ViRtual REality to AiD recoverY post-ICU:

VR-READY

VERSION 4.0 10.03.2025

Sponsor:	Cwm Taf Morgannwg University Health Board
Sponsor ref:	CT/1790
Funder:	Health and Care Research Wales Research for Public and Patient Benefit
Funder ref:	RfPPB-21-1870(P)
REC ref:	23/NE/0113
IRAS number:	323989
Q-Pulse Document Template Number :	TPL/003/36

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the relevant study regulations, GCP guidelines, and CTR's SOPs.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

Sponsor: **Name**	**Signature**	**Date**
Chief Investigator: **Name**	**Signature**	**Date**

General Information This protocol describes the VR-READY study and provides information about the procedures for entering participants into the study. The protocol should not be used as a guide, or as an aide-memoire for the treatment of other participants. Every care has been taken in drafting this protocol; however, corrections or amendments may be necessary. These will be circulated to the known Investigators in the study. Problems relating to the study should be referred, in the first instance, to CTR

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Study Co-ordination:

The VR-READY study is being coordinated between the Centre for Trials Research (CTR), Cardiff University, a Clinical Research Collaboration (UKCRC) registered trials unit and Cwm Taf Morgannwg University Health Board.

This protocol has been developed by the VR-READY Study Management Group (TMG)

For **all queries** please contact the VR-READY team through the main study email address. Any clinical queries will be directed through the Study Manager to either the Chief Investigator or a Co-Investigators

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Glossary of abbreviations

CF	Consent Form
CI	Chief Investigator
CRF	Case Report Form
CTM UHB	Cwm Taf Morgannwg University Health Board
CTR	Centre for Trials Research
CTU	Clinical Trials Unit
CU	Cardiff University
GCP	Good Clinical Practice
HB	Health Board
HCRW	Health Care Research Wales
HE	Health Economics
HRA	Health Research Authority
IC	Informed consent
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
ISF	Investigator Site File
NHS	National Health Service
PI	Principal Investigator
PICS	Post Intensive Care Syndrome
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality control
QL (QoL)	Quality of Life
R&D	Research and Development
REC	Research Ethics Committee
RN	Research Nurse
SMF	Study Master File
SMG	Study Management Group
SSC	Study Steering Committee
SOP	Standard Operating Procedure
VR	Virtual Reality

1 Amendment History

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version.

Amendment No.	Protocol version no.	Date issued	Summary of changes made since previous version
NSA1	1.1	26.07.2023	The time restriction on two of the inclusion criteria for the Phase 1 focus groups have been relaxed from five years to ten years to maximise inclusivity of those who wish to share their experiences.
NSA2	1.2	28.08.2023	Addition of remote consent for ease for participants undertaking on-line focus groups for phase 1
SA1	2.0	12.01.2024	Addition of evaluation questionnaire at the end of Phase 1 focus groups
SA2	3.0	12.06.2024	Amendments for Phase 3 feasibility study based on outcomes of Phase 1 which include; - Inclusion/ exclusion criteria - Intervention content - Intervention delivery - Feasibility study design
NSA3	4.0	10.03.2025	Increase to phase 3 recruitment sample size

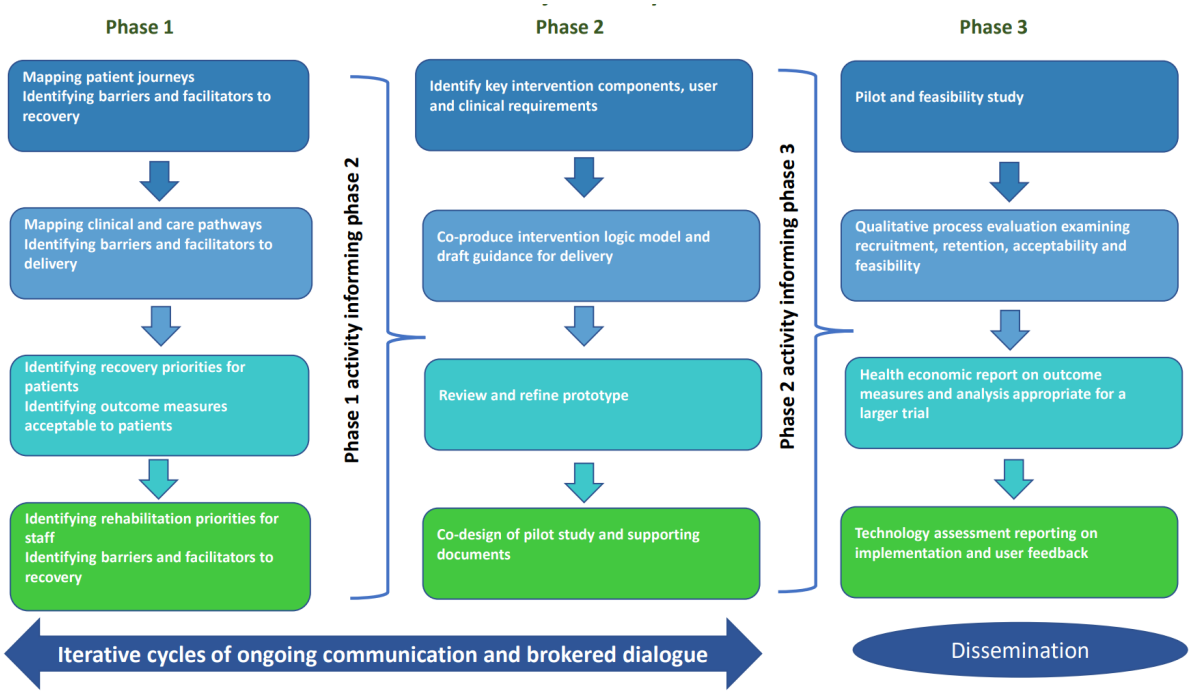
2 Synopsis

Short title	VR-READY
Acronym	VR-READY
Internal ref. no.	UID1363
Funder and ref.	RfPPB-21-1870(P)
Study design	Intervention Development and Feasibility
Study participants	People who have been admitted to intensive care with critical illness and have/ have had ongoing recovery and rehabilitation needs and those healthcare professionals involved in the supporting that recovery and rehabilitation
Planned sample size	Phase 1 – 8 ICU survivors/ family member, 8 HCPs Phase 3 – up to 25 participants (plus all willing research delivery staff)
Planned number of sites	1
Inclusion criteria	The inclusion criteria for Phase 1 focus groups are: - people with a previous admission to critical care within the last ten years - family members/ carers of a patient with a previous admission to critical care in the last ten years. - NHS employees involved in the care of critical care patients in ICU - NHS employees involved in the care and recovery of patients discharged from critical care (e.g. physiotherapists, psychologists, occupational therapists etc.) The inclusion criteria for the Phase 3 feasibility study are; - Current hospital admission involving a stay in critical care, requiring organ support for more than 48 hours OR the / relative/loved one of someone admitted to critical care and is participating in the Phase 3 study - FOR ICU PATIENTS ONLY: If normal vocalization is not possible (due to tracheostomy) then the participant must have an established method of communication with bedside nurse/ ward staff
Exclusion criteria	The exclusion criteria for the Phase 1 focus groups are; - Any person unable to provide informed consent - Any person unable to communicate in English The exclusion for the Phase 3 feasibility study are; - FOR PATIENTS ONLY: Any person experiencing delirium as assessed daily using CAM-ICU - A history of severe motion sickness - A history of photosensitive epilepsy - Any physical or anatomical contraindications to using VR headsets (e.g. severe visual or hearing impairment, major skull or facial surgery) [This does not include those that may require assistance to place the headset due to muscle weakness from ongoing admission.] - Any person unable to communicate in English
Follow-up duration	Phase 1 – 6 months Phase 3 - up to 12 weeks
Planned study period	24 months
Primary objective	Phase 1;

	- Determine the recovery pathway of ICU survivors; including identification of critical components underpinning effective recovery and facilitators and barriers affecting these. Phase 2; - Co-produce a VR mediated home based intervention to aid recovery in ICU survivors Phase 3; - Determine feasibility and acceptability of the developed intervention in a home-based setting
Secondary objectives	Phase 1; - Determine applicable outcome measures of relevance to all stakeholders Phase 3; - Determine the feasibility and acceptability of selected outcome measures for use in future efficacy and cost-effectiveness studies for ICU recovery -Generate a framework for DR.VR adaptation that can be applied to other healthcare settings
Primary outcomes	Phase 3 Study: Feasibility
Secondary outcomes	To be determined by the Phase 1 activities

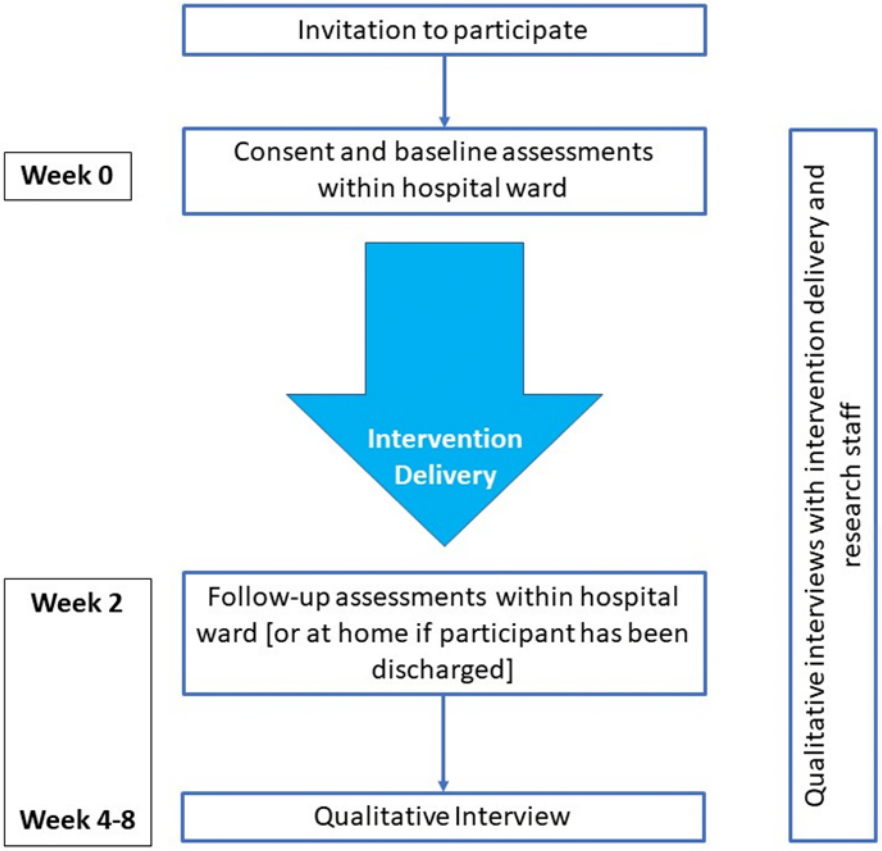
3 Study summary & schema

3.1 Study schema



3.2 Participant flow diagram

Participant flow for the Phase 3 feasibility study


Invitation to participate
Week 0
Consent and baseline assessments within hospital ward
Intervention Delivery
Week 2
Follow-up assessments within hospital ward [or at home if participant has been discharged]
Week 4-8
Qualitative Interview
Qualitative interviews with intervention delivery and research staff

3.3 Study lay summary

People admitted to intensive care (ICU) often experience ongoing health problems once they leave and have returned home. This is described as Post Intensive Care Syndrome (PICS) and can include problems with memory and thinking, physical impairments and reduced psychological wellbeing. This can result in a reduced quality of life, which also affects family members and friends. Although improvements have been made in caring for people within ICU, there is no standard approach to care after leaving ICU to support patients' recovery. A lack of staff and resources have also been a barrier to standard post -ICU care. With the recent increase in admissions to ICU, there is an urgent need to find ways of supporting the recovery of people with PICS that is readily available to patients. A recent review of how to combat PICS suggested that home-based and virtual care plans would be one way of making sure that as many people as possible could take advantage of rehabilitation support.

Immersive virtual reality (VR) can be accessed simply with an easy -to-use headset. VR has already been shown to be useful in helping relaxation and in combatting pain and anxiety. We think that VR might help support people recovering from critical illness and this study is aimed at developing a VR program (intervention) that can address the current inadequacies in post-critical care support.

In order to do this, we are proposing a three stage program of research. First, we need to understand what the recovery journey looks like. We will conduct a series of focus groups with ICU survivors, their family members and healthcare professionals involved in the care and rehabilitation of ICU patients. In these sessions, we will explore what the patient recovery journey looks like and what the critical parts of recovery are. We will also work with these groups to determine, in terms of recovery, what is important to measure (known as outcomes) to find out whether or not a virtual reality-based intervention works.

The second stage will use data from the focus groups which will then be used to alter an existing VR set-up (DR.VR) to specifically support the recovery of ICU patients, working with previous ICU

patients and their family members to inform the design. We will also ask this group what features need to be included when testing the intervention and use this input to design the next stage of the project.

In the third part of the study, we will test the adapted VR intervention in a small group of patients who have previously been admitted to ICU. The aim of this study will be to see if using a VR intervention is possible and if people are happy and willing to use it. We will also explore how acceptable participants find the outcomes selected from the earlier focus groups. We will do this by interviewing participants about their experience. We will also interview the healthcare professionals involved in the care and rehabilitation of these participants to gather their views on the VR intervention. The interview data will be analysed qualitatively to provide an in-depth understanding of the intervention and outcomes. This data can then be used to inform the design of larger studies in the future to test how effective the VR intervention is at supporting the recovery of ICU patients.

At the end of the study, we will share the results with all of the study participants and more widely through appropriate web pages, social media and organisations concerned with the care of ICU patients.

4 Background

Improvements in knowledge and new therapeutic interventions have brought about increased survival rates from critical illness. However, despite prominence as an outcome measure in critical illness research, survival is not the sole outcome of importance to patients, with quality of life following critical illness increasingly recognised as a cornerstone of the recovery journey. It is therefore essential that critical illness research also focuses on survivors' quality of life.

Post intensive care syndrome (PICS) is common following an ICU stay and can be significantly debilitating. Characterized by cognitive, psychological and physical impairments, PICS profoundly impacts the lives of patients and their families: a third of patients do not return to work, another third are unable to do the same work. A quarter of patients still require assistance in activities of daily living a year after ICU admission often affecting the working lives of family members[1]. It has been suggested that "critical illness associated with ICU admission should be treated as a lifetime diagnosis with associated excess mortality, morbidity and the requirement for ongoing health support"[2]. In terms of prudent healthcare, large investments made during intensive care are only sustained when continued support is in place following discharge[3].

There are several well described interventions currently used as the gold standard in PICS prevention during an ICU stay (choice of sedation drugs, sedation breaks, spontaneous breathing trials and early mobilisation) but there is no standardised approach to post -ICU care. Despite published NICE guidance on rehabilitation after critical care in 2009, with quality standards in 2017[4,5] currently less than a third of ICU patients in the UK receive dedicated outpatient follow-up 2-3 months after ICU discharge[6-8]. A recent editorial in the British Medical Journal highlighted the lack of adequate post-ICU rehabilitation, emphasising the serious consequences for individuals and association of increasing costs to the NHS, particularly from unplanned readmissions. It stated that research to determine the most clinically and cost -effective rehabilitation strategies should be a priority, with collaboration between patients, funders and researchers to identify and address evidence gaps[8].

UK Guideline for the Provision of Intensive Care Services (GPICS2)[3] explains that leaving ICU is only the start of a long recovery process which may take months to years, and that there may be considerable residual impact on patient's morbidity and longevity. It also emphasizes the need for further research in this area. Recommendations include the monitoring of outcomes and recovery progression using measures appropriate for the stage of recovery, individual therapy and dependent on local resources including personnel, equipment and finance and additionally a specialist rehabilitation coordinator to facilitate oversight of the rehabilitation pathway. Delivery of services to these standards, especially after leaving hospital, is rare. A recent survey found that delivery to these standards occurred in only 18% of sites[9] mainly due to a lack of funding and staff. The need to think of alternative strategies to deliver therapeutic interventions such as home-based services and virtual platforms to "ensure maximum inclusivity for patients into rehabilitation programs" has been

considered against the limited availability of resources[10]. However, the need for careful management to prevent issues such as digital poverty and literacy from limiting access was also mentioned. GPICS2 further recommends a rehabilitation plan addressing all relevant domains for patients including physical, functional, communication, social, spiritual, nutritional and psychological elements[3] whilst simultaneously acknowledging that "the service-user voice is often missing in shaping research" in this area[3]. The current literature highlights that research into improving post-ICU recovery is essential and is strongly suggestive that the development of accessible, inclusive interventions to aid recovery should be of central prominence.

One potential method of doing this is using immersive virtual reality (VR). VR has been utilised in a variety of healthcare settings and has demonstrated promise in a range of clinical areas[11-14]. Immersive VR been shown to be beneficial in reducing pain and anxiety, to help with relaxation, and been found to be safe and acceptable to intensive care patients[15]. Additionally, VR has shown equal effectiveness to conventional therapies in rehabilitation after stroke, with the added benefits of independent use, more accurate feedback and the ability to stimulate users more than traditional methods[9].

4.1 Rationale for current study

Building on our previous work employing immersive VR in an ICU setting[15,16] we believe that VR provides a unique opportunity to develop an effective, safe and acceptable intervention to aid recovery in PICS affected patients. However, there remain a number of unknowns as to how this might be realistically achieved in a real-world setting. Therefore, we are proposing a program of work which centres service users in understanding what elements would be required to aid recovery and how we may best measure the effectiveness of any such intervention in future studies. We will research the patient experience of recovery from critical illness to identify intervention priorities and outcome measures considered important and acceptable to ICU survivors, their loved ones and relevant ICU and rehabilitation staff. Working with a local Welsh business (Rescape), we will adapt an existing, CE marked VR kit (DR.VR) already in use within the NHS to co-produce a VR-mediated intervention to aid recovery and rehabilitation following an ICU stay. The resulting intervention will then be tested in a group of patients admitted to ICU to examine the feasibility and acceptability of the intervention and its delivery..

This proposal will contribute to understanding of advancing health technologies and their translation and implementation for patient benefit across the NHS. We are focusing here on recovery from PICS, but we will also identify the critical aspects of DR.VR adaptation and intervention development for application to other healthcare priorities and settings. This framework can then be used in the development of interventions aimed at promoting physical and psychological well-being for a variety of patients, which will have wide-reaching benefits across the NHS.

5 Study objectives/endpoints and outcome measures

The overall aim of this study is to co-design an accessible VR mediated intervention to improve in-patient experiences as an aid to recovery in people admitted to critical care. This will occur in 3 phases and the study objectives are defined accordingly.

5.1 Primary objectives

Phase 1;

- Determine the recovery pathway of ICU survivors; including identification of critical components underpinning effective recovery and facilitators and barriers affecting these.

Phase 2;

- Co-produce a VR mediated intervention to improve in-patient experiences as an aid to recovery in ICU survivors

Phase 3;

- Determine feasibility and acceptability of the developed intervention within a hospital setting

5.2 Secondary objectives

Phase 1;

- Determine applicable outcome measures of relevance to all stakeholders

Phase 3;

- Determine the feasibility and acceptability of selected outcome measures for use in future efficacy and cost-effectiveness studies for ICU recovery

-Generate a framework for DR.VR adaptation that can be applied to other healthcare and at-home settings

5.3 Primary outcomes measure(s)

For the phase 3 study, the primary outcome measure will be feasibility as determined by: recruitment, retention, data completeness and intervention adherence. Each measure of feasibility will be assessed according to the pre-defined criteria outlined below.

Variable		Progression Criteria		
		Red	Amber	Green
	No approached willing to participate	<5%	5-19%	20%

Recruitment	No screened actually recruited	<50%*	50-74%	75-100%
	No. recruited	< 6 in total	6-12	12-25
Retention	No of partially active trial participants at primary end point	<50%	50-79%	80%
Adherence	Completion of intervention sessions*	<50%	50-79%	80%
Data Completeness	Completion of baseline measures	<50%	50-79%	80%
	Completion of follow up measures	<50%	50-69%	70%

*to be refined following intervention development in Phase 1 and Phase 2.

5.4 Secondary outcomes measure(s)

Secondary outcome measures will include determining the acceptability of the intervention and trial design to participants through a comprehensive process evaluation. The outcome measures (up to ten maximum) to be used in the feasibility study will be determined during the phase 1 activities. The potential measures for inclusion are discussed in more depth in section 11.

6 Study design and setting

The study is focussed on intervention development and feasibility testing of that intervention. The study is split into three phases:

Phase 1: In this phase of the study we will run a series of focus groups with a group of ICU survivors and/or their family members/ care partners and a group of health care professionals involved in facilitating the rehabilitation and recovery of ICU survivors. These sessions will focus on mapping the recovery pathway and identifying potential barriers and facilitators to the use of a home-based VR mediated intervention. Additionally, these sessions will be used to explore and identify the most relevant outcomes to measure the utility of an intervention to aid recovery in ICU survivors. The locations of focus groups will be chosen on a pragmatic basis for those involved, and will likely be within the hospital setting, at a neutral third party location nearby or online.

Phase 2: Information gathered in phase 1 on the essential components for effective recovery and the experiences of ICU survivors will be used to modify existing DR.VR content, guided by ICU survivors to co-design a VR mediated intervention for home use to aid recovery following an ICU stay.

Phase 3: In this final part of the study, we will examine the feasibility and acceptability of the co-designed VR intervention in up to 25 people admitted to ICU in Cwm Taf Morgannwg University Health Board. This part of the study will also examine the feasibility and acceptability of outcome measures selected on the basis of the data gathered in Phase 1. Evaluation of the intervention and outcomes will be conducted as part of a comprehensive process evaluation.

6.1 Risk assessment

A Study Risk Assessment has been completed to identify the potential hazards associated with the study and to assess the likelihood of those hazards occurring and resulting in harm. This risk assessment considers;

- The known and potential risks and benefits to human subjects
- How high the risk is compared to normal standard clinical practice
- How the risk will be minimised/managed

This study has been categorised as a low-risk study where the level of risk is comparable to the risk of standard medical care. A copy of the study risk assessment may be requested from the Study Manager. The study risk assessment is used to determine the intensity and focus of monitoring activity (see section 22.1).

7 Site and Investigator selection

This study will be carried out at a single participating site within Wales. Before the site can begin recruitment the Principal Investigator must be identified. The following documents must be in place and copies sent to the CTR team prior to study opening at site:

- The letter confirming capability and capacity from the site's R&D Department, following sharing of the local information pack
- A signed Study Agreement
- Current, signed Curriculum Vitae and GCP training certificate of the Principal Investigator (PI)
- Completed Site Delegation Log and Roles and Responsibilities document
- Full contact details for all host care organisation personnel involved, indicating preferred contact
- A copy of the most recent approved version of the Participant Information Sheets and Consent Forms on host care organisation headed paper

Upon receipt of all the above documents, the Study Manager will send written confirmation to the Principal Investigator detailing that the centre is now ready to recruit participants into the study. This email must be filed in the site's Study Site File. Along with the written confirmation, the site should receive a study pack holding all the documents required to recruit into the Study.

Occasionally during the study, amendments may be made to the study documentation listed above. CTR will issue the site with the latest version of the documents as soon as they become available. It is the responsibility of the CTR to ensure that they obtain confirmation of capability and capacity from local R&D organisations to implement the new documents.

8 Participant selection

Participants are eligible for the study if they meet all of the following inclusion criteria and none of the exclusion criteria apply. All queries about participant eligibility should be directed to the Study research nurse before registration.

8.1 Inclusion criteria

The inclusion criteria for Phase 1 focus groups are:

- people with a previous admission to critical care within the last ten years
- family members/ carers of a patient with a previous admission to critical care in the last ten years
- NHS employees involved in the care of critical care patients in ICU
- NHS employees involved in the care and recovery of patients discharged from critical care (e.g. physiotherapists, psychologists, occupational therapists etc.)

The inclusion criteria for the Phase 3 feasibility study are;

- Adults with capacity to consent

- Current hospital admission involving a stay in critical care, requiring organ support for more than 48 hours OR the loved one/ relative of someone admitted to critical care and is participating in the Phase 3 study

- FOR ICU PATIENTS ONLY: If normal vocalization is not possible (due to tracheostomy) then the participant must have an established method of communication with bedside nurse/ ward staff

8.2 Exclusion criteria

The exclusion criteria for the Phase 1 focus groups are;

- Any person unable to provide informed consent
- Any person unable to communicate in English

The exclusion for the Phase 3 feasibility study are;

- FOR PATIENTS ONLY: Any person experiencing delirium as assessed daily using CAM-ICU

- A history of severe motion sickness
- A history of photosensitive epilepsy
- Any physical or anatomical contraindications to using VR headsets (e.g. severe visual or hearing impairment, major skull or facial surgery). [This does not include those that may require assistance to place the headset due to muscle weakness from ongoing admission.]

- Any person unable to communicate in English

9 Recruitment, Screening and registration

9.1 Participant identification

Phase 1

Participants for the focus groups (ICU survivors and/ or their relatives and care partners) will be identified through the local ICU survivors support group, of which our PPI co-applicant is a member. Other participants will be identified and invited by the local research team within the health board. Additionally, ICU survivors may be identified and invited through the UK wide support network, ICU Steps through their mail out or other electronic communications such as twitter.

Health care professionals will be identified locally by the research team and study collaborators. Additional participants may be sought through advertising through professional networks.

Participants interested in taking part in the focus groups will be asked to register their interest by emailing the study team. They will be then sent a participant information sheet with details of the focus groups to be held.

Phase 3

Phase 3 participants will be identified by the local PI and research team in the critical care wards including ICU and High dependency unit (HDU). This is an active research centre where daily participant screening for inclusion in research is routine practice. Potential participants will be provided with a study information sheet, which has been co-produced by ICU survivors following discussion with their consulting clinician or member of the research team. Those interested in taking part can confirm their interest with the research team.

The data collected in Phase 1 indicated that ICU patient family members and support partners may also experience significant anxiety and issues with well-being as a result of their loved one's admission to ICU. At the suggestion and input from those with lived experience, the intervention will also be offered to those family members and support partners. Inclusion of this group will be in two ways- as users of the VR intervention and/or as providers of information relating to intervention delivery and usage in their family member/ loved one.

This group will be identified as those visiting patients within the ICU or HDU who have already provided consent to be part of phase 3. Potential participants will be approached as above if their family member/ loved one has agreed to take part in the study.

9.2 Screening logs

A screening log of all ineligible and eligible but not consented/not approached will be kept at the site to provide information on the feasibility of recruitment. For those approached to participate in the

phase 3 feasibility study will be asked to provide a reason for non-participation, but if the person does not want to provide a reason, this will not be mandated and will be marked as 'no reason given'. Free text answers will be stored in the screening log for subsequent analysis. When at site, logs may contain identifiable information but this **must** be redacted prior to being sent to the CTR. The screening log should be sent to the CTR study personnel every 2 months (see section 19 for further detail on data monitoring/quality assurance).

9.3 Recruitment rates

We will aim to recruit up to 25 participants from ICU at an expected rate of 3.5-4 per month. Family member/ loved ones will be additional to that target sample and we do not expect to include more than 15 family members/ loved ones.

9.4 Informed consent

The participant's informed consent must be obtained using the study Consent Form (CF), which follows the Participant Information Sheet (PIS). The participant should be given sufficient time after the initial invitation to participate before being asked to sign the CF. Informed consent must be obtained prior to the participant undergoing procedures that are specifically for the purposes of the study. Consent may be taken by any suitably qualified member of the research team.

Please note, only when informed consent has been obtained from the participant and they have been enrolled into the study can they be considered a study participant.

Participants should always be asked to provide informed consent where one copy of the consent form should be given/sent to the participant, but the original copy should be kept in the investigator site file and a further copy should be kept with participant's hospital notes (if applicable).

The right of the participant to refuse to participate in the study without giving reasons must be respected. Similarly, the participant must remain free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing his/her further treatment.

<u>Consent arrangements for Phase 1 Focus Groups</u>

Participants attending focus groups will be asked to sign the consent form prior to the beginning the focus group session.

If focus groups need to be held on-line rather than in person, then a consent form will be sent to the participant ahead of time and they will be asked to sign that at the beginning of the focus group session and send a copy (scan or picture) via email to the study email address. Alternatively, the participant can provide remote consent, which a member of the research team will go through each statement and initial each box that the participant has consented to. The consent will also be recorded at the

beginning of the online focus group session. The consent form will also ask participants to indicate if they are willing to be contacted for and/or take part in phase 2 activities.

Consent can be taken by any suitably qualified and trained member of the research team.

Phase 3

When a potential participant indicates an interest in taking part in the feasibility study consent will be taken before any research activities are performed. Consent will be taken by either the site PI or another delegated and appropriately trained member of the research team. These personnel are very experienced in obtaining consent for research studies in critical care.

If the participant struggles to hold a pen adequately (but still has adequate capacity to provide consent) then a witness may sign the consent form for them. This will be documented in the participants notes. Where participants are unable to provide a signature but can consent verbally or by other established methods of communication, this will be detailed on the consent form and in the patient notes. This is an established practice within the healthcare setting.

9.5 Registration

Once a participant has provided informed consent their details will be entered into the participant management database held at the participating site. This will indicate which part of the study that person is taking part in and if they are willing to take part in other phases of the study.

10 Withdrawal & lost to follow-up

10.1 Withdrawal

Participants have the right to withdraw consent for participation in any aspect of the study at any time. The participant's care will not be affected at any time by declining to participate or withdrawing from the study.

If a participant initially consents but subsequently withdraws from the study, clear distinction must be made as to what aspect of the study the participant is withdrawing from. These aspects could be:

- Withdrawal of permission to use data already collected
- Withdrawal of permission to use direct quotations
- Complete withdrawal from any future data collection
- Withdrawal from the intervention only

The withdrawal of participant consent shall not affect the study activities already carried out and the use of data collected prior to participant withdrawal unless specifically requested.

In all instances participants who consent and subsequently withdraw, a withdrawal form will be completed on the participant's behalf by the researcher/clinician based on information provided by the participant.

10.2 Lost to follow up

For the phase 3 feasibility study, participants will be deemed to be lost to follow-up if they fail to complete the follow-up assessments and final assessment interview (see Table 2).

11 Study procedures

The activities of this study are split into three phases;

Phase 1 – Determining critical intervention components and outcomes
Phase 2 – Intervention development and final study design
Phase 3 – Feasibility study of designed intervention.

11.1 Phase 1 – Determining Critical Intervention Components and Outcomes

Phase 1 activities will consist of a series of interactive focus groups consisting of critical care survivors, their loved ones and relevant critical care and rehabilitation staff. There will be a series of focus groups with ICU survivors and their family members/ care partners and a parallel series of focus groups with HCPs involved in the recovery and rehabilitation of ICU survivor (Table 1). It is expected that there will be 4-6 weeks between each focus group, so participants would be expected to be participating in this part of the study for up to 6 months. All participants in the ICU survivor/ family member focus group will receive payment for their attendance at each session in addition to reimbursement of any travel costs incurred. Participants in the HCP focus groups will also receive a voucher as a thank you for their participation.

Using elicitation activities and brokered dialogue, these focus groups will be used to gain an in-depth understanding of the patient experience of recovery from critical illness. This will allow us to identify the essential components, along with facilitators and barriers for recovery in people discharged from ICU. These will include such factors as digital literacy and digital poverty and how these can be addressed to provide equitable access to the planned interventions.

The focus groups will also be used to identify outcome measures for determining the effectiveness of any intervention designed to aid recovery post ICU and considered important and acceptable to all stakeholders. Common and popular outcomes cited in the literature, including ICU related core outcomes, will be used as a starting point within each stakeholder group to determine the relevance and relative importance of various measures across the variety of stakeholders. This will also include discussion around applicable resource use and what factors need to be considered for understanding the wider economic impact of post-ICU rehabilitation and recovery. It is anticipated that this will include questions and discussion on the impact on daily living, ability to work, and use of health care services, to provide initial guidance on important cost drivers to aid design of a study specific resource use measure.

The specific activities of each focus group will be directed using a guide developed with the input of co-applicants to identify key areas for discussion, whilst still encouraging free form dialogue and idea generation. Activities to be included are described in Table 1.

Table 1. Focus group activities

	Patient and family group	Critical care and rehabilitation staff group
Elicitation activity	Patient timeline to understand the experience of ICU and recovery journey	Staff map of patient journey and care through ICU
Focus Group 1	Understanding and mapping patient journey Initiate brokered dialogue activity – questions to raise with staff	Understanding and mapping the patient pathway Initiate brokered dialogue activity – questions to raise with patients and their family
Elicitation activity	ICU Castaway (adaptation of desert island discs) to explore psychological and well-being needs of patients following a stay in ICU	ICU Castaway to explore outcomes important to staff in recovery and rehabilitation
Focus Group 2	Feedback from staff focus group; Identification of recovery needs and outcomes important to patients, barriers and facilitators Intervention mapping	Feedback from patient focus group; Identification of recovery needs and outcomes important to staff, barriers and facilitators Intervention mapping
Focus Group 3	Brokered dialogue and responses including returned comments from FG 2 Demonstration of DR.VR including a review of content and feedback around application and deployment Identification of key scenarios/experiences and user requirements	Brokered dialogue and responses including returned comments from FG 2 Demonstration of DR.VR including a review of content and feedback around application and deployment Identification of key scenarios/experiences and clinical requirements
Focus Group 4	Brokered dialogue and responses/questions from staff group including returned comments from FG 3 Prototype review and co-production of Intervention and logic model	Brokered dialogue and responses/questions from patient group including returned comments from FG 3 Prototype review and con-production of Intervention and logic model

Data collected within these focus groups will be used to;

- Identify outcomes for evaluation of the feasibility and acceptability of the VR intervention in a feasibility study, with the selection of approximately 10 of the most important outcomes across all stakeholders.
- Determine the critical cost drivers of post-ICU recovery to develop a study specific resource measure to include in the pilot and future efficacy studies.
- Generate a logic model to aid the development of a VR mediated intervention to support recovery following discharge from the ICU.

Participants from the phase 1 focus groups (both ICU survivors and health care professionals) will be invited to contribute to phase 2, although there will be no obligation for doing so.

Participants from the phase 1 focus groups (both ICU survivors and health care professionals) will be asked to complete a post-participation evaluation questionnaire once all four focus groups have been completed. The questionnaire will focus on evaluation of the methods used and what the participants thought about the content and conduct of the focus groups, including the use of on-line meetings. Participants will be emailed a link to the questionnaire which will be hosted by Online surveys. All responses will be anonymous. Participants may receive up to two reminders for completion of survey, dependent on response rates.

11.2 Phase 2 – Intervention development

Data gleaned from the focus groups in phase 1 will be used to co-design a VR mediated intervention to support the recovery of ICU survivors as a collaboration with our lived experience group. This will involve the adaption of content already available with DR.VR to suit the needs of ICU survivors and support their recovery. The adaptation of DR.VR will centre on two key domains;

i) mental health and wellbeing
ii) quality of life.

Alongside the co-development of the VR intervention to support post-ICU recovery, we will also co-develop accessory documentation for the use of the VR intervention that will be used in the feasibility testing in phase 3, such as a participant instruction manual and training materials for research staff.

Additionally, those contributing to Phase 2 will be asked to contribute to the final design of the feasibility study. Whilst the general framework of the study has been determined, the specifics of certain aspects of the study such as the outcome measures to be used, the length of intervention period and the length of the follow-up period will be informed by contributions from Phase 1 and Phase 2 participants. It is anticipated that this process of co-design will result in a study design that is feasible and has high levels of acceptability, thus increasing the chances of success for the phase 3 feasibility study.

11.3 Phase 3 – Feasibility Study

Following the development of the VR intervention, its use will be piloted in a small, one arm feasibility study. Up to 25 participants will be recruited to receive the intervention for 2 weeks in the in-patient setting. If participants are discharged prior to completion of the 2-week intervention delivery, they will be able to take the headset home with them.

Following the provision of consent, participants will complete the baseline assessments. We anticipate that for the majority of participants, they will be unable to complete self-report items independently. Therefore, a member of the research team will aid completion by reading out questions and confirming the participants response, which will be entered directly into REDCap using a tablet or laptop.

Where participants are required to complete follow-up assessments at home, they will be asked for their preferred method for completion (either on paper, electronically or research team assisted via the telephone) and guidance for how to complete the assessments will be provided.

The participant will be provided with a VR headset and instructed on how to use the equipment and how to engage with the intervention. A written instruction manual will also be provided. For at least the first two days of the intervention, the participant will be assisted by a member of the research team to guide use of the VR apparatus, troubleshoot any problems with use and ensure that the participant isn't experiencing any undue problems from using the headset. Beyond this, if the participant continues to struggle with using the apparatus independently (i.e. through muscle weakness) then a member of the research team will be available daily to assist. Participants in the in-patient setting will be assessed for any current episodes of delirium prior to using the headset using the CAM-ICU. If a participant progresses to independent use of the VR headset, formal delirium assessments will not be performed as it would be expected that any bout of delirium would preclude independent usage, but research staff will continue to check in with participants regularly.

Participants will be asked to engage with the VR content for at least 5-10 minutes a day. This is consistent with current literature that suggests this is sufficient time for people to benefit from the virtual reality environment. The amount of time spent interacting with VR content is recorded within the hard drive of the VR headset. Usage stats recorded on headset include duration and identification of content accessed.

DR.VR Content and Interface

When the user puts on the headset they will be able to view the 'home screen' menu which details the content contained on the device. This is divided into four sections;

1) Exploration – contains several different immersive environments with simple narration to introduce the user to that environment and invite them to explore the setting.
2) Mindfulness and Motivation – this section consists largely of original DR.VR content, with the addition of a bespoke motivational exercise.
3) Breathing – this section contains the original breathing exercises featuring in DR.VR, but which have been modified in terms of their speed, tailored to the expected capabilities of the participant population
4) Information – this contains a number of information videos featuring key staff roles encountered by patients when they are admitted to critical care.

When the user/ participant chooses a specific menu item they will be presented with the relevant sub-menu that details the specific content within that section.

Diversion/ Exploration

i) Underwater – a guided exploration of an underwater scene featuring a range of marine wildlife. "*From the warm Caribbean Sea to the clear waters of the Pacific Ocean, you'll get to swim with some of the most majestic and endangered creatures on our planet. "*

ii) Cities – a guided exploration of a busy city scape. "*Travel to various cities from around the world. Enjoy your time there whilst listening to the history behind some of the world's most famous landmarks. "*

iii) Travel – this provides the opportunity to experience a range of different worldwide locations. "*The world is full of wonder and beauty. You'll get to travel to see some of the hidden wonders of the world, from exploding volcanoes to salmon fishing with black bears.*"

iv) Wild Hikes - "A wild hike off the beaten track to amazing landscapes, remote beaches, extraordinary mountain ranges and lush green forests."

v) Wildlife - "Sit and experience life up close and personal with some of the worlds most endangered animals from being as small as a bug to looking up at the tallest giraffe!"

vi) Space - Who hasn't dreamt of flying across the universe in your own spaceship? Now you can! Visit the surface of mars and the rings of Saturn, with a few surprise stops along the way."

Mindfulness and Motivation

i) Virtualisation for Motivation – this is a motivational script written by the VR READY consultant clinical psychologist in conjunction with the ICU survivors to provide reassurance and motivation to patients still on their recovery journey. The narration is set within a countryside setting, using aspects of the landscape as anchor points for the narrated content, including calming countryside soundscapes to aid relaxation.

ii) Sleep – "*This guided relaxation experience will help you to relax after a long day and take a moment to recentre yourself. Choose from a variety of exercises from Muscle Relaxation to Belly Breathing from the commentary panel on the right and enjoy watching the sunset in a beautiful savanna.*"

iii) Mindful Seeing – "*This session will teach you how to mindfully look at the world. To stop and be in the moment, to take time to look at something beyond its label, and look at its colour, texture and shape.*"

iv) Body Scan – "*This session is a wonderful mindfulness session to reduce anxiety and stress. It will allow you to accept, with gentle curiosity, how your body is feeling.*"

v) Calming Mind – "*This session connects you with the water in a lake. Watching the ripples of water as you gain the space to calm your mind and bring perspective to your thoughts.*"

vi) Mindful Listening – "*This session gives us the space to really listen to the world around us. To stop and be within the moment. Mindful listening will allow you to take this practice into everyday life. really listening to the world around you.*"

Breathing

i) Beach – This features a computer generated beach scene with accompanying soundscape where the user is guided through a breathing exercise "*Relax and practice your breathing in a relaxing beach environment*"

ii) Snow - This features a computer generated snowy scene with accompanying soundscape where the user is guided through a breathing exercise "*Relax and practice your breathing in a relaxing snowy environment"*

iii) Forest - This features a computer generated forest scene with accompanying soundscape where the user is guided through a breathing exercise "*Relax and practice your breathing in a relaxing forest environment"*

Information

i) Meet the psychologist – a consultant psychologist visits the patient in a hospital environment to explain their role and why the patient might interact with them.

ii) Meet the occupational therapist - an occupational therapist visits the patient in a hospital environment to explain their role and why the patient might interact with them.

iii) Meet the dietician - a dietician visits the patient in a hospital environment to explain their role and why the patient might interact with them.

iv) Meet the speech and language therapist - a speech and language therapist visits the patient in a hospital environment to explain their role and why the patient might interact with them.

v) Meet the physiotherapist- a physiotherapist visits the patient in a hospital environment to explain their role and why the patient might interact with them.

Following the end of the intervention delivery period, participants will be asked to perform follow-up assessments at conclusion on intervention delivery at 2wks and 4wks follow-up. If the participant remains an inpatient, participants will be assessed within their current hospital setting. For participants that have been discharged, they will be contacted to complete the follow-up assessments. This will either be by post (for preferred paper completion),by email (for preferred electronic completion) or by telephone.

Once follow-up assessments have been completed, the participant will be contacted to arrange an appointment for a qualitative interview. This will take place approximately 1 month following completion of the follow-up assessments. This may take place either in person at a location determined by the participant, or via secure video conferencing software such as Zoom or Microsoft teams. If the participant chooses to conduct the interview remotely, and has taken the VR equipment home with them at discharge, a separate arrangement will be made for the research team to either collect the DR.VR equipment or have the participant return it.

11.3.1 Assessments

Participants will be asked to undertake assessments at baseline and after they have finished the VR intervention. The timing of the follow-up period will be informed by activities and data in Phases 1 and 2 of this study. Baseline assessments will be conducted in the hospital setting, but the follow-up assessments will be completed by participants at home either on paper to be returned to the research site, or remotely. If participants are having difficulty, or are delayed in completing the

follow-up assessments, they may be contacted by the research team to support the completion of assessments over the telephone.

Assessments will include;

1) Collection of baseline demographic data to understand the diversity of the participant population and to contextualise any additional support requirements the participant may require in engaging with the intervention or completing assessments. This will be obtained from hospital notes for participants.

2) Collection of intervention adherence data, such as number of days the VR headset was used, the average length of time the VR headset was used and what aspects of the content package participants engaged with most. This data will be collected continuously by the DR.VR software during the intervention period and downloaded at the end of the intervention period.

Clinical outcome measures based on the priorities of ICU survivors, their family members and HCPs involved in the rehabilitation of ICU survivors have been selected, detailed in table 1 People with lived experience have been involved in the choice of outcome measures, based on perceived importance and burden of assessment. Name	Construct	Description	Time to Complete	Time point	
EQ-5D	Quality of Life	A well validated outcome measure for assessing quality of life over 5 domains across; usual activities, self-care, mobility, anxiety and depression and pain and discomfort.	5 mins	Baseline and Follow Up	ICU patients and family members

		Participants are also asked to rate their overall quality of life using a visual analogue scale (0-100).			
ICECAP-A	Quality of Life	Another well validated quality of life instrument 5 questions. Wellbeing: feeling settled and secure; love, friendship and support; being independent; achievement and progress; enjoyment and pleasure	5 mins	Baseline and Follow Up	
Brief resilience Scale	Psychological resilience	This consists of 6 items relating to response or coping to adverse life events. Participants are asked to rate each	5 mins	Baseline only	ICU patients and family members
Richards Campbell Sleep Questionnaire	Sleep	This is a 6 item questionnaire designed to address sleep and sleep quality. Participants are asked to respond to questions on a scale of 0-100. Questions cover; sleep depth, latency, awakenings, ability to return to sleep, sleep quality, with an optional item concerning noise.	5 mins	Baseline and Follow Up	ICU Patients only
DASS-10	Depression and Anxiety	This questionnaire consists of 10 items. Respondents are asked to rate how much has each item has applied to them over the past week on a scale of 0-4.	7 mins	Baseline and Follow Up	ICU patients and family members

3) Qualitative interviews will be conducted with;

i) phase 3 study ICU participants

ii) phase 3 study family member/ loved ones

iii) research/ clinical staff involved in recruitment, assessment and intervention delivery

For phase 3 study participants (ICU patients and family members/loved ones), interviews will be conducted following the end of the intervention period. For research/ clinical staff involved in recruitment, assessment and intervention delivery, these will take place during the recruitment and follow-up period.

These interviews will constitute a qualitative evaluation of the feasibility and acceptability of;

- The DR.VR intervention and its use in a hospital setting, including evaluation of technology acceptance
- Selected outcome measures to participants
- Selected outcome measures to research and intervention delivery staff

Qualitative interviews will be conducted either in person, on the telephone or via secure video-conferencing platforms such as Zoom or Teams and will be dictated by participant preference. Interviews will be audio recorded for transcription and analysis (see data management and analysis sections for further details).

Table 2. Schedule of enrolment and assessments[1]

Procedures	**Visits**				
	Screening (-2days - -1 day)	**Baseline (Wk 0)**	**Intervention Delivery (Wk 1-2)**	**Follow Up**	
				Wk 2	**Wk 4-8**
Informed consent	x				
Demographics		x			
Eligibility assessment	x				
Outcome measures from table 1.		x		x	

[1] Taken from the HRA CTIMP protocol template (2016).

VR READY intervention			x		
Intervention adherence			x		
Qualitative interviews Phase 3 participants and family members					x
phase 3 delivery staff)			x		

12 Safety reporting

The PI is responsible for ensuring that all site staff involved in this trial are familiar with the content of this section.

All Serious Adverse Events (SAEs) that meet requirements of an SAE must be reported immediately (and within 24 hours of knowledge of the event) by the PI at the participating site to the VR READY study team unless the SAE is specified as not requiring immediate reporting (see section 13.2).

12.1 *Definitions*

Term	Definition
Adverse Event (AE)	"Any untoward medical occurrence in a patient or clinical trial participant taking part in health care research, which does not necessarily have a causal relationship with the research."
Serious Adverse Event (SAE)	Any adverse event that - • Results in death • Is immediately life-threatening • Requires hospitalisation or prolongation of existing hospitalisation • Results in persistent or significant disability or incapacity • Is an important medical condition (if they jeopardise the subject or require an intervention to prevent one of the above).
Serious Adverse Reactions (SARs)	Any SAE occurring in a clinical trial participant for which there is a reasonable possibility that it is related to the intervention.

Suspected Unexpected Serious Adverse Reactions (SUSARs)	A SAR, the nature and severity of which is not consistent with the Reference Safety Information (RSI) for the intervention.

12.2 *Study Specific SAE Reporting Requirements*

In this patient population, recovering from critical illness, death, organ failure and readmission to intensive care are expected outcomes.

There are no anticipated adverse events that should be specially reported as SAEs for the purposes of this study.

12.3 *Causality*

Causal relationship will be assessed for the intervention and procedures:

Intervention: VR READY mediated by DR.VR

The PI (or another delegated medically qualified doctor from the trial team) will assess each SAE to determine the causal relationship and the Chief Investigator (CI) (or another appropriately qualified member of the Trial Management Group (TMG)) can also provide this assessment where necessary:

Relationship	**Description**	**Reasonable possibility that the SAE may have been caused by the intervention?**
Unrelated	There is no evidence of any causal relationship with the intervention	No
Unlikely	There is little evidence to suggest there is a causal relationship with the intervention (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).	No
Possible	There is some evidence to suggest a causal relationship with the intervention (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).	Yes

Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	Yes
Definite	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	Yes

12.4 *Expectedness*

The clinical CI (or another delegated appropriately qualified individual) will assess each SAE to perform the assessment of expectedness.

SAEs which add significant information on specificity or severity of a known, already documented adverse event constitute unexpected events. For example, an event more specific or more severe than that described in the protocol is considered unexpected.

Expected adverse events from use of virtual reality headsets
Motion sickness (usually mild)
Headache (usually mild)

12.5 *Reporting Procedures*

12.5.1 Participating Site Responsibilities

The PI (or delegated appropriately qualified doctor from the research team) should sign and date the SAE CRF to acknowledge that he/she has performed the seriousness and causality assessments.

A completed SAE form for all events requiring immediate reporting should be submitted via email to the VR READY study team within **24 hours** of knowledge of the event. A separate form must be used to report each event, irrespective of whether or not the events had the same date of onset.

The participant will be identified only by trial number and initials. The participant's name should not be used on any correspondence. It is also required that sites respond to and clarify any queries raised on any reported SAEs and report any additional information as soon as it becomes available (or at least within 24 hours of the information becoming available) through to the resolution of the event. Additionally, the VR READY study team may request additional information relating to any SAEs and the site should provide as much information as is available to them in order to resolve these queries.

Serious Adverse Event (SAE) email address:

VRREADY@cardiff.ac.uk

Serious adverse events should be reported from time of signature of informed consent, throughout the treatment period up to, and including completion of the follow-up timepoint.

For each **SAE** the following information will be collected:

- full details in medical terms and case description
- event duration (start and end dates, if applicable)
- action taken
- outcome
- seriousness criteria
- causality (i.e. relatedness to intervention), in the opinion of the investigator.

An SAE form is not considered as complete unless the following details are provided:

- Full participant trial number
- An Adverse Event
- A completed assessment of the seriousness, and causality as performed by the PI (or another appropriately medically qualified doctor registered on the delegation log).

If any of these details are missing, the site will be contacted and the information must be provided by the site to the VR READY study team within 24 hours.

All other AEs should be reported on the relevant CRF in the study database following the CRF procedure described in Section 16.

12.5.2 VR READY study team Responsibilities

Following the initial report, all SAEs should be followed up to resolution wherever possible, and further information may be requested by the VR READY study team. For follow-up information, sites to update the initial copy of the SAE form and put a single line through the old information and new information added.

The VR READY study team should continue reporting SAEs until the participant receives the last part of the intervention.

Once an SAE is received by the VR READY study team, it will be evaluated by the VR READY study team and sent to the CI (or their delegate) for an assessment of expectedness.

For all non-CTIMP studies, including clinical investigations of medical devices, only reports of related and unexpected SAEs should be submitted to the REC. These should be sent within 15 days of the CI becoming aware of the event. Reports of related and unexpected SAEs in double-blind trials should be unblinded. There is no requirement for Annual Safety Reports (ASRs) in addition to the information provided through the annual progress report.

12.6 *Procedure following disclosure of psychological distress*

If any participant answers that they are severely or extremely anxious or depressed on the EQ5D, has a raw score of 13 or more on the DASS-10 or a score of more than 0 on DASS-10 item 12 for suicidal thoughts, this should be flagged to the clinical CI and the Critical Care clinical psychologist (contact details below).

Contact Critical Care Clinical Psychologist: Details to be added

If no one is available from the Psychology team, the Crisis team: can be contacted on:

Royal Glamorgan - 01443 443443 x73674

Prince Charles - 01443 443443 x26952

13 Statistical considerations

13.1 Sample size

This study is focussed on intervention development and the piloting of the resulting intervention in a small number of participants to determine feasibility and acceptability of the intervention. Based on pragmatic reasons for running a focus group, we expect each focus group to contain no more than 8 participants each (16 in total across the two groups). For the feasibility study, no quantitative analysis will be performed. We have selected a sample size of up to 25 participants as a pragmatic target for how many people can be recruited from a single site over the given timeframe and at a level that sufficient data will be generated for our planned analysis.

13.3 Procedures for reporting deviation(s) from the original SAP

There will be no quantitative analysis of the data collected, so no SAP will be generated.

13.4 Inclusion in analysis

All evaluable participants will be included in the analysis.

14 Analysis

14.1 Qualitative analysis

Data analysis across all phases will be purely qualitative. Audio recordings of focus groups in phase 1 and participant and HCP/ researcher interviews from the feasibility study will be transcribed verbatim. Transcripts will be subject to analysis using a framework and mapping approach followed

by a thematic analysis informed by Braun & Clarke[23] and Adu[24] using NVivo software as a data management tool.

14.2 Quantitative analysis

In phase 3 of the study, we will ask participants to complete the outcome measures selected through the Phase 1 activities, however, data from the completed outcome measures in phase 3 will not be analysed. Outcome measure data will be collated and summarised in a tabular format for triangulation with the interview data using a mixed methods approach[25] to complement their qualitative evaluation.

15 Data Management

This study will consist largely of qualitative data, with some quantitative data being collected in Phase 3, but with no plans for formal statistical analysis.

Source Data is defined as *"All information in original records and certified copies of original records of clinical findings, observations or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents."* There is only one set of source data at any time for any data element, as defined in site source data agreement.

Study data	*Source Data*				
	Participant medical notes	*CRF (paper)*	*CRF (electronic)*	*Audio file saved on S Drvie*	*Site file*
Consent	*x*				*x*
Focus group data				*x*	
Selected outcome measures		*x*	*x*		
Interview data				*x*	
Withdrawal	*x*		*x*		*x*

15.1 Data collection

Phase 1 Focus groups:
All focus groups will be audio recorded for verbatim transcription. During the interactive sessions, we will collate patient maps of ICU recovery and rehabilitation, as well as polling and prioritisation data from discussion on outcome measures.

Phase 3 Pilot Study:
Data from the pilot study will be largely qualitative stemming from interviews conducted with participants, family members/ loved ones and health care professionals. This data will be collected at two main
time points; one during the delivery of the intervention to gather contemporaneous reflections on the use of the intervention and one at the end of the follow-up period to gather data on the acceptability and relevance of outcome measures,. Data on the selected
outcome measures will be collected prior to intervention delivery and at the end of the follow-up period as part of assessing their acceptability.

15.2 Completion of CRFs

For the phase 3 feasibility study, participants will be able to complete outcome assessments on paper or electronically. The participant's preference for CRF completion will be ascertained at the point of assessment and prior to hospital discharge (if applicable).

15.2.1 Paper CRFs

Paper CRFs will be provided to the participant by post for the follow-up assessment if requested. Completed paper CRFs will be returned to the research site using a pre-paid envelope. CRFs should be returned within four weeks of completion. Participants may be contacted by telephone if the return of paper CRFs are outstanding. This may include support for the completion of paper CRFs via telephone with a study researcher.

CRF pages and data received by the research site from participants will be checked for missing, illegible or unusual values (range checks) and consistency over time.

If missing or questionable data are identified, a researcher may contact the participant for clarification and a record of the data query will be made to inform feasibility outcomes. The case report form pages should not be altered.

Data from paper CRFs will be entered into an Excel spreadsheet by a member of the research team delegated to the study. A proportion of data entry will be checked by a second researcher on a periodic basis.

15.2.2 Electronic CRFs

Remote completion of study outcomes will be enabled through a web-based platform such as REDCap. This is a secure encrypted system accessed by an institutional password, and complies with the General Data Protection Regulation 2016. The system can be accessed on:

<

"Add link here"

A user password will be supplied to investigators upon completion of all processes required prior to opening. To enable participants to complete outcome assessments remotely, a personal link will be emailed to them.

15.3 Data storage and access

All study records will be identified via a unique study identifier. Any hard copy documentation containing study data will be stored in locked cabinets in the Clinical Research Centre, Cwm Taf Morgannwg University Health Board. Only the consent forms will contain identifiable personal data. Only employees of Cwm Taf Morgannwg University Health Board will have access to these documents.

All electronic study records will be held on secure servers and be protected using personal network passwords. Pseudonymised study records will be made accessible to collaborating investigators from institutions outside the sponsor organisation through secure file sharing software such as Microsoft Teams.

Personal identifiable data (largely restricted to participant contact details) will be held within the sponsor organisation in a participant management database that will be protected by additional password encryption. Access will be restricted to limited individuals on the delegation log. Where participants may contact the study team to indicate their interest in taking part in the study or for general correspondence with the research team about their participation in the study, they will do so via the VRReady@cardiff.ac.uk address. The shared mailbox enables monitoring of study correspondence, management of the study and other key activities to be performed by several different team members. This reduces the onus on a single team member to attend to all issues and means that there is no single point of failure in study management. Participants contacting the shared mailbox will involve sharing their contact details (name and e-mail address) outside of the sponsor organisation and will be done voluntarily by the participants.

16 Protocol/GCP non-compliance

The Principal Investigator should report any non-compliance to the study protocol or the conditions and principles of Good Clinical Practice to the CTR in writing as soon as they become aware of it.

17 End of Study definition

The end of the study is defined as the date of final data capture to meet the study endpoints. In this case end of study is defined as the completion of the final qualitative interview in Phase 3 of the study.

Sponsor must notify the main REC of the end of a clinical study within 90 days of its completion or within 15 days if the study is terminated early.

18 Archiving

The SMF and SSF containing essential documents will be archived at an approved external storage facility for a minimum of 10 years. The CTR will archive the SMF and SSFs on behalf of the Sponsor. The Principal Investigator is responsible for archival of the ISF at site on approval from Sponsor. Essential documents pertaining to the study shall not be destroyed without permission from the Sponsor.

19 Regulatory Considerations

19.1 Ethical and governance approval

This protocol has approval from a Research Ethics Committee (REC) that is legally "recognised" by the United Kingdom Ethics Committee Authority for review and approval.

This study protocol will be submitted through the relevant permission system for global governance review dependant on the location of the lead site (e.g. Health Care Research Wales (HCRW) research permissions)

Confirmation of capability and capacity to support the study will be obtained from the host care organisation who will consider local governance requirements and site feasibility. The Research Governance approval of the host care organisation must be obtained before recruitment of participants within that host care organisation.

19.2 Data Protection

Participant confidentiality will be maintained throughout the study. Any data relating to participants will only be stored using the participants unique study identification number. Any personal data (e.g. name and contact details) will be held securely at Cwm Taf Morgannwg University Health Board and Cardiff University in a password protected database on secure servers, according to GCP guidelines and with the participants consent.

The CTR will act to preserve participant confidentiality and will not disclose or reproduce any information by which participants could be identified, except where specific consent is obtained. Data will be stored in a secure manner and will be registered in accordance with the General Data Protection Regulation 2016. The data custodian for this study is the study lead.

19.3 Indemnity

- Non-negligent harm: This study is an academic, investigator-led and designed study sponsored by Cwm Taf Morgannwg University Health Board and coordinated by the CTR. The Co-Chief

Investigators, local Investigators and CTR do not hold insurance against claims for compensation for injury caused by participation in a clinical study and therefore cannot offer any non-negligent harm indemnity. The Association of the British Pharmaceutical Industry (ABPI) guidelines will not apply.

- Negligent harm: In accordance with Technical Note 12 Indemnity for Clinical Research for research Sponsored by a Welsh body, Welsh Risk Pool Services provides indemnity cover against successful negligence claims arising from the management and conduct of the study. Where NHS employees are responsible for the design of a study, indemnity cover will also be provided for negligent harm arising from the study design. Cwm Taf Morgannwg University Health Board does not accept liability for any breach in the other NHS Organisations duty of care, or any negligence on the part of employees of these NHS Organisations.

All participants will be recruited at NHS sites and therefore the NHS indemnity scheme/NHS professional indemnity will apply with respect to claims arising from harm to participants at site.

19.4 Study sponsorship

The study is being sponsored by Cwm Taf Morgannwg University Health Board. The health board shall be responsible for ensuring that the study is performed in accordance with the following:

- Conditions and principles of Good Clinical Practice.
- Declaration of Helsinki (1996)
- UK Policy Framework for Health and Social Care Research.
- The General Data Protection Regulation (2016).
- Other regulatory requirements as appropriate.

The Sponsor has delegated certain responsibilities to Cardiff University (CTR) and other stakeholder organisations as appropriate in accordance with the relevant agreement that is informed by regulation and study type.

19.5 Funding

VR-READY is funded by the Health Care Research Wales Research for Public and Patient Benefit scheme. Additional resource is provided in kind by Rescape Ltd. Who are responsible for the manufacture and adaptation of DR.VR.

20 Study management

This study will be managed via a core project team (PT) and study management group. PT meetings will consist of the Co-CI's and lead study research nurse. Additional members of the research team will be included where required. PT meetings will occur on a frequency dictated by the stage/ urgency of project related issues. In the first instance, this is expected to occur weekly or bi-weekly, reducing to monthly meetings once set-up is complete.

20.1 SMG (Study Management Group)

The VR-READY study management group will consist of all the study co-applicants (as listed at the beginning of this protocol) who will meet at least bi-monthly throughout the course of the project. The SMG will contribute to study design, conduct and delivery as well as analysis and dissemination through these meetings. SMG members will be required to sign up to the remit and conditions as set out in the SMG Charter.

21 Quality Control and Assurance

21.1 Monitoring

The clinical study risk assessment has been used to determine the intensity and focus of central and on-site monitoring activity in the VR-READY study. Due to the low risk nature of the research and the lack of quantitative data collection, there will be no planned monitoring at site. There will be low levels of monitoring in place for qualitative data and study progress. This will be detailed in the monitoring plan.

21.2 Audits & inspections

The study may also be subject to inspection and audit by Cwm Taf Morgannwg University Health Board under their remit as Sponsor.

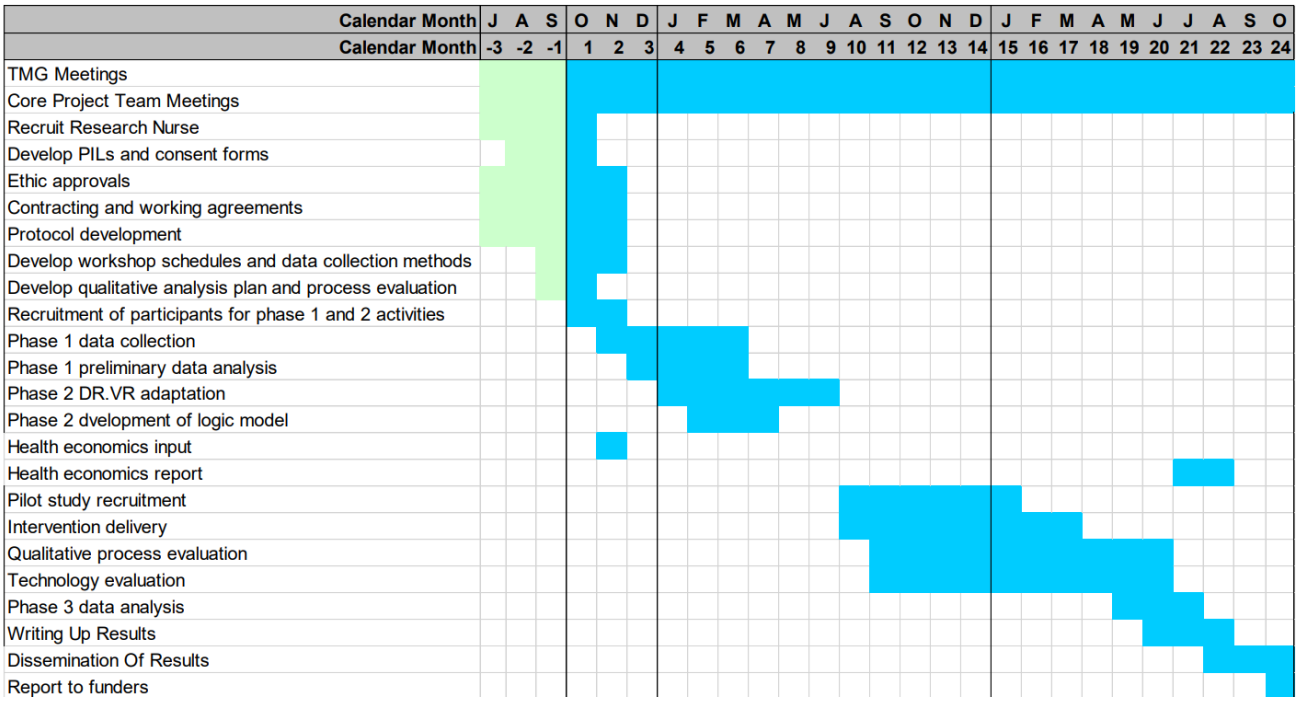
22 Publication policy

A comprehensive publication policy will be developed which will detail all contributors to the project and outline any planned publications relating to the study, including lead and contributing authors. All publications and presentations relating to the study will be authorised by the Study Management Group.

The results of the study will be disseminated in the peer reviewed literature and also with those who have taken part in the study (both ICU survivors and health care professionals) via directed mailing and

23 Milestones

Proposed study timelines



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