoperative stress.[17] Additionally, exposure through VR appears to be an effective treatment modality for several mental health disorders, including PTSD, depression, and anxiety, in a non-ICU setting.[18-21] It provides an innovative modality that is generalizable and could improve the relatives' understanding of what is happening to long-stay ICU patients, without increasing staff workload. We hypothesized that offering treatment- and environment-related information about the ICU via VR increases relatives' understanding of ICU treatment and environment and improves psychological well-being and quality of life.

METHODS AND ANALYSIS

Study design and setting

This study will be a multicentre, clustered randomized trial conducted in the mixed medical-surgical ICUs of four hospitals in Rotterdam, the Netherlands. Cooperating hospitals are: the Erasmus MC (university hospital), Franciscus Gasthuis & Vlietland hospital, Ikazia hospital and Maasstad hospital (all teaching hospitals). The Medical Ethics Committee of the Erasmus MC approved this study (NL73670.078.20, approved December 14, 2020), and local approval was obtained from each participating centres' institutional ethic review board. The study will be conducted from January to December 2021. Participants will be followed for 6 months after patient's ICU discharge. Any modifications to the study protocol, which may impact the conduct of the study or participant 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 Medical Ethics Committee of the Erasmus MC prior to implementation, and the health authorities will be informed in accordance with local regulations.

Study participants

We aim to include relatives, or close friends in absence of relatives, of 160 ICU patients. Relatives ≥ 18 years of age, who are a first/second degree relative of the ICU patient, are responsible for decision making, or sharing the same household are eligible for inclusion. Multiple relatives per patient can participate. In this case, they will be clustered to the same randomization allocation. Relatives with no formal address, unable to understand the Dutch language, not in possession of a smartphone or tablet to watch ICU-VR-F at home, or relatives of patients with an expected ICU-LOS less than 72 hours will

be excluded. Close friends are eligible for inclusion in the case that no relative is available. Close friends are considered close friends if they address themselves as close friends and are responsible for decision making.

Intervention

An interdisciplinary team of three intensivists, a psychologist, and a VR/film director designed an Intensive Care Unit-specific Virtual Reality for relatives (ICU-VR-F) of ICU patients. Based on these focus group meetings and previous studies, the following information was included in the module: 1) an introduction by an intensivist and an ICU nurse to welcome the relative to the ICU and VR environment explaining daily movements at an ICU, 2) explanation of monitors and noises in an ICU room, 3) information regarding mechanical ventilation, intubation and tracheal tube suction, 5) necessity of central/peripheral lines and IV/drips, 6) information and necessity of the treatment team and ICU workflow.[22 23] The ICU-specific VR module was designed with the aim to show relevant and truthful treatment- and ICU environment-related information . The point of view for the camera was the field of vision of the mock patient lying in a hospital bed.

Study procedures

Outcome variables will be collected at each time point, see *Figure 1*. Relatives or close friends will be approached by an investigator of the research team within 2 days after ICU admission. After inclusion, they will receive a first set of questionnaires (T0), consisting of a self-composed questionnaire regarding demographics, psychological well-being , and quality of life. Participants are asked to fill in the first set of questionnaires retrospectively, in order to obtain a measure of participant's anxiety and depression

levels and quality of life prior to the current episode of the patient's illness leading to ICU admission. Hereafter, randomization will be done.

After randomization, participants in the intervention group will receive ICU-VR using head-mounted display VR (Oculus Go, Irvine, CA, CE: R-CMM-OC8-MH-A). Thereafter, they receive cardboard VR glasses and an access link to watch ICU-VR-F at home, which can also be used without the cardboard VR glasses. Participants who are not allowed to visit the hospital due to COVID-19 regulations, i.e., mandatory self-quarantine, inability to visit the ICU, or a limited number of visitors, will only receive ICU-VR-F using cardboard VR glasses via the access link. The number of times a participant watches ICU-VR-F will be logged. Participants have access to the module during the entire study period, including follow-up. Participants will receive a second set of questionnaires during ICU discharge of their relative to assess their understanding of ICU procedures and environment, and will receive follow-up questionnaires at 1 month, 3 months, and 6 months after ICU discharge (*Table 1*).

The study procedures of participants in the intervention group who are allowed to visit the hospital are presented in *Figure 2* and for those who are not allowed to visit the hospital in *Figure 3*.

Randomization and masking

Randomization will be on a 1:1 ratio, clustered based on the ICU patient (i.e., if multiple relatives of one ICU patient participate, they will all be randomized to the same group), stratified for study site and the ability to visit the hospital with regard to COVID-19 regulations. Randomization will be performed using

a centralized internet-based randomization procedure (Castor EDC, Amsterdam, the Netherlands). Due to the nature of the intervention, blinding is not possible.

Outcomes and measurements

The primary endpoint is the effect of ICU-VR-F on psychological well-being and quality of life in participants up to six months after ICU discharge. Psychological well-being will be expressed as the presence and severity of PTSD-, anxiety-, and depression-related symptoms, and will be assessed using the Impact of Event Scale-Revised (IES-R) and Hospital Anxiety and Depression Scale (HADS).[24] [25] Quality of life will be assessed using the RAND-36.[26] The secondary endpoint is the participants' understanding of ICU procedures, i.e., monitors, sounds and daily work practice. Understanding of ICU procedures will be assessed using a subset of the Consumer Quality Index – Relatives in the ICU (CQI-Relatives in the ICU).[27] Additional outcomes are adequate understanding about the ICU environment and procedures (devices, treatment team, alarm noises, procedures) and the perspectives of participants about ICU-VR-F, assessed using the Caregivers Strain Index (CSI), a self-composed 'perceived stress factors' questionnaire, and a self-composed 'perspectives on the ICU-VR intervention' questionnaire.

The IES-R comprises 22 items, assesses subjective distress caused by a traumatic event, and has been previously validated in ICU survivors.[28] The IES-R yields a total score (ranging from 0 to 88, with higher scores indicating more severe symptoms), and subscale scores can be calculated for symptoms of intrusion, avoidance and hyperarousal. An IES-R sum score ≥24 will be considered as PTSD.[29] [30]

The HADS comprises 14 items and is commonly used to determine the levels of anxiety and depression that a person is experiencing. A sum score > 8 on either the depression (7 questions) or anxiety (7 questions) subscale will be classified as depression and anxiety, respectively.[24 31 32]

The RAND-36 consists of 8 scaled scores, which 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 equal weight. The 8 sections are vitality, physical functioning, bodily pain, general health perception, physical role functioning, emotional role functioning, social role functioning and mental health. In addition, a mental- and physical component scale can be calculated, giving a perception of a person's physical and mental health.[26]

The CQI-Relatives in the ICU was designed by the Healthcare Institute of the Netherlands in collaboration with several hospitals to measure the perceived quality of care by relatives of ICU patients.[27] The subset used in the present study was carefully tailored to the needs of the current study. Therefore, unnecessary items for this study were removed, and additional VR-specific questions were added. The subset consists of 38 items, distributed across 4 sections; 1) general questions, 2) questions regarding information provision and understanding of the ICU environment, 3) questions regarding care offered to relatives and 4) questions regarding the communication with the ICU staff.

The self-composed perceived stress factors questionnaire was based on existing literature regarding risk factors for the development of PICS-F, including time spent for visitation, worries about the physical, cognitive and psychological state of the patient, worries about family and familiarity with an ICU. The final questionnaire comprises 18 questions ranging from 0 (Not at all) to 4 (A lot) on a Likert scale.

The self-composed perspectives on the ICU-VR intervention questionnaire comprises 13 questions.

Data management

Data will be uploaded, stored, and maintained on the electronic data capture system of Castor (Castor EDC, www.castoredc.com, Amsterdam, the Netherlands). The study team will be responsible for all data entry and quality control activities. The 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 ICUs of the participating hospitals. Questionnaires will be sent digitally using Castor EDC or hardcopy via postal mail whenever requested.

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

Sample size calculation

To the best of our knowledge, this study will be the first of its kind for which no previous conducted studies can be used to define the expected effect estimate. Due to expected non-normality of PTSD, depression, and anxiety scores at 6 months after ICU discharge, this calculation could represent an overestimation of the effect estimate. Based on our clinical experience, and experience with a pilot study studying the effects of ICU-VR on ventilated ICU patients for which we found Cohen's *d* effect size of 0.77, we expect that a clinically meaningful Cohen's *d* effect size of 0.55 could be expected in relatives.[23] When taking this into account, using a two-sided alpha of 0.05, and a power of 0.80, assuming an

expected loss-to-follow-up of 20%, we aim to include relatives of 160 ICU patients. We expect a needed time of six months on the admission rate history of the participating hospitals.

Statistical analysis

Baseline demographics and treatment-related characteristics will be quantified using descriptive statistics. Continuous variables will be presented as mean (SD) or as median (95% range), based on the distribution of the variable. Categorical variables will be presented as absolute number and relative frequency.

A sensitivity analysis will be performed in which missing data (completely) at random will be dealt with utilizing both multiple imputation according to the Markov-chain Monte Carlo and the Last Observation Carried Forward Method.[33 34] We will correct for multiple testing using the false discovery rate with a maximum of 5% false negatives.[35]

For the primary outcome, the effect of ICU-VR on PTSD, anxiety, depression, and quality of life, we will analyse differences in the IES-R sum score (PTSD), the HADS anxiety- and depression score, and the RAND-36 subscales (quality of life) between participants in the intervention and the control group at each follow-up time-point (e.g., 1 month, 3 months, and 6 months after ICU discharge) using a mixed effect linear regression model with a random intercept for each study site and/or participants based on model comparisons using the Akaiki information criteria. In case of multiple participants for one ICU patient, these participants will be considered as clustered, and a random intercept for each cluster will be used. Between-group differences in variables of interest throughout follow-up were studies by introducing the product of time*treatment group to the model.

Differences in the proportion of participants in the intervention group and participants in the control group with clinically relevant symptoms of PTSD (IES-R sum score ≥ 22), depression (HADS depression score > 8) or anxiety (HADS anxiety score > 8) will be analysed using a mixed effect logistic regression model. Also, changes from baseline will be computed dividing the parameter value at specific time points into the baseline value expressed as percentile changes (% of baseline). The magnitude of change among PTDS, depression, and anxiety at specific time points and differences will be tested using a mixed effect linear regression model.

For the secondary outcome, understanding of the ICU and quality of care in the ICU, we will analyse differences between study groups per question using a mixed effect logistic regression model. By combining the numeric values of the answers given, a sum score and subscales for the different sections can be calculated for each participant. The association between the intervention and these sum scores will be examined using mixed effect linear regression models.

The explorative outcomes, the perceived stress factors and the perspectives of relatives on the ICU-VR-F intervention, will be described using descriptive statistics. Differences in continuous outcomes of the self-composed questionnaire regarding perceived stress factors and the sum score of the CSI will be analysed using mixed effect linear regression models. Differences in categorical outcomes of the self-composed questionnaire regarding perceived stress factors will be analysed using mixed effect logistic regression models.

In analysis, participants will be stratified on the ability to watch the intervention within the hospital to address possible difference in effectiveness. All data will be gathered using Castor EDC (Castor EDC,

Amsterdam, the Netherlands). Analyses will be performed using SPSS (version 27.0; SPSS Inc., Chicago, IL) and R for Statistics (R Foundation for Statistical Computing, Vienna, Austria, 2015). A *P*-value ≤ 0.05 will be considered statistically significant.

Ethics and dissemination

This study will be conducted in accordance with the principles of the Declaration of Helsinki (version October 2013; www.wma.net) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and other guidelines, regulations, and acts. We received approval from the Medical Ethics Committee (METC) of the Erasmus MC, and local approval has been obtained from each participating centre. If deviation from the protocol is necessary, then it will not be implemented without the prior review and approval of the METC. Signed informed consent will be obtained from all participants. Previous research demonstrated that (ICU-)VR is safe.[17 22 23 36] Informed-consent forms will be kept in a locked cabinet in a limited-access room at the Erasmus MC. 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 national and international scientific conferences to publicize the research to healthcare professionals, health services authorities and the public. A summary of the results will be made available to the study patients if requested.

Patient and public involvement statement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Tables

Table 1. Questionnaire per follow-up moment.

Questionnaire:	**T0.** At ICU admission	**T1.** At ICU discharge	**T2/T3/T4** Follow-up (1/3/6 months)
Baseline demographics	X	X	X
HADS (Anxiety and Depression)	X (retrospectively)		X
IES-R (Post-Traumatic Stress Disorder)		X	X
RAND-36 Quality of Life	X (retrospectively)		X
Subset CQI-Relatives in the ICU Understanding ICU procedures		X	
CSI Caregiving Concerns			X
Perceived Stress Factors		X	
Perspectives on the ICU-VR-F intervention		X	X

Abbreviations: CSI, caregivers strain index; CQI, consumer quality index; HADS, hospital anxiety and depression scale; ICU, intensive care unit; ICU-VR-F, intensive care unit-specific virtual reality for relatives; RAND-36; research and development 36-item questionnaire.

Figures

Figure 1. Flow-diagram of the study.

Abbreviations: CSI, caregivers strain index; HADS, hospital anxiety and depression scale; ICU, intensive care unit; ICU-LOS, Intensive Care Unit length-of-stay; ICU-VR-F, Intensive Care Unit-specific Virtual Reality for Family members/relatives; IES-R, impact of event scale-revised; RAND-36, research and development 36-item questionnaire.

Figure 2. Overview of procedures for relatives in the intervention group who are allowed to visit the hospital.

Figure 3. Overview of procedures for relatives in the intervention group who are not allowed to visit the hospital.

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Authors' contributions

J.V., J.v.B., E.W., D.G., and M.v.G. conceived the study and initiated the study design. M.v.G. is the coordinating investigator and grant holder. D.G. is the principal investigator. T.K. provided statistical expertise in the clinical trial design, and J.V. and T.K. wrote the statistical analysis plan. J.v.B., E.W., J.L., and A.S. are the local principal investigators at each study site. All the authors contributed to the refinement of the study protocol and approved the final manuscript. J.V. and M.v.B. wrote the first manuscript draft. J.V. and M.H. composed the questionnaires used in the study. J.V. and M.v.B. will collect the data and conduct the study.

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Competing interests statement

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

Patient and public involvement statement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Data Sharing statement

Not applicable.

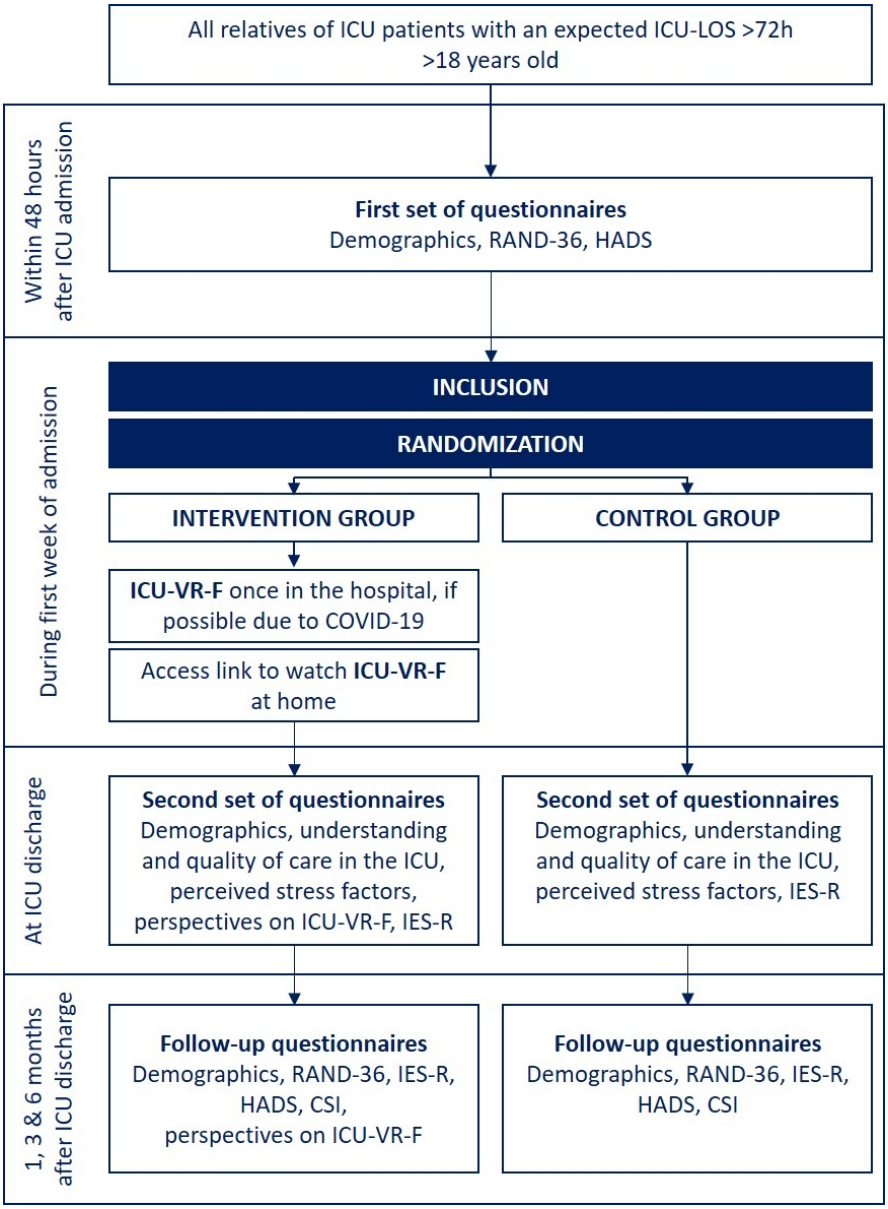

Figure 1. Flow-diagram of the study.
Abbreviations: CSI, caregivers strain index; HADS, hospital anxiety and depression scale; ICU, intensive care unit; ICU-LOS, Intensive Care Unit length-of-stay; ICU-VR-F, Intensive Care Unit-specific Virtual Reality for Family members/relatives; IES-R, impact of event scale-revised; RAND-36, research and development 36-item questionnaire.

147x200mm (150 x 150 DPI)

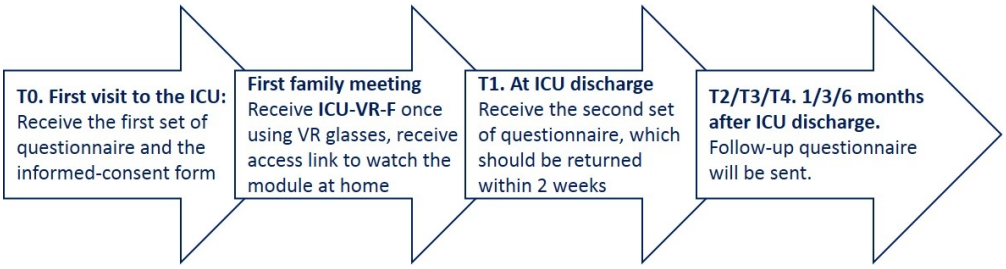

Figure 2. Overview of procedures for relatives in the intervention group who are allowed to visit the hospital.

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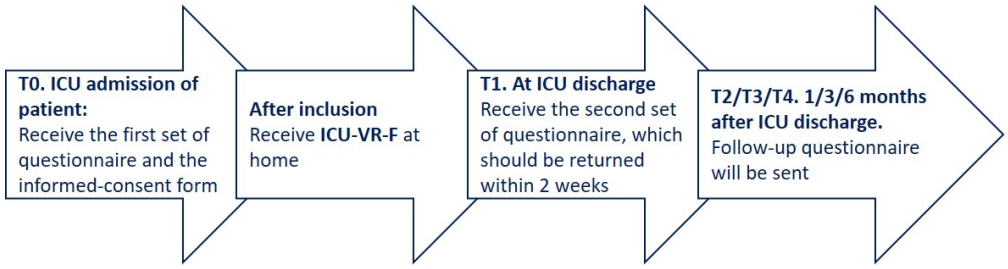

Figure 3. Overview of procedures for relatives in the intervention group who are not allowed to visit the hospital.

199x52mm (150 x 150 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

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		Reporting Item	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
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	17
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	17

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#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	17
Roles and responsibilities: committees	#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)	11
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	1-2
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	N/A
Objectives	#7	Specific objectives or hypotheses	2
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, non-inferiority, exploratory)	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
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will	6

		perform the interventions (eg, surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6
Interventions: modifications	#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
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	N/A
Interventions: concomitant care	#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	8-9
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
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
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	7

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	7
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	7
Methods: Data collection, management, and analysis			
Data collection plan	#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	9
Data collection plan: retention	#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	9
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
Statistics: outcomes	#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	10
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10

Statistics: analysis population and missing data	#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)	10
Methods: Monitoring			
Data monitoring: formal committee	#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
Data monitoring: interim analysis	#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	11
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	6, 11
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)	N/A
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
Consent or assent: ancillary studies	#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	9

Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	9
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: trial results	#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	11
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
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

BMJ Open

Virtual reality for relatives of ICU patients to improve psychological sequelae: study protocol for a multicentre, randomized controlled trial.

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Virtual reality for relatives of ICU patients to improve psychological sequelae: study protocol for a multicentre, randomized controlled trial.

Johan H. Vlake, BSc[1,2]; Jasper Van Bommel, MD, PhD[1]; Evert-Jan Wils, MD, PhD[2]; Tim I.M. Korevaar, MD, PhD[3,4]; Merel E. Hellemons, MD, PhD[5]; Eva Klijn, MD, PhD[1]; Anna F.C. Schut, MD, PhD[6]; Joost A.M. Labout, MD, PhD[7]; Marten P. van Bavel, BSc[1]; Margo M.C. van Mol, PhD[1]; Diederik Gommers, MD, PhD[1]; Michel E. van Genderen, MD, PhD[1,]

[1] Department of Intensive Care, Erasmus Medical Centre, Rotterdam, the Netherlands

[2] Department of Intensive Care, Franciscus Gasthuis & Vlietland, Rotterdam, the Netherlands

[3] Department of Internal Medicine, Erasmus Medical Centre, Rotterdam, the Netherlands

[4] Academic Centre for Thyroid Diseases, Erasmus Medical Centre, Rotterdam, the Netherlands

[5] Department of Pulmonology Medicine, Erasmus Medical Centre, Rotterdam, the Netherlands

[6] Department of Intensive Care, Ikazia Hospital, Rotterdam, the Netherlands

[7] Department of Intensive Care, Maasstad Hospital, Rotterdam, the Netherlands

Corresponding author:

Michel van Genderen

M.vanGenderen@erasmusmc.nl

Tel.: +31 10 704 0 704

ORCID: 0000-0001-5668-3435

Department of Intensive Care

Erasmus Medical Centre

Doctor Molewaterplein 40

3015 GD Rotterdam, the Netherlands

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ABSTRACT

Introduction Intensive Care Unit (ICU) admission of a relative might lead to psychological distress and complicated grief (post–intensive care syndrome–family; PICS-F). Evidence suggests that increased distress during ICU stay increases risk of PICS-F, resulting in difficulty returning to their normal lives after the ICU experience. Effective interventions to improve PICS-F are currently lacking. In the present trial, we hypothesized that information provision using Intensive Care Unit-specific Virtual Reality for Family members/relatives (ICU-VR-F) may improve understanding of ICU and subsequently improve psychological well-being and quality of life in relatives of patients admitted to the ICU.

Methods and analysis This multicentre, clustered randomized controlled trial will be conducted from January to December, 2021, in the mixed medical-surgical ICUs of four hospitals in Rotterdam, the Netherlands. We aim to include adult relatives of 160 ICU patients, with an expected ICU length-of-stay over 72 hours. Participants will be randomized clustered per patient in a 1:1 ratio to either the intervention or control group. Participants allocated to the intervention group will receive ICU-VR-F, an information module that can be watched in VR, while the control group will receive usual care. Initiation of ICU-VR-F will be during their hospital visit, unless participants cannot visit the hospital due to COVID-19 regulations, than VR can be watched digitally. The primary objective is to study the effect of ICU-VR-F on psychological well-being and quality of life up to 6 months after ICU discharge of the patient. The secondary outcome is the degree of understanding of ICU treatment and ICU modalities.

Ethics and dissemination The Medical Ethics Committee of the Erasmus Medical Centre, Rotterdam, the Netherlands, approved the study, and local approval was obtained from each

participating centre (NL73670.078.20). 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, NL9220, registered January 25, 2021).

Strengths and limitations of this study

- A randomized controlled trial examining the effect of an intensive care unit-specific virtual reality intervention for family members/relatives (ICU-VR-F) on psychological well-being and quality of life using an innovative and uniform modality.
- ICU-VR-F represents an easy applicable, safe, and immersive modality to improve communication through better information provision regarding treatment- and environment-related information about the ICU, enabling relatives to receive uniform and complete information.
- ICU-VR-F is an innovative method that is generalizable and makes information easy accessible and immersive.
- Blinding of patients or investigators is not possible due to the nature of the intervention.

INTRODUCTION

An Intensive Care Unit (ICU) admission is known to be a stressful experience for both patients and their relatives. As a result, relatives of ICU patients are at risk of developing several psychological symptoms, such as symptoms of post-traumatic stress disorder (PTSD), anxiety, depression, and complicated grief in the unfortunate event of a patient deceasing during ICU treatment; clinically relevant symptoms of PTSD occur in 21% of relatives of ICU patients, especially in relatives of adult patients, clinically relevant symptoms of anxiety occur in 40%, and clinically relevant symptoms of depression occur in 23%.[1-11] These impairments are collectively referred to as the Post-Intensive Care Syndrome Family (PICS-F).[6] [12 13]

PICS-F frequently results in loss of employment, financial burden, lifestyle interference, and a profound impact on quality of life.[14] These consequences often last a long time and already start during ICU stay of their kin.[3] Important risk factors for the development of PICS-F are the unexpectedness of critical illness, the dramatic nature of the relatives' experience leading to emotional stress, the level of communication of the ICU staff, and the use medical jargon, that frequently makes it hard for the relative to understand the treatment explanation.[1 8 10 11 15 16] As such, relatives may witness invasive treatments with unfamiliar medical procedures and devices in an environment they do not understand. Therefore, communication between ICU staff and families is essential in the care process, and good communication and information provision improves the relatives' understanding of ICU treatment, satisfaction, limit lawsuits, and is associated with lower prevalence of PTSD during the ICU stay.[5 17 18] As such, good

information provision to relatives of ICU patients is essential in improving the relatives' comprehension of ICU procedures and ICU surrounding during the ICU stay.

During the COVID-19 pandemic, many hospitals worldwide disallowed visitors for all adult inpatients including all COVID-19 and non-COVID ICU patients. Relatives of ICU COVID-19 patients are therefore confronted with the impracticableness of visiting their relative in the ICU or to receive good communication from the ICU staff, which may result in a higher psychological burden.[19 20] In the face of mounting the increase in PICS-F-related sequelae, several interventions, such as information brochures, family conferences, and educational programs for relatives, have been tested, but did not result in a clinically meaningful improvement in psychological well-being or quality of life.[21 22] The COVID-19 pandemic has resulted in the disruption of an integral aspect of care in most ICUs across the world and the importance of generalizable and on demand information has been addressed. To date, a clinically meaningful, simple and generalizable intervention remains unavailable.

Virtual Reality (VR) is a relatively new technique that allows the user to fully immerse within a virtual environment. As such, it allows relatives to experience what the patient is experiencing during ICU treatment, possibly leading to a better comprehension of ICU stay. Information provision using VR has shown to decrease preoperative anxiety in both adult and pediatric patients, to help women and their partner to feel better prepared for cesarean delivery, to successfully deliver healthcare related information to adults with intellectual disabilities, and to be an appropriate tool to deliver additional treatment-related information to increase patients' satisfaction.[23-26] Additionally, exposure through VR appears to be an effective treatment modality for several mental health disorders, including PTSD,

depression, and anxiety, in a non-ICU setting.[27-30] It provides an innovative modality that is generalizable and could improve the relatives' understanding of what is happening to long-stay ICU patients, without increasing staff workload. We hypothesized that offering treatment- and environment-related information about the ICU via VR increases relatives' understanding of ICU treatment and environment and improves psychological well-being and quality of life.

METHODS AND ANALYSIS

Study design and setting

This study will be a multicentre, clustered randomized trial conducted in the mixed medical-surgical ICUs of four hospitals in Rotterdam, the Netherlands. Cooperating hospitals are: the Erasmus MC (university hospital), Franciscus Gasthuis & Vlietland hospital, Ikazia hospital and Maasstad hospital (all teaching hospitals). The Medical Ethics Committee (MEC) of the Erasmus MC approved this study (NL73670.078.20, approved December 14, 2020), and local approval was obtained from the institutional ethic review boards of each participating hospital, i.e., the Franciscus Gasthuis & Vlietland hospital, the Ikazia hospital, and the Maasstad hospital. The study will be conducted from January to December 2021. Participants will be followed for 6 months after patient's ICU discharge. Any modifications to the study protocol, which may impact the conduct of the study or participant 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 of the Erasmus MC and local approval will be obtained from the institutional ethic review boards of each participating hospital prior to implementation. Accordingly, the health authorities will be informed in accordance with local regulations.

Study participants

We aim to include relatives, or close friends in absence of relatives, of 160 ICU patients. Relatives ≥ 18 years of age, who are a first/second degree relative of the ICU patient, are responsible for decision making, or sharing the same household are eligible for inclusion. Additionally, relatives should be able to understand the Dutch language to understand ICU-VR-F and should in possession of smartphone,

tablet or computer to watch ICU-VR-F at home. Multiple relatives per patient can participate; the primary contact person of the ICU patient will be approached firstly and will be invited to share the study information with other relatives that could be interested. There is no maximum number of relatives per patients that can participate. In the case of multiple relatives of the same patient participating, relatives of the same patient will be clustered to the same randomization allocation. Relatives with no formal address or relatives of patients with an expected ICU-LOS less than 72 hours will be excluded. Close friends are eligible for inclusion in the case that no relative is available. Close friends are considered close friends if they address themselves as close friends and are responsible for decision making. Relatives of patients who decease during ICU treatment will retrospectively be excluded from the main analysis.

Intervention

Patients will be randomized to receive standard care with additionally ICU-VR-F (intervention group) or standard care alone (control group).

The Intensive Care Unit-specific Virtual Reality for relatives of ICU patients (ICU-VR-F) was based on the previously described ICU-VR intervention for ICU patients and was designed by an interdisciplinary team of three intensivists, a psychologist, a former ICU patient, and a VR/film director. Based on these focus group meetings and previous studies, the following information was included in the module: 1) an introduction by an intensivist and an ICU nurse to welcome the relative to the ICU and VR environment explaining daily movements at an ICU, 2) explanation of monitors and noises in an ICU room, 3) information regarding mechanical ventilation, intubation and tracheal tube suction, 5) necessity of

central/peripheral lines and IV/drips, 6) information and necessity of the treatment team and ICU workflow.[31 32] The ICU-specific VR module was designed with the aim to show relevant and truthful treatment- and ICU environment-related information, and was hospital specific. The point of view for the camera was the field of vision of the mock patient lying in a hospital bed. The hospital specific ICU-VR-F from the Erasmus MC can be found here, from the Franciscus Gasthuis & Vlietland can be found here, and from the Ikazia hospital can be found here. The uniform video script can be found in the Supplementary Data.

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

Study procedures

Outcome variables will be collected at each time point, see *Figure 1*. The primary contact person of the ICU patient will be approached by an investigator of the research team within 2 days after ICU admission and will be asked to share the study information with other relatives. In case that other relatives were interested in participation, their contact details were shared by the primary contact person with the investigator so informed consent could be obtained. A translation of the information for participants and the informed consent form can be found in the Supplementary Data. After inclusion, they will receive a first set of questionnaires (T0), consisting of a self-composed questionnaire regarding demographics, psychological well-being , and quality of life. Participants are asked to fill in the first set of questionnaires

retrospectively, in order to obtain a measure of participant's anxiety and depression levels and quality of life prior to the current episode of the patient's illness leading to ICU admission. Hereafter, randomization will be done.

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

After randomization, participants in the intervention group will additionally receive ICU-VR using head-mounted display VR (Oculus Go, Irvine, CA, CE: R-CMM-OC8-MH-A). Thereafter, they receive cardboard VR glasses and an access link to watch ICU-VR-F at home, which can also be used without the cardboard VR glasses. Participants who are not allowed to visit the hospital due to COVID-19 regulations, i.e., mandatory self-quarantine, inability to visit the ICU, or a limited number of visitors, will only receive ICU-VR-F using cardboard VR glasses via the access link. The number of times a participant watches ICU-VR-F will be logged. Participants have access to the module during the entire study period, including follow-up. Participants will receive a second set of questionnaires during ICU discharge of their relative to assess their understanding of ICU procedures and environment, and will receive follow-up questionnaires at 1 month, 3 months, and 6 months after ICU discharge (*Table 1*).

The study procedures of participants in the intervention group who are allowed to visit the hospital are presented in *Figure 2* and for those who are not allowed to visit the hospital in *Figure 3*.

Randomization and masking

Randomization will be on a 1:1 ratio, clustered based on the ICU patient (i.e., if multiple relatives of one ICU patient participate, they will all be assigned to the same group), stratified for study site and the ability to visit the hospital with regard to COVID-19 regulations. Randomization will be performed using a centralized internet-based randomization procedure (Castor EDC, Amsterdam, the Netherlands). Due to the nature of the intervention, blinding is not possible.

Outcomes and measurements

The primary endpoint is the effect of ICU-VR-F on psychological well-being and quality of life in participants up to six months after ICU discharge. Psychological well-being will be expressed as the presence and severity of PTSD-, anxiety-, and depression-related symptoms, and will be assessed using the Impact of Event Scale-Revised (IES-R) and Hospital Anxiety and Depression Scale (HADS).[33 34] Quality of life will be assessed using the SF-36.[35 36] The secondary endpoint is the participants' understanding of ICU procedures, i.e., monitors, sounds and daily work practice. Understanding of ICU procedures will be assessed using a subset of the Consumer Quality Index – Relatives in the ICU (CQI-Relatives in the ICU).[37] Additional outcomes are adequate understanding about the ICU environment and procedures (devices, treatment team, alarm noises, procedures) and the perspectives of participants about ICU-VR-F, assessed using the Caregivers Strain Index (CSI), a self-composed 'perceived stress factors' questionnaire, and a self-composed 'perspectives on the ICU-VR intervention' questionnaire.

The IES-R comprises 22 items, assesses subjective distress caused by a traumatic event, and has been previously validated in ICU survivors.[38 39] The IES-R yields a total score (ranging from 0 to 88, with higher scores indicating more severe symptoms), and subscale scores can be calculated for symptoms of intrusion, avoidance and hyperarousal. An IES-R sum score ≥24 will be considered as PTSD.[40 41]

The HADS comprises 14 items and is commonly used to determine the levels of anxiety and depression that a person is experiencing. A sum score > 8 on either the depression (7 questions) or anxiety (7 questions) subscale will be classified as depression and anxiety, respectively.[33 42 43]

The RAND-36 consists of 8 scaled scores, which 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 equal weight. The 8 sections are vitality, physical functioning, bodily pain, general health perception, physical role functioning, emotional role functioning, social role functioning and mental health. In addition, a mental- and physical component scale can be calculated, giving a perception of a person's physical and mental health.[44]

The CQI-Relatives in the ICU was designed by the Healthcare Institute of the Netherlands in collaboration with several hospitals to measure the perceived quality of care by relatives of ICU patients.[37] The subset used in the present study was carefully tailored to the needs of the current study (Supplementary Data). Therefore, unnecessary items for this study were removed, and additional VR-specific questions were added. The subset consists of 38 items, distributed across 4 sections; 1) general questions, 2) questions regarding information provision and understanding of the ICU environment, 3)

questions regarding care offered to relatives and 4) questions regarding the communication with the ICU staff.

The self-composed perceived stress factors questionnaire was based on existing literature regarding risk factors for the development of PICS-F, including time spent for visitation, worries about the physical, cognitive and psychological state of the patient, worries about family and familiarity with an ICU. The final questionnaire comprises 18 questions ranging from 0 (Not at all) to 4 (A lot) on a Likert scale. The self-composed perspectives on the ICU-VR-F intervention questionnaire comprises 13 questions. Outcomes of these self-composed questionnaires will be used to determine different aspects of information that relatives were missing or were in need of in the current ICU-VR-F intervention. This data will be used to further improve the VR intervention and its content so it will better meet the needs of relatives. Translations of the self-composed questionnaires can be found in the Supplementary Data.

Data management

Data will be uploaded, stored, and maintained on the electronic data capture (EDC) system of Castor (Castor EDC, www.castoredc.com, Amsterdam, the Netherlands). The study team will be responsible for all data entry and quality control activities. The 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 ICUs of the participating hospitals. Questionnaires will be sent digitally using Castor EDC or hardcopy via postal mail whenever requested.

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

Sample size calculation

To the best of our knowledge, this study will be the first of its kind for which no previous conducted studies can be used to define the expected effect estimate. Due to expected non-normality of PTSD, depression, and anxiety scores at 6 months after ICU discharge, this calculation could represent an overestimation of the effect estimate. Based on our clinical experience, and experience with a pilot study studying the effects of ICU-VR on ventilated ICU patients for which we found Cohen's *d* effect size of 0.77, we expect that a clinically meaningful Cohen's *d* effect size of 0.55 could be expected in relatives.[32] When taking this into account, using a two-sided alpha of 0.05, and a power of 0.80, assuming an expected loss-to-follow-up of 20%, we aim to include relatives of 160 ICU patients. We expect a needed time of six months on the admission rate history of the participating hospitals.

Statistical analysis

Baseline demographics and treatment-related characteristics will be quantified using descriptive statistics. Continuous variables will be presented as mean (SD) or as median (95% range), based on the distribution of the variable. Categorical variables will be presented as absolute number and relative frequency.

A sensitivity analysis will be performed in which missing data (completely) at random will be dealt with utilizing both multiple imputation according to the Markov-chain Monte Carlo and the Last Observation Carried Forward Method.[45 46] We will correct for multiple testing using the false discovery rate with a maximum of 5% false negatives.[47]

For the primary outcome, the effect of ICU-VR on PTSD, anxiety, depression, and quality of life, we will analyse differences in the IES-R sum score (PTSD), the HADS anxiety- and depression score, and the RAND-36 subscales (quality of life) between participants in the intervention and the control group at each follow-up time-point (e.g., 1 month, 3 months, and 6 months after ICU discharge) using a mixed effect linear regression model with a random intercept for each study site and/or participants based on model comparisons using the Akaiki information criteria. In case of multiple participants for one ICU patient, these participants will be considered as clustered, and a random intercept for each cluster will be used. Between-group differences in variables of interest throughout follow-up were studies by introducing the product of time*treatment group to the model.

Differences in the proportion of participants in the intervention group and participants in the control group with clinically relevant symptoms of PTSD (IES-R sum score ≥ 22), depression (HADS depression score

> 8) or anxiety (HADS anxiety score > 8) will be analysed using a mixed effect logistic regression model. Also, changes from baseline will be computed dividing the parameter value at specific time points into the baseline value expressed as percentile changes (% of baseline). The magnitude of change among PTDS, depression, and anxiety at specific time points and differences will be tested using a mixed effect linear regression model.

For the secondary outcome, understanding of the ICU and quality of care in the ICU, we will analyse differences between study groups per question using a mixed effect logistic regression model. By combining the numeric values of the answers given, a sum score and subscales for the different sections can be calculated for each participant. The association between the intervention and these sum scores will be examined using mixed effect linear regression models.

The explorative outcomes, the perceived stress factors and the perspectives of relatives on the ICU-VR-F intervention, will be described using descriptive statistics. Differences in continuous outcomes of the self-composed questionnaire regarding perceived stress factors and the sum score of the CSI will be analysed using mixed effect linear regression models. Differences in categorical outcomes of the self-composed questionnaire regarding perceived stress factors will be analysed using mixed effect logistic regression models.

The main analyses will be conducted per protocol. In these, all patients who have received ICU-VR-F, either both in the hospital as at home or only at home, will be compared with those who did not, and patients of whom the relative has deceased during ICU treatment will be excluded. To determine whether there is a difference in effect between having watched ICU-VR-F the first time in the hospital

and having watched the ICU-VR-F only at home, we will use a dummy variables (ICU-VR-F in the hospital and at home / ICU-VR-F only at home / no ICU-VR-F) instead of the randomization variables in the mixed effects regression models, and determine whether that dummy variable has a significant contribution to the model. We will additionally perform an analysis in which 1) patients who did not watch ICU-VR-F in the hospital will be excluded and 2) patients who watched ICU-VR in the hospital will be excluded to determine whether there is a difference in effect.

All data will be gathered using Castor EDC (Castor EDC, Amsterdam, the Netherlands). Analyses will be performed using SPSS (version 27.0; SPSS Inc., Chicago, IL) and R for Statistics (R Foundation for Statistical Computing, Vienna, Austria, 2015). A *P*-value ≤ 0.05 will be considered statistically significant.

Ethics and dissemination

This study will be conducted in accordance with the principles of the Declaration of Helsinki (version October 2013; www.wma.net) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and other guidelines, regulations, and acts. We received approval from the Medical Ethics Committee (MEC) of the Erasmus MC, and local approval has been obtained from the institutional ethic review boards of each participating hospital, i.e., the Franciscus Gasthuis & Vlietland hospital, the Ikazia hospital, and the Maasstad hospital. If deviation from the protocol is necessary, then it will not be implemented without the prior review and approval of the MEC of the Erasmus MC and each participating hospital's institutional ethic review board. Signed informed consent will be obtained from all participants. Previous research demonstrated that (ICU-)VR is safe.[23 31 32 48] Informed-consent forms will be kept in a locked cabinet in a limited-access room at the Erasmus MC. 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 national and international scientific conferences to publicize the research to healthcare professionals, health services authorities and the public. A summary of the results will be made available to the study patients if requested.

Patient and public involvement statement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Tables

Table 1. Questionnaire per follow-up moment.

Questionnaire:	**T0.** At ICU admission	**T1.** At ICU discharge	**T2/T3/T4** Follow-up (1/3/6 months)
Baseline demographics	X	X	X
HADS (Anxiety and Depression)	X (retrospectively)		X
IES-R (Post-Traumatic Stress Disorder)		X	X
RAND-36 Quality of Life	X (retrospectively)		X
Subset CQI-Relatives in the ICU Understanding ICU procedures		X	
CSI Caregiving Concerns			X
Perceived Stress Factors		X	
Perspectives on the ICU-VR-F intervention		X	X

Abbreviations: CSI, caregivers strain index; CQI, consumer quality index; HADS, hospital anxiety and depression scale; ICU, intensive care unit; ICU-VR-F, intensive care unit-specific virtual reality for relatives; RAND-36; research and development 36-item questionnaire.

Figures

Figure 1. Flow-diagram of the study.

Abbreviations: CSI, caregivers strain index; HADS, hospital anxiety and depression scale; ICU, intensive care unit; ICU-LOS, Intensive Care Unit length-of-stay; ICU-VR-F, Intensive Care Unit-specific Virtual Reality for Family members/relatives; IES-R, impact of event scale-revised; RAND-36, research and development 36-item questionnaire.

Figure 2. Overview of procedures for relatives in the intervention group who are allowed to visit the hospital.

Figure 3. Overview of procedures for relatives in the intervention group who are not allowed to visit the hospital.

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Declarations

Authors' contributions

J.V., J.v.B., E.W., D.G., and M.v.G. conceived the study and initiated the study design. M.v.G. is the coordinating investigator and grant holder. D.G. is the principal investigator. T.K. provided statistical expertise in the clinical trial design, and J.V. and T.K. wrote the statistical analysis plan. J.v.B., E.W., J.L., and A.S. are the local principal investigators at each study site. All the authors contributed to the refinement of the study protocol and approved the final manuscript. J.V. and M.v.B. wrote the first manuscript draft. J.V. and M.H. composed the questionnaires used in the study. J.V. and M.v.B. will collect the data and conduct the study.

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Competing interests statement

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

Patient and public involvement statement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Data Sharing statement

The de-identified individual clinical trial participant-level data will be shared as supplementary material when publishing about the findings of the study.

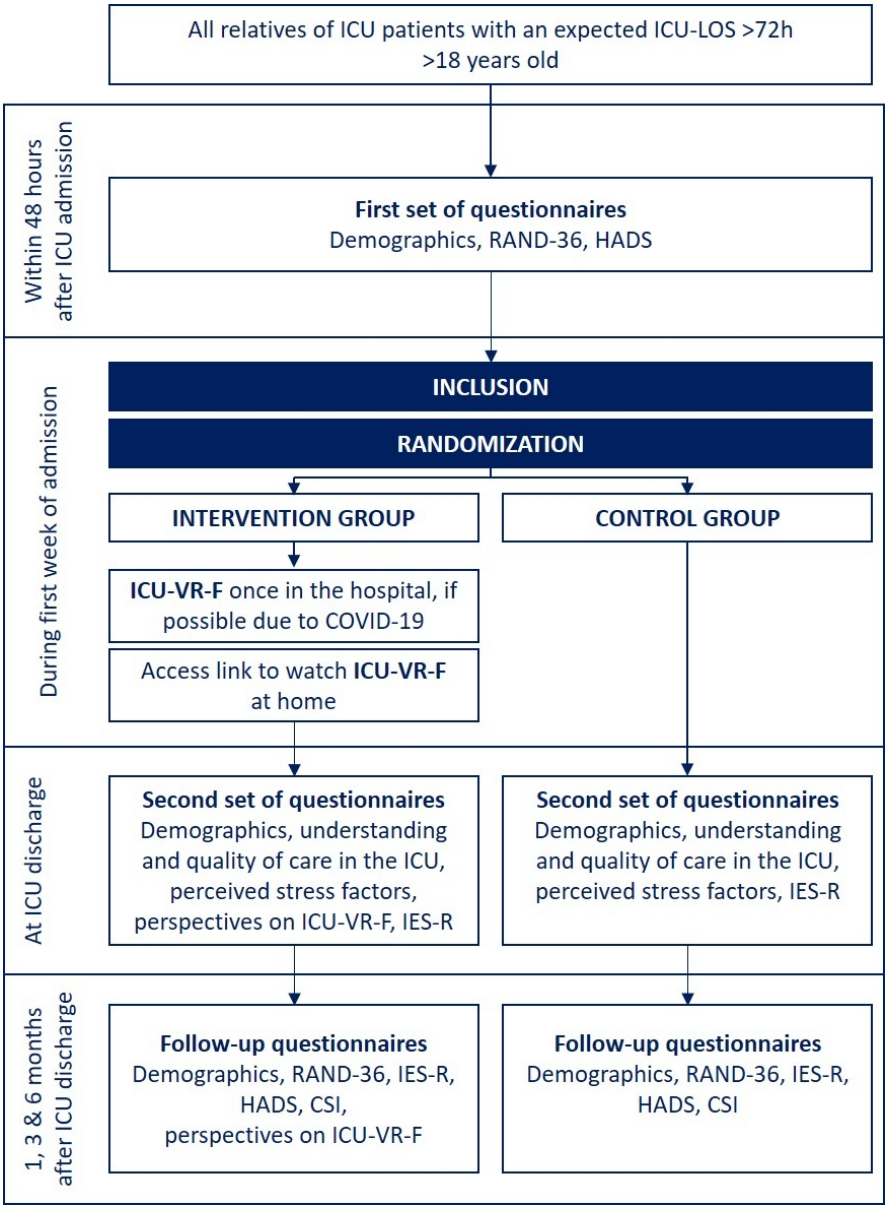

Figure 1. Flow-diagram of the study. Abbreviations: CSI, caregivers strain index; HADS, hospital anxiety and depression scale; ICU, intensive care unit; ICU-LOS, Intensive Care Unit length-of-stay; ICU-VR-F, Intensive Care Unit-specific Virtual Reality for Family members/relatives; IES-R, impact of event scale-revised; RAND-36, research and development 36-item questionnaire.

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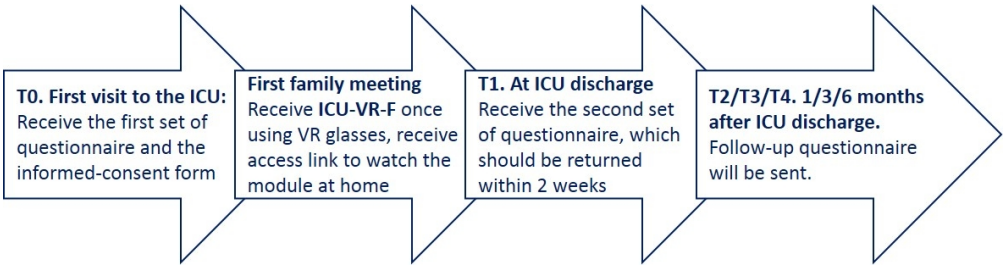

Figure 2. Overview of procedures for relatives in the intervention group who are allowed to visit the hospital.

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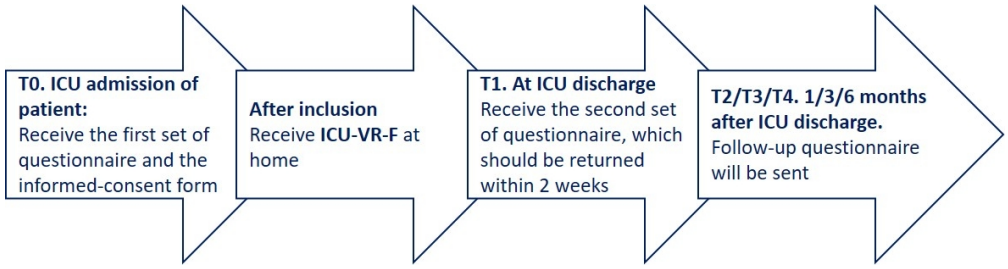

Figure 3. Overview of procedures for relatives in the intervention group who are not allowed to visit the hospital.

199x52mm (150 x 150 DPI)

Supplemental Data

Supplement to: Johan H. Vlake, Jasper van Bommel, Evert-Jan Wils, Tim I.M. Korevaar, Merel E. Hellemons, Eva Klijn, Anna F.C. Schut, Joost A.M. Labout, Marten P. van Bavel, Margo M.C. van Mol, Diederik Gommers, Michel E. van Genderen. Virtual reality for relatives of ICU patients to improve psychological sequelae: study protocol for a multicentre, randomized controlled trial.

Content

Supplementary data 1. Translation of the video script for the ICU-VR-F intervention.

Scene 1. Introduction by an ICU physician and a nurse.

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 receive this information because your relative has been admitted to the ICU. In this virtual environment, you will experience different facets of an ICU treatment, and receive explanation about the treatment in an Intensive Care Unit.

ICU nurse: We will join you during this experience, but we will first lay you down on an ICU bed.

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

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

Setting: The ICU physician and ICU nurse will bring the relative 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. 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. If you look around, you'll see the intensive care department. At the nurse post, nurses are present throughout the day, as are monitors. Nurses can also monitor patients physically through the windows of the room, which allows nurses to be able to continuously keep an eye on your relative.

Setting: The relative arrives at the ICU room, and the ICU physician and ICU nurse place the relative 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.

Scene 2. Explanation of the devices and alarm noises.

Voice-over: There are several devices next to you, such as a monitor, medication pumps and a mechanical ventilator; look around you. These devices are needed to monitor your relative. Each device has its own functions and alarm noise. We will now explain these 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 relative, 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 your relative's heart rate, blood pressure, respiratory rate, and oxygen saturation. If, for instance, your relative's blood pressure is too low, the following alarm signal is produced.

<ALARM SIGNAL SURVEILLANCE MONITOR>

Setting: The explanation window in front of the relative 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 relative, 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 relative's medication is almost empty.

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

Voice-over: Because your relative was critically ill, we can decide to support your relative's breathing. This was done to maintain the appropriate amount of oxygen in your relative's body. To support the breathing, we inserted a tracheal tube through the mouth into the trachea. Because this procedure is often uncomfortable, your relative will be 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. Hereby, mucus will be removed to prevent infections. 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.

Setting: A white arrow appears that points from the mechanical ventilator to an explanation window in front of the relative, where the mechanical ventilated is animated.

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 relative's breathing. If you hear the following sound,

<ALARM SIGNAL MECHANICAL VENTILATOR>

the nurse is 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.

Scene 3. Explanation concerning the drips, infusions and gastric tube.

Setting: The explanation window disappears, and the ICU physician appears.

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 disappears.

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 relative's 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 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.

Scene 4. Explanation about the treatment team and their responsibilities.
Setting: The explanation window disappears, and an ICU physician, nurse and resident enter the room.

Voice-over:	In the ICU, your relative is 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 relative's 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 your relative to discuss how you are doing. This will take place in your relative's room.
ICU resident:	Hello, my name is '**name resident**', I am a resident in the ICU. This means I am being trained to become an ICU physician. Together with my fellow residents, I am responsible for the daily medical care for your relative. Hereby, we are always supported by the ICU physicians.
ICU nurse:	My fellow ICU nurses and I will look after your relative, monitor your relative continuously and are trained to operate the devices for your treatment. Your relative will be taken care of by the same nurse every shift.

Setting: The treatment team leaves the room.

Scene 5. 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 your relative received in the ICU. This is the end of this video, you can remove the VR glasses.

Supplementary Data 2. Translation of the information for participants and informed consent form.

Participant information about participation in medical research.

Virtual Reality for family members / relatives of patients admitted to the ICU.

Official title: Intensive Care Unit specific Virtual Reality for family members (ICU-VR-F) of patients in the ICU.

Introduction

Dear sir, madam,

Using this letter, we would like to inquire whether you are interested in participation in medical research. Participation is on a voluntary basis. You have received this letter because your family member or relative has been admitted to the Intensive Care Unit (ICU) of the Erasmus MC, Franciscus Gasthuis & Vlietland, Ikazia hospital or Maasstad hospital.
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 informed consent form, which can be found on the last page of this letter.

Ask questions

You can use the information provided in this letter to make your decision. Besides, we would like to encourage 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]
- Read the information provided on www.rijksoverheid.nl/mensenonderzoek.

1. General information

This study was initiated by the Erasmus MC. We will refer to the Erasmus MC as the sponsor. Investigators, which can be personified by doctors, nurses and student-researchers, conduct the study in several hospitals, namely the Erasmus MC, the Franciscus Gasthuis & Vlietland, the Ikazia hospital, and the Maasstad hospital, all in Rotterdam.
For this research, we have a required sample size of 160 participants. The medical ethics committee of the Erasmus MC has approved this study.

2. Objectives of the study.

In the current study, we want to study whether information provision using an Intensive Care Unit-specific Virtual Reality intervention for Family Members, ICU-VR-F, can effectively mitigate psychological impairments after ICU treatment of a loved one. Additionally, we will study whether ICU-VR-F helps family members/relatives understand the environment and treatment in the ICU, and whether ICU-VR-F can attribute to the quality of life of relatives of former ICU patients.

To study this, we will compare family members/relatives who do not receive ICU-VR-F, the control group, with family members/relatives who do receive ICU-VR-F, the intervention group.

ICU-VR-F is an information film about the Intensive Care Unit which can be watched using virtual reality. Virtual reality, or VR, represents a virtual or apparent reality. ICU-VR-F lasts approximately 14 minutes. During ICU-VR-F, you are given explanation about several facets of the ICU environment and treatment. During this explanation, you will be laid down in an ICU bed. You can always interrupt ICU-VR-F. In the latter case, you may decide to continue watching ICU-VR-F later on, or to not continue watching ICU-VR-F.

3. Background of the study

An Intensive Care Unit treatment of a family member or relative in the ICU can be a stressful experience. It has been demonstrated that a considerable part of the family members/relatives of ICU patients develop psychological impairments in the period after the patient's ICU treatment. These impairments can comprise symptoms of a post-traumatic stress disorder (PTSD), anxiety disorder, or a depression. Additionally, family members/relative can experience a complicated grief in the unfortunate event of a patient deceasing in the ICU. It is known that proper information provision can help reducing or preventing the development of such complaints.

4. Progress of the study

How long will participation last?

Are you participating in this study? Participation will last until six months after your family member's/relative's discharge from the ICU.

Step 1: Are you suitable for participation?

We will first examine whether you are suitable for participation. All family members/relatives of patient admitted to ICU, of whom the doctors expect that they will be treated there for at least 72 hours, are eligible for participation. Because the explanation in ICU-VR-F is given in Dutch, and because the questionnaires for this study are written in Dutch, it is important that you have sufficient understanding of the Dutch language. You will also need to be in possession of a smartphone, tablet, or laptop which is compatible to use the VR function in YouTube, as you are given the opportunity to watch the intervention at home as well.

In the unfortunate event of your family member/relative deceasing in the ICU, we will ask you to reconsider participation. We will, of course, understand if you no longer wish to participate.

Step 2: Informed Consent

Within two days after your family member's/relative's ICU admission, the investigator has given information about the study, either by telephone or in person, and has sent you this letter. We ask you to carefully and thoroughly read this letter, and consider participation.

If you decide to participate in this study, you can sign the informed consent form which can be found on the last page of this letter. By signing the informed consent form, you confirm that you have been given enough information about the study, that you have been given the opportunity to ask questions, and, based on this information, wish to participate in the study.

Step 3: Randomization

Participants in this study will be randomly assigned to **two groups**. This randomization, comparable with a lottery, decides to which group you are assigned. The investigator or doctor **does not have any influence** on the outcome of the randomization.

The two groups are as following:

1) The control group. Participants assigned to this group will not receive ICU-VR during the study period.
2) The intervention group. Participants assigned to this group will receive ICU-VR-F once in the hospital and will be provided with an access link and cardboard VR glasses, making them able to watch ICU-VR-F at home as many times as wanted. If you are not allowed to visit the hospital due to COVID-19 regulations, you will only receive an access link and the cardboard VR glasses to watch ICU-VR-F at home.

Randomization will be conducted immediately after your decision to participate in the study.

Step 4a. Participants in the control group

Participants, who are assigned to the control group, will receive 'care as usual'. This means that nothing will change with regard to how family members/relatives are normally treated in the ICU.

We will however ask you to fill out several questionnaires. You will receive the first one at the time you decide to participate in the study. With this first questionnaire, we aim to determine your psychological state and quality of life prior to the hospitalization of your family member/relative and how you have experienced the ICU admission of your family member/relative. Completing this questionnaire will take approximately **30 minutes**.

Step 4b. Participants in the intervention group

Participants, who are assigned to the intervention group, will receive ICU-VR-F once within the hospital, if they are allowed to visit the hospital with regard to COVID-19 regulations. This will take place as soon as possible after you have decided to participate. To offer ICU-VR-F, we will use our virtual reality glasses. In **Figure 1** you will find a picture of the VR glasses on the left, and a person using the VR glasses on the right. Before you will receive ICU-VR-F, you will be explained how to use the VR glasses, and how to behave in the virtual environment. After you have received ICU-VR-F once with our VR glasses, you

will receive an access link and cardboard VR glasses. Using these, you can use ICU-VR-F again at home, as many time as wanted. You are also free to offer ICU-VR-F to friends or family. Family members/relatives, who are due to COVID-19 regulations not allowed to visit the hospital, will only receive the access link and cardboard VR glasses to watch ICU-VR-F at home.

Also, you will be asked to fill out several questionnaires. You will receive the first one at the time you decide to participate in the study. With this first questionnaire, we aim to determine your psychological state and quality of life prior to the hospitalization of your family member/relative and how you have experienced the ICU admission of your family member/relative. Completing this questionnaire will take approximately 30 minutes.

Figure 1. Picture of the VR glasses and its controller which will be used when offering ICU-VR-F in the hospital (left). On the right, you see a person using the VR glasses. VR glasses use light that is safe for your eyes. You can keep your own glasses on when using these VR glasses.

Step 5. After your family member's/relative's discharge from the ICU.

After your family member/relative has been discharge from the ICU, we will sent the second questionnaire. Follow-up questionnaire will thereafter be sent after 1 month, 3 months and 6 months. Using these questionnaires, we will measure you psychological state and quality of life. Completing these questionnaires will take approximately 30 minutes per time.

After you have completed the last questionnaire, which will be sent six months after your family member's/relative's ICU discharge, you will be finished with the study.

5. Which 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:

- You watch ICU-VR-F for the first time in the hospital in the way the investigator has explained, if you are allowed to visit the hospital.
- If you are not allowed to visit the hospital, you will watch ICU-VR-F at least once at home using the access link and cardboard VR glasses.
- You cannot participate in another medical study, unless the investigator has granted you permission. Permission can only be given if the other study will not confound the outcomes of this study.

- You complete the questionnaire at the described time-points. If you are unable to fill out the questionnaire by yourself, you may ask a family member or friend to help. If there are no family members or friends available, you may ask the investigator to complete the questionnaire by telephone.
- You contact the investigator in the following situations:
    - You no longer wish to participate in the study
    - Your phone number, home address, or e-mail address changes

6. Safety considerations

In previous studies, we have demonstrated the use of an Intensive Care Unit-specific Virtual Reality intervention is safe in healthy volunteers and in patients. Virtual reality can however cause short-term complaints, such as nausea, dizziness, or a spinning feeling during its use. These complaints are commonly mild or nature, lasts for several minutes, and will resolve spontaneously. If the complaints do not resolve, you can contact the investigator. You will find his phone number on page 9 of this letter.

7. Benefits and disadvantages of participation

Participation in this study can have benefits and disadvantages. We will describe these here. Consider these when considering participation, and talk about them with others.

A possible benefit of participation in this study is that receiving ICU-VR-F may improve understanding of the ICU and thereby reduce psychological complaints and improve quality of life after your relative's/family member's ICU treatment. This is however not certain and will be studied in this study.

The most important disadvantage of participation in this study, it that completing the questionnaire will take a considerable amount of time. Also, you have to honour the commitments as described in paragraph 5, and you may experience short-lasting complaints during ICU-VR-F, as described in paragraph 6.

If you 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 or your family member/relative is treated in the ICU.

8. End of the study.

The investigator will inform you when there is new information about the study, which is important for you as participant. The investigator will then ask you if you want to continue your participation.

In the following situations, the study will end for you:

- If you have completed the last questionnaire, which is sent to you six months after your family member's/relative's discharge from the ICU.
- If you decide that you no longer wishes 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 you or your family member/relative.
- If one of the following organization decide that the study should be terminated:
    - The Erasmus MC (sponsor)
    - The governance
    - The medical ethics committee which approved the study.

What happens if you decide that you no longer wishes to participate

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. After the study.

Approximately 6 months after you have completed your last questionnaire, the investigator will inform you about the most important findings of the study.

10. Usage of your data

If you participate in this study, you also consent to collect, use, and store your data.

Which data do we store?

We will store the following data:

- Your name
- Your gender
- Your (e-mail) address
- Your date of birth
- Data regarding your psychological well-being, extracted from the questionnaires
- Data which is collected during the study
- Treatment-related characteristics of your family member/relative.

Why do we collect, use, and store your data?

We collect, store, and use your data to answer the research 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 your family member/relative is 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 have access to you 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.

For how long will be store your data?

We will store your data for 15 years in the hospital.

Can you withdraw your consent for 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 on page 9 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.

Erasmus MC:

E-mail: [redacted]

Phone number: [redacted]

Franciscus Gasthuis & Vlietland

[redacted]

E-mail: [redacted]

Phone number: [redacted]

Ikazia hospital:

E-mail: [redacted]

Phone number: [redacted]

Maasstad hospital:

Legal Affairs Department / Data Protection Officer

Postal address: [redacted]

Phone number: [redacted]

Where to find more information about this study?

You may find more information about this study on www.TrialRegister.nl. When the study has ended, you may find a summary of the results of the study on this site. You can find the study by searching for 'ICU-VR for Family members' (number: NL73670.078.20).

11. Financial compensation for participation in this 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. Insurance.

The Erasmus MC has taken out an insurance for all participants in this study. The insurance will pay for damage due to participation in the study. This comprises damage during the study, or within 4 years after participation in the study. If you need a reimbursement, you should report damage within 4 years at the insurance company.

Have you suffered damage due to your participation in the study? You should report this to the insurer:

The contact details of the study's insurer are:	
Name:	[redacted]
Address:	[redacted]
	[redacted]
Phone number:	[redacted]
E-mail:	[redacted]

The insurance will cover a maximum of € 650.000 per participant, a maximum of € 5.000.000 for the entire study and € 7.500.000 per year for all studies initiated by the Erasmus MC.

Pay attention: the insurance will not cover the following damage:

- Damage due to a risk about which we informed you in this letter. However, if the damage turns out to be higher than we anticipated, or if the risk was very low, the insurance will cover this damage.
- Damage to your health which would have also developed if you hadn't participated in the study.
- Damage which is a direct consequence of not following given instructions or recommendations of the study team.
- Damage to the health of your children or grandchildren.
- Damage due to a treatment strategy which is already evidence based, or due to a study investigated an evidence-based treatment strategy.

These provisions are set out in the 'Compulsory insurance for medical research involving humans 2015 Decree'. This decision can be found in the Laws of the Government (https://wetten.overheid.nl).

13. Informing the general practitioner

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 below. Would you like to be advised by someone who is not involved in the study team? You can then contact dr. [redacted] (e-mail: [redacted], phone number: [redacted]). 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.

If you have complaints about the study, we would recommend to first discuss these with the investigators of the study or the doctor who is treating your relative. 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.

The treatment team involves:

- [redacted], executive investigator, primary contact for this study
  E-mail: [redacted]
  Phone number: [redacted]
- [redacted], coordinating investigator
  E-mail: [redacted]
  Phone number: [redacted]
- [redacted], principle investigator Erasmus MC
  E-mail: [redacted]
  Phone number:
  Intensive Care Unit: [redacted]
  Hospital: [redacted]
- [redacted], principle investigator Franciscus Gasthuis & Vlietland
  E-mail: [redacted]
  Phone number:
  Intensive Care Unit: [redacted]
  Hospital: [redacted]
- [redacted], principle investigator Ikazia hospital
  E-mail: [redacted]
  Phone number:
  Intensive Care Unit: [redacted]
  Hospital: [redacted]
- [redacted], principle investigator Maasstad hospital
  E-mail: [redacted]
  Phone number:
  Intensive Care Unit: [redacted]
  Hospital: [redacted]

15. Consent for this 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.

Informed consent form for participants

Related to: *'Virtual Reality for family members/relatives of patients in the Intensive Care Unit.'*

- 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 do ☐ / do not ☐ (**please indicate you choice**) give permission to contact me after this study to ask if I am interested to participate in another, related study.
- I want to participate in the study.

My name is (participant): ……

Signature: …… Date: __ / __ / __

I declare that I have fully informed this participant about the current 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 investigator (or its representative):……

Signature:…… Date: __ / __ / __

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

Supplementary data 3. Translation of the self-composed questionnaires.

Questionnaire about your experiences in the Intensive Care Unit.

We would like to know how you have experienced the information provision regarding the ICU admission or your relative.
Therefore, we would like to ask you to answer the following questions as honest as possible.
Are you unsure which of the answers to choose? Choose the answer that applies most to your situation.

1) Prior to your relative's current ICU admission, do you have other experiences with an ICU admission?
   Multiple answers can be given.
   O Yes, I have previously been admitted to an ICU myself.
   O Yes, my relative has also been treated in an ICU previously.
   O Yes, one of my other relatives have been treated in an ICU previously.
   O No, I have no other experiences with an ICU admission.

2) Was the ICU admission of your relatives unexpected for you?
   O Yes
   O No

3) What is the current situation of your relative?
   O My relative is still hospitalized or in another care institution
   O My relative is at home
   O My relative has passed away
   O Other, namely: _____

The following questions are about your experiences with the care and support of relatives in the Intensive Care Unit. When the term “care providers” is used in a question, this refers to all care providers who work in the Intensive Care Unit. Some questions relate to one specific care provider, for example the nurse. In that case, this is mentioned in the question.

Reception and guidance

The following questions are about your first visit to your relative in the Intensive Care Unit.

4) During you first visit to your relative in the Intensive Care Unit, has there been given attention to you as being a relative?

O No, not at all
O A little
O Quite much
O Yes, very much

5) During your first visit to your relative in the Intensive Care Unit, did you receive information about your relative's condition?

O No, not at all
O A little
O Quite much
O Yes, very much

6) Did you receive timely information about your relative's condition during your first visit?

O No
O Yes

7) Were you prepared for your first confrontation with your relative in the Intensive Care Unit?
O No, not at all
O A little
O Quite much
O Yes, very much

8) Have you received general information about the ICU department (about telephone numbers, visiting hours and work flow in the ICU)?
O No
O Yes

9) Did you receive information about how you could contribute to the care, comfort and well-being of your relative?
O No
O Yes

10) Were you given the opportunity to contribute to the care, comfort and well-being of your relative?
O No
O Yes

11) Were you kept informed of your relative's condition?
O No
O Yes

12) Did you feel heard in decision-making about your relative's medical treatment?
O Never
O Sometimes
O Usually
O Always

13) Has there been given attention to your needs?
O No
O Yes

Explanation in the Intensive Care Unit
The following questions are about the information you received in the Intensive Care Unit.

14) Have you received explanation about the treatment of your relative in the Intensive Care Unit?
O No, not at all
O A little
O Quite much
O Yes, totally

15) Have you received explanation about the different devices in the Intensive Care Unit?
O No, not at all
O A little
O Quite much
O Yes, very much

16) Did you receive explanation about the different alarm sounds in the Intensive Care Unit?
O No, not at all
O A little
O Quite much
O Yes, very much

17) Have you received explanation about mechanical ventilation of your relative?
O No, not at all
O A little
O Quite much
O Yes, very much

18) Have you been given explanation about the different IV drips and lines used for your relative and their usefulness?
O No, not at all
O A little
O Quite much
O Yes, very much

19) Were you given explanation of the treatment team that cared for your relative, and their corresponding duties?
O No, not at all
O A little
O Quite much
O Yes, very much

20) Have you received explanation of the different transition times/consultation times of the care providers?
O No, not at all
O A little
O Quite much
O Yes, very much

21) In general, was the information you received relevant/useful?
O No, not at all
O A little
O Quite much
O Yes, very much

22) Are you, in general, satisfied with the completeness of the information you have received?
O No, not at all
O A little
O Quite much
O Yes, very much

23) Was the information and explanation you received in general understandable for you?
O No, not at all
O A little
O Quite much
O Yes, very much

Additional help

You may have been offered additional help for you as a relative. This concerns practical or emotional support from social workers, spiritual counsellors and/or psychologists. The following questions will ask you about this help.

24) Was there attention to your needs as a relative?
O No, not at all
O A little
O Quite much
O Yes, very much

25) Have you been informed about keeping a diary during the ICU period?
O Yes
O No

If yes; did you keep a diary about your relative's Intensive Care period?
O Yes
O No

26) Have you been informed about social work, spiritual care or psychological help for yourself?
Multiple answers can be given.
O No
O Yes, about social work
O Yes, about spiritual care
O Yes, about psychological help

27) Have you been in contact with the social worker, chaplain or psychologist in the hospital?
Multiple answers can be given.
O Yes, with the social worker
O Yes, with the spiritual caretaker
Oh yes, with the psychologist
O No

If yes; was the social worker, spiritual counsellor or psychologist easily accessible for you?
O Yes
O No

If yes; did you experience the contact with the social worker, spiritual counsellor or psychologist as supportive?
O Yes
O No

28) Were you informed about the possibility to talk to a care provider about your experiences, after your relative's discharge from the ICU or the death of your relative in the ICU?
O Yes
O No

29) Did the visiting hours match your needs?
O No, not at all
O A little
O Quite much
O Yes, very much

Contact with healthcare staff

30) Were you kept informed of your relative's situation by the same doctor during your relative's Intensive Care Unit admission?

O No, often by different doctors
O Yes, mostly by the same doctors, but also by other doctors.
O Yes, almost always by the same doctor, but sometimes by a different doctor.
O Yes, always by the same doctor.

31) Were you kept informed of your relative's situation by the same nurses during your relative's Intensive Care Unit admission?

O No, often by different nurses
O Yes, mostly by the same nurse, but also by other nurses.
O Yes, almost always by the same nurse, but sometimes by a nurse.
O Yes, always by the same nurse.

32) How often have you had contact by telephone with a doctor about your nurse's condition?
_____ times a week

33) How often have you had contact by telephone with a doctor about your nurse's condition?
_____ times a week

34) How often did you have contact in person with a doctor about your relative in person?
_____ times a week

35) How often did you have contact in person with a nurse about your relative?
_____ times a week

General judgment

We would like to ask you to indicate below what rating you would give various aspects of Intensive Care Unit. 0 means that you were very unsatisfied, 10 means that it couldn't be better.

36) What number from 0 to 10 (where 0 is very bad and 10 is very good) do you give for the information you received in the Intensive Care Unit?

0	1	2	3	4	5	6	7	8	9	10
O	O	O	O	O	O	O	O	O	O	O

37) Which number from 0 to 10 (where 0 is very bad and 10 is very good) do you give for the explanation about the treatment and the environment of the Intensive Care Unit?

0	1	2	3	4	5	6	7	8	9	10
O	O	O	O	O	O	O	O	O	O	O

38) What number from 0 to 10 (where 0 is very bad and 10 is very good) do you give the doctors in the ICU for their way of communicating?

0	1	2	3	4	5	6	7	8	9	10
O	O	O	O	O	O	O	O	O	O	O

39) On a scale from 0 to 10 (where 0 is very bad and 10 is very good), what number do you give the nurses in the ICU for their way of communicating?

0	1	2	3	4	5	6	7	8	9	10
O	O	O	O	O	O	O	O	O	O	O

40) What number from 0 to 10 (where 0 is very bad and 10 is very good) do you give the care and guidance of relatives in the ICU?

0	1	2	3	4	5	6	7	8	9	10
O	O	O	O	O	O	O	O	O	O	O

Questions about your perspectives on the ICU-VR-F intervention.

We are interested in how you experienced receiving information about the Intensive Care Unit admission and the Intensive Care Unit environment through Virtual Reality. That is why we would like to ask you to answer the questions below as honestly as possible.

1) I liked to receive explanation about the Intensive Care Unit treatment of my relative in this way

O Not at all
O Almost not
O Neutral
O A little
O Very much

2) Virtual Reality is a nice way to obtain information for me.

O Not at all
O Almost not
O Neutral
O A little
O Very much

3) For me, Virtual Reality is a better way of obtaining information than an information folder.

O Not at all
O Almost not
O Neutral
O A little
O Very much

4) For me, Virtual Reality is a better way of obtaining information than a 'normal' video

O Not at all
O Almost not
O Neutral
O A little
O Very much

5) The Virtual Reality information film has ensured that I understand the treatment of my relative in the Intensive Care Unit.

O Not at all
O Almost not
O Neutral
O A little
O Very much

6) The Virtual Reality information film has helped me with processing the Intensive Care Unit admission of my relative.

O Not at all
O Almost not
O Neutral
O A little
O Very much

7) The Virtual Reality information film allows me to empathize with my relative's experience when he/she was in the Intensive Care Unit.

O Not at all
O Almost not
O Neutral
O A little
O Very much

8) I recommend this Virtual Reality information film for other relatives of Intensive Care Unit patients

O Not at all
O Almost not
O Neutral
O A little
O Very much

9) Do you think there was information missing in the Virtual Reality information film that you would have liked to have explained?

O Yes
O No

If yes, what information did you miss?

_____

_____

_____

10) Have you shown the Virtual Reality information film to others to explain to them about the Intensive Care Unit?

Oh yes, to my family
Oh yes, to my friends
Oh yes, to both my family and my friends
O Yes, to others, namely: _____
O No

11) How often have you watched the Virtual Reality information film at home?

O Not at all, only once in the hospital
O 1-3 times
O 4-6 times
O 7-10 times
O More than 10 times

12) How did you watch the information film at home?

O Only through Virtual Reality, with the cardboard VR glasses
O Only in 2D, without the cardboard VR glasses
O Usually through Virtual Reality, with the cardboard VR glasses, but also in 2D, without the cardboard VR glasses
O Usually in 2D, without the cardboard VR glasses, but also through Virtual Reality, with the cardboard VR glasses.
O Just as often by means of Virtual Reality, with the cardboard VR glasses, as in 2D, without the cardboard VR glasses.

Questions about perceived stress factors during your relative's Intensive Care Unit treatment.

With the questions below we want to investigate which factors caused you concerns during the Intensive Care Unit admission of your relative. The first question asks how many hours per week you spent on the ICU admission of your relative. In the questions that follow, we want to know how much you were concerned about the topics mentioned during the ICU admission of your relative.

1) How much time per week did you spend in total on the Intensive Care Unit treatment of your relative, which you would not otherwise have spent on your relative?
Think of travel time to the hospital, visiting times, tasks in the household that you normally did not do

   Approximately _____ hours

2) What other activities related to your relative's ICU admission did you spend time on, and how much time did you spend on these activities?

Activity *For example, visiting time, travel time, etc.*	Time per week (in hours)
1. Visiting time	__ __ hour
2. Travel time	__ __ hour
3.	__ __ hour
4.	__ __ hour
5.	__ __ hour
6.	__ __ hour
7.	__ __ hour
8.	__ __ hour
9.	__ __ hour
10.	__ __ hour

3) To what extent were you concerned about your relative's mental health?

O Not at all
O A little
O Neutral
O Pretty much
O Very much

4) How concerned are you about your relative's cognitive recovery?
Thinking speed, memory, planning, understanding, etc.

O Not at all
O A little
O Neutral (not much, not little)
O Pretty much
O Very much

5) How concerned were you about your relative's resumption of work?

O Not at all
O A little
O Neutral (not much, not little)
O Pretty much
O Very much

6) How concerned are you about your own mental health?

O Not at all
O A little
O Neutral
O Pretty much
O Very much

7) To what extent were you concerned about being able to carry out your own daily work?

O Not at all
O A little
O Neutral (not much, not little)
O Pretty much
O Very much

8) To what extent were you concerned about your financial situation as a result of your relative's Intensive Care Unit admission?

O Not at all
O A little
O Neutral (not much, not little)
O Pretty much
O Very much

9) To what extent were you concerned about the travel time spend to visit your relative in the Intensive Care Unit?

O Not at all
O A little
O Neutral (not much, not little)
O Pretty much
O Very much

10) To what extent did you find it frightening to visit your relative in the Intensiive Care Unit for the first time?

O Not at all
O A little
O Neutral (not much, not little)
O Pretty much
O Very much

11) Did you still find it frightening to visit your relative in the Intensive Care Unit?

O Not at all
O A little
O Neutral (not much, not little)
O Pretty much
O Very much

12) To what extent were you concerned about supporting your family during your relative's Intensive Care Unit admission?

O Not at all
O A little
O Neutral (not much, not little)
O Pretty much
O Very much

13) To what extent were you concerned about the household during your relative's Intensive Care Unit admission?

O Not at all
O A little
O Neutral (not much, not little)
O Pretty much
O Very much

14) To what extent were you concerned about the transfer from the Intensive Care Unit to the normal ward?

O Not at all
O A little
O Neutral (not much, not little)
O Pretty much
O Very much

15) To what extent were you concerned about the necessary medical care for your relative after hospitalization?

O Not at all
O A little
O Neutral (not much, not little)
O Pretty much
O Very much

16) How was your night's sleep during your relative's Intensive Care Unit admission?

O Very bad
O Bad
O Neutral
O Good
O Very good

17) To what extent did you feel responsible for the treatment of your relative?

O Not at all
O A little
O Neutral (not much, not little)
O Pretty much
O Very much

18) To what extent did you feel involved in the treatment of your relative?

O Not at all
O A little
O Neutral (not much, not little)
O Pretty much
O Very much

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	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
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	17
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	17

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#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	17
Roles and responsibilities: committees	#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)	11
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	1-2
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	N/A
Objectives	#7	Specific objectives or hypotheses	2
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, non-inferiority, exploratory)	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
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will	6

		perform the interventions (eg, surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6
Interventions: modifications	#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
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	N/A
Interventions: concomitant care	#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	8-9
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
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
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	7

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	7
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	7
Methods: Data collection, management, and analysis			
Data collection plan	#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	9
Data collection plan: retention	#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	9
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
Statistics: outcomes	#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	10
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10

Statistics: analysis population and missing data	#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)	10
Methods: Monitoring			
Data monitoring: formal committee	#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
Data monitoring: interim analysis	#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	11
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	6, 11
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)	N/A
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
Consent or assent: ancillary studies	#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	9

Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	9
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: trial results	#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	11
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
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