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The Psychological IMpact of surviving an intensive care admission due to COronaVIrus Disease 2019 (COVID-19) on patients in the United Kingdom

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The Psychological IMpact of surviving an intensive care admission due to COronaVIrus Disease 2019 (COVID-19) on patients in the United Kingdom

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ABSTRACT

Introduction

Psychological distress is common in intensive care survivors and is anticipated in those who were treated for severe COVID-19 infection. This trainee-led, multi-centre, observational, longitudinal study aims to assess the psychological outcomes of ICU survivors treated for COVID-19 infection in the United Kingdom.

Methods and analysis

Questionnaires will be provided to study participants 3, 6 and/or 12 months after discharge from intensive care, assessing for anxiety, depression, post-traumatic stress symptoms, health-related quality of life and physical symptoms. Demographic, psychosocial and clinical data will also be collected to explore risk factors for psychological distress using latent growth curve modelling. Study participants will be eligible to complete questionnaires at any of the three timepoints online, by telephone or by post.

Ethics

The study was approved by the Health Research Authority (East Midlands - Derby Research and Ethics Committee, reference: 20/EM/0247).

Trial registration number

NCT05092529; Pre-results

ARTICLE SUMMARY

Strengths and Limitations

1. Trainee-led, multi-centre observational study assessing the psychological outcomes in ICU survivors with COVID-19 in the United Kingdom
2. Outcomes are assessed at multiple time points after ICU discharge, allowing an assessment of the trajectory of patient symptoms
3. Findings will be enriched by the inclusion of qualitative data from patient interviews, a survey of team members and an evaluation of available follow-up services.
4. Participants are eligible to join the study at any point up to 12 months post ICU discharge, which improves the temporal scope of the sampling but may lead to variation in response rates at the 3, 6 and 12 month timepoints.

BACKGROUND

Coronavirus disease 2019 (COVID-19) has led to an extraordinary demand for intensive care support for patients severely affected by SARS-CoV-2. There is an anticipated psychological impact of these intensive care admissions[1] based on previous evidence from intensive care unit (ICU) survivors with acute respiratory distress syndrome (ARDS)[1 2] and from patients treated during previous coronavirus pandemics, namely Severe Acute Respiratory Syndrome (SARS) in 2002-2003 and Middle East Respiratory Syndrome (MERS) in 2012-2013.[3]

Psychological symptoms after an ICU admission may form part of Post Intensive Care Syndrome (PICS), which can also include cognitive and physical impairments that are new or have worsened following ICU admission and persist on discharge from hospital.[4] Between 23 and 38% of ICU patients diagnosed with non-COVID-19 ARDS, prolonged symptoms of anxiety, depression and post-traumatic stress disorder (PTSD) were found, with a median duration of symptoms between 33 and 39 months.[2] Admission to critical care is itself associated with a significant burden of psychological sequelae. Symptoms of anxiety, depression and PTSD have been reported to affect up to 73% of ICU survivors.[5-7] Furthermore, symptoms of anxiety, depression and PTSD can persist in up to 34% of ICU survivors after one year following critical care admission.[5-7] At the peak of the SARS outbreak, patients reported significantly higher stress levels than healthy controls,[8] with 64% of patients reporting symptoms suggesting psychiatric morbidity at 12 months.[9] Data are conflicting regarding the influence of sex on risk for experiencing psychological distress and developing long-term psychiatric morbidity after an ICU admission.[5-7 9 10]. Recognised risk factors for emotional distress following ICU admission include previous psychiatric morbidity, receipt of benzodiazepines in ICU, physical restraint and psychiatric symptoms during their admission.[5-7 11] Data from previous pandemics suggests that pandemic-related factors such as quarantine may also have an impact on the psychological wellbeing of ICU survivors.[3]

This will be the first intensive care trainee-led multi-centre study to be conducted in the United Kingdom, facilitated by the Trainee in Intensive Care (TRIC) Network and with support from the National Institute of Health Research (NIHR).

Study Aims and Objectives

In this study, we aim to assess the short- and long-term psychological impact on patients who have survived an admission to intensive care due to COVID-19 in the United Kingdom, and identify possible predictors of anxiety, depression and post-traumatic stress symptoms in this patient group.

Our primary objective is to identify the proportion of patients surviving an admission to intensive care due to COVID-19 who experience anxiety, depression and/or post-traumatic stress symptoms at 6 months post-discharge, assessed using the Hospital Anxiety and Depression Scale (HADS) and the Impact of Event Scale-6 (IES-6), respectively. Secondary objectives are to identify demographic, clinical, physical and/or psychosocial risk factors for depression, anxiety and/or post-traumatic stress symptoms at 3, 6 and 12 months post discharge from ICU and to assess the feasibility of using a self-reported online questionnaire to examine psychological distress in patients following ICU admission.

METHODS AND ANALYSIS

Study Protocol

Study Design and Setting

PIM-COVID is a multicentre, longitudinal study involving intensive care units in National Health Service (NHS) hospitals in England, Northern Ireland, Scotland and Wales. Study participants will be invited to participate after discharge from intensive care, following assessment of inclusion and exclusion criteria (see Table 1).

Table 1: PIM-COVID Study Eligibility Criteria

Inclusion Criteria	Exclusion Criteria
Adult patients aged ≥18 years Diagnosed positive for COVID-19 Survived to intensive care / high dependency unit discharge following an admission of ≥24 hours	Unable or unwilling to consent Unable to complete questionnaires Unable to speak, understand or communicate in English Patients with diagnosed pre-existing cognitive impairment (at the time of ICU admission) Patients with no fixed abode, at which postal questionnaire might be not received, and who have no access to a personal email address.

The study has two related components:

(1) A multiple cohorts design will be used for point prevalence estimates. We are seeking to obtain a large sample spanning a long time period. Thus, patients meeting the inclusion criteria will be approached up to 12 months post ICU discharge, with some entering the study at 3, 6 and 12 month timepoints. Separate prevalence estimates will be made for each follow-up, with risk factor analysis from clinical data at each timepoint.

(2) A nested single cohort design will provide longitudinal analysis. Using patients available at the 3- and 12-month timepoints, we will estimate individual changes over time and conduct a longitudinal analysis of risk factors.

Study Outcomes

The primary outcome of the study is the prevalence of anxiety, depression and post-traumatic stress symptoms in ICU survivors who have been treated for COVID-19 infection. Anxiety and depression will be assessed using the HADS. Post-traumatic stress symptoms will be assessed using the IES-6. Exploratory outcomes will use demographic, clinical and physical data (outlined in Table 2) to identify demographic, clinical, physical and/or psychosocial predictors of depression, anxiety and/or post-traumatic stress symptoms at 3, 6 and 12 months after discharge from ICU. Evaluation of psychosocial predictors will use metacognitive beliefs and processes (thoughts about beliefs and thought processes) and these will be assessed using the Cognitive Attentional Syndrome Scale-1 (Revised).[12] The feasibility of using a self-reported online questionnaire to assess anxiety, depression and post-traumatic stress symptoms in patients following ICU admission will be evaluated using recruitment numbers, recruitment rate (proportion of those deemed eligible recruited), retention rate (proportion of participants who provide data at subsequent data capture points), and rate of missing key data.

Table 2: Data collected in PIM-COVID study		
Demographic Data	Age Sex Highest education level obtained Employment status Socioeconomic status (postcode-linked deprivation index)	
Clinical Data	Length of stay in ICU Laboratory diagnosis or suspicion of COVID-19 infection Mental health co-morbidities Physical health co-morbidities Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) II score Ventilatory support during ICU admission Diagnosis of delirium during ICU admission Benzodiazepine requirement during ICU admission (other than as required for intubation) Date of death (if during 12 month study period)	
Physical Data	EQ-5D-5L (used as a subjective assessment of the physical function of participants)	
Psychological Data	*Anxiety:*	Hospital Anxiety and Depression Scale (HADS)* EQ-5D-5L*
	Depression:	Hospital Anxiety and Depression Scale (HADS)* EQ-5D-5L*
	Trauma symptoms:	Impact of Event Scale-6 (IES-6)*
Metacognitive beliefs and processes	Cognitive Attentional Syndrome Scale-1 Revised (CAS-1R) *	
** Self reported questionnaires administered at 3, 6 and/or 12 months following ICU discharge*		

Hospital and Anxiety Depression Scale (HADS)

The HADS is a 14-item self-report measure in which participants rate the presence of symptoms of anxiety (7 items) and depression (7 items) over the preceding week using a 4-point Likert scale, with options from 0 (absence) to 3 (extreme presence). Responses are summed to produce two subscale scores, ranging from 0-21, with higher scores indicative of higher anxiety and depression levels, respectively. The HADS is widely used to assess

anxiety and depression in people with physical health difficulties and demonstrates good psychometric properties when used in an intensive care setting.[13] Cut-off scores of ≥8 on anxiety and depression subscales of the HADS have been used to define caseness, with a score of 8-10 being 'borderline abnormal' and a score of 11-21 indicating anxiety or depression.[13 14]

Impact of Event Scale-6 (IES-6)

The IES-6 is a validated tool in survivors of ARDS to screen for post-traumatic stress disorder. It is an abbreviated version of the Impact of Event Scale-Revised (IES-R) test and contains six questions.[15] We selected the IES-6 over the IES-R because it is shorter, has been validated in a very similar patient population,[15] will provide similar information to the IES-R, and is likely to have a higher completion rate by patients because of its length in the context of participants commonly experiencing a reduced concentration span following ICU admission.[4]

EuroQol 5-dimension, 5-level questionnaire (EQ-5D-5L)

The EQ-5D-5L is a five-domain, self-report measure assessing mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Participants are asked to rate each question, indicating no problems, slight problems, moderate problems, severe problems or extreme problems. In addition, participants are invited to rate their health on a visual analogue scale from 0-100, where zero represents the worst health imaginable and 100 represents the best health imaginable. EQ-5D-5L is the recommended questionnaire to assess the HRQoL of critically ill patients.[16]

Cognitive Attentional Syndrome Scale-1 Revised (CAS-1R)

The CAS-1R is a 10-item self-report measure assessing positive and negative metacognitive beliefs, frequency of worry or rumination and the use of a range of counterproductive coping strategies used in response to negative thoughts and feelings.[12] Participants are asked to rate the degree to which they have engaged in a particular coping strategy or thought process during the previous week. Responses are scaled from 0%-100% and are summed to produce a total score. Higher scores indicate greater conviction in metacognitive beliefs and greater use of maladaptive coping strategies to manage distress. The CAS-1R has demonstrated good psychometric properties in physical health populations.[17]

Recruitment

After discharge from ICU, patients will be screened by local study teams against inclusion and exclusion criteria prior to enrolment, with the possibility for enrolment up to 12 months after

ICU discharge. Patients will be invited to participate in person whilst awaiting discharge from hospital, whilst attending an ICU follow up clinic appointment in hospital, or by postal invitation with a unique code to offer the opportunity to complete the consent form. Questionnaires at 3, 6 and/or 12 months will be completed online, by phone or by post.

Database

Study data will be collected and managed using the online Research Electronic Data Capture (REDCap) system hosted at the University of Liverpool.[18 19] Personal data will be added to the secure, web-based software platform only once patients agree to participate in the study and will be held for the study duration. Personal patient data will be pseudo-anonymised for analysis and will be held in compliance with EU General Data Protection Regulations (GDPR) and the UK Data Protection Act (2018).

Patient and Public Involvement

The peer support group charity, ICUsteps, has a group of ex-ICU patients and relatives who feed back on the importance and relevance of the research question and how they view the outcome measures being used. One of the authors in her role as the research manager for ICUsteps asked this group to comment on the draft research protocol using their experience of critical illness. They were also asked to comment on the possible impact for patients of taking part in the study. Patients were not involved in the recruitment to or conduct of the study.

ANCILLARY STUDIES

Three sub-studies were designed and added to the main study, following HRA approval on 28 February 2022. Semi-structured interviews were added to the study to gain a deeper understanding of patient experience, taking into consideration feedback from patients involved in the study that the validated tools utilised in the questionnaire did not allow the nuance of their individual experiences to be conveyed. Surveying sites to understand the services available to COVID-19 survivors across the country was added to gain context to the information provided in the questionnaires in regards to whether patients engaged with follow up services. As PIM-COVID is a trainee-led study, we added a survey of team members to understand the attitudes and opinions of collaborators and to gain their feedback on the study in a structured way.

Sub-study: Semi-structured Interviews

The aim of the semi-structured interviews is to explore the experiences of critical care survivors following COVID-19 infection during their recovery phase, including perceptions

about the care received and support available to them. Study participants who have indicated on a completed questionnaire that they are happy to be contacted by the study team for more information will be approached by telephone or email to discuss their potential participation in a one-on-one interview. A purposive sample of participants will be selected aiming for a sample that is diverse, representative of the cohort (in terms of ethnicity, sex, geographical location, degree of deprivation based on postcode, length of stay in ICU, etc), and inclusive of participants with and without evidence of psychological distress, based on answers to the 3 and 6 month questionnaires, where these have been answered. Participants from the last cohort of patients discharged from ICU will be invited to interview. Interviews will be conducted via Microsoft Teams or by phone and will be recorded. Audio recordings will be transcribed for analysis by a transcription service.

Sub-study: Survey of study team members

We aim to explore factors influencing study team member involvement, understand their attitudes and opinions, and gain feedback on the study. Team members at all study sites will be invited to complete an online survey by email, which will explore the socio-demographic characteristics of study team members, previous academic experience, feedback on involvement in the study, attitudes towards health research, barriers and motivators to contributing to health research, and future research plans.

Sub-study: Survey of study sites

Current national guidelines state that at-risk ICU survivors who have had an admission of more than 4 days should be invited to a follow up clinic 2-3 months after discharge from ICU.[20] However, hospital and community based services to support ICU survivors in their recovery were limited even before COVID-19, with about 70% of hospitals not offering an ICU follow up clinic.[21] In this sub-study we aim to assess geographical differences in the availability and structure of follow-up services offered to patients with critical COVID-19 after hospital discharge. All intensive care units within the UK will be approached by email and/or phone and invited to complete an online survey about follow-up services available for patients having been discharged from hospital after critical illness.

STATISTICAL METHODS

We will report findings of the study using descriptive methods in the absence of a non-COVID or non-ICU comparator group. Data about ICU patients in the United Kingdom were reported by the Intensive Care National Audit and Research Centre (ICNARC) in three temporal groups related to the 'waves' of ICU patients admitted with COVID-19. In keeping with the date ranges used by ICNARC, we will consider study participants who were in ICU prior to 31 August 2020,

between 1 September 2020 and 30 April 2021, and from 1 May 2021 onwards in addition to evaluating the overall cohort.[22]

Multiple cohorts design

Unadjusted point prevalence rates per 100,000 individuals will be estimated with 95% Confidence Intervals at 3-, 6- and 12-month observations. These separate cohorts cannot be directly compared because ICU and broader illness-related variables may change over time and thus may differ between cohorts (e.g., survivor bias attributable to improved ICU care during the course of the pandemic). Clinical risk factors for each cohort will be estimated using binomial logistic regression.

Single cohort design

Separate analyses will be conducted with HADS Anxiety, Depression and IES-6 scores. Trajectories of HADS Anxiety, Depression and IES-6 scores will be described using growth curve analysis. Growth curve analysis is a flexible statistical method for describing population changes over multiple timepoints by flexibly fitting and comparing pre-specified linear or curvilinear models. Risk factors can be identified by fitting predictors to models, allowing for both intra- and inter-participant variations to be analysed.[23-25] To improve power, we will use the full range of scores for the HADS and IES-6.

Latent growth curve modelling (LGCM) is a form of structural equation modelling that allows a population's trajectory across multiple observations to be described with regard to two parameters; an intercept representing the population mean at time=0, and a slope representing sequential changes from that mean.[25] In LGCM pre-specified theoretical models can be tested for adequacy of fit to the data, or parameters can be freely estimated. As the intercept and slope parameters cannot be fully specified in advance for model testing, we will adopt a conventional approach of testing and refining a model of the data starting from an initial fully constrained model. Constraints are systematically relaxed based on fit to the emerging model until good fit is established. Once intercept and slope of each model are identified, putative demographic, clinical, physical and/or psychosocial risk factors can be identified using multivariate analyses, such as regression, to predict intercept and slope.

The initial model will specify known population means for HADS anxiety and depression and IES-6 as intercepts, a linear slope trajectory, with homogenous individual growth, equality of error variance across observations and independence of slope and error estimates assumed. These are initial assumptions in the process of latent growth curve modelling and are outside the scope of this manuscript but are explained in the reference provided here.[23] Parameters

will be relaxed in that order until good fitting models (Comparative Fix Index (CFI) > .95, Root Mean Square Error of Approximation (RMSEA) .05) are identified whilst retaining as many fixed parameters from the initial model as possible. [26 27] Linear and quadratic slope models will be tested; linear models being defined as slope parameters 0, 1, 4, and 12 and quadratic slopes as 0, 1, 8 and 24.

Secondary analyses will be to assess temporal relationships between HADS Anxiety, Depression and IES-6 scores and CAS-1R and EQ-5D-5L variables to identify the roles of the latter as potential mediators of the former.

Missing Data

Missing variable replacement will not be used in the multiple cohorts design. Data replacement for the single cohort design will be achieved by multiple imputation for the logistic regression analysis and unbiased full information maximum likelihood estimation. Some missing variables in the single cohort will derive from the death of participants – the date of death will be provided by study teams into the online study database if the patient has died during the study period. Data will not be replaced in observations missed through death, but data obtained from these participants whilst alive will be used in imputation calculations.[28]

Sub-study: Semi-structured Interviews

Analysis of the interviews will use the principles of the constant comparative method and interpretive thematic analysis. The analysis will be interpretive and consider both latent and manifest aspects of the data, thereby acknowledging both the manner that participants talk as well as the explicit content. Analysis will progress in parallel with recruitment and will end when theoretical saturation is reached. Systematic data coding will be performed; exceptional case analysis will be discussed within the research team; and data will be triangulated with quantitative data from the PIM-COVID study to enriching findings and interpretation.

Sub-studies: Survey of Study Team Members & Survey of Study Sites

The findings of both surveys will be reported using descriptive methods.

RESEARCH ETHICS APPROVAL

The study was approved by the Health Research Authority (East Midlands - Derby Research and Ethics Committee, reference: 20/EM/0247).

DATA SHARING STATEMENT

Upon the conclusion of the study, the dataset may be made available from the corresponding author on reasonable request.

AUTHOR CONTRIBUTIONS

AW, BW and AB conceived the study. The protocol was developed with the expertise of MGC, PF, SB and CJ in clinical psychological research, and CJ has advocated for patients and has represented their perspective. SB created the plan for statistical analysis. AW, MGC and IW received funding to conduct this study. AW, IW and KW have key roles in study implementation. AW wrote the first draft of this protocol. All authors refined the study protocol and approved this manuscript.

COMPETING INTERESTS

None of the authors have any competing interests that may have influenced the submitted work.

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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	1
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	1
Funding	#4	Sources and types of financial, material, and other support	2
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	2

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	2
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	2
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)	N/A
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	N/A
Objectives	#7	Specific objectives or hypotheses	4
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)	5
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	5
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will	12

		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	N/A
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	5
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)	5
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	N/A
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	5
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	N/A

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	N/A
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N/A
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
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	N/A
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	7
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	N/A
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	7
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	9
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	N/A
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	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	8
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	7

Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	11
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	11
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	N/A
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	11
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

PIM-COVID study: protocol for a multi-centre, longitudinal study measuring the psychological impact of surviving an intensive care admission due to COVID-19 on patients in the United Kingdom

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PIM-COVID study: protocol for a multi-centre, longitudinal study measuring the psychological impact of surviving an intensive care admission due to COVID-19 on patients in the United Kingdom

Study Acronym:

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ABSTRACT

Introduction

Psychological distress is common in intensive care unit (ICU) survivors and is anticipated in those who were treated for severe COVID-19 infection. This trainee-led, multi-centre, observational, longitudinal study aims to assess the psychological outcomes of ICU survivors treated for COVID-19 infection in the United Kingdom at 3, 6 and/or 12 months after ICU discharge and explore whether there are demographic, psychosocial and clinical risk factors for psychological distress.

Methods and analysis

Questionnaires will be provided to study participants 3, 6 and/or 12 months after discharge from intensive care, assessing for anxiety, depression, post-traumatic stress symptoms, health-related quality of life and physical symptoms. Demographic, psychosocial and clinical data will also be collected to explore risk factors for psychological distress using latent growth curve modelling. Study participants will be eligible to complete questionnaires at any of the three timepoints online, by telephone or by post.

Ethics

The PIM-COVID study was approved by the Health Research Authority (East Midlands - Derby Research and Ethics Committee, reference: 20/EM/0247).

Trial registration number

NCT05092529; Pre-results

ARTICLE SUMMARY

Strengths and Limitations

1. Trainee-led, multi-centre, longitudinal, observational study assessing the psychological outcomes in ICU survivors with COVID-19 in the United Kingdom
2. Outcomes are assessed at multiple time points after ICU discharge, allowing an assessment of the trajectory of patient symptoms
3. Findings will be enriched by the inclusion of qualitative data from patient interviews, a survey of team members and an evaluation of available follow-up services.
4. Participants are eligible to join the study at any point up to 12 months post ICU discharge, which improves the temporal scope of the sampling but may lead to variation in response rates at the 3, 6 and 12 month timepoints.

BACKGROUND

Coronavirus disease 2019 (COVID-19) has led to an extraordinary demand for intensive care support for patients severely affected by SARS-CoV-2. There is an anticipated psychological impact of these intensive care admissions[1] based on previous evidence from intensive care unit (ICU) survivors with acute respiratory distress syndrome (ARDS)[1 2] and from patients treated during previous coronavirus pandemics, namely Severe Acute Respiratory Syndrome (SARS) in 2002-2003 and Middle East Respiratory Syndrome (MERS) in 2012-2013.[3] Evidence is emerging on the impact of COVID-19 on hospitalised patients in the UK and internationally.[4-7] We anticipate that the PIM-COVID study will be the largest longitudinal, observational study in the UK to assess the psychological outcomes of critically ill patients who have been treated for COVID-19 infection.

Psychological symptoms after an ICU admission may form part of Post Intensive Care Syndrome (PICS), which can also include cognitive and physical impairments that are new or have worsened following ICU admission and persist on discharge from hospital.[8] In a study assessing the psychological wellbeing of ICU survivors up to five years after discharge from hospital, up to 38% of ICU patients diagnosed with non-COVID-19 ARDS were found to have prolonged symptoms of anxiety, depression and post-traumatic stress disorder (PTSD), with a median duration of symptoms between 33 and 39 months.[2] Admission to critical care is itself associated with a significant burden of psychological sequelae. Symptoms of anxiety, depression and PTSD have been reported to affect up to 73% of ICU survivors.[9-11] Furthermore, symptoms of anxiety, depression and PTSD can persist in up to 34% of ICU survivors after one year following critical care admission.[9-11] At the peak of the SARS outbreak, patients reported significantly higher stress levels than healthy controls,[12] with 64% of patients reporting symptoms suggesting psychiatric morbidity at 12 months.[13] Recognised risk factors for emotional distress following ICU admission include previous psychiatric morbidity, receipt of benzodiazepines in ICU, physical restraint and psychiatric symptoms during their admission.[9-11 14 15] Data are conflicting regarding the influence of sex on risk for experiencing psychological distress and developing long-term psychiatric morbidity after an ICU admission.[9-11 13 16] Data from previous pandemics suggests that pandemic-related factors such as quarantine may also have an impact on the psychological wellbeing of ICU survivors.[3]

Study Aims and Objectives

In this study, we aim to assess the short- and long-term psychological impact on patients who have survived an admission to intensive care due to COVID-19 in the United Kingdom, and

identify possible predictors of anxiety, depression and post-traumatic stress symptoms in this patient group. This is the first intensive care trainee-led multi-centre study to be conducted in the United Kingdom, facilitated by the Trainee in Intensive Care (TRIC) Network and with support from the National Institute of Health Research (NIHR). The TRIC Network is a UK-wide group of trainees, with an interest in intensive care medicine, who aim to facilitate and inspire audit, quality improvement and research among trainees (interns/residents) and ICU-affiliated clinicians.

Our primary objective of the study is to identify the proportion of patients surviving an admission to intensive care due to COVID-19 who experience anxiety, depression and/or post-traumatic stress symptoms at 6 months post-discharge, assessed using the Hospital Anxiety and Depression Scale (HADS) and the Impact of Event Scale-6 (IES-6), respectively. Secondary objectives are to identify demographic, clinical, physical and/or psychosocial risk factors for depression, anxiety and/or post-traumatic stress symptoms at 3, 6 and 12 months post discharge from ICU and to assess the feasibility of using a self-reported online questionnaire to examine psychological distress in patients following ICU admission.

METHODS AND ANALYSIS

Study Protocol

Study Design and Setting

PIM-COVID is a multicentre, longitudinal study involving intensive care units in National Health Service (NHS) hospitals in England, Northern Ireland, Scotland and Wales. Study participants have been invited to participate after discharge from intensive care, following assessment of inclusion and exclusion criteria (see Table 1). The study started in November 2020 and is due to be completed, inclusive of the sub-studies, in November 2023.

Table 1: PIM-COVID Study Eligibility Criteria	
Inclusion Criteria	**Exclusion Criteria**
Adult patients aged ≥18 years Diagnosed positive for COVID-19 Survived to intensive care / high dependency unit discharge following an admission of ≥24 hours	Unable or unwilling to consent Unable to complete questionnaires Unable to speak, understand or communicate in English Patients with diagnosed pre-existing cognitive impairment (at the time of ICU admission) Patients with no fixed abode, at which postal questionnaire might be not received, and who have no access to a personal email address.

The study has two related components:

(1) A multiple cohorts design will be used for point prevalence estimates. We are seeking to obtain a large sample spanning a long time period. Thus, patients meeting the inclusion criteria will be approached up to 12 months post ICU discharge, with some entering the study at 3, 6 and 12 month timepoints. Separate prevalence estimates will be made for each follow-up, with risk factor analysis from clinical data at each timepoint.

(2) A nested single cohort design will provide longitudinal analysis. Using patients available at the 3- and 12-month timepoints, we will estimate individual changes over time and conduct a longitudinal analysis of risk factors.

Study Outcomes

The primary outcome of the study is the prevalence of anxiety, depression and post-traumatic stress symptoms in ICU survivors who have been treated for COVID-19 infection. Anxiety and depression will be assessed using the HADS. Post-traumatic stress symptoms will be assessed using the IES-6. Exploratory outcomes will use demographic, clinical and physical data (outlined in Table 2) to identify demographic, clinical, physical and/or psychosocial predictors of depression, anxiety and/or post-traumatic stress symptoms at 3, 6 and 12 months after discharge from ICU. Evaluation of psychosocial predictors will use metacognitive beliefs and processes (thoughts about beliefs and thought processes) and these will be assessed using the Cognitive Attentional Syndrome Scale-1 (Revised).[17] The feasibility of using a

self-reported online questionnaire to assess anxiety, depression and post-traumatic stress symptoms in patients following ICU admission will be evaluated using recruitment numbers, recruitment rate (proportion of those deemed eligible recruited), retention rate (proportion of participants who provide data at subsequent data capture points), and rate of missing key data.

Table 2: Data collected in the PIM-COVID study

Demographic Data	Age Sex Highest education level obtained Employment status Socioeconomic status (postcode-linked deprivation index)	
Clinical Data	Length of stay in ICU Laboratory diagnosis or suspicion of COVID-19 infection Mental health co-morbidities pre-admission (self-reported and as documented in medical records) Physical health co-morbidities pre-admission Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) II score † Ventilatory support during ICU admission Diagnosis of delirium during ICU admission Benzodiazepine requirement during ICU admission (other than as required for intubation) Date of death (if during 12 month study period)	
Functional Data	EuroQol 5-dimension, 5-level questionnaire * (EQ-5D-5L, assessing health-related quality of life. Used as a subjective assessment of the physical function of participants)	
Psychological Data	*Anxiety:*	Hospital Anxiety and Depression Scale (HADS)* EQ-5D-5L*
	Depression:	Hospital Anxiety and Depression Scale (HADS)* EQ-5D-5L*
	Psychological trauma symptoms:	Impact of Event Scale-6 (IES-6)*
Metacognitive beliefs and processes	Cognitive Attentional Syndrome Scale-1 Revised (CAS-1R) *	

** Self-reported questionnaires administered at 3, 6 and/or 12 months following ICU discharge*

† The APACHE II score is an ICU illness severity scoring applied within the first 24 hours of admission.

Hospital and Anxiety Depression Scale (HADS)

The HADS is a 14-item self-report measure in which participants rate the presence of symptoms of anxiety (7 items) and depression (7 items) over the preceding week using a 4-point Likert scale, with options from 0 (absence) to 3 (extreme presence). Responses are summed to produce two subscale scores, ranging from 0-21, with higher scores indicative of higher anxiety and depression levels, respectively. The HADS is widely used to assess anxiety and depression in people with physical health difficulties and demonstrates good psychometric properties when used in an intensive care setting.[18] Cut-off scores of ≥8 on anxiety and depression subscales of the HADS have been used to define caseness, with a score of 8-10 being 'borderline abnormal' and a score of 11-21 indicating anxiety or depression.[18 19]

Impact of Event Scale-6 (IES-6)

The IES-6 is a validated tool in survivors of ARDS to screen for post-traumatic stress disorder. It is an abbreviated version of the Impact of Event Scale-Revised (IES-R) test and contains six questions.[20] We selected the IES-6 over the IES-R because it is shorter, has been validated in a very similar patient population,[20] will provide similar information to the IES-R, and is likely to have a higher completion rate by patients because of its length in the context of participants commonly experiencing a reduced concentration span following ICU admission.[8] Each of the six items in IES-6 is marked on a scale of 0-4, where zero indicates absence of distress and four indicates extreme distress. The mean of the six items is then calculated to give the IES-6 score. Cut-off scores of ≥1.75 indicate probable symptoms of PTSD in survivors of ARDS.[20]

EuroQol 5-dimension, 5-level questionnaire (EQ-5D-5L)

The EQ-5D-5L is a five-domain, self-report measure assessing mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Participants are asked to rate each question, indicating no problems, slight problems, moderate problems, severe problems or extreme problems. In addition, participants are invited to rate their health on a visual analogue scale from 0-100, where zero represents the worst health imaginable and 100 represents the best health imaginable. EQ-5D-5L is the recommended questionnaire to assess the health-related quality of life of critically ill patients.[21] Whilst we will report all domains of the EQ-5D-5L, the HADS will be used to assess rates of anxiety and depression.

Cognitive Attentional Syndrome Scale-1 Revised (CAS-1R)

The CAS-1R is a 10-item self-report measure assessing positive and negative metacognitive beliefs, frequency of worry or rumination and the use of a range of counterproductive coping

strategies used in response to negative thoughts and feelings.[17] Participants are asked to rate the degree to which they have engaged in a particular coping strategy or thought process during the previous week. Responses are scaled from 0%-100% and are summed to produce a total score. Higher scores indicate greater conviction in metacognitive beliefs and greater use of maladaptive coping strategies to manage distress. The CAS-1R has demonstrated good psychometric properties in physical health populations.[22]

Recruitment

After discharge from ICU, patients will be screened by local study teams against inclusion and exclusion criteria prior to enrolment, with the possibility for enrolment up to 12 months after ICU discharge. Patients will be invited to participate in person whilst awaiting discharge from hospital, whilst attending an ICU follow up clinic appointment in hospital, or by postal invitation with a unique code to offer the opportunity to complete the consent form. Questionnaires at 3, 6 and/or 12 months will be completed online, by phone or by post.

Database

Study data will be collected and managed using the online Research Electronic Data Capture (REDCap) system hosted at the University of Liverpool.[23 24] Personal data will be added to the secure, web-based software platform only once patients agree to participate in the study and will be held for the study duration. Personal patient data will be pseudo-anonymised for analysis and will be held in compliance with EU General Data Protection Regulations (GDPR) and the UK Data Protection Act (2018).

Patient and Public Involvement

The peer support group charity, ICUsteps, has a group of ex-ICU patients and relatives who feed back on the importance and relevance of the research question and how they view the outcome measures being used. One of the authors in her role as the research manager for ICUsteps asked this group to comment on the draft research protocol using their experience of critical illness. They were also asked to comment on the possible impact for patients of taking part in the study. Patients were not involved in the recruitment to or conduct of the study.

ANCILLARY STUDIES

Three sub-studies were designed and added to the main study, following HRA approval on 28 February 2022. Semi-structured interviews were added to the study to gain a deeper understanding of patient experience, taking into consideration feedback from patients involved in the study that the validated tools utilised in the questionnaire did not allow the nuance of

their individual experiences to be conveyed. Surveying sites to understand the services available to COVID-19 survivors across the country was added to gain context to the information provided in the questionnaires in regards to whether patients engaged with follow up services. As PIM-COVID is a trainee-led study, we added a survey of team members to understand the attitudes and opinions of collaborators and to gain their feedback on the study in a structured way.

Sub-study: Semi-structured Interviews

The aim of the semi-structured interviews is to explore the experiences of critical care survivors following COVID-19 infection during their recovery phase, including perceptions about the care received and support available to them. The structure of the interview is outlined in the 'Interview Guide', which can be found in the supplementary material. Study participants who have indicated on a completed questionnaire that they are happy to be contacted by the study team for more information will be approached by telephone or email to discuss their potential participation in a one-on-one interview. A purposive sample of participants will be selected aiming for a sample that is diverse, representative of the cohort (in terms of ethnicity, sex, geographical location, degree of deprivation based on postcode,[25-28] length of stay in ICU, etc), and inclusive of participants with and without evidence of psychological distress, based on answers to the 3 and 6 month questionnaires, where these have been answered. Participants from the last cohort of patients discharged from ICU will be invited to interview. Interviews will be conducted via Microsoft Teams or by phone and will be recorded. Audio recordings will be transcribed for analysis by a transcription service.

Sub-study: Survey of study team members

We aim to explore factors influencing study team member involvement, understand their attitudes and opinions, and gain feedback on the study. Team members at all study sites will be invited to complete an online survey by email, which will explore the socio-demographic characteristics of study team members, previous academic experience, feedback on involvement in the study, attitudes towards health research, barriers and motivators to contributing to health research, and future research plans.

Sub-study: Survey of study sites

Current national guidelines state that at-risk ICU survivors who have had an admission of more than 4 days should be invited to a follow up clinic 2-3 months after discharge from ICU.[29] However, hospital and community based services to support ICU survivors in their recovery were limited even before COVID-19, with about 70% of hospitals not offering an ICU follow up clinic.[30] In this sub-study we aim to assess geographical differences in the

availability and structure of follow-up services offered to patients with critical COVID-19 after hospital discharge. All intensive care units within the UK will be approached by email and/or phone and invited to complete an online survey about follow-up services available for patients having been discharged from hospital after critical illness.

STATISTICAL METHODS

We will report findings of the study using descriptive methods in the absence of a non-COVID or non-ICU comparator group. Data about ICU patients in the United Kingdom were reported by the Intensive Care National Audit and Research Centre (ICNARC) in three temporal groups related to the 'waves' of ICU patients admitted with COVID-19. In keeping with the date ranges used by ICNARC, we will consider study participants who were in ICU prior to 31 August 2020, between 1 September 2020 and 30 April 2021, and from 1 May 2021 onwards in addition to evaluating the overall cohort.[31] SPSS and MPlus software will be used to conduct statistical analysis.

Multiple cohorts design

The objective is to document 3, 6 and 12-month point prevalence estimates of HADS anxiety and depression and IES-6 scores, by demographic, clinical, treatment and psychiatric history variables. Unadjusted point prevalence rates per 100,000 individuals will be estimated with 95% Confidence Intervals at 3-, 6- and 12-month observations. These separate cohorts cannot be directly compared because ICU and broader illness-related variables may change over time and thus may differ between cohorts (e.g., survivor bias attributable to improved ICU care during the course of the pandemic). Demographic, clinical, treatment and psychiatric history risk factors for each cohort will be estimated using binomial logistic regression.

Single cohort design

The objective is to estimate temporal trajectories of HADS anxiety and depression, and IES-6 scores, and to prospectively predict these trajectories from demographic, clinical, treatment, psychiatric and CAS-1R scores. Trajectories of HADS Anxiety, Depression and IES-6 scores will be described using latent growth curve modelling (LGCM). Risk factors can then be identified by fitting predictors to models, allowing for both intra- and inter-participant variations to be analysed.[32-34] To improve power, we will use the full range of scores for the HADS and IES-6, not categories based on putative clinical cutoff scores.

LGCM is a form of structural equation modelling that allows a temporal trajectory to be precisely estimated with regard to two parameters; a slope representing sequential changes across observations, and an intercept representing the population mean at time=0. In this

study, the intercept represents an immediate post-discharge value which will be estimated from the first (three-month) observation and slope estimates.[34] We will adopt a conventional approach by modelling HADS anxiety and depression and IES-6 intercepts and slopes, starting from theoretical assumptions and adjusting these in relation to observed model parameters until the best compromise between initial parameters and observed data is achieved. The initial model will use known population means for HADS anxiety and depression and IES-6 as intercepts, a linear slope trajectory, with homogenous individual growth, equality of error variance across observations and independence of slope and error estimates assumed. Linear and quadratic slope models will be specifically tested; linear models being defined as slope parameters 1, 2, and 4, representing a linear progression between 3, 6 and 12-month observations, and quadratic slopes defined as 1, 4 and 16. Constraints on parameters will be relaxed until good fitting models (Comparative Fix Index (CFI) > .95, Root Mean Square Error of Approximation (RMSEA) < .05) are achieved. [35 36] Once intercept and slope of each model are identified, putative demographic, clinical, physical and/or psychosocial risk factors can be identified using multivariate analyses, such as regression, to predict intercept and slope. Secondary analyses will be conducted to assess temporal relationships between HADS anxiety and depression and IES-6 scores and demographic, clinical, treatment, psychiatric, CAS-1R and EQ-5D-5L variables to identify the roles of the latter as potential mediators of the scores.

Missing Data

Missing variable replacement will not be used in the multiple cohorts design. Data replacement for the single cohort design will be achieved by multiple imputation for the logistic regression analysis and unbiased full information maximum likelihood estimation. Some missing variables in the single cohort will derive from the death of participants – the date of death will be provided by study teams into the online study database if the patient has died during the study period. Data will not be replaced in observations missed through death, but data obtained from these participants whilst alive will be used in imputation calculations.[37]

Sub-study: Semi-structured Interviews

Analysis of the interviews will use the principles of the constant comparative method and interpretive thematic analysis. The analysis will be interpretive and consider both latent and manifest aspects of the data, thereby acknowledging both the manner that participants talk as well as the explicit content. Analysis will progress in parallel with recruitment and will end when theoretical saturation is reached. Systematic data coding will be performed; exceptional case analysis will be discussed within the research team; and data will be triangulated with quantitative data from the PIM-COVID study to enriching findings and interpretation.

Sub-studies: Survey of Study Team Members & Survey of Study Sites
The findings of both surveys will be reported using descriptive methods.

RESEARCH ETHICS APPROVAL

The study was approved by the Health Research Authority (East Midlands - Derby Research and Ethics Committee, reference: 20/EM/0247).

DATA SHARING STATEMENT

Upon the conclusion of the study, the dataset may be made available from the corresponding author on reasonable request.

AUTHOR CONTRIBUTIONS

AACW, BWJ and AJB conceived the study. The protocol was developed with the expertise of MGC, PF, SB and CJ in clinical psychological research, and CJ has advocated for patients and has represented their perspective. SB created the plan for statistical analysis. AACW, MGC and IDW received funding to conduct this study. AACW, IDW and KW have key roles in study implementation. AACW wrote the first draft of this protocol. All authors refined the study protocol and approved this manuscript.

COMPETING INTERESTS

None of the authors have any competing interests that may have influenced the submitted work.

FUNDING

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LICENCE STATEMENT

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PIM-COVID Study: SUPPLEMENTARY MATERIAL

Cognitive Attentional Syndrome Scale-1 Revised (CAS-1R)

The author of the CAS-1R questionnaire has granted permission for the use of CAS-1R in the study but has stated '…the measure cannot be re-published or reproduced in a published paper as it is copyright protected and also part of the PATHWAY treatment manual that is protected by a non-disclosure'.

PIM-COVID INTERVIEW GUIDE

Interviews will be arranged at a time convenient for the participant and will be conducted via telephone, an online secure platform (e.g. MS Teams or Zoom), or in person as per the participant's preference and current government guidance regarding lockdowns.

Closed questions are to be avoided as much as possible. To ensure that the research questions are addressed, a semi-structured approach should be used. Interruptions from the interview should be kept to a minimum, with the interviewer reflecting, prompting and summarising, with open or closed questions and probing where appropriate. Participants should be encouraged to speak about their specific experience.

Before the interview commences, ensure that the participant has read the information sheet. Questions and prompts below are resources on which the interviewer can draw and only relevant questions should be asked.

1. Introduction

2. Reassurance of confidentiality

Ensure the participant that their answers will be treated confidentially, and their interview will be anonymised before being analysed. Confidentiality will only be broken if they say something that indicates risk to themselves or others.

3. Clarification of research aims and the interview purpose

4. Time for questions from the participant about the interview and/or information sheet

Remind participants that the interview will be recorded.

5. Interview questions

The format and sequencing will be guided by the patient's responses.

- What has your experience been since leaving intensive care?
- What psychological and/or physical symptoms have you experienced, including:
  - Difficulty concentrating
  - Breathlessness
  - Coughing
  - Difficulties sleeping
  - Nightmares
  - Pain
  - Weakness
  - Fatigue
  - Intrusive thoughts
  - Seeing insects
- Have your psychological and/or physical symptoms changed over the course of your recovery?
  - If so, how?
- Do you think your physical symptoms (e.g. breathlessness, pain, weakness) have affected your mental well-being?
- How do you think that COVID-19 has affected your recovery, if at all?
- How have any of the following COVID-19 related factors influenced your recovery:
  - Restricted family/friend visiting whilst in hospital
  - Staff wearing PPE
  - Difficulty getting face to face appointments with your GP
  - Reminders about COVID-19 in the media.
  - Family support. Limits on family/friends visiting when at home because of lockdown. Or more family support because of furlough.
- What follow-up services have you been offered?
- Have you attended ICU follow-up clinic?
  - If no, why not?
  - If yes, did you find it helpful and what services were offered as part of that (ICU doctor, physio, dietician, respiratory physician)
- Were you given a phone number to contact for advice?
- Did you use it?
  - If no, why not?

- Is there any other support that you would have liked to have been offered?
- Were you contacted to attend a follow-up clinic? Would you have preferred to have been contacted once you got home (at an earlier time point that being invited for follow-up clinic)?
- At what time frame would you have found that helpful?
- What support do you think you would have benefitted from?
- Did you feel you knew what to expect during your recovery?
- Were you given any information regarding what experiences to expect during your recovery e.g. timespan / symptoms?
    - If so what information was given?
    - Where you satisfied with the information given?
- Specifically - were you given information about ICU recovery / ICUsteps / locally available support services?

6. Close

- Is there anything else you would like to share?

Thanks for taking part.

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	1
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	1
Funding	#4	Sources and types of financial, material, and other support	2
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	2

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	2
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	2
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)	N/A
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	N/A
Objectives	#7	Specific objectives or hypotheses	4
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)	5
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	5
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will	12

		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	N/A
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	5
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)	5
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	N/A
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	5
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	N/A

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	N/A
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N/A
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
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	N/A
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	7
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	N/A
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	7
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	9
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	N/A
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	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	8
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	7

Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	11
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	11
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	N/A
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	11
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