Study Title: Evaluating the musculoskeletal health state of Intensive Care Unit Survivors: A multicentre observational study

Internal Reference Number / Short title: The MSK-ICU Study

Ethics Ref: 21/NS/0143

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Funder:	National Institute of Health Research – Integrated Clinical Academic Programme
Chief Investigator Signature:	

Statistician Signature: N/A

Please declare any/no potential conflicts of interest.

There are no potential conflicts of interest

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

Trial Title: Evaluating the musculoskeletal health state of Intensive Care Unit Survivors: A multicentre observational study
Protocol Date and Version No: 6/7/22 v3

Protocol signature page

The undersigned has read and understood the trial protocol detailed above and agrees to conduct the trial in compliance with the protocol.

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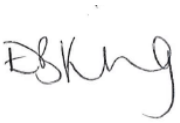
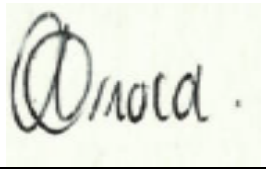
Principal Investigator (Please print name) Elizabeth King		**Signature** 		**Site name or ID number** Oxford University Hospitals		**Date** 9/5/21
Principal Investigator (Please print name) Amy Arnold		**Signature** 		**Site name or ID number** Great Western Hospitals		**Date** 17/5/21

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1. KEY CONTACTS

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2. LAY SUMMARY

2.1 Background
The intensive care unit (ICU) is a vital part of hospital care, with more patients requiring treatment on ICU each year. However, patients who survive ICU often experience long term physical problems resulting in a poor quality of life. There have been several studies investigating rehabilitation after ICU. These have demonstrated little benefit on physical function, exercise capacity or quality of life. Musculoskeletal (MSK) problems are those that affect bone, muscle and joints. MSK problems affect 25% of the UK population and limit people's ability to work. To date, there has been a small amount of research which has shown that ICU survivors are likely to experience MSK problems that would potentially benefit from physiotherapy.
2.2 Aims
The aim of this study is to evaluate the overall MSK health of patients, six months after they were admitted to ICU.
2.3 Study design
There will be four parts to this research study:
Firstly, patients will be phoned six months after they were admitted to ICU and asked several questionnaires. These questionnaires will gather information on their MSK health, employment and quality of life.
Patients who report having MSK problems will be invited to one of two assessment visits and to participate in a qualitative sub study:
A group of patients will undergo a full MSK assessment with a physiotherapist. This will include pain, muscle and joint assessment.
A smaller group of patients with severe MSK problems will undergo the same MSK assessment as above plus some additional tests which will be performed at Oxford Brookes University. They will be asked about their function, have an ultrasound scan, undertake a walking test and be given a wristband to records how active they are for a week after their visit.
A group of patients as well as their adult family members will be interviewed about their experiences of living with or supporting those with MSK problems. Staff in related services such as follow-up clinics or rehabilitation settings will also be invited to be interviewed regarding their experiences of supporting patients with their recovery and the clinical services they provide.
2.4 Dissemination
The findings of this research study will aim to be published in research journals, presented at national and international conferences, and using social media e.g. Twitter. Locally the findings will be presented to patients, staff and researchers.
The findings will help to advise the future development of treatments to improve MSK problems and physical function in survivors of ICU.

3. SYNOPSIS

Study Title	Evaluating the musculoskeletal health state of Intensive Care Unit Survivors: A multicentre observational study		
Internal ref. no. / short title	The MSK-ICU Study		
Study registration	The study will be registered on ISRCTN following ethical approval		
Sponsor	Oxford University Hospitals NHS Foundation Trust Joint Research Office, Oxford University Hospitals NHS FT, Second Floor, OUH Cowley, Unipart House Business Centre, Garsington Road, Oxford. OX4 2PG		
Funder	National Institute of Health Research – Integrated Clinical Academic Programme, Clinical Doctoral Research Fellowship		
Study Design	Multicentre longitudinal cohort study		
Study Participants	Participants admitted to ICU for >48 hours		
Sample Size	332		
Planned Study Period	The project will run between 1st December 2021 and 31st October 2023. All participants will be followed up at a single time point, 6 months following admission to ICU		
Planned Recruitment period	18st February 2021 – 28h February 2022		
	Objectives	Outcome Measures	Timepoint(s)
Primary	To quantify the musculoskeletal health state using the MSK Health Questionnaire (MSK-HQ). Assess the relationship between MSK-HQ and quality of life, employment, anxiety and depression, and symptoms of post-traumatic stress disorder.	MSK Health Questionnaire (MSK-HQ) And European Quality of Life: 5 Dimensions (EQ-5D-5L) utility score, Hospital Anxiety and Depressions Scale (HADS), Impact of Events Scale-Revised (IES-R), and Employment questionnaire.	Telephone follow-up at 6 months following admission to ICU.
Secondary	To identify prognostic factors for a lower MSK-HQ score after critical illness.	MSK Health Questionnaire (MSK-HQ) and 15 potential baseline variables.	Variables collected at baseline as part of usual ICU care and MSK-HQ collected as above.

	To characterise the specific musculoskeletal complications experienced by patients using a standardised comprehensive musculoskeletal assessment.	Joint range of movement, Visual Analog Scale (VAS), Fear-Avoidance Beliefs Questionnaire (FABQ), DN4, Medical Research Council Sum Score (MRC SS), hand held dynamometry.	Physical assessment 6 months following admission to ICU.
	To evaluate patient mobility and upper limb function, and the extent of the relationship to muscle structure and function in those patients with poor musculoskeletal health.	Ultrasound scan of quadriceps and biceps, isokinetic dynamometry, 6-minute walk test, Life-Space Questionnaire, Quick DASH, accelerometry.	Physical assessment 6 months following admission to ICU.
	To explore patients and relatives' experiences of MSK disorders in relation to activities of daily living, employment, social engagement/community activities, wellbeing and subsequent healthcare activity.	Lived experiences Aspects of service provision identified	Interviews 6-9 months following admission to ICU.
	To explore healthcare professionals' experiences of delivering services	Lived experiences Aspects of service provision identified	Nil specific time point.

	for patients with MSK impairment		
Intervention(s)	N/A		
Comparator	N/A		

4. ABBREVIATIONS

ADLs	Activities of daily living
CI	Chief Investigator
CRF	Case Report Form
DN4	Douleur Neuropathique 4 Questions
EQ-5D-5L	European Quality of Life: 5 Dimensions
FABQ	Fear-Avoidance Beliefs Questionnaire
GCP	Good Clinical Practice
GP	General Practitioner
HADS	Hospital Anxiety and Depressions Scale
HRA	Health Research Authority
ICF	Informed Consent Form
ICU	Intensive Care Unit
IES-R	Impacts of Events Scale-Revised
IKD	Isokinetic dynamometry
MOReS	The Centre for Movement, Occupational and Rehabilitation Sciences
MRC SS	Medical Research Council Sum Score
MSK	Musculoskeletal
MSK-HQ	Musculoskeletal Health Questionnaire
NHS	National Health Service
OBU	Oxford Brookes University
PI	Principal Investigator
PIS	Participant/ Patient Information Sheet
QD	Quick DASH
QoL	Quality of life
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
RES	Research Ethics Service

ROM	Range of movement
TMF	Trial master file
USS	Ultrasound scan
VAS	Visual Analogue Scale
6MWT	Six minute walk test

5. BACKGROUND AND RATIONALE

5.1 What is the Problem being addressed?

The number of admissions to intensive care units (ICU), complexity of illness and cost of critical care is increasing over time. This is representative of both an aging critical care population presenting with a variety of pre-existing co-morbidities, and an increase in survival rates due to improvements in ICU services and delivery.[1] Survivors of critical illness frequently experience long-term physical impairment, persistent exercise limitation and decreased health-related quality of life (QoL).[2] The subsequent socioeconomic burden of critical illness is also high. Patients report significant healthcare utilisation after discharge from hospital, with up to 40% re-admitted to hospital at least once in the first year after discharge.[3] Rates of return to employment following admission to ICU are also extremely low, with up to 31% of patients not returning to work within 5 years of ICU admission.[4] Despite extensive longitudinal investigation of survivors of critical illness, there has been limited investigation into the reason for poor physical function and unemployment.

There have been a large number of studies investigating early rehabilitation interventions within ICU. They demonstrate that although early rehabilitation in ICU may improve levels of mobility and strength in hospital, none to date have shown long term post discharge improvements in physical function.[5] Multiple recent studies investigating rehabilitation interventions after ICU and hospital discharge have failed to demonstrate positive primary outcomes, which have included patient reported physical function and exercise capacity.[6,7,8] The interventions employed in these studies are based on the successful group exercise programmes used in cardiac and pulmonary rehabilitation,[9] constituting cardiopulmonary and general strengthening exercises. However, unlike the patient populations attending cardiac and pulmonary rehabilitation programmes, ICU patients vary significantly in terms of their pre-morbid state, duration and severity of illness and post hospital discharge physical problems.

At present, it is unclear if general weakness and/or decreased exercise capacity are significantly impacting physical function in ICU survivors, or indeed what other problems might be limiting this function. Our previous research[10] found that a high proportion of ICU patients experience functionally limiting shoulder impairment six months following discharge from hospital. However, no post-ICU studies have investigated or provided interventions to address any specific musculoskeletal (MSK) conditions after critical illness, or included quantification of MSK outcome measures. Therefore, as the reasons for impaired physical function in ICU survivors are currently unknown, the most appropriate rehabilitation methods are also unknown. To inform the development of future interventions to improve physical function in ICU survivors, more information on the long term physical problems experienced is required.

For the development of a complex intervention, according to best practice[11] it is important to explore the experiences of key stakeholders such as patient, family members and clinicians and services currently provided.

5.2 Why is this research important in terms of improving the health of the public and/or patients and the NHS?

MSK conditions are wide ranging and cover problems affecting bone, muscle and joints. They are the leading cause of pain and disability in the UK with 25% of the population affected.[12] They are characterised by pain and loss of function and can diminish QoL and impact on family and social relationships. Given the rates of muscle mass loss of up to 20% in the first week of ICU admission,[13] it is reasonable to expect that patients will subsequently develop MSK complications after discharge from ICU.

MSK conditions also have a significant socioeconomic impact. They are the second leading cause of sickness absence at work, with 30.8 million working days lost in the UK in 2016 due to MSK problems.[14] Therefore, it is possible that long term MSK complications are contributing to poor physical function, QoL and return to work in ICU survivors.

This potential source of long-term disability in ICU survivors is under-investigated, despite fitting into several key areas for ICU research in the UK. Investigating how patients can best be supported following discharge home from ICU was identified by the James Lind Alliance[15] as their second highest priority. Further investigation into MSK complications in ICU survivors would also fulfil other high priority areas for research identified, including: investigating what rehabilitation methods both during and after ICU achieve best outcomes for patients; and what is the best way to support recovery from the physical consequences of critical illness.

Investigating MSK complications following critical illness was also deemed an important area for research by patients locally. Our initial research idea was presented to the Oxford Critical Care Patient Forum, where patients reported MSK conditions being a key factor in preventing them resuming their activities of daily living (ADLs).

The current lack of identification of the specific physical impairment limiting a patients' ability to execute activities is impeding the design and evaluation of post-ICU rehabilitation interventions and care pathways. Therefore, the proposed research will return to the International Classification of Functioning, Disability, and Health (ICF) framework.[16] We will firstly identify specific physical dysfunction in the form of MSK conditions, along with patients' global MSK health state, prior to evaluating the impact on patients' ability to execute activities. A qualitative element of this study will allow meaningful understanding beyond functioning at the level of a body part and encompass the whole person, and correspondingly within their environment.

The findings from this research will be essential in developing future rehabilitation interventions aimed at improving long term physical function in ICU survivors. This will subsequently improve patients QoL, expedite return to work and decrease healthcare and social services utilisation.

3. Review of the existing evidence – How does the existing literature support this proposal?

A scoping review of long-term MSK complications following critical illness was conducted which highlighted only a small number of studies. Of the 4500 studies screened, 32 included an evaluation of at least one aspect of MSK health after hospital discharge.

Most studies evaluated a single aspect of MSK health, with peripheral muscle weakness, chronic pain and abnormal neuromuscular function being the most commonly assessed and reported problems. Three studies[2,10,17] investigated peripheral joint complications, of which our prospective cohort study[10] was the only study to undertake a standardised physical assessment of patients that included multiple aspects of MSK health. Results from this study identified that shoulder impairment was present in 67% of patients at 6 months after hospital discharge, and had a severely detrimental effect on upper limb function. Patients reported being unable to undertake every day activities such as: putting a coat on; reaching food from a cupboard; and holding their child. The shoulder was also the most commonly identified location for chronic pain following critical illness.[18] These findings were relevant as the post-ICU studies to date[6,7,8] have had little or no upper limb component to their intervention.

The problems identified were not only limited to the upper limb. The majority of studies also identified impaired muscle or nerve function evaluating the lower limb.[19] One study[20] included an evaluation of gait and postural control and demonstrated that those patients with poor lower limb muscle power had worse gait parameters. This is important as exercise capacity in post-ICU rehabilitation studies is commonly evaluated using the 6-minute walk test (6MWT). However, this assessment does not reveal why patients achieve low scores, which limits its use in patients with limited mobility due reasons other than decreased exercise tolerance.

The nature of critical illness and its long term consequences, along with the prevalence and detrimental effect of MSK conditions, means that it is highly likely that MSK conditions are having a negative impact on patient's physical function and QoL. The post-ICU rehabilitation studies to date have failed to demonstrate an improvement in physical function, however none have provided interventions to address MSK complications or included an MSK outcome measure. The small number of studies investigating long-term MSK complications in this population to date have identified some individual MSK problems, but there has been no evaluation of patients' global MSK health state and very limited physical assessment. There is no agreement as to the factors associated with MSK complications in this population, therefore it is unclear which patients and which factors need to be targeted for successful rehabilitation interventions.

There is a wealth of qualitative studies exploring patient experiences of living with musculoskeletal conditions such as rheumatoid or osteoarthritis. Whilst these are insightful for the methodological approaches, these conditions are in clinical silos compared to the vast array of impairments for survivors of critical care. Similarly, there is a growing body of qualitative literature exploring the psychosocial factors survivors of critical illness transition beyond the acute setting, and the experiences of care givers.

In order to develop rehabilitation interventions to improve long term physical function and QoL in ICU survivors, more detail regarding the reasons for physical impairment need to be established. The proposed research seeks to address this.

6. OBJECTIVES AND OUTCOME MEASURES

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)
Primary Objective To quantify the musculoskeletal health state using the MSK Health Questionnaire (MSK-HQ). Assess the relationship between MSK-HQ and quality of life, employment, anxiety and depression, and symptoms of post-traumatic stress disorder.	MSK Health Questionnaire (MSK-HQ) And European Quality of Life: 5 Dimensions (EQ-5D-5L) utility score, Hospital Anxiety and Depressions Scale (HADS), Impact of Events Scale-Revised (IES-R), and Employment questionnaire.	Telephone follow-up at 6 months following admission to ICU.
Secondary Objectives To identify prognostic factors for a lower MSK-HQ score after critical illness.	MSK Health Questionnaire (MSK-HQ) and 15 potential baseline variables.	Variables collected at baseline as part of usual ICU care and MSK-HQ collected as above. Physical assessment 6 months following admission to ICU.
To characterise the specific musculoskeletal complications experienced by patients using a standardised comprehensive musculoskeletal assessment. To evaluate patient mobility and upper limb function, and the extent of the relationship to muscle structure and function in those patients with poor musculoskeletal health.	Joint range of movement, Visual Analog Scale (VAS), Fear-Avoidance Beliefs Questionnaire (FABQ), DN4, Medical Research Council Sum Score (MRC SS), hand held dynamometry. Ultrasound scan of quadriceps and deltoid, isokinetic dynamometry, 6-minute walk test, Life-Space Questionnaire, Quick DASH, accelerometery.	Physical assessment 6 months following admission to ICU.
Secondary To explore patients and relatives' experiences of MSK disorders in relation to activities of daily living, employment, social engagement/community activities, wellbeing and subsequent healthcare activity.	Lived experiences Aspects of service provision identified	Interviews 6-9months following admission to ICU.
To explore healthcare professionals' experiences of delivering services for patients	Lived experiences	Nil specific time point

with MSK impairment following critical illness.	Aspects of service provision identified	

7. STUDY DESIGN

Our research question is: What is the musculoskeletal health state of, and how does it impact physical function in, ICU survivors six months after admission to ICU?

Our aim is to conduct a longitudinal investigation to determine and characterise the musculoskeletal health state of ICU survivors six months following admission to ICU, in order to inform future development of targeted rehabilitation interventions.

The proposed research plan is a multicentre, prospective, longitudinal, cohort study using a telephone follow-up questionnaire, with two sub-studies involving physical assessments (see participant flowchart – Appendix A) and a qualitative sub-study. This qualitative sub-study will be a case study design including four hospital sites with each making a case whereby patient, adult family members and staff will be drawn upon within the methodology. This will also include documentary analysis of policy documentation (hospital and ICU) and patient facing materials. Four centres will be included in this study: Oxford, Reading, Milton Keynes and Swindon. The variety in size and type of recruiting hospitals is representative of ICU's across the UK, allowing for increased generalisability and a larger sample size.

The majority of previous studies investigating musculoskeletal complications are historical retrospective cohort studies or prospective studies with a small sample size. The largest threat to validity in a prospective ICU follow-up study is selection bias through a high loss to follow-up rate. To counter this, the proposed study is multicentre (across a range of hospitals), uses a telephone questionnaire and clear recording of participant contact information.

All patients will be followed up at a single time point, six months after admission to ICU, receiving a telephone follow-up where five questionnaires will be asked. These questionnaires consist of the primary outcome measure (MSK-HQ) and the recommended core outcome set for ICU follow-up studies (EQ-5D-5L, HADS, IES-R). Due to the limited time available, a single time point will allow for a greater number of patients to be assessed compared to multiple time points.

Participants who identify as having a new MSK problem will be invited to participate in one of two sub studies involving a physical assessment (please see section 9.8 for further detail) and a qualitative sub-study involving qualitative interviews seeking insight about the lived experience of post ICU MSK impairments. Each sub study involves a single follow-up appointment at the participants earliest convenience following their telephone follow-up (please see section 9.8 for further detail).

Study Flow Chart

Milestone	2022				2023			
	Jan-Mar	Apr-Jun	Jul-Sep	Oct-Dec	Jan-Mar	Apr-Jun	Jul-Sep	Oct-Dec
Study Recruitment								
Primary Study - Telephone Follow-Up								
Sub Study 1 - MSK Assessments								
Sub Study 2 – Muscle and Mobility and Function Assessments								
Qualitative Sub Study – Interviews								
Data Cleaning And Analysis								

8. PARTICIPANT IDENTIFICATION

8.1. Study Participants

Participants who have been admitted to ICU for 48 hours or more.

8.2. Inclusion Criteria

- Participant aged 18 years or above.
- Admitted to an ICU for >48 hours.

Sub study 1

- Participants identifying as having any MSK problem

Sub Study 2

- Participants with an MSK-HQ score of 35 or less

Qualitative Sub Study

A. Participants

- Participants with an MSK-HQ score of 35 or less

B. Families

- Adult family member (aged 18 years or above) of patient participant who has been discharged from hospital with an MSK-HQ score of 35 or less who has regular contact with the participant from the outset of the injury or illness

C. Healthcare staff

- A member of NHS staff involved in the care of patients following discharge from ICU.

8.3. Exclusion Criteria

The participant may not enter the study if ANY of the following apply:

- Patients who are judged to lack capacity at the time of consent as defined by the Mental Capacity Act (2005).
- Proven or suspected primary brain pathology, spinal cord injury or other neuromuscular disease resulting in permanent or prolonged weakness.
- Admitted to ICU with musculoskeletal complications or trauma.
- Patients who have a palliative diagnosis/treatment pathway.
- Patients who were dependent for activities of daily living in the month prior to current intensive care unit admission (gait aids acceptable).
- Prisoners.
- Patients with no fixed abode.
- Patients who are unable to communicate clearly in English over the telephone for 20 minutes.
- Patients refusing consent.

9. PROTOCOL PROCEDURES

9.1. Recruitment

The four recruiting centres have been identified and have agreed to participate in the study. They represent a variety of size and type of ICU which will increase the generalisability of the study findings.

All patients admitted to one of the recruiting ICUs for greater than 48 hours will be screened for eligibility by delegated ICU staff. The wider ICU clinical care team will also be asked to consider potential patients for the study. Any patients that are deemed potentially suitable will be asked by a member of the clinical team if they are happy for a member of the research team to come and discuss a research study that they may be eligible for. The clinical team will also provide the participant with a Participant Information Sheet (PIS). If the patient agrees to this introduction, then a member of the research team will introduce and discuss the study, and ask them to consider giving informed consent. If the patient would like more time to consider the information then the member of the research team will arrange to return at another time.

9.2. Screening and Eligibility Assessment

Primary Study – Telephone follow-up

The screening process will involve a review of patient medical records by members of the ICU who have been trained to screen for study participants. Each participant must satisfy all the inclusion and exclusion criteria. For patients who are not included in the study, their hospital number, initials and reason for exclusion will be recorded on a screening log. Participants must be consented and recruited to the study prior to being discharged from the recruiting hospital site.

Participants who self-identify as having a MSK problem at the telephone follow-up, will be invited to participate in two of three sub studies.

Sub Study 1 – MSK assessments

Participants identifying as having any MSK problem (and report an MSK-HQ score of greater than 35) will be invited to participate in Sub Study 1.

Sub Study 2 – Muscle, mobility and function assessments

Participants who identify as having a severe MSK problem (an MSK-HQ score of 35 or less) will be invited to participate in Sub Study 2. If they do not wish to travel to Oxford then they will be invited to participate in Sub Study 1.

Qualitative Sub Study

Patient participants from Oxford, Reading, Milton Keynes or Swindon who identify as having a severe MSK problem (an MSK-HQ score of 35 or less) will be invited to participate in the Qualitative Sub Study. Alongside the patient participant group, their adult family members will also be invited to participate in this Qualitative Sub Study.

Staff members in either follow up services, post ICU rehabilitation services or community services providing rehabilitation for ICU survivors from Oxford, Reading, Milton Keynes or Swindon will be invited to participate in the Qualitative Sub Study.

Service leads for four localities will be approached for information about current service provision in the form of questions.

9.3. Informed Consent

The participant must personally sign and date the latest approved version of the Informed Consent form before any study specific procedures are performed.

Written versions of the Participant Information Sheet and Informed Consent will be presented to the participants detailing no less than: the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, without affecting their legal rights, and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as they wish to consider the information, and the opportunity to question the Investigator or other independent parties to decide whether they would like to participate in the study. Written Informed Consent will then be obtained by means of participant-dated signature and dated signature of the person who presented and obtained the Informed Consent. The person who obtained the consent must be suitably qualified and experienced and have been authorised to do so by the Chief/Principal Investigator. A copy of the signed Informed Consent will be given to the participant and added to their medical notes or uploaded into the patients electronic health record. The original signed form will be retained at the study site. Written Informed Consent must be

gained prior to discharge from hospital to be included in the study. Patients will be assigned a unique participant number at the point of consent. On all study-specific documents, other than the signed consent form and record of participant contact information, the participant will be referred to by the study participant number/code, not by name.

Sub Study 1&2

Participants who are eligible for sub study one or two will be invited to participate at the telephone follow-up. Verbal versions of the relevant sub study Participant Information will be presented to the participants as above. If the participant provisionally agrees to participate, a written version of the Participant Information will be posted or emailed to them. They will then be booked an appointment to attend a physical assessment, and asked to contact the research team to cancel that appointment if they no longer wish to participate or wish to have more time to consider the information. The participant will have at least 48 hours between telephone follow-up and the physical assessment appointment. At the appointment written Informed Consent will be obtained as above.

Qualitative Sub Study

Patient and adult family member participants who are eligible for the qualitative sub study will be invited to participate at the telephone follow-up or at a further convenient telephone call. Verbal versions of the Patient Information will be presented to the participants as above. If the participant provisionally agrees to participate, a written version of the Patient Information will be posted or emailed to them. They will then be booked an appointment to attend a face-to-face, video conference with audio recording or telephone interview, and asked to contact the research team to cancel the appointment if they no longer wish to participate or wish to have more time to consider the information. At a face-to-face appointment written Informed Consent will be obtained as above. If a participant prefers a video conferencing or telephone interview, an electronic version of the consent will be gained.

Staff who are in principle who are willing to engage following receipt of the Patient Information from the service leads' emails will email the research team. They will then be booked to attend an appointment to attend a face-to-face, video conference or telephone interview, and asked to contact the research team to cancel the appointment if they no longer wish to participate or wish to have more time to consider the information. At a face-to-face appointment written Informed Consent will be obtained as above. If a participant prefers a video conferencing or telephone interview, an electronic version of the consent will be gained.

9.4. Enrolment

This is a non-randomised longitudinal cohort study, and therefore after informed consent has been gained, participants will be enrolled via the REDCap online system (https://projectredcap.org/about/) used by Oxford Brookes University. Participant contact information will be recorded on a separate database within REDCap.

9.5. Blinding and code-breaking

There is no blinding or code breaking procedure in the study.

9.6. Description of study intervention(s), comparators and study procedures (clinical)

There is no study intervention or comparator.

9.7. Baseline Assessments

Prognostic factors collected as baseline data will include: demographics (age, gender, body mass index); admission information (reason for admission, severity of illness, ICU and hospital length of stay); ICU interventions (invasive ventilation and duration, neuromuscular blocking agents, prone positioning, mobilisation activity); and pre-admission function and comorbidities (Functional Comorbidity Index, Clinical Frailty Scale, MSK history). Data will be collected on a CRF within REDCap.

9.8. Subsequent Visits

Visit/Contact 1 – Telephone Follow-up

Admission to ICU was chosen as the time zero and therefore all participants will receive a telephone follow-up at six months following their admission to ICU. Prior to the phone call, patients electronic health record will be checked for their current health status and location i.e. in hospital, at home or died. At the start of the phone call, participants will be asked if it is a convenient time to talk and that the questionnaires will take approximately 20 minutes (additional time will be required to introduce Sub Study 1 or 2 to eligible participants). If it is not a convenient time, the researcher will arrange to call the participant back at a time that is more convenient for them. Participants will confirm their identity through their full name, date of birth and address. Participants will then be asked five questionnaires in the following order: MSK-HQ, employment questionnaire, EQ-5D-5L, HADS and IES-R. Data will be captured on a CRF entered into RedCap. If the participants are eligible for enrolment into Sub Study 1 or 2 or the Qualitative Sub Study based on the eligibility assessment, then they will be invited to participate as above, including arranging an appointment time.

Visit 2a (Sub Study 1)

Participants from Oxford will either be assessed at their home or at the ICU follow-up clinic at the John Radcliffe Hospital. Participants from Milton Keynes and Reading will be assessed at the ICU follow-up clinics at their respective hospitals. Participants attending their follow-up clinic for assessment will receive reasonable reimbursement of their travel expenses that will be agreed in advance. Researchers undertaking the participant assessments at their home will do so in full compliance with the OUH NHS FT lone working policy. Following confirmation of their identity (as above), participants will undergo a three part MSK assessment that will take approximately 45 minutes (including informed consent). Firstly participants will be asked to record their current pain severity and location using a visual analogue scale (VAS) and body map, prior to being asked the Fear-Avoidance Belief Questionnaire (FABQ) and DN4 questionnaire. Secondly, participants upper and lower limb range of movement (ROM) will be assessed. Finally, participant strength will be assessed using manual muscle testing and hand held dynamometry. All assessment data will be captured on a CRF entered directly into RedCap using a laptop.

Visit 2b (Sub Study 2)

Participants will be assessed in the movement laboratory at MOReS (Oxford Brookes University). All participants will be reimbursed their travel expenses (as above). Participants will confirm their identity and answer a series of questions regarding their physical health before undergoing the same assessment as Sub Study 1 (above). Participants will then have an ultrasound scan and isokinetic dynamometry assessment (IKD) of their quadriceps and biceps. Participants will undertake a 6 minute walk test prior to

being asked the Life-Space and QuickDASH (QD) questionnaires. Finally participants will be provided with an accelerometer and stamped addressed envelope, which they will be asked to wear for one week prior to posting back to MOReS. The assessment will take no more than two hours (including informed consent). All assessment data will be captured on a CRF entered directly into RedCap using a laptop.

Visit 2c (Qualitative Sub Study)

Participants will be interviewed at a convenient time and location to them; either their respective follow up clinic, via videoconferencing or telephone, or in the movement laboratory at Oxford Brookes University (for Oxford participants only.) At the start of the interview, participants will confirm their identity via their full name, date of birth and address. If not a convenient time, the researcher will arrange to call back or to schedule a call for the participant at a time that is more convenient. The interview will take up to 60 minutes, and the duration will be guided by the participant.

Face to face interviews will be held either in a meeting room away from the clinical area or (for staff) in a quiet room in or alongside the clinical care, as chosen by the participant. Videoconferencing or telephone interviews will be conducted in a private office. Face to face, telephone and video conferencing interviews will be audio recorded only using two 20ictaphones.

The interviews will be conducted using a semi-structured topic guide based on systematic review data and background literature review. Due to the iterative nature of qualitative interviews, the topic guide will evolve during the process to ensure any emerging themes are explored.

9.9. Sample Handling

No sample will be taken

9.10. Early Discontinuation/Withdrawal of Participants

During the course of the study a participant may choose to withdraw early from the study at any time. This may happen for several reasons, including but not limited to:

- The occurrence of what the participant perceives as an intolerable AE.
- Inability to comply with study procedures
- Participant decision

Data obtained up until the point of participant withdrawal will be retained for use in the study analysis. No further data would be collected after withdrawal.

In addition, the Investigator may discontinue a participant from the study follow-up at any time if the Investigator considers it necessary for any reason including, but not limited to:

- Ineligibility (either arising during the study or retrospectively having been overlooked at screening)
- Clinical decision

The type of withdrawal and reason for withdrawal will be recorded in the CRF.

If the participant is withdrawn due to an adverse event, the Investigator will arrange for telephone calls until the adverse event has resolved or stabilised.

9.11. Definition of End of Study

The end of study is the point at which all the study data has been entered into the CRF and queries resolved.

10. SAFETY REPORTING

The safety reporting window for the study is during the physical assessments for Sub Studies 1 and 2 described above, ending when the individual participant physical assessment is completed. Investigator's will follow up any serious adverse events, which occur during the safety reporting window, until event resolution or stabilisation.

10.1. Definition of Serious Adverse Events

A serious adverse event is any untoward medical occurrence that:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- consists of a congenital anomaly or birth defect.

Other 'important medical events' may also be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

Possible expected adverse events that may occur during the physical assessments for Sub Studies 1 and 2 include trips, slips and falls during walking tests. Risks will be minimised with an assessed protocol.

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

10.2. Reporting Procedures for Serious Adverse Events

A serious adverse event (SAE) occurring to a participant should be reported to the REC that gave a favourable opinion of the study where in the opinion of the Chief Investigator the event was 'related' (resulted from administration of any of the research procedures) and 'unexpected' in relation to those procedures. Reports of related and unexpected SAEs should be submitted within 15 working days of the Chief Investigator becoming aware of the event, using the HRA report of serious adverse event form (see HRA website).

11. STATISTICS AND ANALYSIS

11.1. Statistical Analysis Plan (SAP)

The plan for the statistical analysis of the study is outlined below. There is not a separate SAP document in use for the study.

11.2. Description of the Statistical Methods

Primary Study

We will undertake descriptive analysis of the MSK-HQ, employment questionnaire, EQ-5D-5L utility score, HADS and IES-R using counts and percentages, means and standard deviations, or medians and interquartile ranges.

Multivariable linear regression will be used to assess for association of the baseline variables collected with the MSK-HQ score.

The relationships between MSK-HQ and employment, EQ-5D-5L, HADS and IES-R will be analysed through correlation statistics.

Sub Study 1

We will undertake descriptive analysis of the individual aspects of the MSK assessment (FABQ, ROM, VAS, MRC SS, dynamometry) using counts and percentages, means and standard deviations, or medians and interquartile ranges. I will explore the relationships between the individual aspects of assessment and the MSK-HQ score using correlation statistics.

Sub Study 2

I will undertake descriptive analysis of the individual components of the assessment (USS, IKD, 6MWT, life-space questionnaire, accelerometery, QD) using counts and percentages, means and standard deviations, or medians and interquartile ranges. We will investigate the relationships between the results at impairment and function domains in the upper and lower limb through correlation statistics.

Qualitative Sub Study

Interview transcripts will be recorded verbatim and transferred into qualitative analysis software (Nvivo). We will complete a phenomenological analysis to illuminate the lived experiences of patient, adult family members and staff participants from the interviews. The focus on lived experiences allows insight into how a person within a given context relates that the phenomenon. Anonymised quotes will be used in research reports and publications.

Case study documentation will be collated through description and aggregation of questions and resources. Narrative analysis will be undertaken and include critical discussion amongst the research team (including the supervisory team). Critical discussion is an essential component of narrative analysis of qualitative data. It involves dialogue between qualitative researchers to facilitate the identification and analysis of patterns or themes in a given data set and enhance the researcher's reflective and thoughtful engagement with their data.

11.3. Sample Size Determination

Primary Study

We have based the sample size calculation on the primary purpose of the data analysis, which is to identify prognostic factors for the development of a lower MSK-HQ score at six months after admission to ICU.

Using local case mix data for the John Radcliffe and Churchill ICUs in Oxford, Royal Berkshire ICU in Reading and the ICU at the Milton Keynes District General Hospital, approximately 2,840 patients are admitted each year. Of those, 1,340 have an ICU length of stay greater than 48 hours and are discharged to a ward within the hospital. Approximately 180 patients would be ineligible for participation in the study, and when accounting for an inpatient mortality of 7%, 1,100 eligible patients would be expected to survive to discharge from hospital.

For the ends of developing a prediction model, the MSK-HQ score will be treated as a continuous variable. There are 15 potential baseline prognostic factors identified. Based on this number of predictors and assuming an approximately normal distribution of residuals, the minimum sample size required to estimate a multiplicative margin of error of 0.1 would be 249 individuals. Allowing for a 25% loss to follow-up, it is necessary to recruit 332 participants. This sample size and number of predictors would also ensure the estimation of a shrinkage factor ≥ 0.9 and a difference between apparent and adjusted R^2 ≤ 0.02, even with a moderate anticipated R^2 of 0.6.

Sub Study 1

The scoping review we conducted identified that previous ICU follow-up studies that have included a physical assessment of some aspect of MSK health, have varied in sample size from 11 to 127. Our previous single centre prospective cohort study[10] had a sample size of 61 at six months following hospital discharge with an 18 month recruitment period. As the aim of this part of the study is to describe the specific MSK conditions and their prevalence, across three sites the target sample size is 115 patients.

Sub Study 2

As this part of the study is exploratory in nature, a formal power calculation has not been undertaken. The single previous study to more comprehensively evaluate mobility in ICU survivors included 24 patients.[20] As the patients will be a sub group based on MSK health state and locality to Oxford, the sample size is likely to be relatively small compared to the other parts of the study. Therefore our target sample size is 35.

Qualitative Sub Study

Our target sample size is 10-15 patient and family participants and 10-15 staff across all four sites. We are seeking to gain information power from the richness of the interviews. The information power model suggests that the more information held within a sample that is relevant to the study; lower numbers of participants are therefore required.

Analysis populations

All participants will be included in the analysis. Participants who have baseline data collected but withdraw prior to the telephone follow-up will have their baseline data included in the analysis.

12. DATA MANAGEMENT

The plan for the data management of the study are outlined below. There is not a separate Data Management document in use for the study.

12.1. Source Data

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, correspondence, topic guides, reflexive notes, memo notes, audio files, field notes and qualitative theme documentation.

CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant number/code, not by name.

12.2. Access to Data

Direct access will be granted to authorised representatives from the Sponsor and host institution for monitoring and/or audit of the study to ensure compliance with regulations.

12.3. Data Recording and Record Keeping

At each site the trial master file (TMF) containing essential information for the conduct of the study, and participant consent forms will be stored in a locked filing cabinet, behind a swipe-access door.

All study data will be recorded electronically and entered directly onto REDCap (https://projectredcap.org/about/), which is a secure platform for building and managing online databases. Patients will be assigned a unique participant number at the point of consent. All patient data will be connected to this number when stored electronically on the secure REDCap database. Participant name, date of birth and contact details (address and phone number) which are required for follow-up will also be recorded electronically and stored on REDCap, however this will be held in a separate project to the study data.

All interview audio recordings and questions to service leads will be downloaded and stored on a secure Oxford University Hospitals server as a password protected file.

All data undergoing analysis will be pseudo-anonymised, identifiable through participant study number only. All pseudo-anonymised data required for analysis will be transferred and stored on a secure Oxford University Hospitals server as a password protected file, and recorded on the information asset register in compliance with NHS Trust information governance policy.

Personal identifiable data, including participant contact information and screening logs will be kept for 12 months on a secure Oxford University Hospitals server, until all of the study data has been cleared

and the results published in case any of the data needs further evaluation or checking. Research data will be kept for five years (see section 20).

13. QUALITY ASSURANCE PROCEDURES

The study may be monitored, or audited in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures.

13.1. Risk assessment

Not applicable

13.2. Study monitoring

Not applicable

13.3. Study Committees

External advisory committee

The external advisory committee will meet to evaluate participant recruitment rates, outcome measure completion and interim data analysis. The committee will comprise of clinicians and researchers from the three participating sites, the study investigators and members of the Oxford ICU patient forum. The committee will be chaired by Dr David McWilliams, meet quarterly during study recruitment and at least annually outside of this.

14. PROTOCOL DEVIATIONS

A study related deviation is a departure from the ethically approved study protocol or other study document or process (e.g. consent process or administration of study intervention) or from Good Clinical Practice (GCP) or any applicable regulatory requirements. Any deviations from the protocol will be documented in a protocol deviation form and filed in the study master file.

15. SERIOUS BREACHES

A “serious breach” is a breach of the protocol or of the conditions or principles of Good Clinical Practice which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the trial subjects; or

(b) the scientific value of the research.

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the C.I., the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the approving REC committee and the relevant NHS host organisation within seven calendar days.

16. ETHICAL AND REGULATORY CONSIDERATIONS

16.1. Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

16.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

16.3. Approvals

Following Sponsor approval the protocol, informed consent forms and participant information sheets will be submitted to an appropriate Research Ethics Committee (REC), and HRA (where required) and host institutions for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

16.4. Other Ethical Considerations

Participants who are identified as having a new MSK impairment at any of the three potential assessment points (telephone follow-up, sub study 1 or sub study 2) will be given appropriate self-care advice (which may include attending their GP surgery), and have a comprehensive written summary of findings sent to their local ICU follow-up clinic and GP.

The questionnaires being used at the telephone follow-up or the interviews may have the potential to result in distress to participants. Prior to commencing the questionnaires or interviews the researcher will explain that the participant is free to ask to pause or stop at any time, and will offer to stop or pause the questionnaires if the participant becomes distressed during the telephone conversation. Participants will be offered advice on avenues for support such as ICU support groups.

Any clinically concerning information that is reported by participants at any point will be discussed with their GP and appropriate referrals made within the existing hospital system. This will be done through the weekly ICU follow-up clinic which is run by ICU Consultants and Psychiatrist, who have a specialist interest and expertise in issues for patients and families following critical illness. Patients presenting with a more serious clinical problem will be advised to attend their local Minor Injuries Unit or Emergency Department, or an ambulance will be called as appropriate.

16.5. Reporting

The CI shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, HRA (where required) host organisation, Sponsor and funder (where required). In addition, an End of Study notification and final report will be submitted to the same parties.

16.6. Transparency in Research

Prior to the recruitment of the first participant, the study will have been voluntarily registered on a publicly accessible database.

Where the study has been registered on multiple public platforms, the study information will be kept up to date during the study, and the CI or their delegate will upload results to all those public registries within 12 months of the end of the study declaration.

16.7. Participant Confidentiality

The study will comply with the General Data Protection Regulation (GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. The processing of the personal data of participants will be minimised by making use of a unique participant study number only where possible on study documents and any electronic database(s), with the exception of the screening log and record of participant contact information in REDCap . All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data.

16.8. Expenses and Benefits

For participants in Sub study 1, 2 and the Qualitative Sub Study will receive reasonable travel expenses for any visits additional to normal care will be reimbursed on production of receipts, or a mileage allowance provided as appropriate. Participants for Sub studies 1 and 2 will receive a retail voucher to the value of £20 to compensate them for their time. Participants in Sub study 2 will receive a stamped addressed envelope to return the accelerometer.

17. FINANCE AND INSURANCE

17.1. Funding

The study is funded by the NIHR Integrated Clinical Academic programme through the Clinical Doctoral Research Fellowship obtained by Owen Gustafson.

17.2. Insurance

NHS bodies are legally liable for the negligent acts and omissions of their employees. If you are harmed whilst taking part in a clinical research study as a result of negligence on the part of a member of the study team this liability cover would apply.

Non-negligent harm is not covered by the NHS indemnity scheme. The Oxford University Hospitals NHS Foundation Trust, therefore, cannot agree in advance to pay compensation in these circumstances.

In exceptional circumstances an ex-gratia payment may be offered.

17.3. Contractual arrangements

Appropriate contractual arrangements will be put in place with all third parties.

18. PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by the NIHR. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

19. DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY

Not applicable.

20. ARCHIVING

Following completion of the study, all participant consent forms will be scanned and converted to an electronic file and subsequently shredded on site. All research data will be transferred to a digital archive in a secure file space on an Oxford University Hospitals server for a minimum of 5 years in accordance with Oxford University Hospitals research and development, and will be disposed of securely if it is confirmed that they are no longer required. When appropriate all data will be destroyed and wiped. In line with GDPR policy, only the investigators involved in this study will have access to the data generated by the study.

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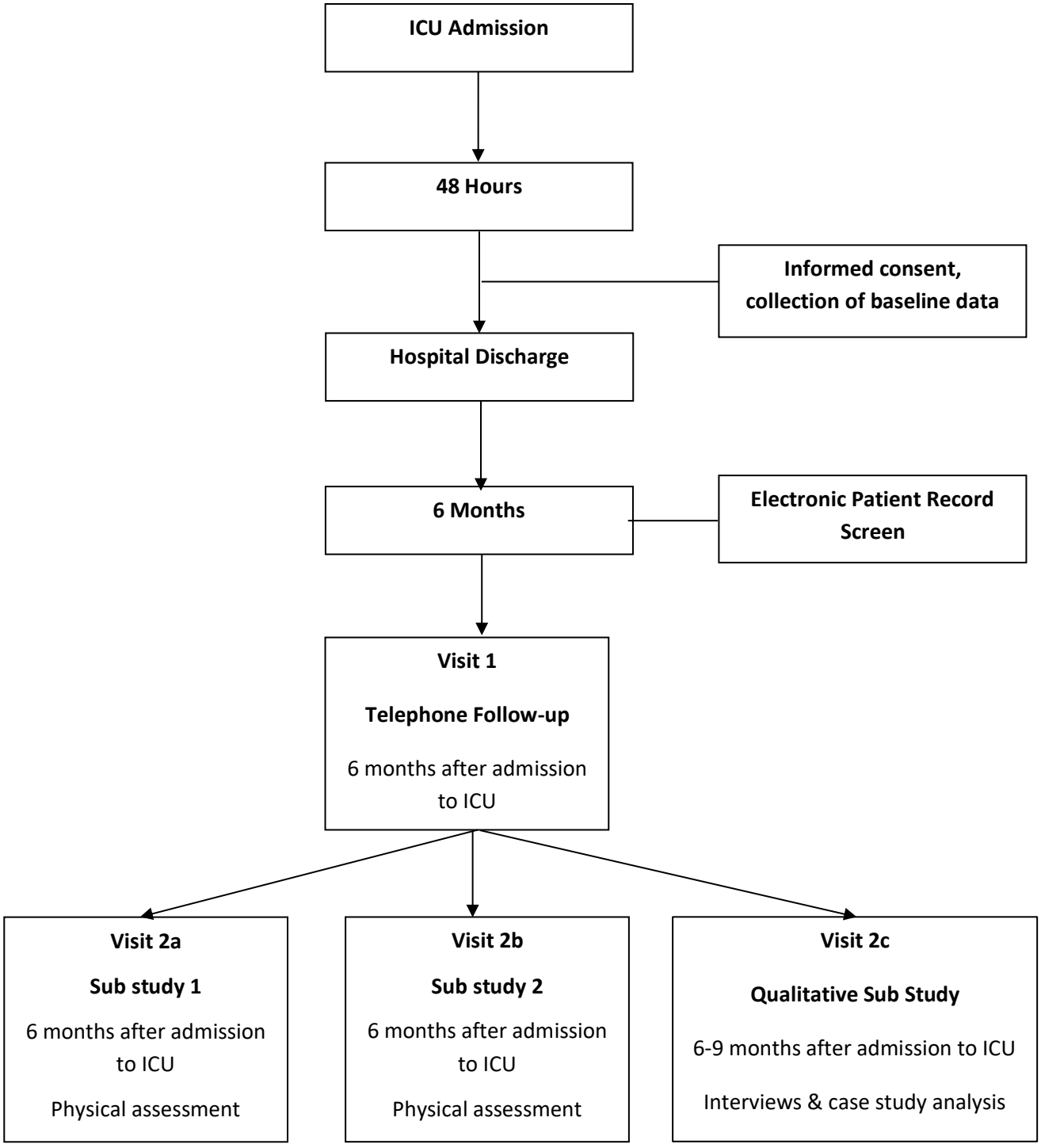
22. APPENDIX A: PARTICPIANT FLOW CHART



23. APPENDIX B: SCHEDULE OF STUDY PROCEDURES

Procedures	**Visits**					
	Day 2 - hospital discharge	**Day 2 – hospital discharge**	**6 months**	**6 months**	**6 months**	**6 - 9 months**
	Screening	**Baseline**	**Visit 1**	**Visit 2a**	**Visit 2b**	**Visit 2c**
Informed consent	15 min			15 min	15 min	15min
Demographics		5 min				
Medical history		10 min				
Telephone Follow-up			35min			
Sub study 1 - Physical assessment				30 min		
Sub Study 2 – Physical assessment					1 hour 45min	
Sub Study 3 - Interviews						1 hour
Sub Study 3 – Case study						1 hour

24. APPENDIX C: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	v3	27/5/22	Elizabeth King	Addition of qualitative sub study Change of PI at Oxford to Elizabeth King Addition of Great Western Hospital as a site Addition of Annabel Williams, Sarah Vollam and Elizabeth King to the study team as qualitative experts Extension of recruitment and study end dates
2	v4	4/12/22	Owen Gustafson	An increase in sample size by 10 (from 322 to 332) due to a recalculation of the number of participants required for the statistical analysis.

List details of all protocol amendments here whenever a new version of the protocol is produced.

Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee and HRA (where required).