FULL STUDY PROTOCOL v2.0

Paediatric Early Rehabilitation/Mobilisation during InTensive Care

Sponsor	University of Birmingham
Funder	National Institute for Health Research (NIHR) Health Technology Assessment (HTA) 17/21/06
Chief Investigator	Dr Barney Scholefield
Sponsor reference number	ERN_18-1134
ISRCTN number (clinicaltrials.gov)	NCT04110938
REC reference number	19/ES/0102
Date	16th June 2020

UNIVERSITY OF BIRMINGHAM

NHS
National Institute for Health Research

CI Signature Page

This protocol has been approved by:

Trial Name:	PERMIT Full Study Protocol
Protocol Version Number:	Version: 2.0
Protocol Version Date:	16/06/2020

CI Name:	Dr. Barney Scholefield
Trial Role:	Chief Investigator
Signature and date:	 16/06/2020

Sponsor statement:

Where the University of Birmingham takes on the sponsor role for protocol development oversight, the signing of the IRAS form by the sponsor will serve as confirmation of approval of this protocol.

Funder Statement

"This study/project is funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme (17/21/06). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care"

1. Protocol Amendments

Protocol Amendments				
The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version				
Amendment number	**Date of amendment**	**Protocol version number**	**Type of amendment**	**Summary of amendment**
1	16th June 2020	2.0	Major addition	Addition of Phase 1a Survey, Phase 1c Review, Phase 2b Review and Phase 3 Pilot. Formatting and layout

2. Administrative Information

Contact details are available upon request: iia-permitstudy@contacts.bham.ac.uk

Sponsor	
University of Birmingham	Sponsor contact: Dr Birgit Whitman Head of Research Governance and Integrity Room 117, University of Birmingham Birmingham, B15 2TT

Chief investigator	
Dr Barney Scholefield	NIHR Clinician Scientist
Birmingham Acute Care Research Group, Institue of Inflammation and Ageing. University of Birmingham	

Sponsor's Medical Expert for the Trial	
Dr Barney Scholefield	NIHR Clinician Scientist / Paediatric Intensive Care Consultant

Co-investigator (s)	
Rob Forsyth	Consultant Neurologist
Institute of Health and Society Newcastle University	
Tim Rapley	Professor
Northumbria University	
Jennifer McAnuff	Academic Occupational Therapist
Institute of Health and Society, Newcastle University	
Nazima Pathan	Consultant in Paediatric Intensive Care
Department of Paediatrics, The Chancellor, Masters, and Scholars of the University of Cambridge	
Stephen Brett	Consultant in Intensive Care
Department of surgery and cancer, Imperial College of Science, Technology and Medicine	
Joseph Manning	NIHR /HEE Clinical Lecturer; Charge Nurse Paediatric Critical Care Outreach
The University of Nottingham and Nottingham University Hospitals NHS Trust	
David Moore	Senior Lecturer
Institute of Applied Health University of Birmingham	
Michelle Geary	Physiotherapist
Child Health, University Hospital Southampton NHS Foundation Trust	
Fenella Kirkham	Professor of Neurology
Child Health, University Hospital Southampton NHS Foundation Trust	
Gillian Colville	Psychologist

Paediatric Psychology Service, St George's University Hospitals, NHS Foundation Trust	
Julie Menzies	Senior PICU Research Nurse
Paediatric Intensive Care, Birmingham Children's Hospital NHS Foundation Trust	
Kevin Morris	Honorary Professor of Paediatric Intensive Care
Paediatric Intensive Care, Birmingham Children's Hospital NHS Foundation Trust	
Roger Parslow	Senior Lecturer
University of Leeds Child Health	
Dr Richard Feltbower	Principal Investigator PICANet
PICANet, University of Leeds Child Health	
Sophie Lockley	PPI Representative

Trial Office Contact Details	
Faaria Hussain	Project Manager for PERMIT study
Institute of Microbiology and Infection NG20, Ground Floor, Biosciences Building College of Medical and Dental Sciences University of Birmingham Edgbaston Birmingham B15 2TT	
Jacqueline Y. Thompson	Research Fellow for PERMIT study
Rm 237, Level 2, Public Health Building, Institute of Applied Health Research, University of Birmingham Birmingham, B15 2TT	

Trial Steering Committee	
Dr Shane Tibby	Chair, Clinician, Trialist, London
Prof Mark Peters	Prfo Intensive Care medicine, Clinician, London
Dr Kerry Woolfall	Senior Lecturer Health Services Research Qualitative Researcher, Liverpool
Ms Suzanne Dottin-Payne	PPI representative
Prof Jim Leswey	Professor Medical Statistics, Glasgow

Data Monitoring and Ethics Committee	
Prof Bronagh Blackwood	Chair, Clinician, Trialist, Belfast
Dr Siva Oruganti	PICU consultant, Cardiff
Ms Cliona Mcdowell	Statistican, Belfast

3. Table of Contents

4.Table of Figures

5.PERMIT Study Overview

This is the combined FULL STUDY PROTOCOL for the multi-phase PERMIT study programme. It comprises the individual protocols for each Phase and Sub-Phases of PERMIT.

This section describes an overview of the PERMIT study aims and objectives and relationship to phases and sub-phases of the PERMIT programme.

Due to the evolution of the PERMIT programme, individual sub-phase protocol will be submitted for required regulatory and ethical review at different stages, time points and to different ethics review boards as appropriate. The timing, submission and regulatory boards are indicated for each individual sub-phase protocol.

5.1. Aims and Objectives of PERMIT study

5.1.1.Aims:

To prepare for a definitive ERM trial, we will: i) identify current ERM practice, ii) specify the content of an ERM intervention; ii) establish the patient population for whom ERM may be appropriate; iii) determine patient-centred outcomes of ERM, and appropriate measures; iv) explore the feasibility and acceptability of an ERM future trial.

5.1.2.Objectives: PHASE 1 (months 1-6): Understand current practice

1.1 Identify & describe current ERM practice in UK PICs

1.2 Assess capability of UK PICs to deliver ERM

1.3 Establish and model how many/which CYP would be appropriate for ERM in the PIC population

1.4 Review the literature supporting current ERM practice

PROTOCOL	Linked Objectives	Page no.
PROTOCOL: Phase 1a Survey.	1.1,1.2	17
PROTOCOL: Phase 1b Observational study.	1.1,1.2,1.3	24
PROTOCOL Phase 1c: Literature Review.	1.4	57

5.1.3.Objectives: PHASE 2 (7-16 months): Develop ERM intervention and select patient centred-outcomes

2.1 Co-design manual of ERM interventions

2.2 Identify relevant primary and secondary patient-centred outcomes

2.3 Rapid literature review to identify outcome assessment tools

2.4 Explore feasibility and acceptability of ERM interventions and trial designs

2.5 Manualise the proposed ERM intervention

PROTOCOL	Linked Objectives	Page no.
PROTOCOL: Phase 2a Workshop & Interviews with Children and Young People.	2.1,2.2, 2.4	61
PROTOCOL: Phase 2a Workshops & Interviews with Experts and Health Professionals	2.1, 2.2, 2.4	73
PROTOCOL: Phase 2b: Literature Review	2.3	83

5.1.4. Objectives: PHASE 3 (months 17-21): Assessment of feasibility of proposed ERM intervention and outcome measures

3.1 Test, refine and adapt manualised ERM intervention

3.2 Explore feasibility of manualised ERM intervention in a two centre non-randomised pilot study

PROTOCOL	Linked Objectives	Page no.
PROTOCOL: Phase 3 Feasibility study	3.1,3.2	86

5.1.5. Objectives: PHASE 4 (months 22-24): Synthesise data and report findings

4.1 Combine population, intervention, and standard care and outcome definitions for future trial evaluation proposal

4.2 Build consensus on intervention for feasible/acceptable ERM trial

4.3 Explore methodological approaches and future trial design

4.4 Disseminate findings and full HTA report.

PROTOCOL	Linked Objectives	Page no.
PROTOCOL: Phase 4	4.1,4.2	In development

5.2. Summary of PERMIT study phases, protocol version and ethical review bodies & dates.

Phase of PERMIT	Section	Details
Phase 1a survey	Protocol version	PERMIT Phase 1a: SURVEY PROTOCOL v1.0 05FEB2019
	Ethics	University of Birmingham 5FEB2019 BMS_1819_03
	Amendment	None
Phase 1b Observational study	Protocol version	Final: PERMIT_Observational_Study_Protocol_IRAS Project ID-263127_v1.0_03Oct2019
	Ethics	REC approval: 02 September 2019 19/ES/0102
	Clinical Trials ref	NCT04110938
	Amendment	Amendment approved: 23/12/2019: Minor amendment (study sites added) from original REC approved: PERMIT+obervational+study+protocol_IRAS+Project+ID-263127_v0.3+11Jul2019
Phase 1c Review	Protocol version	PHASE 1c: Systematic Review /Scoping Review v1.0 16JUNE2020
	Ethics	Not applicable
	Amendment	None
Phase 2a Workshop interview: parents, children and young people.	Protocol version	The PERMIT feasibility study – Paediatric Early Rehabilitation/Mobilisation during InTensive care (workshops and interviews with parents, children, and young people) [PERMIT version 3.0 Phase 2 Protocol] 13FEB2020
	Ethics	REC approval: 28 February 2020 **19/LO/1987**
	Amendment	None
Phase 2a Workshop Health care professionals	Protocol version	PERMIT Phase 2a protocol - workshops and interviews with professional's protocol version is 0.2 20 July 2019
	Ethics	Newcastle University approval (Ref 14224/2018). on 01/08/2019
	Amendment	None
Phase 2b Rapid review outcome tools	Protocol version	PHASE 2b: RAPID REVIEW OUTCOME TOOLS v1.0 16JUNE2020
	Ethics	Not applicable
	Amendment	None
Phase 3 Feasibility study	Protocol version	*Draft* version of: PERMIT_Feasibility_Study_Protocol_v0.1 29_04_2020
	Ethics	Awaited
	Clinical Trials ref	Awaited
	Amendment	-
Phase 4 Synthesise data	Protocol version	Awaited
	Ethics	N/A
	Amendment	-

6. Background and Rationale

6.1. Background

6.1.1. Problem being addressed

Annually in the UK, critical illness or injury affects 19,000 children (0-18 years) (1) and warrants admission to the paediatric intensive care unit (PICU) for the receipt of life-sustaining treatments. Survival rates from PICU is at an all-time high (>96%). However, low levels of mortality have been offset by an increase in morbidity. The impact of being critically ill and exposed to the PICU is multiple. Weakness, cognitive impairment, organ dysfunction, and psychological problems have been reported to emanate from deconditioning. Subsequently, post-PICU many CYP experience significant and residual physical, cognitive, and psychosocial morbidities that impact on their quality of life (2-8). Subsequently, contemporary focus has turned to the development, testing and implementation of interventions to minimise the iatrogenic harm of critical care and maximise patient outcomes (9).

Early rehabilitation/mobilisation (ERM) encompasses patient-tailored interventions, delivered individually (10, 11) or in a bundled package (12), provided by health professionals from multiple disciplines and care-givers within intensive care settings to promote recovery, both physical (e.g. movement, functional activities, ambulation) and non-physical (e.g. speech, play, psychological, cognitive) (13-19).

Rehabilitation has been shown to improve quality of life and patient outcomes; reduce health inequalities, and make significant savings to the health and care system (20). Benefits have been demonstrated in the use of ERM in adult ICU populations in relation to patient outcomes as well as healthcare utilisation (16, 21). Furthermore, studies indicate that the intervention is safe and feasible, reduces delirium and increases ventilator-free days, improves day-to-day functioning and reduces hospital readmissions (17, 22-25). However, in the UK, understanding of current ERM practices (including content, barriers, facilitators, feasibility, and safety) and their impact on the outcomes of paediatric ICU patients is limited. This has stifled an evidence-based approach to ERM which has resulted in disparity in the adoption and utilisation of ERM interventions in PICUs across the UK.

6.1.2. Why is the research important in terms of improving the health of the public and/or to patients and the NHS?

In adult intensive care, ERM has been shown in clinical trials to improve long term physical functioning and return to independence (21). It can also shorten the length of ventilation and stay in intensive care and hospital with significant economic benefit, and is recommended by NICE (17, 22-25). There are potential benefits of ERM in Paediatric Intensive Care (PIC). With practical interventions appropriate to the CYP condition and age, there is potential to positively impact the emotional, behavioural, cognitive and functional outcomes of CYP and to benefit their caregivers' quality of life (26-30). There is clearly an opportunity for improvement of care for CYP and their families in the NHS. Challenges to ERM in critically ill children include the wide age range, heterogeneous disease processes, and a high proportion of children with preceding chronic co-morbidities (1, 26, 31). Several international studies have demonstrated feasibility, acceptability, and safety of ERM in this population using physiotherapy (PT)(14, 16), occupational therapy (OT)(13), video games(10) and exercise equipment (e.g. in bed cycling)(11). However, the evidence base for ERM in the paediatric ICU populous in a UK context is scant.

In order to design clinical trials to investigate the potential benefits of ERM in critically ill children, it is crucial to understand current utilisation and potential feasibility in a UK context. PERMIT will generate much-needed knowledge for future multi-centre interventional trials to test the effectiveness of ERM on short and long-term outcomes in children as well as healthcare utilisation. Therefore this research is important as it will contribute to establishing the health benefits of ERM in critically ill children and impact on services and NHS resources.

6.1.3.Why this research is needed now?

The use of ERM in the paediatric ICU population offers significant potential to: prevent morbidities associated with being critically ill; facilitate recovery, and improve patient outcomes. Whilst there is good evidence to support the safe and effective use of ERM in adult ICU populations (25), there is insufficient evidence of such an effect in children. Despite the absence of robust evidence, it is apparent from communication with the national network of NHS PICUs that some units have implemented ERM into their clinical practice. In some cases this does not appear to have been undertaken systematically, nor has the impact on patient outcomes, service utilisation, or resources been evaluated. High quality, effective, and efficient services that meet the needs of patients are key priorities for the NHS as outlined in the NHS mandate (32) and the Five Year Forward View. It is therefore timely and relevant that research is undertaken to build the evidence base to inform the utilisation of ERM in PICU clinical practice.

We have engaged extensively with international research consortia to share expertise during the PERMIT study development which in turn has supported optimising efficiency and collaboration in advancing knowledge (33). However, we recognise it is unlikely that research conducted outside of UK NHS practice alone, will be able to suitably address current knowledge gaps on whether the ERM is valuable to the NHS. Existing uncertainties around ERM that relate to: (1) its current use in the UK, (2) how it has been operationalised and implemented, and (3) its feasibility as a possible intervention cannot be addressed by the existing body of literature. Therefore, the primary research we propose in the PERMIT study needs to be undertaken to inform a definitive trial of effectiveness that will, in turn, determine the value of ERM within the NHS PIC population. Specifically, the Phase 1 study, outlined in this protocol, will provide essential findings that will inform subsequent phases of this programme of work.

6.1.4.Theoretical framework

Our proposed research plan draws on and integrates three established frameworks of particular relevance to the conceptualisation, development, and implementation of ERM interventions: (i) the World Health Organization's International Classification of Functioning, Disability, and Health; (34) (ii) the Medical Research Council's guidance on developing and evaluating complex interventions (35, 36) and (iii) Normalisation Process Theory. (37, 38)

Throughout the proposed study, we will use the International Classification of Function, Disability, and Health (ICF), (34) to provide a common language for conceptualising, measuring, and documenting hypothesised outcomes of ERM interventions. ERM interventions are hypothesised to impact on multiple aspects of children's functioning, at the level of their body functions (e.g. neuro-musculoskeletal, movement-related, and/or mental functions), activities (e.g. mobility, learning, communication, and/or self-care, activities of daily living), and participation (e.g. education, play, recreation, and leisure), as well as on service delivery and economic outcomes (e.g. length of intensive care/overall hospital stay). (15, 39) As a comprehensive, multidisciplinary framework integrating biological, individual, and social perspectives, the ICF will enable us to clearly and consistently specify the functional outcomes that may be targeted by ERM interventions. It will also enable us to categorise the environmental factors (e.g. clinician knowledge, skills, and beliefs, PIC unit culture), and children's personal factors (e.g. chronological and developmental age, premorbid functional ability), that may play an important role in the implementation or effectiveness of ERM interventions. (15, 39)

To guide our development and clear specification of the content ('active ingredients') of ERM interventions, we will draw on the Medical Research Council's (MRC) methodological framework for developing complex interventions. (35, 36) We conceptualise rehabilitation as a complex intervention in that it: (i) consists of a number of interacting components within the intervention, delivered by a range of multidisciplinary clinicians; (ii) targets numerous and various functional outcomes related to children's level of physical function, activities, and participation; and (iii) requires a high degree of flexibility and tailoring in its delivery across individuals and clinical populations. (35) In line with MRC recommendations, (35) we propose to (i) identify the existing evidence base about the content, outcomes, delivery, and implementation of ERM interventions; (ii) identify and develop theory about how ERM interventions are hypothesised to lead to changes in children's functioning; and (iii) continuously model the process and outcomes of ERM interventions by progressively refining

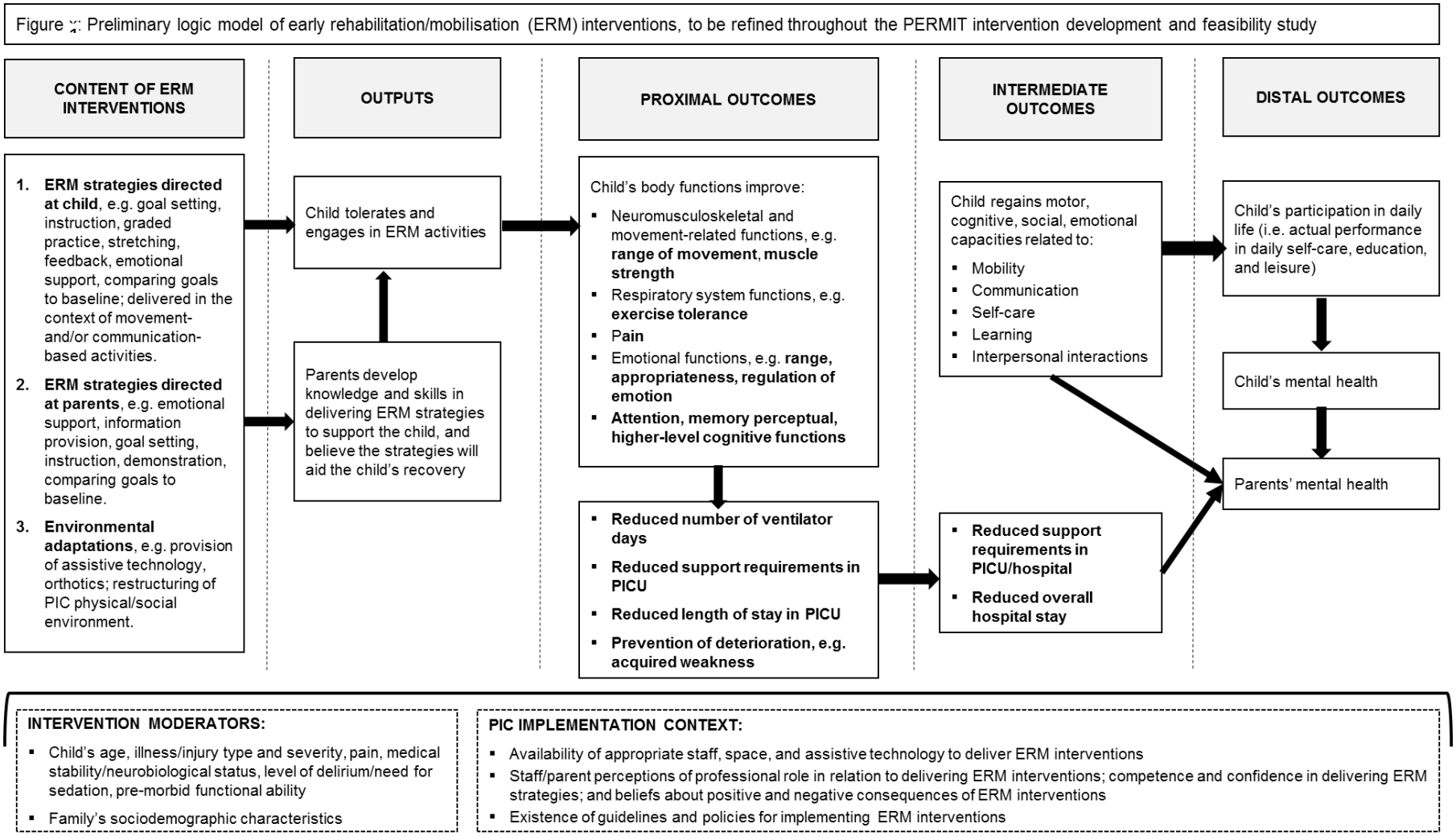
intervention prototypes, and producing a manual of feasible and acceptable ERM interventions in preparation for a future definitive evaluation study.

The MRC framework also incorporates guidance for assessing the feasibility of complex interventions, for example establishing whether interventions can be delivered as intended. We plan to consider implementation issues as early as possible in our intervention development process, which will enable us to further improve the design and sustainability of ERM interventions, explore their future use if later found to be cost-effective, and reduce the chance of implementation failure. (40) We will use Normalisation Process Theory (NPT), (37, 38) as our theoretical framework for exploring factors that may promote or inhibit the routine implementation of ERM interventions as standard practice in UK NHS PICUs. The explicit use of NPT throughout the study will support theoretical and practical understanding of how ERM interventions may be best introduced to clinical settings, both in the context of a randomised controlled trial and implementation as part of usual rehabilitation care.

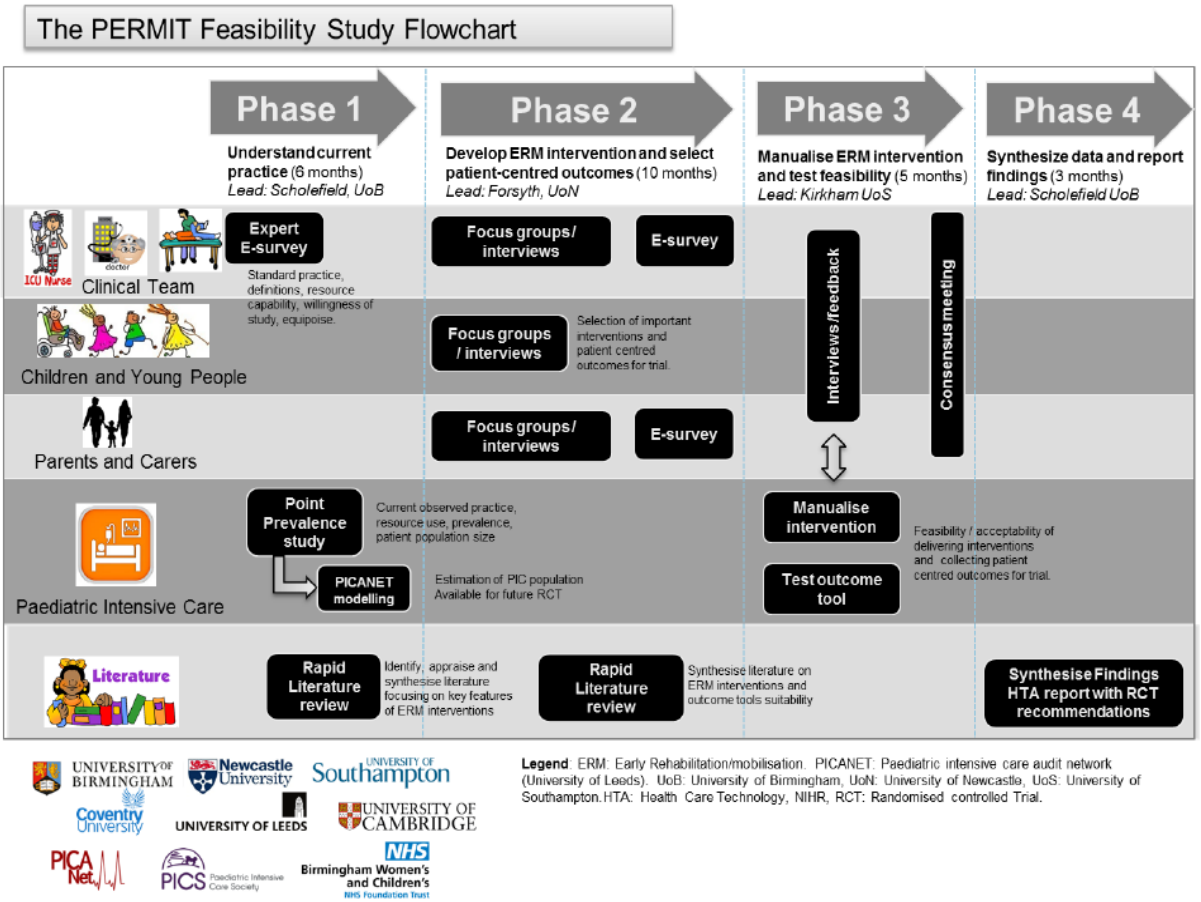
We have developed a preliminary logic model (41, 42) (**Error! Reference source not found.**), based o n current literature (15, 39) and the clinical expertise within the research team, to represent our understanding of the content of ERM interventions, their hypothesised proximal, intermediate, and distal outcomes, potential intervention moderators, and key contextual factors that may influence their implementation. The logic model will facilitate communication within the research team throughout the study by making our multidisciplinary assumptions about ERM interventions more transparent. We will develop the logic model throughout the study, using and refining it within each phase to inform data collection, analysis, and synthesis, and will present a summative model as a key study output to inform next-stage research on ERM interventions.

It is proposed that the findings from this Phase 1 study (outlined in this protocol) will contribute to developing and refining the ‘content’, ‘moderators’ and ‘context’ components of the logic model (Figure 1).

Figure 1 PERMIT study logic model



6.1.5. Overview of PERMIT study Phases



Legend: ERM: Early Rehabilitation/mobilisation. PICANET: Paediatric intensive care audit network (University of Leeds). UoB: University of Birmingham, UoN: University of Newcastle, UoS: University of Southampton. HTA: Health Care Technology, NIHR, RCT: Randomised controlled Trial.

PHASE 1a PROTOCOL: Survey

7.PHASE 1a: SURVEY PROTOCOL

7.1. Survey Protocol development and sign off

Protocol Contributors	
The following people have contributed to the writing of this protocol:	
Name:	Affiliation and role:
Dr Barney Scholefield	Chief Investigator – University of Birmingham
Dr Joseph Manning	Co-Investigator – The University of Nottingham
Jacqueline Thompson	Research Fellow – The University of Birmingham

7.2. Trial Summary

Title	Paediatric Early Rehabilitation/Mobilisation during InTensive care feasibility Survey
Short Title	PERMIT Survey
Sponsor Name and Reference	University of Birmingham REF ERN_18-1134
Funder Name and Reference	NIHR HTA 17/21/06
Study Design	Survey

Overall Aim	The survey will enable us to map current ERM practice: including factors influencing the decision to offer ERM; what is the content of ERM; how is it delivered; what 'dose' is used; how do HCP think it works; what resources are available nationally; what outcome measures do people think are useful to measure; funding availability for ERM; contextual implementation features; and the existence of local ERM protocols.
Study Objectives	1.1 Identify & describe current ERM practice in UK PICUs 1.2 Assess capability of UK PICUs to deliver ERM
Population & Inclusion Criteria	We plan to sample at least 3 lead health care practitioners (1 allied health, 1 medical and 1 nursing) from all 28 UK and Irish PICs (total number of participants n=84). We will also approach other health care professionals and therapists at individual PICs.
Study Centres	28 UK NHS PICUs: 1 Addenbrooke's Hospital, Cambridge 2 Noah's Ark Children's Hospital for Wales, Cardiff 3 Royal Manchester Children's Hospital 4 Great Ormond Street Hospital, London (PICU/NICU) 5 Evelina London Children's Hospital 6 King's College Hospital, London 7 Leeds General Infirmary 8 Freeman Hospital, Newcastle upon Tyne 9 Great North Children's Hospital, Newcastle upon Tyne 10 Royal Stoke University Hospital 11 Queen's Medical Centre, Nottingham 12 John Radcliffe Hospital, Oxford 13 Royal Brompton Hospital, London 14 Alder Hey Children's Hospital, Liverpool 15 Sheffield Children's Hospital 16 Southampton Children's Hospital 17 St George's Hospital, London 18 St Mary's Hospital, London 19 Birmingham Children's Hospital 20 Bristol Royal Hospital for Children 21 Glenfield Hospital, Leicester 22 Leicester Royal Infirmary 23 Royal Hospital for Sick Children, Edinburgh 24 The Royal London Hospital 25 Royal Hospital for Children, Glasgow 26 Royal Belfast Hospital for Sick Children 27 Our Lady's Children's Hospital, Crumlin, Dublin 28 Temple Street Children's University Hospital, Dublin

7.3. Background

7.3.1.Overview:

The PERMIT study is a National Institute Health Research (NIHR) Health Technology Assessment (HTA) funded study. The award has been granted to Dr Barney Scholefield, (Chief Investigator). This project is a survey of health care practitioners and is being classed as a 'sub study' of the PERMIT study. This is separate to the ongoing IRAS/ REC application for the main PERMIT study. The project is an opportunity for two undergraduate BMedSci students at University of Birmingham (UoB to be involved and supported in the conduct of research as a dissertation project. We are therefore requesting University of Birmingham approval for conduct of the survey. We believe this will be of low ethical risk as the study involves communication and data capture of health care practitioners in the NHS and minimum personal data storage.

7.3.2.Background to PERMIT study:

Annually in the UK, critical illness or injury affects 19,000 children (0-18 years) and warrants admission to the Paediatric Intensive Care Unit (PICU) for the receipt of life sustaining treatments. Survival rates from PICU is at an all-time high (>96%). However, low levels of mortality have been offset by an increase in morbidity. Weakness, cognitive impairment, organ dysfunction, and psychological problems have been reported to emanate from deconditioning. Early rehabilitation/ mobilisation (ERM) provided in PICU may reduce the process of decondition. ERM encompasses patient-tailored interventions, delivered individually or in a bundled package, provided by health care professionals from multiple disciplines within intensive care settings to promote recovery. This includes both physical (e.g. movement, functional activities, and ambulation) and non-physical (e.g. speech, play, psychological, cognitive) factors.

In adult intensive care, ERM has been shown in clinical trials to improve long term physical functioning and return to independence. It can also shorten length of ventilation and stay in intensive care and hospital with significant economic benefit, and is recommended by NICE. There are therefore potential benefits of ERM in Paediatric Intensive Care (PIC). However, the evidence base for ERM in PICU patients is scant and the provision of ERM can be expensive and not sustainable for some NHS Trusts.

We will undertake a short online survey (using Smartsurvey – as approved by UoB Research Governance) of senior health care practitioners (medical, nursing and allied health professionals) from all UK PICUs.

7.4. Aims and objectives

7.4.1.Aims

The aim of the survey is to understand more about current ERM service provision and whether a future trial in the UK is feasible.

The survey will enable us to map current ERM practice. This will include factors influencing the decision to offer ERM ; what is the content of ERM; how is it delivered; what 'dose' is used; how do HCP think it works; what resources are available nationally; what outcome measures do people think are useful to measure; funding availability for ERM; contextual implementation features; and the existence of local ERM protocols.

7.4.2.Objectives

1.1 Identify & describe current ERM practice in UK PICs

1.2 Assess capability of UK PICs to deliver ERM

7.5. Data collection/analysis:

The survey will be designed and piloted by the PERMIT co-applicant study team. It will be distributed via established networks of known lead clinicians (Paediatric Intensive Care Society – Study Group, PICU physiotherapy and occupational therapy networks). We anticipate >75% return rate following previous practice surveys. Numeric and textual data will be analysed using descriptive statistics and framework analysis respectively.

7.5.1.Target population:

We plan to sample at least 3 lead health care practitioners (1 allied health, 1 medical and 1 nursing) from all 28 UK and Irish PICs (total number of participants n=84). We will also approach other health care professionals and therapists at individual PICs if the original three responders are unable to answer questions (e.g. regarding service provision of occupational therapy or dietitians.

List of planned NHS and Irish PICUs.

1 Addenbrooke's Hospital, Cambridge
2 Noah's Ark Children's Hospital for Wales, Cardiff
3 Royal Manchester Children's Hospital
4 Great Ormond Street Hospital, London (PICU/NICU)
5 Evelina London Children's Hospital
6 King's College Hospital, London
7 Leeds General Infirmary
8 Freeman Hospital, Newcastle upon Tyne
9 Great North Children's Hospital, Newcastle upon Tyne
10 Royal Stoke University Hospital
11 Queen's Medical Centre, Nottingham
12 John Radcliffe Hospital, Oxford
13 Royal Brompton Hospital, London
14 Alder Hey Children's Hospital, Liverpool
15 Sheffield Children's Hospital
16 Southampton Children's Hospital
17 St George's Hospital, London
18 St Mary's Hospital, London
19 Birmingham Children's Hospital
20 Bristol Royal Hospital for Children
21 Glenfield Hospital, Leicester
22 Leicester Royal Infirmary
23 Royal Hospital for Sick Children, Edinburgh
24 The Royal London Hospital
25 Royal Hospital for Children, Glasgow
26 Royal Belfast Hospital for Sick Children
27 Our Lady's Children's Hospital, Crumlin, Dublin
28 Temple Street Children's University Hospital, Dublin

7.5.2.Recruitment

Senior health care practitioners will be identified through the Paediatric Intensive Care Society, physiotherapy and occupational health membership lists. Permission for distributing to the email list will be obtained from the Chair or Vice Chairman of the Paediatric Intensive Care Study Group. Emails will be sent out by the Paediatric Intensive Care Society directly and the PERMIT researchers will not have access to participants' individual emails. The survey will be sent out with an introductory email *(PERMIT_Study_Survey_Invite v2.0 31JAN2019)* and a PIS *(PERMIT_Survey_PIS Version 2.0 31/01/2019)*. Reminders will be sent out a further two times, at weekly intervals. The reminders will be sent to all original invitees (surveys will be completed anonymously so there will be no way of knowing who has already completed the survey). Those who have already completed the survey will be asked not to complete it again.

7.5.3.Consent

Potential participants will be sent an introductory email *(PERMIT_Study_Survey_Invite v2.0 31JAN2019)* containing an introduction to the aims and objectives of the PERMIT study survey, explicitly stating that completion of the survey is optional, but that completion and submission implies informed consent. A more detailed PIS *(PERMIT_Survey_PIS v2.0 31012019)* will be attached to this email, which potential participants will be encouraged to read.

7.5.4.Participant feedback

Participants will be invited to take part in future aspects of the PERMIT study (focus groups).

We will also publish the results of the PERMIT study survey as part of the full HTA project report and associated published manuscripts and this will be available to all participants to read. Links will be provided via the Paediatric Intensive Care Society mailing list.

In the invitation email and patient information sheet, the participants are informed of their right to decline participation or to withdraw before the survey is submitted. Once they have submitted their answers they will not be able to withdraw from the questionnaire study and this is detailed in the PIS and at the beginning of the survey.

As the survey results will be anonymous it will not be possible to remove a participant's data after the survey has been submitted. This information is clearly outlined in the PIS *(PERMIT_Survey_PIS v2.0 31012019)*

7.6. Data protection

7.6.1.Confidentiality

Completed surveys will be submitted anonymously. If participants choose to give their contact details in order to take part in a future focus group, these will not be linked to their completed questionnaire.

All information collected about participants during the study will be treated confidential, and will be handled, stored and destroyed in accordance with the Data Protection Act 2018.

Data will be stored securely with [SmartSurvey] while the survey is ongoing, and will be stored securely on the University of Birmingham server once data collection is complete.

Survey answers will be kept for 10 years after the end of the PERMIT study. If contact details are provided, these will be deleted within 6 months of the end of the study.

7.6.2.Storage and access to data

Survey answers will be stored securely on SmartSurvey until the data collection period is complete. Responses will then be exported to spreadsheets and stored securely on University of Birmingham servers. Only Dr Scholefield will have access to this SmartSurvey account.

All co-investigators and research students under Dr Scholefield supervision will have access to anonymised data once exported.

Data will be deleted from SmartSurvey once data collection is complete and data has been exported to University of Birmingham servers. In accordance with the data will be securely deleted from University of Birmingham servers after the end of the PERMIT study + 10 years

7.6.3. Optional contact details obtained from survey participants – identifiable

Participants' details will be stored securely on SmartSurvey until the data collection period is complete. Participants details will then exported to password protected spreadsheets and stored securely on University of Birmingham servers.

Deleted from SmartSurvey once data collection complete and data has been exported to University of Birmingham servers. Securely deleted from University of Birmingham servers

7.7. Significance/ benefits

This important piece of work is a key component of the larger PERMIT feasibility study and will inform the design and feasibility of future research into ERM in paediatric critical care. Importantly it will improve our understanding of current practice and provision of ERM in the UK and guide the development of a future intervention trial of ERM in critically ill children.

7.8. Risks

This survey poses no risk to research staff or participants.

The study involves the sharing of contact information for involvement in future components of the PERMIT study. Provision of this contact information is optional and data storage procedures as outlined above and in the Patient Information leaflet will minimise risk of data breach and ensure compliance to GDPR regulations.

7.9. Ethics approval

The University of Birmingham granted institutional ethical approval on 05/02/2019, Sponsor reference ERN_18-1134. Consent was implied through survey completion.

PHASE 1b PROTOCOL: Observational Study

8. PHASE 1b: OBSERVATIONAL STUDY PROTOCOL

8.1. Observational Study Protocol development and sign off

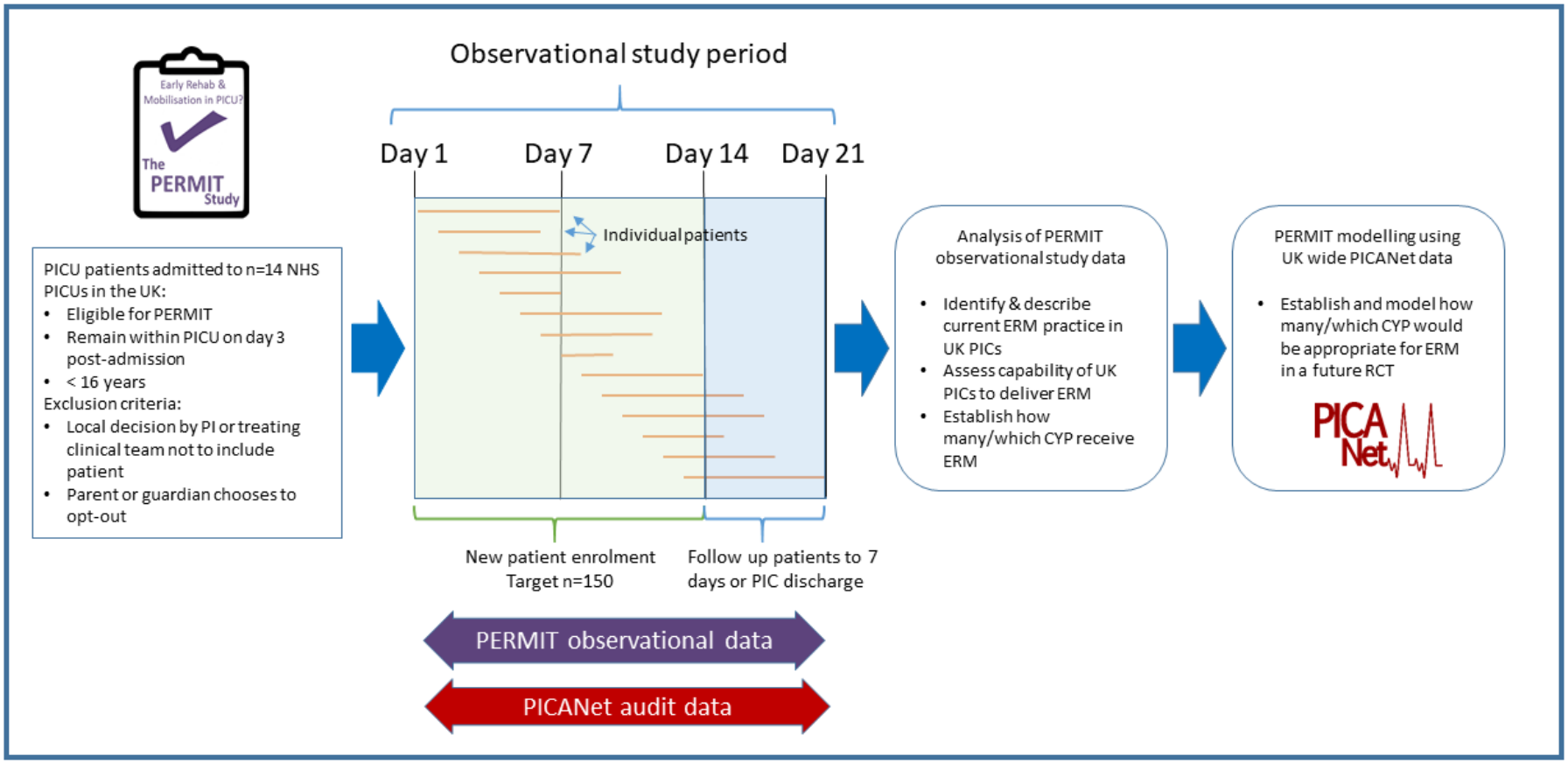
Protocol Contributors	
The following people have contributed to the writing of this protocol:	
Name:	Affiliation and role:
Dr. Barney Scholefield	Chief Investigator – University of Birmingham
Dr. Joseph Manning	Co-Investigator – The University of Nottingham
Jacqueline Thompson	Research Fellow – The University of Birmingham

8.2. Trial Summary

Title	Paediatric Early Rehabilitation/Mobilisation during InTensive care feasibility Observational study
Short Title	PERMIT Observational study
Sponsor Name and Reference	University of Birmingham REF ERN_18-1134
Funder Name and Reference	NIHR HTA 17/21/06
Study Design	Observational cohort study
Overall Aim	To prepare for a definitive ERM trial, we will: i) Identify current ERM practice, and ii) Establish the patient population for whom ERM may be appropriate
Study Objectives	1.1 Identify & describe current ERM practice in UK PICUs 1.2 Assess capability of UK PICUs to deliver ERM 1.3 Establish and model how many/which CYP would be appropriate for ERM in the PIC population
Population & Inclusion Criteria	Inclusion: All Children and Young Persons (CYP) (0-<16 years) Admitted to PICU Remain within PICU on day 3 post-admission Exclusion: Local decision by PI or treating clinical team not to include patient Parent or guardian chooses to opt-out
Study Centres	14 UK NHS PICUs: 1. Addenbrooke's Cambridge 2. Alder Hey Children's NHS Foundation Trust 3. Birmingham Children's Hospital 4. Evelina London Children's Hospital 5. Freeman Hospital, Newcastle upon Tyne Hospitals NHS Foundation Trust 6. GOSH CICU and GOSH PICU, Great Ormond Street Hospital for Children NHS Foundation Trust 7. Great North Children's Hospital, Newcastle 8. Nottingham Children's Hospital 9. Oxford University Hospitals 10. Royal Hospital for Children Glasgow

	11. Royal Manchester Children's Hospital 12. Southampton Children's Hospital, Southampton General Hospital 13. St Mary's Hospital, Imperial London 14. University Hospital Leicester and Glenfield Hospital, Leicester 15. King's College Hospital NHS Foundation Trust, London 16. Leeds Children's Hospital, Leeds General Infirmary 17. The Royal Hospital for Children and Young People, Edinburgh (RHCYP)
Follow up duration	7 days
Definition of End of study	Final report 24 months after commencement
Planned study period	24 months

Figure 2 PERMIT Observational study flow chart



8.3. List of Abbreviations

CRF: Case report form

CV: Curriculum Vitae

CYP: Children and young persons

DoB: Date of birth

HQIP: Healthcare Quality Improvement Partnership

ICH-GCP: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use – Good Clinical Practice

NICU: Neonatal Intensive Care Unit

PCCMDS: Paediatric critical care minimum dataset – data provided to PICANet

PICANet: Paediatric Intensive Care Audit Network (PICANet)

PICU: Paediatric Intensive Care Unit

PIS: Patient Information Sheet

REC: Regional Ethics Committee

REDCAP: Research Electronic Data Capture

SOP: Standard Operating Procedure

8.4. Trial Rationale

8.4.1. Justification for participant population

Observation of infants and children in PICU who may receive early rehabilitation and mobilisation (ERM) interventions as part of standard care.

8.4.2. Justification for design

Observational study to observe staff performing ERM interventions within PICU will provide real-world data that would inform aspects of the study. The observational approach of this design, combined with the use of routine data will reduce the burden of data collection for PERMIT and minimise the impact on parents and families during a difficult time.

8.5. Aims, Objectives and Outcome Measures

8.5.1. Aims and Objectives

Aims:

- Identify current ERM practice,
- Using routinely collected data, establish the patient population for whom ERM may be feasible.

Objectives:

- Identify & describe current ERM practice in UK PICUs
- Assess the capability of UK PICUs to deliver ERM
- Establish and model how many/which CYP may be suitable for ERM in the PICU population using routinely collected data.

8.6. PERMIT observational study Outcome Measures

8.6.1. Primary outcome

- Prevalence of delivery of ERM on day 3 post PICU admission.

8.6.2. Primary outcome assessment

- The prevalence and scope of ERM will be described as the proportion of patients with any 'active interaction' delivered on day 3 post-admission.

8.6.3. Secondary outcomes

- Prevalence and incidence of ERM delivery between day 3 and day 10 post PICU admission, quantification of ERM delivered per patient, characteristics of patients receiving ERM, type of ERM interventions delivered, and factors associated with variability of delivery between PICUs.

8.6.4. Secondary outcome assessment

- Cumulative prevalence for each day in PICU after day 3, up to day 10 post-admission with whom ERM may/may not be considered appropriate.
- Quantification of dose (duration, measured in minutes) of ERM on each day and characteristics of patients receiving ERM will be presented using standard descriptive statistics.
- Further analysis will be undertaken to understand factors associated with ERM and the incidence of ERM.
    - Multilevel multivariable logistic regression models with random effects for PICU site will be used to evaluate predictors of ERM provided on day 3. Predictors of interest will be established following the Phase 1a survey and expert group consensus (examples include: age, presence of PICU protocol, diagnostic category, sedation level and PIM3 probability of mortality score).
- To calculate incidence rates and incidence rate ratios for number or ERM interventions, accounting for variable length of PICU stay, we will use a multilevel multivariable Poisson Model.

8.7. Study Design and Setting

This is an observational study to ascertain current practice, identifying current ERM practices within the PICU settings and barriers/facilitators to ERM delivery.

We plan to directly observe current ERM practices within UK PICUs, identify patients who do and do not receive ERM, describe variation between PICUs and factors associated with ERM practices.

Following the observation of current ERM delivery and identification of patients who may benefit from ERM in selected PICs, we will use this information to model how many patients may be available in the UK for a potential future RCT. This will be achieved by comparing and modelling the patient demographic information with the existing full PICANet dataset.

8.8. Target population/setting:

8.8.1.Inclusion:

- All Children and Young Persons (CYP) (0-<16 years)
- Admitted to PICU
- Remain within PICU on day 3 post-admission

8.8.2.Exclusion:

- Local decision by PI or treating clinical team not to include patient
- Parents or guardians choose to opt-out.

The broad inclusion criteria will allow observation of all types of patients admitted for PICU care (acute and elective e.g. post-surgical recovery) and all age ranges without the requirement for 48hrs ventilatory. (23)

8.8.3.Sampling of sites

We will purposely select 14 UK PICUs of three varying sizes (n=6 large: >800 admissions/year, n=5 medium: 500-800 admissions/year, n=3 small: <500 admissions/year) with varying activity level of ERM practice (e.g. high, low users) identified from PERMIT survey responses.

8.8.4.Patient identification and screening

Local sites will screen all current patients daily at 09:00 within their PICU for eligibility to participate in PERMIT study over a 14 day observation period. When patients become eligible then case report forms (CRF) will be completed for each patient and each active ERM interaction performed. (See data collection)

8.8.5.Recruitment/enrolment:

All eligible patients will be included in PERMIT observational study unless parents/guardians choose to opt-out of data sharing (see consent).

8.8.6.Strategies to maximise recruitment

Daily screening by local research staff of patients will identify eligible patients and patients becoming eligible the following day. Each participating site will have a designated research co-ordinator to identify patients and collect data on delivered ERM activities by clinical staff.

8.9. Outcomes

8.9.1. Primary outcome:

- The prevalence and scope of ERM will be described as the proportion of patients with any 'active interaction' provided on day 3 post-admission.

8.9.2. Secondary outcomes:

- Cumulative prevalence for each day in PICU after day 3, up to day 10 post-admission will be calculated.
- Quantification of doses of ERM on each day and characteristics of patients receiving ERM will be presented using standard descriptive statistics.
- Further analysis will be undertaken to understand factors associated with ERM and the incidence of ERM.
    - Multilevel multivariable logistic regression models with random effects for PICU site will be used to evaluate predictors of ERM provided on day 3. Predictors of interest will be decided by expert group consensus (examples include: age, presence of PICU protocol, diagnostic category, sedation level and PIM3 probability of mortality score).
- To calculate incidence rates and incidence rate ratios for number or ERM interventions, accounting for variable length of PICU stay, we will use a multilevel multivariable Poisson Model.

8.10. Data collection

To maximise efficiency and ensure we can estimate point prevalence, all study sites will recruit and collect data over the same 21 day observation period (either in November 2019 or January 2020). Patients will be recruited through the first two weeks of the PERMIT study period (e.g. study day 1 to 14) with a further week to complete follow up (study day 15-21). Individual patient data collection and observations will occur for up to 7 days after patients are eligible and recruited or until PICU discharge, whichever is sooner (e.g. data collection commenced day 3 post-admission and continued up to day 10 post-admission).

8.10.1. Unit level data

Data will be collected on each study day (1-21) at a unit level to record the following

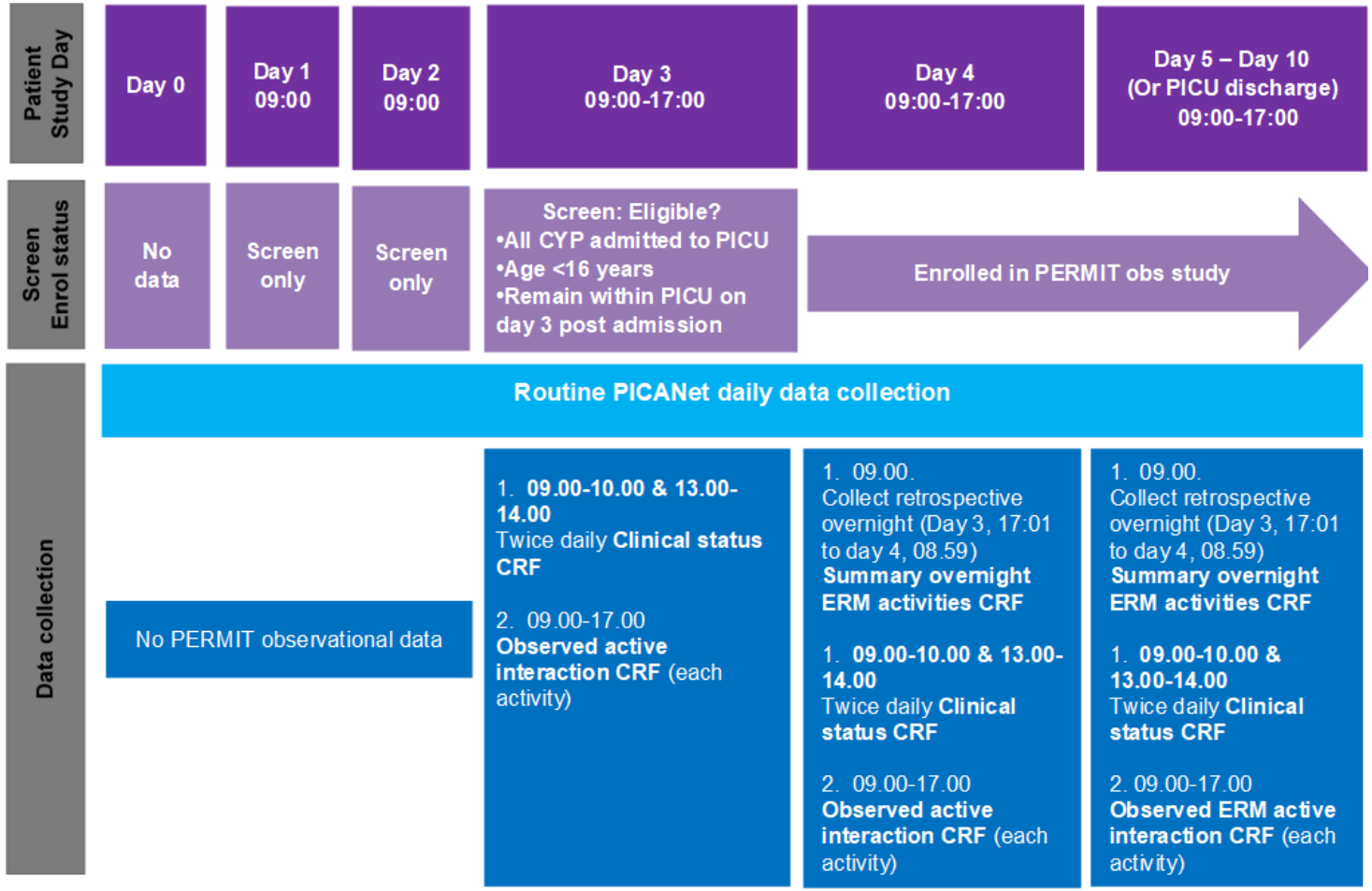
- Number of staff available in PICU (divided by grade and speciality) at 09:00.
- Census of the number of patients in the PICU at 09:00.
- Number of beds open to admissions at 09:00.
- Nursing number to patient ratio at 09:00.

8.10.2. Patient-level data

Two categories of patient-level data will be collected.

1) Routine PICANet data which include the PCCMDS (Paediatric critical care minimum data set).
2) PERMIT study observational data (new data).

Figure 3: Screening and data collection schema for individual patients



Day 0 = day of admission. Day 1 = 1st day at 9.00. CRF = Case Report Form. PICANet = Paediatric Intensive Care Audit Network

8.10.3. PICANET routinely collected data

Participating sites already collect PICANet defined data items and submit to PICANet web. For patients included in the PERMIT study, local sites will collate the PICANet data already collected for that patient and combine this data with the PERMIT observational data below. This data will be pseudo-anonymised at the local site prior to secure transfer to the PERMIT trials office.

Currently, all patients admitted to PICU have data recorded via the Paediatric Intensive Care Audit Network (PICANet). PICANet has permission to collect patient identifiable data under section 251 of the NHS Act 2006 (originally enacted under Section 60 of the Health and Social Care Act 2001). We will use the PICANet data to supplement and reduce the burden of data collection for PERMIT. Patient characteristics (e.g. reason for admission, severity of illness score (e.g. PIM3 (43)), critical care interventions) and individual patient PIC resource use (mechanical ventilation days, renal replacement therapy, vasoactive drug use). A full list of data items and data definitions can be found at www.picanet.org.uk/documentation.

8.10.4. PERMIT observational study patient level data

Figure 3: Screening and data collection schema for individual patients displays the daily planned data collection for individual patients.

From Day 3 of PICU admission onwards, until the patient is discharged from PICU (or day 10 of admission, whichever is sooner), patient-level data will be collected for the PERMIT study.

1) Clinical status

This will include health care interventions, ventilator requirement, sedation and coma level, presence of delirium, inotropic support and neuromuscular blocking drug usage. This data will supplement routinely collected PICANet data. Data will be collected twice, between 09:00 and 10:00 and between 14:00 and 15:00 each day.

2) Observed ERM active interaction

We will undertake a behavioural mapping procedure (44) to capture ‘active interaction’ versus ‘no interaction’ with a patient in a therapeutic rehabilitation context after local researcher training, and piloting of observation case report form. Frequency, quantity, and type of ‘active interaction’ of ERM delivered by physiotherapy, occupational therapy, speech & language, play, psychology, nurse and parent will be recorded.

Clinical staff performing the activity will be instructed to record planned activity and delivered activity duration in medical records. A research nurse will use this data to complete active interaction CRF.

CRFs will be collated hourly between 9 am and 5 pm by the local site research nurse. ‘Active ERM interaction/interventions’ will be defined using the PERMIT logic model (**Error! Reference source not found.**) and based on paediatric modification of published ICU mobility scales. (45)

With the addition of free-text for any activity performed outside of the standardized mobility scales.

This data will be recorded on the “Observed ERM active interaction” CRF.

3) Summary of overnight ERM activities

Daily at 09:00 researchers will retrospectively review the clinical case records to record any ERM activities that occurred overnight. Overnight is defined as the time from the end of Observed active interaction period 17:01, until 08:59 prior to the start of the next Observed active interaction period.

This data will be recorded on the *Summary of overnight ERM activities* CRF.

8.11. Sample Size

We aim for a sample size of n=150 CYP. Accepting our hypothesis that there is wide variability in the current prevalence of ERM delivery across PICUs (e.g. 20%-80%: (reference: personal communication with Glasgow, Nottingham, Birmingham, Southampton PIC clinicians) we anticipate identifying any ERM use in 75/150 patients (prevalence of 50%). With 150 participants a confidence interval with a width of 8% either side of the estimate (41.7%-58.3) can be produced. This degree of accuracy is adequate for our purposes.

8.12. Future RCT Sample Size Modelling:

Using the primary outcome of the prevalence of ERM, PICU and patients characteristics, we will subsequently use the UK PICANet database to identify and count potential trial population sample size using national anonymised data for all UK and Irish PICUs. Anonymised PICANet data has been used efficiently for previous NIHR HTA funded PIC RCTs (FEVER study: HTA 15/44/01*, CHiP study:* HTA 05/506/03). Using PICANet admission data, on average 20,000 patients are admitted per year across 28 PICUs (averaging 2 patients/unit/day). Of these 40-45% of patients stay on PICU for ≥3 days (20% > 7 days), on average 5.5 to 6 patients/unit/week will be eligible. Enrolling patients admitted over a 14-day recruitment window in 14 units, 150 patients will be included (average n=11 patients/PICU/14 days). (1)

8.13. Consent

As the study is purely observational, it will not affect the treatment the children receive, we propose to conduct the PERMIT observational study without seeking consent from parents/legal representatives.

This is to avoid any unnecessary burden for parents/legal guardians in approaching consent during a very sensitive time. Information about the study will be provided to all eligible patients and displayed with public areas of participating PICUs. This will explain the study to parents, family and friends and children who are able to make autonomous decisions. Parents/legal guardians may opt the child's data out of the study at any time and that the future care their child will receive will not be affected. We will also mention that no identifiable data for the PERMIT observational study will be collected.

This procedure has been acceptably used by the FEVER observational study (REC 17/NW/0026), an observational study of critically ill children's exposure and management to fever within UK PICUs, where posters and information leaflets explaining the study were available to family and friends explaining their rights to withdraw from the study at any time.

8.14. PICANET Modelling

Following the collection of PERMIT observational study data, we use the identified key patient characteristics for patients who may benefit from ERM and model the number for patients available in the UK for a future RCT by analysing the full PICANet dataset.

PICANet has ethical approval granted by the Trent Medical Research Ethics Committee (ref 05/MRE04/17) and the National Information Governance Board (NIGB) to collect personally identifiable data without consent. All PICANet data used within the PERMIT study will be anonymised prior to sharing from the local sites to the PERMIT trials office. Also, any PICANet data used to model future RCT feasibility will also be anonymised. (1)

8.15. Study procedures and assessments

8.15.1. Summary of assessments

Figure 4 Schedule of assessments for each PICU

TIMEPOINT	*Study Day 1*	*Study Day 2-14*	*Study Day 15-21*
ENROLMENT:			
Eligibility screening (daily)	X	X	
Enrolment to PERMIT (daily)	X	X	
ASSESSMENTS:			
Complete Unit staff and patient census (daily)		X	X
Patient-level: Clinical Status CRF. Twice daily		XX	XX
Patient-level: Observed ERM active interaction CRF (for each active interaction)		X	X
Patient-level: Summary of overnight ERM activity CRF		X	X
Ensure completion of PICANet routine data	X	X	X

Study day 1 = **First day** on the week of trial starting

Study day 2 = **Second day** on the week of trial starting

Study day 14 = **Final day** of enrolment of eligible patients

Study day 15-21 = Completion of up to 7 days of data collection for enrolled patients. No new patient enrolled during this period.

Figure 5 Schedule of assessments for individual patients

TIMEPOINT	*Patient Day 2 (09:00)*	*Patient Day 3 (09:00-17:00)*	*Patient Day 4-10 (09:00-17:00)**
ENROLMENT:			
Eligibility screen	X		
Enrolment to PERMIT		X	
ASSESSMENTS:			
Patient level: Clinical Status CRF. Twice daily		XX	XX
Patient-level: Observed ERM active interaction CRF (for each active interaction)		X	X
Patient-level: Summary of overnight ERM activity CRF		X	X
Ensure complete PICANet routine data has been collected	X	X	X

Patient Day 0 = the day a patient is admitted to PICU which occurs after 09:01 and before 08:59 of the same day.

Patient Day 1 = the 1st day the patient has been in PICU at exactly 09:00. (A patient may have been admitted 10mins prior, or 23 hours prior; however, the census count is that the patient is in PICU at exactly 09:00 on the study day).

Patient Day 2 = the 2nd day the patient has been in PICU at 09:00.

Patient Day 3 = the 3rd day the patient has been in PICU at 09:00 (this is the day that ERM activities will be observed from).

Patient Day 10 is the 10th day the patient has been in PICU at 09:00 (this is the end of the 7 complete days of data collection).

*****Data collection stops earlier than Day 10 if the patient is discharged from PICU/HDU care area which is managed by critical care staff who submit PICANet/PCCMDS data.

8.16. Schedule of Assessments

Figure 4 & Figure 5 summarise the schedule of assessments.

8.16.1. Clinical status

Data will be collected twice, between 09:00 and 10:00 and between 14:00 and 15:00 each day.

8.16.2. Observed ERM active interaction

CRFs will be collated hourly between 9 am and 5 pm by the local site research nurse.

8.16.3. Summary of overnight ERM activities

Daily at 09:00 researchers will retrospectively review the clinical case records to record any ERM activities that occurred overnight. Overnight is defined as the time from the end of Observed active interaction period 17:01, until 08:59 prior to the start of the next Observed active interaction period.

8.16.4. Complete PICANET routine data

Local sites will have existing PICANet routine data collection systems in place. PICANet collected admission data on all patients within 1 hour of PICU admission. PCCMDS data is collected twice a day summarising activities and interventions within each shift. Further details available in PICANet data collection manual https://www.picanet.org.uk/data-collection/data-manuals-and-guidance/

8.17. Adverse Event Reporting

8.17.1. Reporting Requirements

Due to the fact that there is no interventional element to the PERMIT Observational Study no additional adverse event reporting will be required. We will record any unexpected clinical events that occur during the delivery of ERM activities.

8.17.2. Source Data

In order to allow for the accurate reconstruction of the study and clinical management of the subject, source data will be accessible and maintained.

Some data may be entered directly onto the paper-based CRF prior to data entry into the REDCAP database.

The participants' medical notes generated and maintained at the site will act as source data.

8.17.3. Screening CRF Completion

Data reported on each CRF will be consistent with the source data and any discrepancies will be explained. Staff delegated to complete CRFs will be trained to adhere to:

- *Date format and partial dates*
- *Study-specific interpretation of data fields*
- *Which forms to complete and when*
- *What to do in certain scenarios, for example when a parents/guardians opt-out of data sharing from the study*
- *Missing/incomplete data*
- *Protocol and ICH-GCP non-compliances*

In all cases, it remains the responsibility of the local site's Principal Investigator to ensure that the CRF has been completed correctly and that the data are accurate. Where applicable for the study this will be evidenced by the signature of the local site's Principal Investigator

8.18. Data Handling and Record Keeping

8.18.1. Data Management

Data Management

Figure 6 PERMIT study dataflow

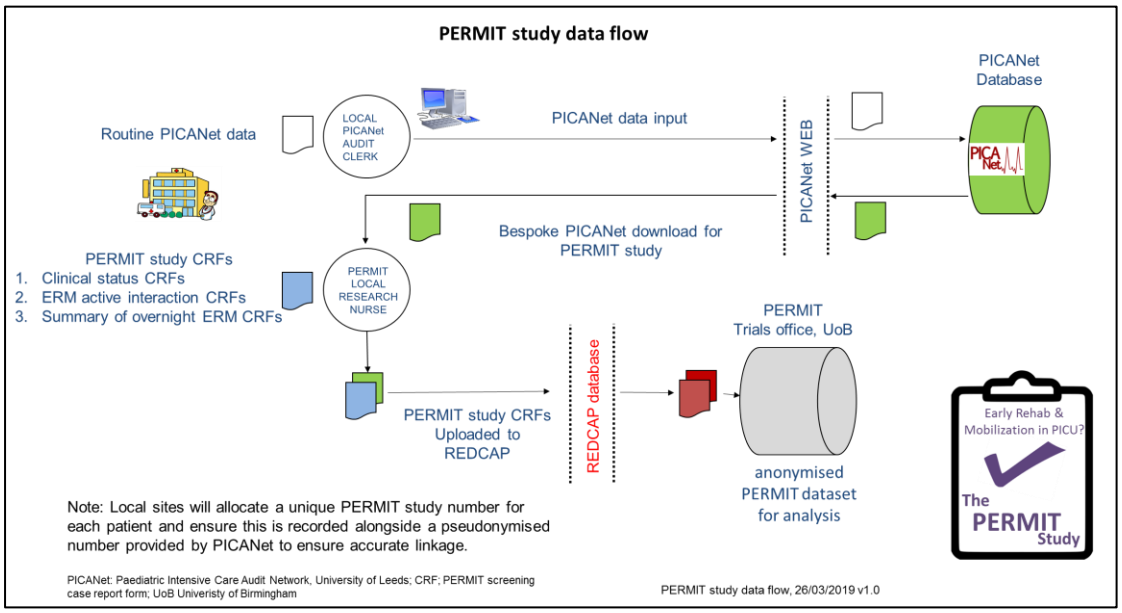


Figure 6 summarises PERMIT study data flow.

Participating sites will screen all eligible patients for PERMIT study. A screening log will be created at each site by the local research team and this will record local patient IDs [NHS number and own hospital Patient Identification number].

For patients that fulfil all inclusion criteria and no exclusion criteria: local research staff will record in the enrolment log 1) a unique PERMIT study ID [local site code + sequential numbered patient; provided by the Trials Office], local patient IDs [NHS number and own hospital Patient Identification number] and PICANet study ID [provided by PICANet] of all enrolled patients.

Local sites will complete CRFs for all enrolled patients using the PERMIT study ID on each record. CRFs will be paper-based initially to aid bedside data collection. At the end of each study day, paper CRFs will be collated and stored in patient-specific site files. Local sites will be responsible for the safe and secure storage of these primary documents (locked in a filing cabinet or office within the PICUs or research offices).

Local sites will input data from the paper-based CRF data onto REDCAP computer database using the PERMIT study ID for patient identification only. No Identifiable patient data will be uploaded to REDCAP or shared with the PERMIT trials office.

Local sites will then access PICANet data via a customised download from the PICANet database using the PERMIT study ID. No patient identifiable data will be included in this customised download

(DoB which will be converted into age in days). The PICANet data download will be uploaded to the REDCAP database to combine with the PERMIT study CRF data.

The PERMIT study trials Office team will only access the anonymised data in the REDCAP database.

Data contained within REDCAP will be transferred securely to the University of Birmingham computer server within the PERMIT study database for statistical analysis and prognostic modelling.

8.18.2. Archiving

At the end of the study, the Chief Investigator will archive securely all centrally-held study-related documents for a minimum of ten years in accordance with ICH-GCP guidelines.

It will be the responsibility of the Principal Investigators at each site to ensure all essential study documentation and source documents (e.g. Investigator Site Files, copies of CRFs, etc.) at their sites are securely retained for at least 10 years.

Guidance on archiving will be provided in the study-specific Standard Operating Procedure (SOP). All archived documents, held centrally and locally, should be available for inspection by appropriate authorities upon request.

8.19. Site Set-up and Initiation

All participating Principal Investigators will be asked to sign the necessary agreements and supply a current CV to the PERMIT Trials Office. All members of the site research team will also be required to sign a site signature delegation log. Before commencing recruitment all sites will undergo a process of initiation and will have completed ICH-GCP training. Key members of the site research team will be required to attend either a meeting or a teleconference covering aspects of the study design, protocol procedures, collection, and reporting of data and record keeping. Sites will be provided with an electronic copy of the Investigator Site File (for local printing on-site) containing essential documentation, instructions, and other documentation required for the conduct of the study. The PERMIT Trials Office must be informed immediately of any change in the site research team.

8.20. Monitoring

8.20.1. On-site Monitoring

Monitoring will be carried out as required following a risk assessment and as documented in the monitoring plan. Any monitoring activities will be reported to the PERMIT Trials Office and any issues noted will be followed up to resolution. Additional on-site monitoring visits may be triggered, for example by poor CRF return, poor data quality, an excessive number of participant withdrawals or deviations. If a monitoring visit is required the PERMIT Trials Office will contact the site to arrange a date for the proposed visit and will provide the site with written confirmation. Investigators will allow the PERMIT study staff access to source documents as requested.

8.20.2. Central Monitoring

The PERMIT Trials Office will be in regular contact with the site research team and PICANet to check on progress and address any queries that they may have. The PERMIT Trials Office will check incoming summary of screened cases and Case Report Forms for compliance with the protocol, data consistency, missing data, and timing. Sites will be asked for missing data or clarification of inconsistencies or discrepancies. Sites will be requested to send in copies of signed Opt-out Forms and other documentation for in-house review. This will be detailed in the monitoring plan.

8.21. Audit and Inspection

The Principal Investigator will permit study-related monitoring, quality checks, audits, ethical reviews, and regulatory inspection(s) at their site, providing direct access to source data/documents. The Principal Investigator will comply with these visits and any required follow up. Sites are also requested to notify the PERMIT Trials Office of any inspections.

8.22. Notification of Serious Breaches

The sponsor is responsible for notifying the REC of any serious breach of the conditions and principles of ICH-GCP in connection with that study or the protocol relating to that study. Sites are therefore requested to notify the PERMIT Trials Office of any suspected study-related serious breach of ICH-GCP and/or the study protocol. Where the PERMIT Trials Office is investigating whether or not a serious breach has occurred sites are also requested to cooperate with the Trials Office in providing sufficient information to report the breach to the REC where required and in undertaking any corrective and/or preventive action.

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or ICH-GCP, and/or poor recruitment. Any major problems identified during monitoring may be reported to the PERMIT Trial Management Group and the REC. This includes reporting serious breaches of ICH-GCP and/or the study protocol to the REC. A copy is sent to the University of Birmingham Clinical Research Compliance Team at the time of reporting to the REC.

8.23. End of Study Definition

The end of the study will be after the three-month follow-up point of the last recruited participant plus an additional 6 months of data cleaning, queries, and analysis period. The PERMIT Trials Office will notify the REC the study has ended and a summary of the clinical trial report will be provided within 12 months of the end of the study.

A copy of the end of study notification, as well as the summary report, is also sent to the University of Birmingham Research Governance Team at the time of sending these to the REC.

8.24. Statistical Considerations

8.24.1. Analysis of Outcome Measures

The prevalence and scope of ERM will be described as the proportion of patients provided with any 'active interaction' on day 3 post-admission. Cumulative prevalence for each day in PICU after day 3, up to day 10 post-admission will be calculated. Quantification of doses of ERM on each day and characteristics of patients receiving ERM will be presented using standard descriptive statistics. Further analysis will be undertaken to understand factors associated with ERM and the incidence of ERM. Multilevel multivariable logistic regression models with random effects for PICU site will be used to evaluate predictors of ERM provided on day 3. Predictors of interest will be established following PERMIT survey and expert group consensus (examples include: age, presence of PICU protocol, diagnostic category, sedation level and PIM3 probability of mortality score). To calculate incidence rates and incidence rate ratios for number or ERM interventions, accounting for variable length of PICU stay, we will use a multilevel multivariable Poisson Model.

Using the primary outcome of the prevalence of ERM, PICU and patients characteristics, we will subsequently use the UK PICANet database to identify and count potential trial population sample size using national anonymised data for all UK and Irish PICUs.

8.25. Trial Organisational Structure

8.25.1. Sponsor

University of Birmingham (see Administrative information page 5)

8.25.2. Trial Management Group

All day-to-day management of the PERMIT Study will be the responsibility of the Trial Management Group (TMG). Members of the TMG will include the PERMIT Chief Investigator, co-applicants, research fellows and project manager. The TMG will meet regularly to discuss the management and progress of the study and findings from other related research. There will be close contact throughout the study with the PICANet trials group.

8.25.3. Project oversight committee/Trial steering committee

An independent trial oversight committee has been appointed by the NIHR in keeping with standard structure and definitions.

Title	First name	Last name	Job Title	Expertise
Dr	Shane	Tibby	Consultant in PICU	Chair, Clinician, Trialist
Prof	Mark	Peters	Professor of Paediatric Intensive Care	Clinician, Trialist
Dr	Kerry	Woolfall	Senior Lecturer Health Services Research	Qualitative Researcher
Ms	Suzanne	Dottin-Payne	Parent representative	PPI representative
Prof	Jim	Lewsey	Professor of Medical Statistics	Statistician

8.25.4. Finance

This is a commissioned study funded by NIHR Health Technology Assessment (HTA) (*NIHR HTA*-17/21/06). It will be eligible for (NIHR CRN) Portfolio adoption. Funding will be provided for local R&D setup, site-specific training, eligibility screening, and CRF completion.

8.26. Ethical Considerations

The study will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, June 1964, amended at the 48th World Medical Association

General Assembly, Somerset West, Republic of South Africa, October 1996 (website: http://www.wma.net/en/30publications/10policies/b3/index.html).

The study will be conducted in accordance with the Research Governance Framework for Health and Social Care, the applicable UK Statutory Instruments, (which include the Medicines for Human Use Clinical Trials 2004 and subsequent amendments and the Data Protection Act 2018 and Guidelines for Good Clinical Practice (ICH-GCP). The protocol will be submitted to and approved by the REC prior to circulation.

Before any participants are enrolled in the study, the Principal Investigator at each site is required to obtain local R&D approval. Sites will not be permitted to enrol participants until written confirmation of R&D approval is received by the Principal Investigator.

For any amendment to the study, the Chief Investigator or designee, in agreement with the sponsor will submit information to the appropriate body in order for them to issue approval for the amendment. The Chief Investigator or designee will work with sites (R&D departments at NHS sites as well as the study delivery team) so they can put the necessary arrangements in place to implement the amendment to confirm their support for the study as amended.

It is the responsibility of the Principal Investigator to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual participants.

PIC admission is known to be stressful for parents (30), with logistical challenges for parents' participation in terms of caring for their child, other children, and travel. PERMIT co-applicants have extensive experience of researching families in PICU, acknowledging these challenges (46, 47).

CYP should be involved in decision making about research (48). This is challenging in PICU when CYP are critically unwell. Following a PICU admission, participation may be challenging for some CYP experiencing residual neurological and cognitive difficulties.

PERMIT is addressing these by:

1) Working with CYP and parent PPI, to ensure the work is designed sensitively and full risk/benefit assessment is conducted.

2) Adopting an inclusive approach, recognising CYP right to self-determination. Accessibility will be facilitated through attention to the language and format of study materials.

4) Adopting methods to accommodate participants' preferences and facilitate involvement.

In order to design clinical trials to investigate the potential benefits of ERM in critically ill children, it is crucial to understand current utilisation and potential feasibility in a UK context. PERMIT will generate much-needed knowledge for future multi-centre interventional trials to test the effectiveness of ERM on short and long-term outcomes in children as well as healthcare utilisation. Therefore this research is important as it will contribute to establishing the health benefits of ERM in critically ill children and impact on services and NHS resources.

The PERMIT study has been conceived, designed and developed by experts in paediatric intensive care, health services research and clinical trials and has been reviewed and approved by independent reviewers on behalf of the funders (National Institute for Health Research (NIHR) Health technology award (HTA) programme). The PERMIT study team includes academics, clinicians, as well as patients, carers and parent involvement and engagement members who have and will inform all aspects of the project design, conduct, and outputs. The study management group will meet regularly to review the progress of the study against timelines and milestones.

8.26.1. Recruitment

There will be no specific recruitment in the PERMIT observational study. Additional data on the use of ERM and potential eligibility into a future RCT of an ERM intervention will be collected alongside routinely collected standard audit data.

8.26.2. Consent

As the study is purely observational, it will not affect the treatment the children receive, we propose to conduct the PERMIT observational study without seeking consent from parents/legal representatives.

This is to avoid any unnecessary burden for parents/legal guardians in approaching consent during a very sensitive time. Information about the study will be provided to all eligible patients and displayed within public areas of participating PICUs. This will explain the study to parents, family and friends and children who are able to make autonomous decisions. Parents/legal guardians may opt the child's data out of the study at any time and that the future care their child will receive will not be affected. We will also mention that no identifiable data for the PERMIT observational study will be collected.

This procedure has been acceptably used by the FEVER observational study (REC 17/NW/0026), an observational study of critically ill children's exposure and management to fever within UK PICUs, where posters and information leaflets explaining the study were available to family and friends explaining their rights to withdraw from the study at any time.

8.26.3. Risk, burdens, and benefits

The PERMIT study is purely observational and will not affect any patient's treatment; however, parents / legal representatives will have the opportunity to withdraw the patient from the study at any time. All data collected before patients opt-out would be used only for study purposes and stored securely in accordance with Data Protection guidelines. This process will be known to them through leaflets and posters that will be accessible on the PICU written in a clear and understandable language. No identifiable information will be accessed directly for the study. It is often the case that those involved in the decision to participate in studies would like to see their data used to improve the care they and other patients are given.

8.26.4. Confidentiality and data protection

No patient identifiable data will be collected or transferred to the PERMIT trials office for the PERMIT observational study. Anonymised data will be stored securely in REDCAP database or nested within the PICANet database. Currently, all patients admitted to PICU have data recorded via the Paediatric Intensive Care Audit Network (PICANet). PICANet has permission to collect patient identifiable data under section 251 of the NHS Act 2006 (originally enacted under Section 60 of the Health and Social Care Act 2001). We will use the PICANet data to supplement and reduce the burden of data collection for PERMIT. However, no identifiable patient data will be collected or used for the PERMIT observational study. As PICANet is part of the Health Quality Improvement Partnership (HQIP), therefore we intend to make a release of data request, and a customised data collection request to HQIP in order to gain access to unidentifiable routine PICANet data and collect the additional data required for this study.

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the General Data Protection Regulation and Data Protection Act 2018.

Participants will always be identified using only their unique study identification number, on the Case Report Form and correspondence between the Trials Office and the participating site. Participants will give their explicit consent for the movement of their Opt-out form, giving permission for the Trials Office to be sent a copy. This will also be used to perform in-house monitoring of the consent process.

The Investigator must maintain documents, not for submission to the Trials Office (e.g. Participant Identification Logs) in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete study records, provided that participant confidentiality is protected.

The Trials Office will maintain the confidentiality of all participants' data and will not disclose information by which participants may be identified to any third party. Representatives of the PERMIT Study Trial Office and sponsor may be required to have access to participant's notes for quality assurance purposes but participants should be reassured that their confidentiality will be respected at all times.

The Chief Investigator will act as the data custodian for the PERMIT observational study.

8.26.5. Conflicts of interest

None.

8.27. Ethical Approval

Formal ethical approval was obtained on 2/9/2019 from the East of Scotland Research Ethics Service, REC Reference: 19/ES/0102, IRAS Project ID: 263127

8.28. Insurance and Indemnity

The University of Birmingham has in place Clinical Trials indemnity coverage for this study which provides cover to the University for harm which comes about through the University's, or its staff's, negligence in relation to the design or management of the study and may alternatively, and at the University's discretion provide cover for non-negligent harm to participants.

With respect to the conduct of the study at Site and other clinical care of the patient, responsibility for the care of the patients remains with the NHS organisation responsible for the Clinical Site and is therefore indemnified through the NHS Litigation Authority.

The University of Birmingham is independent of any pharmaceutical company, and as such, it is not covered by the Association of the British Pharmaceutical Industry (ABPI) guidelines for participant compensation.

8.29. Publication Policy

The results of this study will be submitted for publication in a peer-reviewed journal. The manuscript will be prepared by Dr. Scholefield and authorship will be determined by mutual agreement. All site Investigators actively participating in the study will be invited to co-author the manuscript and fulfil authorship eligibility as per international guidelines.

Any secondary publications and presentations prepared by Investigators must be reviewed by Dr. Scholefield. Submission must not occur prior to the publication of the primary manuscript. Manuscripts must be submitted to Dr. Scholefield in a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues. The authors must acknowledge that the study was performed with the support of the NIHR and the University of Birmingham.

8.30. Abbreviations and Definitions

Term	Description
CRF	Case report form
ERM	Early rehabilitation and Mobilisation
PICANet	Paediatric Intensive Care Audit Network (PICANet)
PICU	Paediatric Intensive Care Unit
PIM	Paediatric Index of Mortality
PIS	Patient Information sheet
Screening Log	Local site screening log of all PICU admission, identifying patients fulfilling eligibility criteria for PERMIT observational study.
Source data	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial
The Trials Office	The team of people, including the Chief Investigator, responsible for the overall management and coordination of the trial. This will be located in the Public Health Building, University of Birmingham.
Trials management group	The Trial Management Group includes those individuals responsible for the day-to-day management of the trial, such as the Chief Investigator, statistician, project manager, research fellow, and co-applicants. The role of the group is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself.
Project oversight committee	The project oversight committee includes those who oversee the process of assuring the quality of the project management and delivery to reduce risk and improve outcomes.

PHASE 1c PROTOCOL: Review

9.PHASE 1c: Systematic Review /Scoping Review

9.1. Introduction

We plan to conduct a scoping review to summarise the evidence for early rehabilitation and mobilisation (ERM) within paediatric intensive care units (ICU). We aim to answer questions regarding commonalities and disparities in paediatric versus adult ICU research.

9.2. Objectives

Our primary outcome of interest is to summarise the type of ERM intervention delivered to patients admitted to Paediatric ICUs, findings of effectiveness and identify gaps in the literature. Secondary outcomes included clinical, functional and psychosocial measures, patient-reported outcome measures (PROMs) of quality of life, adverse events, resource use and cost-effectiveness. The quality of the empirical conclusions will be evaluated to inform guidance on ERM. Where possible, we meaningfully considered the what, why, how as well as barriers of implementing ERM within paediatric ICU.

9.2.1.Review question

(1) What is the efficacy of early mobilization and rehabilitation (ERM) interventions in Paediatric intensive care unit (ICU)?

(2) What outcomes demonstrate a dose-response relationship within Paediatric ICU compared to adult ICU?

(3) What are the gaps in the evidence base for rehabilitation packages used in clinical practice versus interventions evaluated in research studies?

9.3. Methods

Design

The review protocol was registered on PROSPERO international prospective register of systematic reviews, registration ID: CRD42019151050, available via https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019151050 and reported using Preferred Reporting Items for Systematic Reviews and Meta-Analyses: Extension for Scoping Reviews (PRISMA-ScR) guidelines. A study author (JT) developed a search strategy, using search terms of Paediatric Intensive Care and early rehabilitation and mobilisation, combined to identify suitable records. Details of the search strategy have been provided in Appendix 1. No language, duration or publication type restrictions were applied.

We performed a systematic search of relevant medical databases (CENTRAL, CINAHL, EMBASE, MEDLINE, PEDro) from inception until the 13th of December 2019. We will also search websites: US National Institutes of Health Clinicaltrials.gov, the mobilisation-network-org http://www.mobilization-network.org/Network/Welcome.html, HTA, Database of Abstracts of Reviews of Effects (DARE) and the NHS Economic Evaluation Database (NHS EED), and the Grey literature via Open Grey databases for records of eligible studies.

9.3.1. Types of study to be included

All studies designs that include infants, children, and young people will be eligible for inclusion. Mixed-study designs will be included provided qualitative and qualitative data are presented separately. Studies that only include patients recruited during secondary or community-care or after ICU discharge or during out-patient care will be excluded. Corresponding authors of eligible studies will be contacted for details of missing study information or data.

9.3.2. Condition or domain being studied

This review will evaluate all outcomes of ERM delivered among critically ill Paediatric patients.

9.4. Participants/population

9.4.1. Inclusion criteria

Critically ill Paediatric ICU patients (infants, children and young people), 18 years of age or younger, who received early mobilisation or physical rehabilitation including but was not limited to physiotherapy or occupational therapy (within the first week of admission, ideally ≤ 3days) delivered by any health professional or ICU personnel with or without any comparisons or none were included.

Studies were included if they were: (1) original primary research (randomized controlled trials (RCTs), prospective cohort studies, case studies, and retrospective study designs); (3) published in English language. We included surveys and qualitative reports of ERM practice in PICU to enumerate barriers. Systematic reviews were retrieved to perform hand searching of eligible references but were not counted as original records.

9.4.2. Exclusion criteria

Non-English reports and studies with interventions that commenced outside ICU. We excluded incomplete reports from clinical trial registries, were not included in this review.

9.4.3. Intervention(s), exposure(s)

The exposure of interest in this study will be early mobilization and rehabilitation (ERM).

9.4.4. Comparator(s)/control

Studies that include infants, children and young people receiving early mobilization and rehabilitation (ERM) interventions will be compared those not receiving ERM. This will

include all conditions (acute or chronic) during ICU admission. However, in addition, we will include studies that evaluate ERM without a comparator group such as cross-sectional studies, case reports or case series.

9.4.5.Main outcome(s)

To determine the effectiveness of ERM within Paediatric ICU

* Measures of effect

Not applicable. No restriction will be placed on the effect measures included in this study.

9.4.6.Additional outcome(s)

The secondary outcomes of this study will include measures of physical, functional, psychosocial measures. Outcomes of quality of life, adverse events, resource use, and cost-effectiveness will be considered. In addition, we will include studies that evaluate other patient-reported outcome measures (PROMs) and measures of survival.

A summary of interventions effectiveness within ICU will be produced and the feasibility of ERM delivery will also be considered. No restrictions will be placed on how this outcome is defined or measured.

9.4.7.Data extraction (selection and coding)

Studies included in the review will be identified using medical databases and stored in a software - EndNote. The eligibility of studies will be screened at title and abstract to identify relevant records. Studies deemed irrelevant will be excluded. Potentially eligible studies will be evaluated at full-text and ineligible studies will be excluded. Records will be screened by two independent reviewers. Data extraction will be completed using a standardized and piloted data extraction form prepared in excel. This will cover study design, population, intervention and outcome characteristics. Discrepancies at each stage will be resolved by an arbitrator.

9.4.8.Data extraction and quality appraisal

Two reviewers (JT and BS) independently screened the records identified at title and abstract using the study eligibility criteria. Discrepancies were resolved by using a consensus meeting. One reviewer (JT) screened potentially eligible studies for inclusion at full text, and ineligible studies were excluded. We extracted key information on the characteristics of the study, participants, intervention and outcomes. Data extraction was completed using a standardised and piloted data extraction form prepared using excel. The methodological quality of studies was assessed by one reviewer (JT) and independently verified by co-authors (OC, JM, BS). We extracted information on the following domains:

- Study characteristics – PICU setting, i.e. size, severity of illness, comorbidity
- Patient demographics – age, sex, admission diagnosis
- Study design – sample size, intervention, and outcomes (clinical and process)
- Intervention details – intervention types; volume, time-to-initiation, duration, number of mobilisation / rehabilitation sessions, and implementation strategies

The methodological quality of outcomes measures used within PICU research will be assessed by one reviewer and checked by a second. We will supplement results with evidence from qualitative and quantitative reviews conducted critically ill among adults.

9.4.9.Risk of bias (quality) assessment

The Cochrane Risk of bias tool for randomised controlled trials (v2.0) and Risk Of Bias In Non-Randomized Studies - of Interventions (ROBINS-I) will be used to assess the quality of included studies.

9.4.10. Strategy for data synthesis

Results of this systematic review will be narratively synthesized. We anticipate significant heterogeneity across studies, hence data from included studies will not be pooled for meta-analysis. If possible, the results of this review will be grouped into themes and qualitatively described. Thematic analysis will be considered to generate new concepts. Recommendations for future research will be based on the quality of the findings and the overall quality of the evidence.

9.4.11. Analysis of subgroups or subsets

Subgroup analysis based on outcomes reported among infants, children, and young people will be considered. If possible, we will make comparisons between Paediatric and adult populations (identified via scoping reviews) based on interventions and outcomes.

9.4.12. Type and method of review

Intervention, Narrative synthesis, Systematic review

9.4.13. Anticipated or actual start date

01 September 2019

9.4.14. Anticipated completion date

03 February 2020

9.4.15. Funding sources/sponsors

The National Institute of Health Research Health Technology Assessment is acknowledged NIHR HTA. Grant reference: 17/21/06

PHASE 2a PROTOCOL: Workshops

10. PHASE 2a: WORKSHOPS & INTERVIEWS WITH PARENTS, CHILDREN AND YOUNG PEOPLE

10.1. Development and sign off

Protocol Contributors

The undersigned have contributed to this present protocol. They confirm that the following protocol has been agreed and accepted, and that the Primary Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

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

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

Date: 17 September 2019

Primary Investigator
Dr Rob Forsyth
Consultant / Senior Lecturer
Institute of Neuroscience
Newcastle University
(

Co-Investigators
Dr Jennifer McAnuff
Research Fellow / Occupational Therapist
Institute of Health and Society
Newcastle University

Professor Tim Rapley
Co-Director of Research and Innovation
Department of Social Work, Education and Community Wellbeing
Northumbria University

Research Associates

Dr Olivia Craw
Institute of Health and Society
Newcastle University

Dr Laura Cutler
Institute of Health and Society
Newcastle University

10.2. Protocol Summary

Title	Paediatric Early Rehabilitation/Mobilisation during InTensive care feasibility Observational study
Short Title	PERMIT workshops and interviews with parents and children and young people
Sponsor Name and Reference	University of Birmingham RG_19-214
Funder Name and Reference	NIHR HTA 17/21/06
IRAS Number	270791
Sponsor Statement	Where the University of Birmingham takes on the sponsor role for protocol development oversight, the signing of the IRAS form by the sponsor will serve as confirmation of approval of this protocol.
Study Design	Co-design workshops and interviews.
Study Participants	Parents of children and young people previously admitted to PIC, some of whom will have received ERM interventions. Children and young people previously admitted to PIC, some of whom will have received ERM interventions.
Planned Size of Sample (if applicable)	Parents (n=12-18) Children and young people (n=8-14)
Follow up duration (if applicable)	Not applicable
Planned Study Period	November 2019 – June 2020
Research Question/Aim(s)	To develop: (i) detailed intervention prototypes for ERM in PIC settings, and (ii) descriptions of feasible and acceptable ways in which the prototypes can be delivered to different patient groups and in different settings.

10.3. Research question and aims

The aims of the workshops and interviews with parents and CYP are to help develop:

(i) Detailed intervention prototypes for ERM in PIC settings, and
(ii) Descriptions of feasible and acceptable ways in which the prototypes can be delivered to different patient groups and in different settings.

To ensure development of intervention prototypes that are informed by diverse views and experiences we are additionally addressing these aims by undertaking workshops and interviews with health professionals and experts, in a separate but related study which has received Newcastle University ethics approval (reference code: 14224/2018).

10.3.1. Objectives

Our objectives are to:

- Work with parents and CYP to co-design a manual of ERM interventions,
- Identify relevant primary and secondary patient-centred outcomes,
- Explore the feasibility and acceptability of ERM interventions and trial designs.

10.3.2. Outcome

The key outputs for the study will be a manual specifying the content, context, delivery, and implementation of ERM interventions to specific patient populations. The manual will also include a preliminary outline of the feasibility and acceptability of clinical trial designs to key stakeholders.

10.4. Study design and methods of data collection and data analysis

We will undertake a series of workshops and interviews with parents and CYP. To ensure development of intervention prototypes that are informed by diverse views and experiences, different individuals will participate in each of the workshops.

The workshops and interviews will cover the following topics:

- Exploring outcomes of ERM, including physical, functional, and psychosocial outcomes, quality of life, adverse effects, resource use, and cost. Participants will discuss their perceptions of the relevance and usefulness of the outcome constructs identified from the survey and literature review previously conducted within the overall PERMIT study. They will articulate their ideas about how various proximal, intermediate, and distal outcomes relate to each other and to different patient groups. They will also consider which primary and secondary outcomes they believe would be of importance for a future trial.
- Exploring the content, context, and delivery of ERM in relation to different patient groups. Using existing intervention manuals as a starting point, participants will work with researchers to co-design ERM prototypes, and describe feasible and acceptable ways in which they can be delivered to different patient groups and in different contexts.
- As the workshops and interviews progress, participants will review, refine, and build on the outputs from those conducted previously. Finally, we will integrate all outputs into a proposed manual for a fully-specified ERM intervention, and begin to explore with participants the feasibility and acceptability of potential trial designs.

10.5. Data Collection Materials & Procedures

Parents will take part in workshops together so they can feel as comfortable as possible in describing their experiences and expressing their views and preferences. CYP will come together in developmentally appropriate workshops with their peers. Interviews will be conducted with those for whom it is more convenient (i.e. to suit access requirements or practical logistics).

Engaging adult and paediatric stakeholders in abstract concepts related to rehabilitation interventions (e.g. outcomes, content, context, and delivery) is recognised to be challenging. Therefore, our preliminary topic guide draws on published examples where this was successfully achieved, including with CYP. The topic guide will be continuously developed throughout the data collection and analysis.

We do not envisage that parents or CYP will find the data collection particularly upsetting. However, we are prepared to handle that sensitively if the situation does arise, for example by working closely with parents and ensuring CYP understand they can stop at any time. CYP will be offered the option of being accompanied by a familiar adult, and their assent will be reaffirmed on an ongoing basis.

The following key principles and practices will be emphasised during the workshops and interviews with CYP:

- We will enable CYP to prepare in advance if they want to, by providing them (via their parent) with age/developmentally appropriate and accessible materials related to the data collection activities (e.g. CYP PIS for older and younger CYP; see PERMIT phase 2b PIS CYP (younger) v3 and PERMIT phase 2b PIS CYP (older) v3). This will support stimulation of ideas, discussion with trusted adults, reflection on experiences, and preparation of materials on communication aids. It will also keep parents further informed about what their CYP is being asked to do, which is likely to be important to them.
- Supporting ease of access to data collection activities, through visual instructions and explanations, picture prompts, photos, symbols, key words, and mapping; and by minimising reliance on literacy skills and complex language.
- Supporting CYP's choices about how they engage in data collection activities, through diverse task-based approaches that incorporate describing, sorting, choosing etc., and by minimising reliance solely on independent movement and hand control.
- Increasing CYP's confidence to engage in data collection activities, through creative and non-intrusive approaches in which they can express their own beliefs and experiences indirectly through co-constructed characters and scenarios.
- Generating visual and written materials and products, that can be used to convey the content discussed and as a basis for subsequent workshops.

After each workshop and interview, researchers will immediately generate detailed notes reflecting on the discussions and how groups and individuals approached the activities. Key insights and ideas will be recorded in detail. As soon as possible after workshops and interviews, researchers will analyse the outputs in detail for recurring design ideas, and plan how both the outputs and the ideas will be brought back and presented at subsequent workshops and interviews.

Two researchers will conduct each workshop, one of whom (Dr Jennifer McAnuff) has clinical expertise as an allied health clinical academic in paediatric healthcare, specifically working with CYP with complex neurodisability. JMc will oversee the conduct of the CYP interviews, as she has expertise in: (i) adapting communication methods and practical activities to include CYP at varying ages and developmental stages; (ii) safeguarding vulnerable CYP, being familiar with local safeguarding partnership procedures which tend to be consistent across the country (local safeguarding procedures will be clarified with lead clinicians at the three study sites as required); and (iii) sensitive discussion of topics that CYP may find distressing, e.g. their personal experiences of health services. The interviews will be conducted by Dr Olivia Craw.

All data will be audio-recorded, professionally transcribed, stored securely on the Newcastle University password-protected servers, and uploaded to NVivo Pro v11 to support co-ordination of

analysis. We do not plan to return transcripts to participants for comment or correction. We may take photographs of materials produced during the workshops and interviews (e.g. re-designed logic models, drawings of intervention prototypes etc.) – participants will not be in the photographs. Transcripts and field notes will be fully anonymised before data analysis begins. All electronic data will be accessible only to the Newcastle University and University of Birmingham study team. The digital audio recordings will be destroyed at the end of the PERMIT study. Paper data will be disposed of securely. All other records (e.g. transcripts) will be retained in a secure archive setting for 10 years to facilitate future analysis and publication of the study material.

10.5.1. Data Analysis

Data analysis will primarily be thematic analysis in that it will focus on capturing repeated patterns of meaning as well as design ideas. However, we plan to implement a more structured approach by: (i) using an a priori coding framework based on the key results identified in the survey and literature review previously conducted within the overall PERMIT study; and (ii) incorporating key theoretical constructs related to feasibility, acceptability, and implementation of healthcare interventions into the analysis, specifically key constructs from Normalisation Process Theory [2, 3] and the theoretical framework of acceptability of healthcare interventions [4]. The analysis will be led by Dr Olivia Craw and supported and overseen by the wider study team at Newcastle University. This will include double coding sections of transcript and regular critical discussion and reflection in study team meetings.

10.5.2. Study Setting

The workshops and interviews will be conducted across 3 PIC sites, specifically Birmingham, Newcastle and Glasgow. We have selected these sites because: (i) they are diverse in terms of their size, multidisciplinary team, patient population, active/minimal use of ERM, and type of ERM used; and (ii) they enable us to engage stakeholders from diverse geographical locations, and make it more feasible for stakeholders to travel to participate in the research.

Local investigators for each of the 3 participating sites are listed below. All are employed as clinicians in their respective NHS Trusts and will access information provided for the PERMIT study as part of their routine practice. As such, these individuals are both part of the clinical care team and will act as a member of the local research team for their respective PIC site.

Birmingham Children's Hospital (local investigator: Dr Julie Menzies, co-investigator for the wider PERMIT study and Nurse) is the lead centre for PIC for the West Midlands and the largest single centre PIC unit in the UK, specialising in care for respiratory, cardiac, liver, general surgery, spinal, orthopaedics, metabolic, endocrine, neurology and neurosurgery populations.

Great North Children's Hospital and the Freeman Hospital (local investigators: Ms Amanda Carruthers, Physiotherapist, and Dr Rob Forsyth, Principal Investigator of this component of the PERMIT study and Consultant Child Neurologist). Together, these two PIC settings host one of the largest and most comprehensive PIC services in the UK and serve the largest geographical area in England (North East and North Cumbria).

Glasgow Royal Hospital for Children (local investigator: Dr Richard Levin, PIC intensivist), is an integrated critical care unit, providing both intensive and high dependency care, and is the sole provider of heart surgery and cardiac catheter interventional procedures for CYP in Scotland.

10.6. Sample and Recruitment

10.6.1. Eligibility criteria

The study population will be parents (n=12-18) of CYP previously admitted to PIC, some of whom will have received ERM interventions, and CYP (n=8-14) previously admitted to PIC, some of whom will have received ERM interventions. For both the parents and the CYP, we have planned a purposive

sampling strategy with broad preliminary inclusion and exclusion criteria informed by topic expertise within the wider PERMIT study team. These broad criteria will facilitate the inclusion of diverse groups of parents and CYP with experience of PIC:

Inclusion criteria for parents:

- Parent of a child/young person aged 0-16 years at time of PIC admission
- Parent of a child/young person previously admitted to PIC for either acute or elective/post-surgical care
- Parent of a child/young person who remained in PIC on day 3 post admission

In order to engage participants with a diverse range of experience, some parents recruited will have a child/young person who did receive ERM during their admission to PIC, whilst others will have a child/young person who did not receive ERM.

Exclusion criteria for parents:

- Parent of a child/young person who received <48hrs ventilatory support (the requirement for more than 48hrs ventilatory support targets a population at-risk for post ICU syndrome and thought to require rehabilitation. It is also a frequently-used cut-off in rehabilitation research [5])
- Local decision by Family Liaison that it would not be safe and/or appropriate to contact an individual parent about participation in the study

Inclusion criteria for CYP:

- Aged 0-<16 years
- Previously admitted to PIC for either acute or elective/post-surgical care
- Remained in PIC on day 3 post admission
- In order to engage participants with a diverse range of experience, some CYP recruited will have received ERM during their admission to PIC, whilst others will not

Exclusion criteria for CYP:

- <48hrs ventilatory support
- Local decision by Family Liaison that it would not be safe and/or appropriate to contact an individual parent about their child's participation in the study

We anticipate that results from Phase 1 of the overall PERMIT study, together with emergent findings from the proposed workshops and interviews, will provide valuable insights about the parents and CYP for whom ERM may be particularly relevant, important, beneficial, and/or challenging. Furthermore, once these parents and CYP have been identified, it is a core objective of the overall PERMIT study to understand their views on both the acceptability and feasibility of ERM interventions. We therefore plan to iteratively refine our inclusion and exclusion criteria as our understanding of this population develops, and further purposively sample parents and CYP with the desired characteristics that will enable us to gain diverse perspective and best achieve our research objectives.

Desirable characteristics for further purposive sampling of parents may include their child's age, gender, other socio-demographic factors, health condition, location, reason for PICU admission, severity of illness/injury, length of PICU stay, experience of ERM interventions, diagnosis of post-PICU syndrome, and pre-morbid functional ability. Desirable characteristics for further purposively sampling of CYP may include age, gender, other socio-demographic factors, health condition, location, reason for PICU admission, severity of illness/injury, length of PICU stay, experience of ERM interventions, diagnosis of post-PICU syndrome, and pre-morbid functional ability.

10.6.2. Size of sample

We plan to recruit n=12-18 parents and n=8-14 CYP. This sample size will enable us to engage diverse participants with wide-ranging experience of direct relevance to ERM and PIC settings in the UK NHS context. Our proposed sample size is also commensurate with the breadth and depth of analysis we require to deliver our study objectives, and is feasible within the study resources.

10.6.3. Sampling Technique

A purposive sampling strategy will be used to identify parents and CYP. As described in detail above, sampling, recruitment and data collection will be iterative, in that sampling and data analysis in the preliminary workshops and interviews – as well as in the overall PERMIT study – will shape further targeted sampling for the subsequent workshops and interviews. We expect to have a good understanding of the typical population of CYP admitted to PIC settings in the UK from results of the Phase 1 survey of healthcare professionals, literature review and observational study, and this will directly inform which parents and CYP we approach.

10.6.4. Recruitment

For the parents, the sampling and recruitment will be implemented as follows:

1. The first step will be to review the local ERM database at each of the three participating sites (the database is a record of treatment patients received whilst in PIC, including ERM, if applicable). The purpose of this review will be to identify parents who meet the inclusion criteria. The review will be conducted by local investigators employed as clinicians in their respective NHS Trusts who have access to their local ERM database as part of their routine practice.
2. Once a list of parents meeting the inclusion criteria has been identified, the local investigator for the PIC (who, is part of the clinical care team within the PIC) will liaise with local Family Liaison Teams to ensure that it would be safe and appropriate to proceed with recruitment (i.e. to ensure that there are no known significant reasons for avoiding approaching parents, such as their CYP remaining critically ill or having died). Family Liaison Teams have essential insight into the likelihood that significant distress may be caused by approaching potential participants and will know of any parents who are currently having significant problems coping following the critical illness of their CYP. Where local intelligence suggests it would be unsafe or inappropriate, these parents will be removed from the list.
3. Local investigators will then cross-reference the list of parents with their local PIC unit ward admissions books to establish whether these parents' CYP have been transferred to another ward or have been discharged home. They will distribute recruitment packs to the selected parents. For parents whose CYP have been transferred to another ward, local investigators will hand deliver recruitment packs. For parents whose CYP have been discharged home, local investigators will post or email recruitment packs, depending on how their NHS Trust has usually communicated with the parent and in accordance with any known parental preferences around communication. The packs will consist of an invitation letter (PERMIT phase 2b invitation (parents) v2), a Participant Information Sheet (PERMIT phase 2b PIS-parents v3), a consent form (PERMIT phase 2b consent form (parents) v3), and a stamped return envelope (as required).
4. Parents will return their consent forms directly to Dr Olivia Craw (PERMIT research associate at Newcastle University). Dr Craw will then contact parents directly to arrange data collection at their convenience.
5. Researcher(s) will monitor ongoing informed consent throughout the workshops, e.g. by listening and looking out for verbal or non-verbal signs that may indicate parents are uncomfortable or do not wish to continue. If such signs are observed, the researcher(s) will sensitively check if parents wish to continue, and assure them of their right to withdraw at any point without affecting their legal rights or employment.
6. We anticipate that all participants will have the capacity to provide informed consent. However, the PERMIT study team will be vigilant for any signs of limitations in capacity.
7. Parents will receive a thank you letter/email at the end of their study participation.

8. Recruitment packs will be distributed in small batches until the required purposive sample and/or planned sample size have been achieved.

The recruitment of CYP will be implemented as follows:

1. The first step will be to review the local ERM database at each of the three participating sites (the database is a record of treatment patients received whilst in PIC, including ERM, if applicable). The purpose of this review will be to identify CYP who meet the inclusion criteria. The review will be conducted by local investigators employed as clinicians in their respective NHS Trusts who have access to their local ERM database as part of their routine practice.
2. Once a list of CYP meeting the inclusion criteria has been identified, the local investigator for the PIC (who, is part of the clinical care team within the PIC) will liaise with local Family Liaison Teams to ensure that it would be safe and appropriate to proceed with recruitment (i.e. to ensure that there are no known significant reasons for avoiding approaching parents, such as their CYP remaining critically ill or having died). Family Liaison Teams have essential insight into the likelihood that significant distress may be caused by approaching potential participants and will know of any parents who are currently having significant problems coping following the critical illness of their CYP. Where local intelligence suggests it would be unsafe or inappropriate, these parents will be removed from the list.
3. Local investigators will then cross-reference the list of CYP with their local PIC unit ward admissions books to establish whether these CYP have been transferred to another ward or have been discharged home. They will then distribute recruitment packs to the selected CYPs' parents. For CYP who have been transferred to another ward, local investigators will hand deliver recruitment packs to parents. For CYP who have been discharged home, local investigators will post or email recruitment packs to parents, depending on how the NHS Trust has usually communicated with the family and in accordance with any known parental preferences around communication.
4. The recruitment packs will consist of an invitation letter (for CYP: PERMIT phase 2b invitation (young person) v1; and for parent: PERMIT phase 2b invitation (parents-CYP) v1), a Participant Information Sheet for parents (PERMIT phase 2b PIS parents- CYP to participate v3), a consent form (PERMIT phase 2b consent form (CYP participating) v3), a Participant Information Sheet for CYP (PERMIT phase 2b PIS CYP (younger) v3; PERMIT phase 2b PIS CYP (older) v3), a CYP assent form (PERMIT Phase 2b assent form v3), and a stamped return envelope (as required). The pack contains information about the nature and objectives of the study, possible risks associated with participation, and who parents can contact with questions, and actively encourages contact with the study team.
5. Parents will return the parent consent and CYP assent forms directly to Dr Craw (PERMIT research associate at Newcastle University). Dr Craw will then contact parents directly to confirm parents' consent, arrange data collection at their CYP's convenience, and to ensure a good understanding of CYP communication and access requirements for a workshop/interview.
6. Before the start of the workshops and interviews, the researcher will explore informed assent directly with CYP, using the CYP Participant Information Sheet and a CYP assent form. CYP will be assured that they can freely choose whether or not to take part. Assent will be confirmed on an ongoing basis throughout data collection, both explicitly (i.e. by checking with CYP if they want to proceed), and by monitoring CYP's non-verbal interactions (e.g. lack of eye contact, attention, or concentration) and tuning into possible avoidance behaviours (e.g. wanting to go the bathroom frequently).
7. At the end of study participation, CYP and their parents will receive a thank you letter/email for taking part, and CYP will receive a developmentally appropriate certificate of achievement.
8. Recruitment packs will be distributed in small batches until the required purposive sample and/or planned sample size have been achieved.

Note that parents will receive either an invitation for their CYP to participate, or an invitation for themselves to participate as parents, but not both. This is so as to minimise the burden of participating in the study.

10.7. Additional Ethical and Regulatory Considerations

The study will be conducted in accordance with the Research Governance Framework for Health and Social Care, the applicable UK Statutory Instruments, (which include the General Data Protection Regulation, Data Protection Act 2018 and Guidelines for Good Clinical Practice (ICH-GCP)).The protocol will be submitted to and approved by the Research Ethics Committee (REC) prior to circulation.
Before any participants are recruited for the study, the Principal Investigator is required to obtain local Research & Development (R&D) approval. Enrolment of participants will not be permitted until written confirmation of R&D approval is received by the Principal Investigator.

10.7.1. Special considerations for children and young people

Ethical practice for the proposed study will be guided by the Nuffield Council Report on Children and Clinical Research: Ethical Issues [6]. We will follow the ethos that: (i) scientifically valid and ethically robust research that addresses questions of importance to the health of CYP people is an essential and necessary part of the healthcare system; and (ii) CYP have the potential from an early age to play an active role in determining their own lives and in engaging with others, and should be offered the opportunity to participate in research. Should they decide to contribute to research, they need to be protected from harm, which involves the implementation of special considerations. In the present study, this applies to the workshops and interviews with CYP.

The following key principles and practices will, therefore, be emphasised during the workshops and interviews with CYP:

- Participant Information Sheets will apply to parents (PERMIT phase 2b PIS parents- CYP to participate v3) - with a separate information sheet designed to be accessible for CYP (PERMIT phase 2b PIS CYP (younger) v3 and PERMIT phase 2b PIS CYP (older) v3), to facilitate shared decision-making regarding participation.
- The research team will ensure parents and CYP have time to consider research participation, and make themselves available both to discuss the research and respond to queries the parent or CYP may have prior to decision-making.
- CYP's 'assent' for participation in a workshop or interview will be an ongoing process across the study: CYP's views and decisions will be respected.
- We will enable CYP to prepare in advance if they want to, by providing them (via their parent) with any necessary personally tailored accessible materials related to the data collection activities. This will support stimulation of ideas, discussion with trusted adults, reflection on experiences, and preparation of materials on communication aids. It will also keep parents further informed about what their CYP is being asked to do, which is likely to be important to them.
- Supporting ease of access to data collection activities, through visual instructions and explanations, picture prompts, photos, symbols, key words, and mapping; and by minimising reliance on literacy skills and complex language.
- Supporting CYP's choices about how they engage in data collection activities, through diverse task-based approaches that incorporate describing, sorting, choosing etc., and by minimising reliance solely on independent movement and hand control.
- Increasing CYP's confidence to engage in data collection activities, through creative and non-intrusive approaches in which they can express their own beliefs and experiences indirectly through co-constructed characters and scenarios.
- Generating visual and written materials and products, that can be used to convey the content discussed and as a basis for subsequent workshops.

10.7.2. Assessment and management of risk

We do not anticipate encountering any significant risks to participants. However, we are prepared to handle that sensitively if the situation does arise. Dr Jennifer McAnuff has clinical expertise as an allied health clinical academic in paediatric healthcare, specifically working with CYP with complex neurodisability. We do not envisage that CYP will find the data collection upsetting. However we are prepared to handle that sensitively if the situation does arise, for example by working closely with parents and ensuring CYP understand they can stop at any time. CYP will be offered the option of being accompanied during data collection by a familiar adult, and their assent will be reaffirmed on an ongoing basis [6].

10.7.3. Data Protection

The present study requires the collection of personally-identifiable information in order to appropriately conduct research. When personally-identifiable information is held for people who have agreed to take part in research, it is ensured that it is in the public interest. We will use the data in the ways needed to conduct and analyse the research study.

All investigators will comply with the requirements of the Data Protection Act 1998 with regards to the collection, storage, processing, and disclosure of personal information and will uphold the Act's core principles.

All workshops and interviews will be digitally audio-recorded and transcribed by a professional company external to Newcastle University. We may also take photographs of the materials produced during data collection – participants will not be in the photographs. Transcripts will be fully anonymised before data analysis begins. All electronic data will be held on the secure, password protected servers at Newcastle University, and will be accessible only to the study team. The digital audio recordings will be destroyed at the end of the PERMIT study. Paper data will be disposed of securely. All other records (e.g. transcripts) will be retained in a secure archive setting for 10 years to facilitate future analysis and publication of the study material.

We will use participants' names and contact details (e.g. email addresses, telephone numbers) to contact them about the research study, or they will receive the recruitment pack by post. We will use other information (e.g. sociodemographic characteristics) to help us analyse the research data, e.g. to understand how delivery of and views about early rehabilitation/mobilisation interventions may vary across the country. Individuals at Newcastle University and University of Birmingham may look at the research data to check the accuracy of the research study. The only individuals at Newcastle University and University of Birmingham who will have access to information that identifies participants will be the study team, or people who are required to audit the data collection process.

Participants will be informed that they have the following rights: a right of access to a copy of the information comprised in their personal data; a right in certain circumstances to have inaccurate personal data rectified; a right to object to decisions being taken by automated means; and a right to access and request electronic copies of all personal data held about them; a right to correct or request deletion of that information If upon review they find that any of their information is incomplete or inaccurate. We will not pass on any person-identifiable data to any external agency. No personal data will be transferred outside the European Union. Any personal data we hold about them will be destroyed within six months of the end of the study.

10.8. End of study definition

The end of study will be upon completion of the whole PERMIT programme of research (i.e. Phase 1, 2 and 3), plus an additional 6 months. The REC will be notified that the study has ended.

A copy of the end of study notification as well as the summary report is also sent to the University of Birmingham Research Governance Team at the time of sending these to the REC.

10.9. Ethics approval

10.10. References

1. *National Institute for Health and Care Excellence. Rehabilitation after critical illness in adults. NICE; 2017 [cited 2019 Sept 18]. (Quality standard [QS158]). Available from: https://www.nice.org.uk/guidance/qs158*

2. *Medical Research Council. A framework for development and evaluation of RCTs for complex interventions to improve health. London; 2000. Available from: https://mrc.ukri.org/documents/pdf/rcts-for-complex-interventions-to-improve-health/*

3. *May CR, Mair F, Finch T, MacFarlane A, Dowrick C, Treweek S, Rapley T, Ballini L, Ong BN, Rogers A, Murray E. Development of a theory of implementation and integration: Normalization Process Theory. Implementation Science. 2009 Dec;4 (1):29.*

4. *Sekhon M, Cartwright M, Francis JJ. Acceptability of healthcare interventions: an overview of reviews and development of a theoretical framework. BMC health services research. 2017 Dec;17(1):88.*

5. *Morris PE, Goad A, Thompson C, Taylor K, Harry B, Passmore L, Ross A, Anderson L, Baker S, Sanchez M, Penley L. Early intensive care unit mobility therapy in the treatment of acute respiratory failure. Critical care medicine. 2008 Aug 1;36(8):2238-43.*

6. *Bioethics NCo. Children and clinical research: ethical issues. Nuffield Council on Bioethics London; 2015. Available from: http://nuffieldbioethics.org/wp-content/uploads/Children-and-clinical-research-Chapter-1.pdf*

11. PHASE 2a: WORKSHOPS & INTERVIEWS WITH EXPERTS AND HEALTH PROFESSIONALS

11.1. Development and sign off

Protocol Contributors

The undersigned confirm that the following protocol has been agreed and accepted and that the Primary Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

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

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

Date: 24 July 2019

Primary Investigator
Dr Rob Forsyth
Consultant / Senior Lecturer
Institute of Neuroscience
Newcastle University

Co-Investigators
Dr Jennifer McAnuff
Research Fellow / Occupational Therapist
Institute of Health and Society
Newcastle University

Professor Tim Rapley
Co-Director of Research and Innovation
Department of Social Work, Education and Community Wellbeing
Northumbria University

Research Associates

Dr Olivia Craw
Institute of Health and Society
Newcastle University

Dr Laura Cutler
Institute of Health and Society
Newcastle University

11.2. Protocol Summary

Title	The PERMIT feasibility study – Paediatric Early Rehabilitation/Mobilisation during InTensive care (workshops and interviews with experts and health professionals)
Short Title	PERMIT early mobilisation feasibility study – workshops and interviews
Sponsor Name and Reference	University of Birmingham ERN_18-1134
Funder Name and Reference	NIHR HTA 17/21/06
IRAS Number	We are currently clarifying whether HRA approval is required for the management aspects of the study. We do not require NHS REC review.
Sponsor Statement	Where the University of Birmingham takes on the sponsor role for protocol development oversight, the signing of the IRAS form by the sponsor will serve as confirmation of approval of this protocol.
Study Design	Co-design workshops and interviews with international experts and NHS health professionals providing early rehabilitation/mobilisation in intensive care settings.
Study Participants	International experts (e.g. lead clinicians, clinical academics, researchers) NHS multidisciplinary health professionals (e.g. doctors, nurses, allied health professionals)
Planned Size of Sample (if applicable)	International experts (e.g. lead clinicians, clinical academics, researchers) n=12-18 NHS multidisciplinary health professionals (e.g. doctors, nurses, allied health professionals), n=18-24
Follow up duration (if applicable)	Not applicable
Planned Study Period	August – May 2019
Research Question/Aim(s)	To develop: (i) detailed intervention prototypes for early rehabilitation/mobilisation in paediatric intensive care settings, and (ii) descriptions of feasible and acceptable ways in which the prototypes can be delivered to different patient groups and in different settings.

11.3. Research question and aims

The aim of the workshops and interviews with international experts in early rehabilitation/mobilisation and NHS health professionals is to develop:

(iii) Detailed intervention prototypes for early rehabilitation/mobilisation in paediatric intensive care settings, and
(iv) Descriptions of feasible and acceptable ways in which the prototypes can be delivered to different patient groups and in different settings.

11.3.1. Objectives

Our objectives are to:

- Work with international experts and NHS health professionals to co-design a manual of early rehabilitation/mobilisation interventions,
- Identify relevant primary and secondary patient-centred outcomes,
- Explore the feasibility and acceptability of early rehabilitation/mobilisation interventions and trial designs.

11.3.2. Outcome

The key outputs for the study will be a manual specifying the content, context, delivery, and implementation of early rehabilitation/mobilisation interventions to specific patient populations. The manual will also include a preliminary outline of the feasibility and acceptability of clinical trial designs to key stakeholders.

11.3.3. Study design and methods of data collection and data analysis

We will undertake approximately three rounds of co-design workshops and interviews with international experts in early rehabilitation/mobilisation and NHS health professionals. To ensure development of intervention prototypes that are informed by diverse views and experiences, different individuals will participate in each of the three rounds.

Each round of workshops and interviews will cover the following topics:

- Exploring outcomes of early rehabilitation/mobilisation, including physical, functional, and psychosocial outcomes, quality of life, adverse effects, resource use, and cost. Participants will discuss their perceptions of the relevance and usefulness of the outcome constructs identified from a survey and literature review previously conducted within the overall PERMIT study. They will articulate their ideas about how various proximal, intermediate, and distal outcomes relate to each other and to different patient groups. They will also consider which primary and secondary outcomes they believe would be of importance for a future trial.
- Exploring the content, context, and delivery of early rehabilitation/mobilisation, in relation to different patient groups. Using existing intervention manuals as a starting point, participants will work with researchers to co-design early rehabilitation/mobilisation intervention prototypes, and describe feasible and acceptable ways in which they can be delivered to different patient groups and in different contexts.
- In each round, participants will review and refine the outputs from the previous rounds. Finally, we will integrate all outputs into a proposed manual for a fully-specified early

rehabilitation/mobilisation intervention, and begin to explore with participants the feasibility and acceptability of potential trial designs.

Engaging adult and paediatric stakeholders in abstract concepts related to rehabilitation interventions (e.g. outcomes, content, context, and delivery) is recognised to be challenging. Therefore our preliminary topic guide will draw on published examples where this was successfully achieved. The topic guide will be continuously developed throughout the three rounds of data collection and analysis.

Two researchers will conduct each workshop and one researcher will conduct each interview. These will be overseen by Ms Jennifer McAnuff (co-investigator) and Dr Rob Forsyth (primary investigator), both of whom have clinical academic in paediatric healthcare.

After each workshop and interview, researchers will immediately generate detailed notes reflecting on the discussions and how groups and individuals approached the activities. Key insights and ideas will be recorded in detail. As soon as possible after workshops and interviews, researchers will analyse the outputs in detail for recurring design ideas, and plan how both the outputs and the ideas will be brought back and presented at subsequent workshops and interviews.

All data will be audio-recorded, professionally transcribed, stored securely on the Newcastle University password-protected servers, and uploaded to NVivo Pro v11 to support co-ordination of analysis. We do not plan to return transcripts to participants for comment or correction. We may take photographs of materials produced during the workshops and interviews (e.g. re-designed logic models, drawings of intervention prototypes etc.) – participants will not be in the photographs. Transcripts and field notes will be fully anonymised before data analysis begins. All electronic data will be accessible only to the Newcastle University study team.

The digital audio recordings will be destroyed at the end of the PERMIT study. Paper data will be disposed of securely. All other records (e.g. transcripts) will be retained in a secure archive setting for 10 years to facilitate future analysis and publication of the study material.

Data analysis will primarily be thematic analysis in that it will focus on capturing repeated patterns of meaning as well as design ideas. However, we plan to implement a more structured approach by: (i) using an a priori coding framework based on the key results identified in the survey and literature review previously conducted within the overall PERMIT study; and (ii) incorporating key theoretical constructs related to feasibility, acceptability, and implementation of healthcare interventions into the analysis, specifically key constructs from Normalisation Process Theory and the theoretical framework of acceptability of healthcare interventions.

The analysis will be led by Dr Laura Cutler (research associate) and supported and overseen by the wider study team at Newcastle University. This will include double coding sections of transcript and regular critical discussion and reflection in study team meetings.

11.4. Study setting

Workshops and interviews will be conducted face-to-face and via videoconference (e.g. Skype or Zoom). At this point, it is not possible to specify exactly where and when workshops and interviews will take place, because recruitment will be conducted on a national and international level, and we do not yet know who will agree to take part.

For the face-to-face workshops and interviews, we anticipate collecting data at approximately three sites within easy reach of three paediatric intensive care units, for example in Southampton, Birmingham, and Newcastle. We are provisionally proposing these sites because: (i) their local paediatric intensive care units are diverse in terms of their size, multidisciplinary team, patient population, active/minimal use of early rehabilitation/mobilisation, and type of early rehabilitation/mobilisation used; and (ii) a variety of sites would enable us to engage participants from diverse geographical locations, and make it more feasible for participants to travel to take part in the

research. We will review this proposal based on the response to our recruitment strategy, and as we further specify our key desirable sampling characteristics.

Participants will have the opportunity to state their preferences in terms of workshop or interview, timings, and locations. As much as possible, we will organise data collection flexibly around participants' schedules and availability.

We will seek to conduct the face-to-face data collection in comfortable, informal spaces in community sites, University sites, or other suitable locations, although this will depend primarily on access requirements and availability of space. Researchers will create welcoming, informal environments by allowing sufficient time for introductions, refreshments, exploration of the research programme and intervention materials, and regular comfort breaks. We anticipate a duration of 1-2 hours for each workshop, and 30 minutes-1 hour for each interview.

11.5. Sample and recruitment

11.5.1. Eligibility Criteria

The study population will be international clinical and research experts in early rehabilitation/mobilisation in adult and paediatric intensive care settings, and NHS health professionals with and without experience of implementing early rehabilitation/mobilisation in paediatric intensive care settings.

For both the international experts and the NHS health professionals, we do not plan to specify fixed inclusion and exclusion criteria. Instead, we will specify key desirable sampling characteristics based on the results from the earlier phase of the overall PERMIT early mobilisation feasibility study (i.e. the survey, literature review, and observational study – led and managed separately by University of Birmingham). Desirable characteristics may include location of practice, size and specialism of intensive care setting, professional group, active/minimal use or experience of early rehabilitation/mobilisation interventions, type of interventions used or experienced, type of implementation issues described in participants' publications etc. Importantly, because sampling, recruitment, and data collection and analysis will be iterative, key desirable characteristics may change as data collection progresses.

11.5.2. Size of sample

We plan to recruit n=12-18 international experts in early rehabilitation/mobilisation. Our proposed sample size is informed by the scale of early rehabilitation/mobilisation activities in intensive care settings internationally, e.g. how many people are leading research and quality improvement in this topic, how many papers of direct relevance to the PERMIT study have been published etc. The sample size will also enable us to engage a diverse group of international experts, with wide-ranging experience of direct relevance to early rehabilitation/ mobilisation and intensive care settings in the UK NHS context.

We plan to recruit n=18-24 NHS health professionals, many of whom will have direct experience of delivering and implementing early rehabilitation/mobilisation. Our proposed sample size is informed by our current understanding of the characteristics of the paediatric intensive care workforce in the UK NHS, e.g. the different types of professionals involved in early rehabilitation/mobilisation, and the different patient populations served by paediatric intensive care units. The sample size will enable us to engage a diverse group of health professionals, with different perspectives on what early rehabilitation/mobilisation involves, what are the most important outcomes, and what are the key issues related to delivery, implementation, and evaluation.

Our proposed sample size is also commensurate with the breadth and depth of analysis we require to deliver our study objectives, and is feasible within the study resources.

11.5.3. Sampling technique

We will use a purposive sampling strategy to identify international experts and NHS health professionals. Sampling, recruitment, and data collection and analysis will be iterative, in that sampling and data analysis in the preliminary workshops and interviews will shape further targeted sampling for the subsequent workshops and interviews.

The sampling frame for the international experts is a list of individuals leading or supporting early rehabilitation/mobilisation research or quality improvement in intensive care settings (e.g. names, locations, professional roles). The list has been compiled, populated, and prioritised by a PERMIT research associate on the basis of the published literature on this topic, and has been further supplemented by the wider PERMIT study team who have topic expertise and well-established clinical and research networks of direct relevance.

The sampling frame for the NHS health professionals is a list of lead/senior clinicians who participated in a previous survey within the overall PERMIT study, and agreed to be approached about a workshop or interview. The previous survey received ethics review and approval from University of Birmingham, and has now closed to recruitment. From this survey, we expect to have a more detailed understanding of the paediatric intensive care workforce in the UK NHS, i.e. the different types of professionals involved in early rehabilitation/mobilisation, and the patient populations with whom they are working. This will enable us to further specify our inclusion criteria. It will also highlight important limitations in our sampling frame, e.g. if key professional groups are under-represented within survey respondents, we will supplement the list of lead/senior clinicians with further recruitment through targeted professional networks (i.e. Paediatric Intensive Care Society Study Group, allied health professional clinical forums).

11.5.4. Recruitment

For the international experts, sampling and recruitment will be implemented as follows:

- The PERMIT study team (specifically Dr Laura Cutler research associate, and Dr Julie Menzies co-investigator) will prioritise which experts within the sampling frame to approach first, based on the results from the earlier phase of the overall PERMIT early mobilisation/rehabilitation feasibility study.
- The recruitment pack will be emailed directly to experts. Dr Laura Cutler will send the email as she is not known to the experts and therefore will not unduly influence their response.
- A maximum of two reminder emails or follow-up telephone calls will be used.
- When an expert returns his/her consent form, Dr Laura Cutler will follow up with an email or telephone call to establish their preferences regarding a face-to-face or online workshop or interview, and timings and locations.
- Workshops and interviews will be scheduled as much as possible according to participants' preferences.
- Participants will receive a thank you and debriefing letter after taking part in a workshop or interview.
- If an expert does not respond to the recruitment pack or reminders, the PERMIT study team will invite the next highly prioritised expert within the sampling frame.
- Recruitment packs will be distributed in small batches until the required purposive sample is achieved. The PERMIT study team will continuously monitor which key desirable sampling characteristics have been fulfilled, and which are outstanding. This will inform further sampling and recruitment.

For the NHS health professionals, sampling and recruitment will be implemented as follows:

- The PERMIT study team (specifically Dr Laura Cutler research associate, Ms Jennifer McAnuff co-investigator, Dr Julie Menzies co-investigator, and Dr Barney Scholefield Chief Investigator) will prioritise which NHS health professionals within the sampling frame to approach first, based on the results from the earlier phase of the overall PERMIT early mobilisation/rehabilitation feasibility study.
- The recruitment pack will be emailed directly to NHS health professionals, as they previously gave informed consent to be approached about taking part in a workshop or interview. Dr Laura Cutler will send the email as she is not known to the health professionals and therefore will not unduly influence their response.
- A maximum of two reminder emails or follow-up telephone calls will be used.
- When a health professional returns his/her consent form, Dr Laura Cutler will follow up with an email or telephone call to establish their preferences regarding a face-to-face or online workshop or interview, and timings and locations.
- Workshops and interviews will be scheduled as much as possible according to participants' preferences.
- Participants will receive a thank you and debriefing letter after taking part in a workshop or interview.
- If a health professional does not respond to the recruitment pack or reminders, the PERMIT study team will invite the next highly prioritised individual from the same professional group within the sampling frame.
- Recruitment packs will be distributed in small batches until the required purposive sample is achieved. The PERMIT study team will continuously monitor which key desirable sampling characteristics have been fulfilled, and which are outstanding. This will inform further sampling and recruitment.
- If we are unable to satisfactorily fulfil our purposive sampling strategy from the list of lead/senior clinicians who participated in the PERMIT survey and agreed to be approached, we will distribute our recruitment pack through targeted professional networks, i.e. the Paediatric Intensive Care Society Study Group, the Royal College of Occupational Therapists Specialist Section for Children, Young People, and Families (Acute Forum), the Association of Paediatric Chartered Physiotherapists, the Royal College of Speech and Language Therapists Clinical Excellence Networks, the British Dietetic Association, the British Association of Play Therapists, the Healthcare Play Specialist Education Trust, the Association of Clinical Psychologists, and the #PedsICU Twitter hashtag.

11.6. Consent

The process of gaining informed consent will be implemented as follows:

- Potential participants will receive a recruitment pack via email. The recruitment pack will contain an invitation letter, a Participant Information Sheet, and a consent form.
- Both the invitation letter and the Participant Information Sheet will contain information on who to contact with questions. Potential participants will be actively encouraged and assured they are welcome to contact the study team with questions.
- The Participant Information Sheet will contain information about the nature and objectives of the study, and possible risks associated with participation.
- If potential participants would like to take part, they will be instructed to complete the consent form indicating their understanding, and return the form directly to the study team via email.
- The study team will further check participants' informed consent at two specific points in time: (i) when the study team contacts the participant to arrange their workshop or interview, and (ii) before starting the workshop or interview.

- Additionally, researcher(s) will monitor ongoing informed consent throughout the workshops and interviews, e.g. by listening and looking out for verbal or non-verbal signs that may indicate participants are uncomfortable or do not wish to continue. If such signs are observed, the researcher(s) will sensitively check if participants wish to continue, and assure them of their right to withdraw at any point without affecting their legal rights or employment.
- We anticipate that all participants will have the capacity to provide informed consent, by virtue of their daily professional roles as clinicians and researchers. However, the PERMIT study team, specifically those conducting workshops and interviews, will be vigilant for any signs of limitations in capacity.

11.7. Assessment and management of risk

We do not anticipate encountering any significant risks to participants.

11.7.1. Data protection

All investigators must comply with the requirements of the Data Protection Act 1998 with regards to the collection, storage, processing, and disclosure of personal information and will uphold the Act's core principles.

All workshops and interviews will be digitally audio-recorded and transcribed by a professional company external to Newcastle University. We may also take photographs of the materials produced during data collection – participants will not be in the photographs. Transcripts will be fully anonymised before data analysis begins. All electronic data will be held on the secure, password protected servers at Newcastle University, and will be accessible only to the study team. The digital audio recordings will be destroyed at the end of the PERMIT study. Paper data will be disposed of securely. All other records (e.g. transcripts) will be retained in a secure archive setting for 10 years to facilitate future analysis and publication of the study material.

We will use participants' names and contact details (e.g. email addresses, telephone numbers) to contact them about the research study, or they will receive the recruitment pack indirectly through their professional networks. We will use other information (e.g. professional role, where they work) to help us analyse the research data, e.g. to understand how delivery of and views about early rehabilitation/mobilisation interventions may vary across the country. Individuals at Newcastle University may look at the research data to check the accuracy of the research study. The only individuals at Newcastle University who will have access to information that identifies participants will be the study team, or people who are required to audit the data collection process.

Participants will be informed that they have the following rights: a right of access to a copy of the information comprised in their personal data; a right in certain circumstances to have inaccurate personal data rectified; a right to object to decisions being taken by automated means; and a right to access and request electronic copies of all personal data held about them; a right to correct or request deletion of that information If upon review they find that any of their information is incomplete or inaccurate. We will not pass on any person-identifiable data to any external agency. No personal data will be transferred outside the European Union. Any personal data we hold about them will be destroyed within six months of the end of the study.

11.8. Ethical Approval

Formal ethical approval was obtained From Newcastle University ethics committee, 1/8/2019. (Ref 13605/2018).

PHASE 2b PROTOCOL: Review

12. PHASE 2b: RAPID REVIEW OUTCOME TOOLS

12.1. Background

We will conduct a rapid literature review(49, 50) to identify tools available for measuring the patient-centred outcomes prioritised in the workshops/interviews, and summarise the tools' measurement properties and potential for use in the study population. The protocol will be developed using established guidance for reviews of measurement properties,(51) will be registered with NIHR PROSPERO, and reported following the PRISMA guidelines.(52)

12.2. Design

12.2.1. Search strategy:

We will undertake two rounds of electronic searches of the following bibliographic databases: the Cochrane Library (including DARE, HTA and NHS EED), MEDLINE, EMBASE, CINAHL, PubMed, PsychINFO, and Web of Science. The first round will identify tools used to measure the patient-centred outcomes in the study population or comparable populations, and will include all study designs; the second round will identify evidence about the tools' measurement properties (i.e. reliability, validity, and responsiveness), and will include quantitative study designs only. Searches will incorporate key words and relevant medical subject heading (MeSH), where available. Results will be cross-checked with included papers in the Phase 1 literature review of key features of ERM interventions, to ensure capture of relevant papers.

12.2.2. Inclusion criteria:

Papers will be included if: (i) the study **P**articipants are children (aged 0-18 years), AND (ii) the **C**ontext is children's critical care, OR children's secondary and community care / rehabilitation contexts more broadly, AND (iii) the **O**utcome (or, the 'phenomenon of interest') is one of the patient-centred outcomes of interest, OR a measurement property of a related tool. Searches will not be restricted on language or publication year.

12.2.3. Screening and selection:

One reviewer will screen all titles in the first instance,(53) and then screen all remaining abstracts. A second reviewer will screen the abstracts excluded by the first.(54) Both reviewers will screen a 20% random sample of the records eligible for full-text screening, pilot and refine the inclusion/exclusion criteria, and resolve disagreements using a third-party arbiter where required. One reviewer will screen the remaining full-texts. Screening will be managed in EndNote, and documented using Microsoft Excel spreadsheets.

12.2.4. Quality assessment:

We will use the COSMIN scale(55) to assess the quality of studies reporting the development/validation of outcome assessment tools, and established criteria(56) for assessing the quality of the tools themselves. We do not plan to assess the quality of studies describing the use/implementation of the tools, but will use the data extracted to inform the design of our subsequent survey of key stakeholders.

12.2.5. Data extraction and synthesis:

We will extract information and generate comparative summary tables on study characteristics and populations, implementation contexts and issues, content and characteristics of outcome assessment tools, and results of measurement properties. Taking into consideration the number of studies available for each outcome assessment tool, the quality of those studies, the consistency of results, the relevance and consistency of the implementation contexts, and reported implementation issues, we will generate a shortlist of tools whose potential use in a future trial and usual rehabilitation care could be tested in Phase 3. If no suitable tools are identified, we will prioritise next-stage research recommendations for outcome measurement in ERM interventions.

Phase 3: PROTOCOL Pilot Study

The PERMIT Pilot study

Paediatric Early Rehabilitation/Mobilisation during InTensive care pilot study

Sponsor: **University of Birmingham**

Chief Investigator: **Dr Barney Scholefield**

Funder: **National Institute for Health Research (NIHR) Health Technology Assessment (HTA) 17/21/06**

Sponsor reference number	ERN_18-1134
ISRCTN number (clinicaltrials.gov)	Awaiting registration of Phase 3
REC reference number	Ethics awaited

UNIVERSITY OF BIRMINGHAM

NHS National Institute for Health Research

13. Phase 3: PERMIT Pilot Study

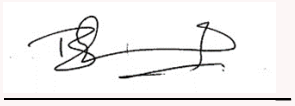
Protocol development and sign off

Protocol Contributors	
The following people have contributed to the writing of this protocol:	
Name:	Affiliation and role:
Dr. Barney Scholefield	Chief Investigator – University of Birmingham
Dr. Fenella Kirkham	Principal Investigator – University College London
Jacqueline Thompson	Research Fellow – The University of Birmingham
Dr. Jennifer McAnuff	Research Fellow – Newcastle University

CI Signature Page

This protocol has been approved by:

Trial Name:	PERMIT Pilot Study
Protocol Version Number:	Version: _0_._1_
Protocol Version Date:	_2_ _9_ / _0_ _4_ / _2_ _0_ _2_ _0_

CI Name:	Dr. Barney Scholefield
Trial Role:	Chief Investigator
Signature and date:	 _0_. _1_ / _0_ _4_ / _2_ _0_ _2_ _0_

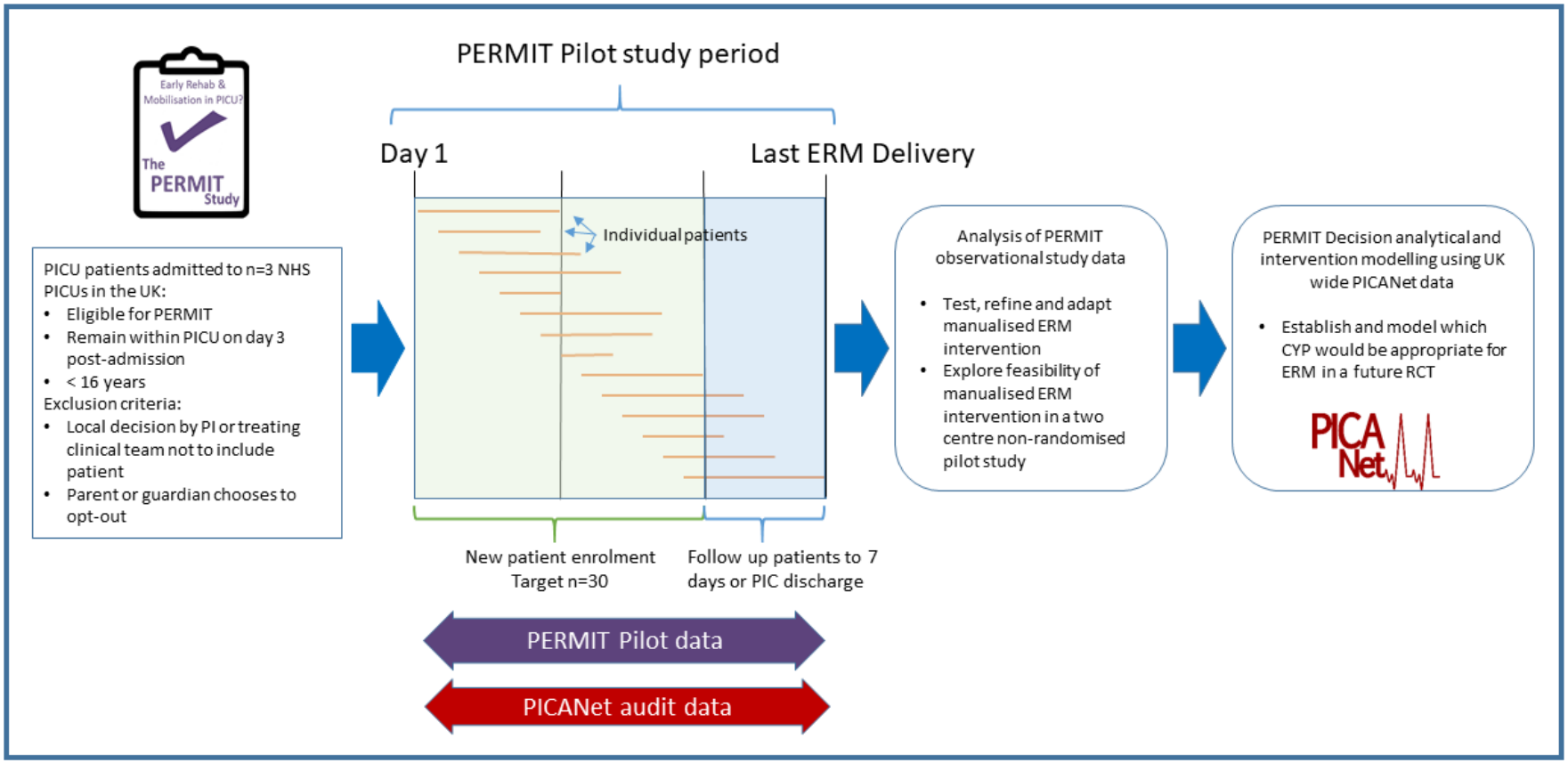
Sponsor statement:

Where the University of Birmingham takes on the sponsor role for protocol development oversight, the signing of the IRAS form by the sponsor will serve as confirmation of approval of this protocol.

TRIAL SUMMARY

Title	Paediatric Early Rehabilitation/Mobilisation during InTensive care feasibility study
Short Title	PERMIT Pilot study
Sponsor Name and Reference	University of Birmingham REF ERN_18-1134
Funder Name and Reference	NIHR HTA 17/21/06
Study Design	Pilot study
Overall Aim	To prepare for a definitive ERM trial, we will: iii) Assess the feasibility of proposed ERM intervention and outcome measures iv) Test ERM and outcome tool feasibility in PICs (design and test in three independent PICs)
Study Objectives	i) Test, refine and adapt manualised ERM intervention ii) Explore feasibility of manualised ERM intervention in a two-centre non-randomised pilot study
Population & Inclusion Criteria	Inclusion: All Children and Young Persons (CYP) (0-<16 years) Admitted to PICU Remain within PICU on day 3 post-admission Exclusion: Local decision by PI or treating clinical team not to include patient Parent or guardian chooses to opt-out
Study Centres	3 UK NHS PICUs: 18. Birmingham Children's Hospital 19. King's College Hospital NHS Foundation Trust, London 20. University Hospital Southampton NHS Foundation Trust
Follow up duration	7 days
Definition of End of study	Final report 24 months after commencement
Planned study period	5 months

PERMIT Pilot study flow chart



List of Abbreviations

CRF: Case report form

CV: Curriculum Vitae

CYP: Children and young persons

DoB: Date of birth

HQIP: Healthcare Quality Improvement Partnership

ICH-GCP: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use – Good Clinical Practice

NICU: Neonatal Intensive Care Unit

PCCMDS: Paediatric critical care minimum dataset – data provided to PICANet

PICANet: Paediatric Intensive Care Audit Network (PICANet)

PICU: Paediatric Intensive Care Unit

PIS: Patient Information Sheet

REC: Regional Ethics Committee

REDCAP: Research Electronic Data Capture

SOP: Standard Operating Procedure

13.1. Trial Rationale

13.1.1. Justification for participant population

A pilot study of infants and children in PICU who receive early rehabilitation and mobilisation (ERM) interventions as part of standard care.

13.1.2. Justification for design

To observe staff performing bespoke study ERM interventions within PICU will provide real-world data on the intervention and implementation element. We will also collect data on the implementation of ERM within UK PICU's. This information would inform the design of a future definitive clinical study.

13.2. Aims, Objectives and Outcome Measures

13.2.1. Aims:

- Test, refine and adapt manualised ERM intervention
- Explore feasibility of manualised ERM intervention in a three-centre non-randomised pilot study

13.2.2. Objectives:

- Confirm the feasibility and acceptability of the interventions and outcome tool
- Adaptation of usable intervention manual in Southampton PICU
- Implementation of intervention within two other selected PICU

13.2.3. Explore feasibility of manualised ERM intervention in a three-centre non-randomised pilot study

The feasibility research questions for Phase 3 are: 1) will clinicians, patients and families accept the proposed ERM intervention and approach(es) to the outcome, 2) can staff implement the ERM intervention and outcome assessments as manualised at the end of Phase 2 and if not, what modifications are necessary overtime and across the other PICU's? 3) To explore the extent to which different factors within PICU such as managerial, economic and organisational affect the implementation process and consequently, the observed effect on outcome measures.

At this stage, details of the feasibility study are generic as the nature of the proposed ERM (and any specifics regarding proposed intervention population) will not be known until the end of Phase 2. In particular, it is not known at this stage whether the ERM will comprise time-limited, defined "intervention episodes" that are delivered repeatedly or whether it will be more of an all-or-nothing "bundle of care" or process-level intervention. We propose two stages to feasibility assessment.

13.2.4. Test, refine and adapt manualised ERM intervention:

Over 2 months, we will prospectively screen and model approaching clinicians and families for consent for eligible patients to receive the proposed new ERM intervention (i.e. discussing recruitment and intervention processes without actually delivering the intervention). This will allow us to understand potential barriers to enrolment in terms of intervention acceptability (to patients, families, and clinicians), and unanticipated obstacles (e.g. specifics of clinical condition, co-morbidities, practicalities of delivering the intervention or outcome assessment) and so test, further refine and adapt the manual.

13.3. PERMIT Pilot Study Outcome Measures

13.3.1. *Primary outcomes:*

- Acceptability of ERM intervention for parents, clinicians and CYP.
- The proportion of eligible CYP successfully recruited;
- Proportion completing intervention;
- Proportion completing outcome assessments.

13.3.2. Primary outcome assessment

Case report forms would be used to record information on the delivery of ERM.

13.3.3. Secondary outcomes

- Rates of and reasons for deviations from the protocol

- Rates of adverse events.
- Ability to deliver intervention at times and for durations proposed in the manual
- Barriers to the recruitment of eligible patients, to delivery of ERM intervention and delivery of outcome measures
- Recommendations regarding further modifications to the protocol

- Other outcomes considered include duration of mechanical ventilation, hospital and PICU length of stay, cognitive and functional measures, parent/carer satisfaction questionnaires, quality of life measures.
- Data on the cost-utility of the study interventions will be collected to assess the economic value of ERM and cost implications with regards to staffing or availability of resources. We will use this data alongside rates of readmission to inform the design of the definitive PERMIT study.

13.3.4. Secondary outcome assessment

Purposive sampling would be used to recruit healthcare professionals, patient and public representatives of children who have been admitted to ICU. Audio-recorded interviews will be conducted by an expert qualitative researcher with stakeholders, CYPs and their parents. Text-based data would be collected until saturation is achieved and qualitatively analysed by experts. Data will be thematically analysed using QSR NVIVO software. This will inform the future approach to recruitment and strategies for overcoming local barriers to staged implementation of ERM.

13.4. Study Design and Setting

This is a pilot study to test the ERM interventions and outcomes within the PICU settings and barriers/facilitators to ERM implementation.

We plan to oversee the ERM delivery within UK PICUs. Following the observation of current ERM delivery and identification of patients who may benefit from ERM in selected PICs. We will identify related determinants of successful implementation.

13.4.1. Target population/setting:

13.4.2. Inclusion:

The clinical population defined by the inclusion and exclusion criteria in the manual from Phase 2; their families and treating medical, nursing and Allied Health professionals at University Hospital Southampton, Birmingham Children and Women's NHS Foundation Trust, and King's College Hospital NHS Foundation Trust, PICU.

13.4.3. Exclusion:

- Local decision by PI or treating clinical team not to include patient
- Parents or guardians choose to opt-out.

The broad inclusion criteria will allow observation of all types of patients admitted for PICU care (acute and elective, e.g. post-surgical recovery) and all age ranges without the requirement for 48hrs ventilatory (23)

13.4.4. Patient identification and screening

All patients admitted to PICU will be screened by local research staff with details recorded using the study screening log.

13.4.5. Strategies to maximise recruitment

Daily screening by the local research staff of patients will identify eligible patients and patients becoming eligible the following day. Each participating site will have a designated research co-ordinator to identify patients and record data on ERM and process activities. To ensure validity and reliability, a designated PERMIT research co-ordinator will collect data at all participating sites.

13.4.6. Recruitment/enrolment:

All eligible patients will be included in PERMIT pilot study unless parents/guardians choose to opt-out of data sharing (see consent).

13.4.7. Feasibility study of manualised ERM intervention

We will undertake a three-centre non-randomised pilot study testing the implementation of the manualised ERM intervention, including proposed dose and duration and outcome assessment tool(s). We will investigate whether the ERM intervention and outcome assessment can be delivered as intended, the potential challenges to delivery as intended and participant's experiences of the process.

13.4.8. *Target population/setting:*

CYP as defined by the manual's inclusion and exclusion criteria at University Hospital Southampton, Birmingham Children and Women's NHS Foundation Trust, and King's College Hospital NHS Foundation Trust Great Ormond Street Hospital, PICUs, families of CYP, multi-disciplinary clinicians at PICUs.

13.4.9. Sampling:

30 CYP, their families and treating clinicians at 3 PICU centres.

13.4.10. *Data collection and analysis:*

We will screen all patients admitted to the relevant PICU over the two month study period for proposed inclusion and exclusion criteria recording the incidence of eligible patients. We plan to enrol 10 patients in Southampton PICU in months 19-21, engaging with Medical lead clinicians, Nursing Staff and Allied Health Professionals as well as consenting families (including assenting CYP where feasible). We will also train research and therapy staff at King's University Hospital London and Birmingham Women and Children's Hospital from whom we plan to recruit 10 patients at each centre in the subsequent months (total n=30 CYP).

We will collect patient-level data on demographic patient characteristics, age, pre-admission neurodevelopmental status, the reason for admission, critical care interventions (ventilation, inotrope usage, etc.), and sedation level. We will examine delivery as intended and NHS costs of implementing the ERM intervention at times and for durations proposed in the manual, including all additional NHS staff time. We will also examine and monitor any deviation from the ERM intervention protocol and record any adjustment of the intervention and its timing and duration based on acceptability and feasibility on the relevant PICU. We will document any adverse events using a modification of international consensus adverse outcome guidelines (57)

We will administer outcome measures mandated in the manual, at times prescribed, to determine Feasibility, acceptability and the appropriateness and usability of the candidate primary and secondary outcome measurement tools as well as study protocols. We will report the completion rates of all outcome measures, compliance and adherence to treatment plans.
For the 10 CYP recruited at Southampton, we will interview parents, clinicians and CYP (where possible) to understand their experience of the ERM intervention and outcome tools. We will focus on barriers and facilitators to recruitment, parents and CYP experiences ERM intervention and outcome assessment and clinicians experiences of delivering the intervention. Interviews will, with consent, be audio-recorded, transcribed verbatim and edited to ensure the anonymity of respondent. The analysis will be conducted by a thematic approach informed by key constructs in the Normalisation Process Theory. (37, 58)

13.4.11. Phase 3 Outputs:

Revise manual after testing in the feasibility study, evidence of acceptability and feasibility of proposed ERM intervention and outcome assessment tool used in clinical practice.

13.4.12. Phase 3 stop/go criteria

- Feasibility and acceptability of the interventions and outcome tool
- Adaptation of usable intervention manual to selected PICU's

13.5. Outcomes

13.5.1. Data collection and analysis:

We will screen all patients admitted to PICU over the study period using the proposed inclusion and exclusion criteria. We will approach professionals (n=15-20) with clinical responsibility for potentially eligible CYP. We will undertake brief think-aloud discussions (10-15 minutes) with them about the workability of the ERM interventions for the specific eligible patient, seeking any suggestions for adaptations to the intervention that the treating clinicians consider might improve acceptability and feasibility for the range of eligible CYP. We will refine and adapt the manual throughout this process.

After revisions, we will then approach potentially eligible CYP (n=5-10) and families for 'notional consent' for the ERM intervention. We will undertake brief think-aloud discussions (10-15 minutes) with them about the study, exploring their views on study processes (especially recruitment and outcome assessment) and intervention processes. We will then undertake final revisions and adaptations of the manual. All discussions will, with consent, be audio-recorded, transcribed verbatim and edited to ensure the anonymity of respondent. The analysis will be conducted by a thematic approach informed by key constructs in Normalisation Process Theory (37, 58).

13.5.2. Unit level data (competency assessment for site performance)

Data will be collected on each study day (XX) at a unit level to record the following

- Number of nursing staff to patient ratio at 09:00.
- The number of beds open to admissions at 09:00.
- Census of number of eligible patients in PICU at 09:00 (using screening logs).
- The number of eligible patients who received ERM.

13.5.3. Patient-level outcome data

Two categories of patient-level data will be collected.

3) PERMIT pilot study data (new data).
4) Routine PICANet data which include the PCCMDS (Paediatric critical care minimum data set).

13.5.4. Implementation-level data

Two categories of implementation-level data will be collected.

5) Qualitative data on the role of managers, organisational structure and availability of resources within PICU.
6) PERMIT process-related study data (new data) exploring differences in local team characteristics, local cultures such as communication strategies, interprofessional collaborations and implementation efforts. Availability of mobilisation teams, goal setting on ward rounds using checklists, criteria for mobilisation and daily feedback.

13.5.5. Early Rehabilitation and Mobility (ERM) phase compliance data

Two categories of ERM implementation will be collected.

7) Qualitative data with willing participants – carers and CYP discharged from PICU.
8) PERMIT study data on recruitment approach (new data).

Figure 2a: Timeline for PERMIT Pilot study

Manual Development / Site Initiation Visits (SIVs)

Pilot phase

Site	Preparatory phase (September – December 2020) / 5-month Phase 3 enrolment period (January – May 2021)									
	9	10	11	12	0	1	2	3	4	5
Pilot site 1										
Pilot site 2										
Pilot site 3										

Site 1 = Southampton University Hospital,
Site 2 = Birmingham Children and Women's NHS Foundation Trust,
Site 3 = King's College Hospital NHS Foundation Trust

Site close visits / Qualitative Process evaluation

Figure 2b: Timeline for PERMIT Pilot study

Phase	Stage	Stage date	Number of activities	Minimum required completion rate (%)	Duration (Hours/Days)
Pre-implementation	Co-design + Level of engagement + Debriefs				
	Readiness planning, preparation of educational materials or videos				
	Readiness assessment (baseline infrastructure/equipment, resources + the availability of medical records for retrospective data)				
Implementation	Local opinion leader, PICU staff to patient ratio, training + coaching				
	Feasibility, adherence and fidelity monitoring, i.e. observations / weekly supervision				
	Feasibility (local consensus processes), adherence and fidelity assessment, audit and feedback				
Post-implementation	Competency or performance assessment				

13.5.6. PICANET routinely collected data

Participating sites already collect PICANet defined data items and submit to PICANet web. For patients included in the PERMIT study, local sites will collate the PICANet data already collected for that patient and combine this data with the PERMIT pilot data below. This data will be pseudo-anonymised at the local site before secure transfer to the PERMIT trials office.

Currently, all patients admitted to PICU have data recorded via the Paediatric Intensive Care Audit Network (PICANet). PICANet has permission to collect identifiable patient data under section 251 of the NHS Act 2006 (originally enacted under Section 60 of the Health and Social Care Act 2001). We will use the PICANet data to supplement and reduce the burden of data collection for PERMIT. Patient characteristics (e.g. reason for admission, the severity of illness score (e.g. PIM3 (43)), critical care interventions) and individual patient PIC resource use (mechanical ventilation days, renal replacement therapy, vasoactive drug use). A full list of data items and data definitions can be found at www.picanet.org.uk/documentation.

13.5.7. PERMIT pilot study patient-level data

Figure 3: Screening and data collection schema for individual patients display the daily planned data collection for individual patients.

From Day 3 of PICU admission onwards, until the patient is discharged from PICU, patient-level data will be collected for the PERMIT study. The risk assessment will be conducted using bespoke PERMIT ERM grid mapped against the sickness or acuity levels of patients. Using the rationale for each level of acuity, patients would be assigned to the lowest ERM activity level

4) Clinical status

This will include health care interventions, ventilator requirement, sedation and coma level, presence of delirium, inotropic support and neuromuscular blocking drug usage. This data will supplement routinely collected PICANet data. Data will be collected twice, between XX: XX and XX: XX and between XX: XX and XX: XX each day. Data on adverse events such as dislodgement of endotracheal tubes, or central lines during mobilisation will be collected.

5) Intervention components

We will undertake a behavioural mapping procedure (44) to capture ‘active interaction’ processes with a patient in a therapeutic rehabilitation context after local researcher training, and piloting of observation case report form. Frequency, quantity, and type of ‘active interaction’ of ERM delivered by physiotherapy, occupational therapy, speech & language, play, psychology, nurse and parent will be recorded. Prompts, checklists and menu of activities will be designed to aid clinical decision-making algorithms. Given the heterogeneous nature of the interventions available for management, the choice of treatment will be based on clinical assessment and the decision of the local team.

Clinical staff performing the activity will be instructed to record the planned activity and delivered activity duration in medical records. A research nurse will use this data to complete active interaction CRF. However, further observation of clinical decision-making by multi-disciplinary teams and the delivery of ERM activities may be performed at set times by the study co-ordinator. On completion of the study, the content of intervention menus will be revised to develop comprehensive care testable pathways for the definitive study.

CRFs will be collated hourly between XX am and XX pm by the local site research nurse. ‘Active ERM interaction/interventions’ will be defined using the PERMIT bespoke intervention manual, developed using the logic model (**Error! Reference source not found.**) and based on a paediatric modification o

f published ICU mobility scales. (45) With the addition of free-text for any activity performed outside of the standardised mobility scales.

This data will be recorded on the “Observed ERM active interaction” CRF.

Daily at XX: XX researchers will retrospectively review the clinical case records to record any ERM activities that occurred overnight. Overnight is defined as the time from the end of Observed active interaction period 17:01, until 08:59 prior to the start of the next Observed active interaction period.

6) Implementation components

Regular discussions during ward rounds will be used as platforms to remind staff about the PERMIT study. Study *Implementation activities* CRFs (checklist and audit proforma’s) will be used to record the process of ensuring and maintaining staff engagement, performing clinical assessments and delivering ERM within PICU’s.

13.6. Sample Size

We aim for a sample size of n=30 CYP.

13.7. Future RCT Sample Size Modelling:

Using the outcomes of the recruitment rate, adherence, compliance and adverse events, PICU and patients characteristics, from the pilot study, we will perform sample size calculations for potential trial population sample size using national anonymised data for all UK and Irish PICUs. Anonymised PICANet data has been used efficiently for previous NIHR HTA funded PIC RCTs (FEVER study: HTA 15/44/01*, CHiP study:* HTA 05/506/03). Using PICANet admission data, on average, 20,000 patients are admitted per year across 28 PICUs (averaging 2 patients/unit/day). Of this 40-45 % of patients stay on PICU for ≥3 days (20% > 7 days), on average 5.5 to 6 patients/unit/week will be eligible. (1)

13.8. PICANET Modelling

Pre- and post- PERMIT pilot study data collection, we will use the identified key patient characteristics for patients who may benefit from ERM and model the number for patients available in the UK for a future RCT by analysing the full PICANet dataset. We will also consider differences in the integrated management system and local processes.

PICANet has ethical approval granted by the Trent Medical Research Ethics Committee (ref 05/MRE04/17) and the National Information Governance Board (NIGB) to collect personally identifiable data without consent. All PICANet data used within the PERMIT study will be anonymised before sharing from the local sites to the PERMIT trials office. Also, any PICANet data used to model future RCT feasibility will be anonymised. (1)

13.9. Consent

13.9.1. Consent

As the study is interventional, children admitted to select PICU's will receive additional treatment, we will receive assent from CYPs and consent from patients and parents/guardians to conduct the PERMIT pilot study. This will be conducted by appropriately trained staff designated on the PERMIT study log.

Parents/legal guardians would be provided with information leaflets explaining details of the intervention. Information about the study will be provided to all eligible patients and displayed with public areas of participating PICUs. Research nurses will explain the study to parents, family and friends and children who are able to make autonomous decisions. Parents/legal guardians will be approached on Day 3 of their child's admission for consent and assured that the future care their child will receive would not be affected. We will also mention that no identifiable data for the PERMIT pilot study will be collected. Due to the sensitive nature of the admission time, opt-in consent would be used. Local language translation services will be used to explain the information about the consent process to participants in a preferred format.

This procedure has been acceptably used within UK PICUs (previous NIHR HTA funded PIC RCTs (FEVER study: HTA 15/44/01, CHiP study: HTA 05/506/03) and recommended by the Ottawa Statement(59), where posters and information leaflets explaining the study were available to family and friends explaining their rights to withdraw from the study at any time.

13.9.2. Patient withdrawal

We will record details of children who opt-out or withdraw after enrolment to the study in screening logs. We will include data collected from patients who withdrew after data collection commenced but prior to withdrawal.

13.10. Patient and Public Involvement

We will undertake consultation interviews with parents/legal guardians of children and young people who have been admitted to PICU. Their views would be incorporated in the design, the experience of interventions, acceptability, i.e. choice of patient-relevant outcomes and conduct of the study – active or passive approach to informed consent. We would also ensure their views are reflected in the presentation and outlook of the patient information leaflets (PIS), posters and dissemination of results.

We would also have representatives of senior managers working in PICU to ensure the perspective with regards to the organisation, economic and process-related factors in PICU are discussed. This might take the form of informal chats or short think-aloud meetings. Outcomes of these meetings will be incorporated during the study design.

13.11. Study procedures and assessments

13.11.1. Summary of assessments

Figure 7 Schedule of assessments for each PICU

TIMEPOINT	*Study Day 1 - 2*	*Study Day 3*	*Final Study Day*
ENROLMENT:			
Eligibility screening (daily)	X	X	X
Enrolment to PERMIT (daily)	X	X	X
ASSESSMENTS:			
Complete Unit staff and patient census (daily)		X	X
Patient-level: Clinical Status CRF. Twice daily		XX	XX
Patient-level: Observed ERM active interaction CRF (for each active interaction)		X	X
Patient-level: Summary of overnight ERM activity CRF		X	X
Ensure completion of PICANet routine data / Implementation outcomes CRF	X	X	X

Study day 1 = **First day** on the week of trial starting

Study day 3 = **Third day** on the week of trial starting and commencement of trial in PICU

Study day 60 = **Final day** of enrolment of eligible patients

Study day 61-69 = Completion of up to 7 days of data collection for enrolled patients. No new patient enrolled during this period.

Figure 8 Schedule of assessments for individual patients

TIMEPOINT	*Patient Day 1 -2 (09:00)*	*Patient Day 3 (09:00-17:00)*	*Patient Day 3-60 (09:00-17:00)**
ENROLMENT:			
Eligibility screen	X		
Enrolment to PERMIT		X	X
ASSESSMENTS:			
Patient level: Clinical Status CRF. Twice daily		XX	XX
Patient-level: Observed ERM active interaction CRF (for each active interaction)		X	X
Patient-level: Summary of overnight ERM activity CRF		X	X
Ensure complete PICANet routine data has been collected / Implementation outcomes CRF	X	X	X

Patient Day 0 = the day a patient is admitted to PICU, which occurs after 09:01 and before 08:59 of the same day.

Patient Day 1 = the 1st day the patient has been in PICU at exactly 09:00. (A patient may have been admitted 10mins prior, or 23 hours prior; however, the census count is that the patient is in PICU at exactly 09:00 on the study day).

Patient Day 2 = the 2nd day the patient has been in PICU at 09:00.

Patient Day 3 = the 3rd day the patient has been in PICU at 09:00 (this is the day that ERM activities will be delivered from).

Patient Last Day = is the last or 60th day the patient has been in PICU or end of study enrolment.

13.11.2. Clinical status

Data will be collected twice, between XX: XX and XX: XX and between XX: XX and XX: XX each day.

13.11.3. Observed ERM active interaction

CRFs will be collated hourly between 9 am and 5 pm by the local site research nurse and study co-ordinator.

13.11.4. Summary of overnight ERM activities

Daily at XX: XX researchers will retrospectively review the clinical case records to record any ERM activities that occurred overnight. Overnight is defined as the time from the end of Observed active interaction period 17:01 until 08:59 before the start of the next Observed active interaction period.

13.11.5. Implementation processes

CRFs will be collated hourly between 9 am and 5 pm by the local site research nurse and study co-ordinator. This includes data on fidelity, protocol deviation, compliance and adherence.

13.11.6. Complete PICANET routine data

Local sites will have existing PICANet routine data collection systems in place. PICANet collected admission data on all patients within 1 hour of PICU admission. PCCMDS data is collected twice a day summarising activities and interventions within each shift. Further details available in PICANet data collection manual https://www.picanet.org.uk/data-collection/data-manuals-and-guidance/

13.12. Adverse Event Reporting

13.12.1. Reporting Requirements

Because there is an interventional element to the PERMIT Pilot Study, information on serious adverse events (SAEs) and adverse event (AEs) reporting will be required. We will record any expected and unexpected clinical events that occur during the delivery of ERM activities. Precise definitions for expected adverse events will be provided to ensure consistency.

We will define SAEs as events that require medical intervention, exacerbated the patient's condition or led to death. These events will be reported to the PERMIT CI and study team within 24 hours of occurrence after confirmation by the site PI. A copy of the report should then be faxed to the study team shortly afterwards.

AEs will be defined as events untoward events that occur during intervention delivery or patient's admission but did not require any further intervention or only caused minor disruption of the patient's clinical status. These events will be reported to the PERMIT CI and study team within 2 weeks of admission.

Expected Adverse events

- *Dislodgment of tubes or ETT*
- *Falls*
- *Discomfort, dizziness, tiredness or pain*
- *Change in blood pressure, heart rate or respiratory rate*

Unexpected Adverse events

- *Cardia arrest*
- *Death*

13.12.2. Source Data

To allow for the accurate reconstruction of the study and clinical management of the subject, source data will be accessible and maintained at the site. The participants' medical notes generated and maintained at the site will act as source data. Some data may be entered directly onto the paper-based CRF before data entry into the REDCAP database. Screening CRF Completion

Data reported on each CRF will be consistent with the source data, and any discrepancies will be explained. Staff delegated to complete CRFs will be trained to adhere to:

- *Date format and partial dates*
- *Study-specific interpretation of data fields*
- *Which forms to complete and when*
- *What to do in specific scenarios, for example when a parents/guardians opt-out of data sharing from the study*
- *Missing/incomplete data*
- *Protocol and ICH-GCP non-compliances*

In all cases, it remains the responsibility of the local site's Principal Investigator to ensure that the CRF has been completed correctly and that the data are accurate. Where applicable for the study, this will be evidenced by the signature of the local site's Principal Investigator.

13.13. Data Handling and Record-Keeping

13.13.1. Data Management

Figure 9 PERMIT study dataflow

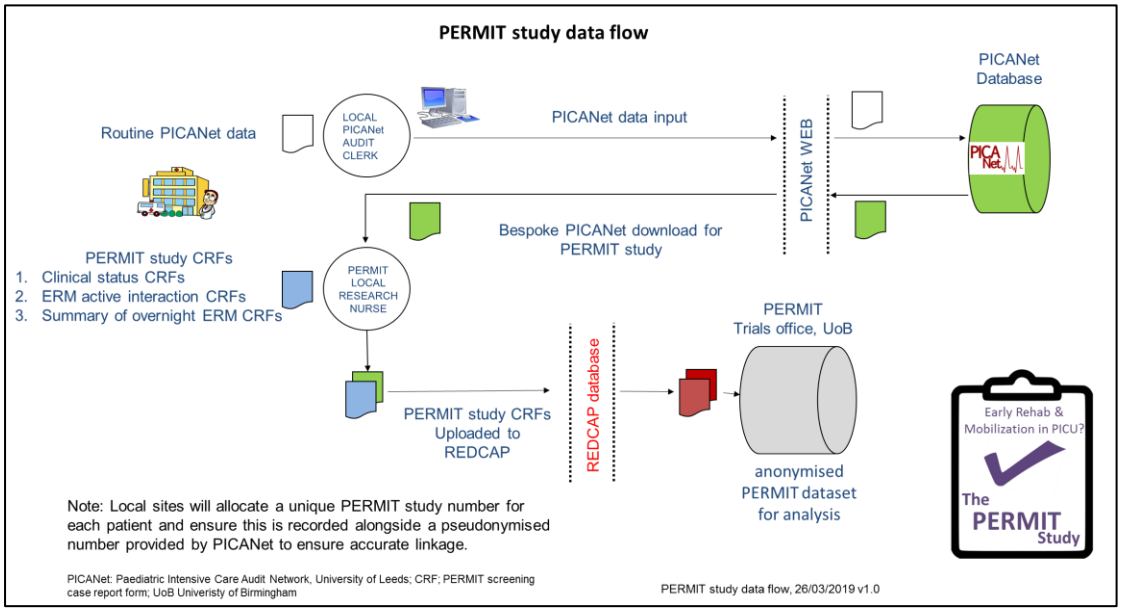


Figure 6 summarises PERMIT study data flow.

Participating sites will screen all eligible patients for PERMIT study. A screening log will be created at each site by the local research team, and this will record local patient IDs [NHS number and own hospital Patient Identification number].

For patients that fulfil all inclusion criteria and no exclusion criteria: local research staff will record in the enrolment log 1) a unique PERMIT study ID [local site code + sequential numbered patient; provided by the Trials Office], local patient IDs [NHS number and own hospital Patient Identification number] and PICANet study ID [provided by PICANet] of all enrolled patients.

Local sites will complete CRFs for all enrolled patients using the PERMIT study ID on each record. CRFs will be paper-based initially to aid bedside data collection. At the end of each study day, paper CRFs will be collated and stored in patient-specific site files. Local sites will be responsible for the safe and secure storage of these primary documents (locked in a filing cabinet or office within the PICUs or research offices).

Local sites will input data from the paper-based CRF data onto REDCAP computer database using the PERMIT study ID for patient identification only. No Identifiable patient data will be uploaded to REDCAP or shared with the PERMIT trials office.

Local sites will then access PICANet data via a customised download from the PICANet database using the PERMIT study ID. No identifiable patient data will be included in this customised download (DoB which will be converted into the age in days). The PICANet data download will be uploaded to the REDCAP database to combine with the PERMIT study CRF data.

The PERMIT study trials Office team will only access the anonymised data in the REDCAP database.

Data contained within REDCAP will be transferred securely to the University of Birmingham computer server within the PERMIT study database for statistical analysis.

13.13.2. Archiving

At the end of the study, the Chief Investigator will archive all centrally-held study-related documents securely for a minimum of ten years in accordance with ICH-GCP guidelines.

It will be the responsibility of the Principal Investigators at each site to ensure all essential study documentation, and source documents (e.g. Investigator Site Files, copies of CRFs, etc.) at their sites are securely retained for at least 10 years.

Guidance on archiving will be provided in the study-specific Standard Operating Procedure (SOP). All archived documents, held centrally and locally, should be available for inspection by appropriate authorities upon request.

13.14. Site Set-up and Initiation

All participating Principal Investigators will be asked to sign the necessary agreements and supply a current CV to the PERMIT Trials Office. All members of the site research team will also be required to sign a site signature delegation log. Before commencing recruitment, all sites will undergo a process of initiation, study training and will have completed ICH-GCP training. Key members of the site research team will be required to attend either a meeting or a teleconference covering aspects of the study design, protocol procedures, collection, and reporting of data and record keeping. Sites will be provided with an electronic copy of the Investigator Site File (for local printing on-site) containing essential documentation, instructions, and other documentation required for the conduct of the study. The PERMIT Trials Office must be informed immediately of any change in the site research team.

13.14.1. Training and Site Initiation Visits (SIVs)

Prior to the study launch, we will arrange meetings and visit sites to understand local processes, patient pathways and organisational factors that may influence the study. Three levels of training will be delivered to ensure consistency and intervention fidelity.

13.14.2. Training for and engagement with Senior management staff

We will develop questions regarding the following hierarchy of decision making for ERM on PICU. Pre- and post-comparisons of the answers provided by sites would be used to inform the design of the definitive clinical trial.

- Who decides that ERM is a priority at an organisational and unit level? This could include managers, multi-disciplinary clinical leads, and funders.
- Who and how is the decision making regarding ERM made during clinical PICU ward rounds?
- Who decides what ERM is suitable for each patient admitted on PICU
- Who decides who will perform the ERM activity on a patient?
- How to the performance of ERM by the designated health professional be assessed as adequately performed?

13.14.3. Ongoing Training for Site PI and research staff

Study training and monitoring of adherence will be performed throughout the study. This data will be reviewed after recruitment at the first recruitment site to identify factors related to recruitment, eligibility, staff buy-in, ease of completing study CRFs. After that, relevant changes will be made to subsequent recruitment phases of the pilot study.

13.14.4. Training for Local Clinical Staff

To ensure engagement

Following the collection of PERMIT pilot study data, we will use identified key patient characteristics for patients who may benefit from ERM and model the number for patients available in the UK for a future RCT by analysing the full PICANet dataset.

13.15. Monitoring

13.15.1. On-site Monitoring

Monitoring will be carried out as required following a risk assessment and as documented in the monitoring plan. Any monitoring activities will be reported to the PERMIT Trials Office and any issues noted will be followed up to resolution. Additional on-site monitoring visits may be triggered, for example, by poor CRF return, poor data quality, an excessive number of participant withdrawals, protocol deviations or AE's. If a monitoring visit is required, the PERMIT Trials Office will contact the site to arrange a date for the proposed visit and will provide the site with written confirmation. Investigators will allow the PERMIT study staff access to source documents as requested.

13.15.2. Central Monitoring

The PERMIT Trials Office will be in regular contact with the site research team and PICANet to check on progress and address any queries that they may have. The PERMIT Trials Office will check the incoming summary of screened cases and Case Report Forms for compliance with the protocol, data consistency, missing data, and timing. Sites will be asked for missing data or clarification of inconsistencies or discrepancies. Sites will be requested to send in copies of signed Opt-out Forms and other documentation for in-house review. This will be detailed in the monitoring plan.

13.16. Audit and Inspection

The Principal Investigator will permit study-related monitoring, quality checks, audits, ethical reviews, and regulatory inspection(s) at their site, providing direct access to source data/documents. The Principal Investigator will comply with these visits, and any required follow up. Sites are also requested to notify the PERMIT Trials Office of any inspections.

13.17. Notification of Serious Breaches

The sponsor is responsible for notifying the REC of any serious breach of the conditions and principles of ICH-GCP in connection with that study or the protocol relating to that study. Sites are therefore requested to notify the PERMIT Trials Office of any suspected study-related serious breach of ICH-GCP and/or the study protocol. Where the PERMIT Trials Office is investigating whether or not a serious breach has occurred sites are also requested to cooperate with the Trials Office in providing sufficient information to report the breach to the REC where required and in undertaking any corrective and/or preventive action.

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or ICH-GCP, and/or poor recruitment. Any major problems identified during monitoring may be reported to the PERMIT Trial Management Group and the REC. This includes reporting serious breaches of ICH-GCP and/or the study protocol to the REC. A copy is sent to the University of Birmingham Clinical Research Compliance Team at the time of reporting to the REC.

13.18. End of Study Definition

The end of the study will be after the three-month follow-up point of the last recruited participant plus an additional 6 months of data cleaning, queries, and analysis period. The PERMIT Trials Office will notify the REC the study has ended, and a summary of the clinical trial report will be provided within 12 months of the end of the study.

A copy of the end of study notification, as well as the summary report, is also sent to the University of Birmingham Research Governance Team at the time of sending these to the REC.

13.19. Statistical Considerations

13.19.1. Analysis of Outcome Measures

The effectiveness of the manualised ERM intervention will be described as the acceptability of ERM intervention for parents, clinicians and CYP. The proportion of eligible CYP successfully recruited; Proportion completing intervention; Proportion completing outcome assessments. Assessment of outcome would involve participants who demonstrate improvement in the chosen study outcome measures. Quantification of doses of ERM on each day and characteristics of patients receiving ERM; Rates of and reasons for deviations from protocol; Rates of adverse events; Ability to deliver intervention at times and for durations proposed in the manual; Barriers to the recruitment of eligible patients, to delivery of ERM intervention and to delivery of outcome measures; Recommendations regarding further modifications to the protocol will be presented using standard descriptive and inferential statistics for normal and non-normally distributed data with confidence limits. Categorical variables will be tabulated using frequencies and proportions.

Further analysis will be undertaken to understand organisational and process factors associated with ERM. Multilevel multivariable logistic regression models with random effects for PICU site will be used to evaluate predictors of ERM provided on day 3 and intervention fidelity. Predictors of interest will be established following PERMIT survey and expert group consensus (examples include: age, presence of PICU protocol, diagnostic category, sedation level and PIM3 probability of mortality score). To calculate incidence rates and incidence rate ratios for the number or ERM interventions, accounting for a variable length of PICU stay, we will use a multilevel multivariable Poisson Model.

13.20. Trial Organisational Structure

13.20.1. Sponsor

The University of Birmingham (see Administrative information page 5)

13.20.2. Trial Management Group

All day-to-day management of the PERMIT Study will be the responsibility of the Trial Management Group (TMG). Members of the TMG will include the PERMIT Chief Investigator, co-applicants, research fellows and project manager. The TMG will meet regularly to discuss the management and progress of the study and findings from other related research. There will be close contact throughout the study with the PICANet trials group.

13.20.3. Project oversight committee/Trial steering committee

An independent trial oversight committee has been appointed by the NIHR in keeping with standard structure and definitions.

Title	First name	Last name	Job Title	Expertise
Dr	Shane	Tibby	Consultant in PICU	Chair, Clinician, Trialist
Prof	Mark	Peters	Professor of Paediatric Intensive Care	Clinician, Trialist
Dr	Kerry	Woolfall	Senior Lecturer Health Services Research	Qualitative Researcher
Ms	Suzanne	Dottin-Payne	Parent representative	PPI representative
Prof	Jim	Lewsey	Professor of Medical Statistics	Statistician

13.20.4. Finance

This is a commissioned study funded by NIHR Health Technology Assessment (HTA) (*NIHR HTA*-17/21/06). It will be eligible for (NIHR CRN) Portfolio adoption. Funding will be provided for local R&D set-up, site-specific training, eligibility screening, and CRF completion.

13.21. Ethical Considerations

The study will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, June 1964, amended at the 48th World Medical Association General Assembly, Somerset West, Republic of South Africa, October 1996 (website: http://www.wma.net/en/30publications/10policies/b3/index.html).

The study will be conducted in accordance with the Research Governance Framework for Health and Social Care, the applicable UK Statutory Instruments, (which include the Medicines for Human Use

Clinical Trials 2004 and subsequent amendments and the Data Protection Act 2018 and Guidelines for Good Clinical Practice (ICH-GCP). The protocol will be submitted to and approved by the REC before circulation.

Before any participants are enrolled in the study, the Principal Investigator at each site is required to obtain local R&D approval. Sites will not be permitted to enrol participants until written confirmation of R&D approval is received by the Principal Investigator.

For any amendment to the study, the Chief Investigator or designee, in agreement with the sponsor will submit information to the appropriate body in order for them to issue an approval for the amendment. The Chief Investigator or designee will work with sites (R&D departments at NHS sites as well as the study delivery team), so they can put the necessary arrangements in place to implement the amendment to confirm their support for the study as amended.

It is the responsibility of the Principal Investigator to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual participants.

PIC admission is known to be stressful for parents (30), with logistical challenges for parents' participation in terms of caring for their child, other children, and travel. PERMIT co-applicants have extensive experience of researching families in PICU, acknowledging these challenges (46, 47).

CYP should be involved in decision making about research (48). This is challenging in PICU when CYP are critically unwell. Following a PICU admission, participation may be challenging for some CYP experiencing residual neurological and cognitive difficulties.

PERMIT is addressing these by:

1) Working with CYP and parent PPI, to ensure the work is designed sensitively and full risk/benefit assessment is conducted.

2) Adopting an inclusive approach, recognising CYP right to self-determination. Accessibility will be facilitated through attention to the language and format of study materials.

4) Adopting methods to accommodate participants' preferences and facilitate involvement.

In order to design clinical trials to investigate the potential benefits of ERM in critically ill children, it is crucial to understand current utilisation and potential feasibility in a UK context. PERMIT will generate much-needed knowledge for future multi-centre interventional trials to test the effectiveness of ERM on short and long-term outcomes in children as well as healthcare utilisation. Therefore this research is important as it will contribute to establishing the health benefits of ERM in critically ill children and impact on services and NHS resources.

The PERMIT study has been conceived, designed and developed by experts in paediatric intensive care, health services research and clinical trials and has been reviewed and approved by independent reviewers on behalf of the funders (National Institute for Health Research (NIHR) Health technology award (HTA) programme). The PERMIT study team includes academics, clinicians, as well as patients, carers and parent involvement and engagement members who have and will inform all aspects of the project design, conduct, and outputs. The study management group will meet regularly to review the progress of the study against timelines and milestones.

13.21.1. Recruitment

Participants who meet the study eligibility criteria will be approached and enrolled after consent from Parents/Legal guardians has been received. Additional data on the use of ERM and potential eligibility into a future RCT of an ERM intervention will be collected alongside routinely collected standard audit data.

13.21.2. Consent

This aspect of the PERMIT study is interventional. Eligible children will receive the study intervention. We will seek consent from parents/legal representatives.

This is to avoid any unnecessary burden for parents/legal guardians in approaching consent during a very sensitive time. Information about the study will be provided to all eligible patients and displayed within public areas of participating PICUs. This will explain the study to parents, family and friends and children who are able to make autonomous decisions. Parents/legal guardians may opt the child's data out of the study at any time and that the future care their child will receive will not be affected. We will also mention that no identifiable data for the PERMIT pilot study will be collected.

This procedure has been acceptably used by the FEVER observational study (REC 17/NW/0026), an observational study of critically ill children's exposure and management to fever within UK PICUs, where posters and information leaflets explaining the study were available to family and friends explaining their rights to withdraw from the study at any time.

13.21.3. Risk, burdens, and benefits

This aspect of the PERMIT study is interventional and will affect the treatment patient's receive; however, parents / legal representatives will have the opportunity to withdraw the patient from the study at any time. All data collected before patients opt-out would be used only for study purposes and stored securely in accordance with Data Protection guidelines. This process will be known to them through leaflets and posters that will be accessible on the PICU written in a clear and understandable language. No identifiable information will be accessed directly for the study. It is often the case that those involved in the decision to participate in studies would like to see their data used to improve the care they and other patients are given.

13.21.4. Confidentiality and data protection

No identifiable patient data will be collected or transferred to the PERMIT trials office for the PERMIT pilot study. Anonymised data will be stored securely in REDCAP database or nested within the PICANet database. Currently, all patients admitted to PICU have data recorded via the Paediatric Intensive Care Audit Network (PICANet). PICANet has permission to collect identifiable patient data under section 251 of the NHS Act 2006 (originally enacted under Section 60 of the Health and Social Care Act 2001). We will use the PICANet data to supplement and reduce the burden of data collection for PERMIT. However, no identifiable patient data will be collected or used for the PERMIT pilot study. As PICANet is part of the Health Quality Improvement Partnership (HQIP), therefore we intend to make a release of a data request, and a customised data collection request to HQIP in order to gain access to unidentifiable routine PICANet data and collect the additional data required for this study.

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored following the General Data Protection Regulation and Data Protection Act 2018.

Participants will always be identified using only their unique study identification number, on the Case Report Form and correspondence between the Trials Office and the participating site. Participants will give their explicit consent for the movement of their Opt-out form, permitting for the Trials Office to be sent a copy. This will also be used to perform in-house monitoring of the consent process.

The Investigator must maintain documents, not for submission to the Trials Office (e.g. Participant Identification Logs) in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete study records, provided that participant confidentiality is protected.

The Trials Office will maintain the confidentiality of all participants' data and will not disclose information by which participants may be identified to any third party. Representatives of the PERMIT Study Trial Office and sponsor may be required to have access to participant's notes for quality

assurance purposes, but participants should be reassured that their confidentiality will be respected at all times.

The Chief Investigator will act as the data custodian for the PERMIT pilot study.

13.21.5. Conflicts of interest

None.

13.22. Insurance and Indemnity

The University of Birmingham has in place Clinical Trials indemnity coverage for this study which provides cover to the University for harm which comes about through the University's, or its staff's, negligence in relation to the design or management of the study and may alternatively, and at the University's discretion provide cover for non-negligent harm to participants.

With respect to the conduct of the study at the site and other clinical care of the patient, responsibility for the care of the patients remains with the NHS organisation responsible for the Clinical Site and is therefore indemnified through the NHS Litigation Authority.

The University of Birmingham is independent of any pharmaceutical company, and as such, it is not covered by the Association of the British Pharmaceutical Industry (ABPI) guidelines for participant compensation.

13.23. Publication Policy

The results of this study will be submitted for publication in a peer-reviewed journal. The manuscript will be prepared by Dr. Scholefield, and authorship will be determined by mutual agreement. All site Investigators actively participating in the study will be invited to co-author the manuscript and fulfil authorship eligibility as per international guidelines.

Any secondary publications and presentations prepared by Investigators must be reviewed by Dr. Scholefield. Submission must not occur prior to the publication of the primary manuscript. Manuscripts must be submitted to Dr. Scholefield in a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues. The authors must acknowledge that the study was performed with the support of the NIHR and the University of Birmingham.

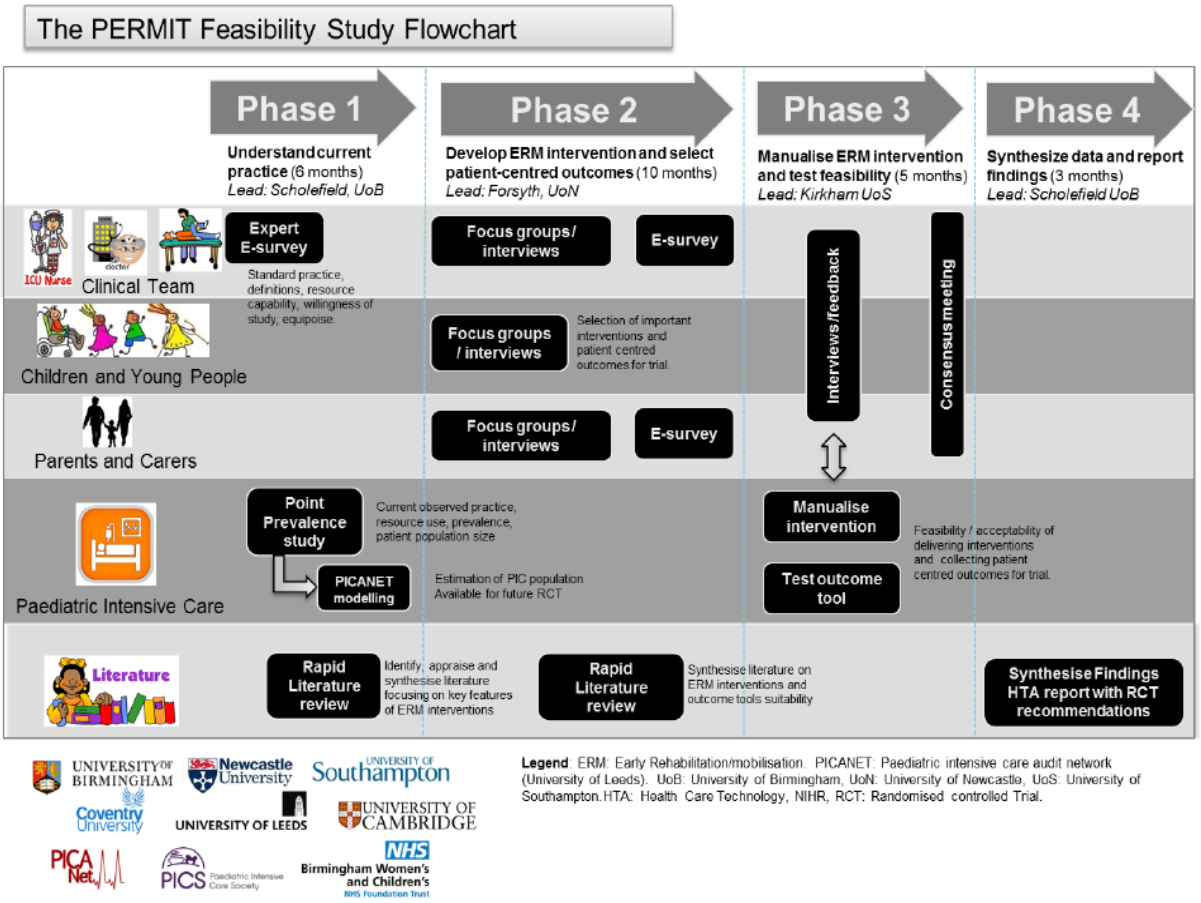
13.24. Abbreviations and Definitions:

Term	Description
CRF	Case report form
ERM	Early rehabilitation and mobilisation
PICANet	Paediatric Intensive Care Audit Network (PICANet)
PICU	Paediatric Intensive Care Unit
PIM	Paediatric Index of Mortality
PIS	Patient Information sheet
Screening Log	Local site screening log of all PICU admission, identifying patients fulfilling eligibility criteria for PERMIT pilot study.
Source data	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial
The Trials Office	The team of people, including the Chief Investigator, responsible for the overall management and coordination of the trial. This will be located in the Public Health Building, University of Birmingham.
Trials management group	The Trial Management Group includes those individuals responsible for the day-to-day management of the trial, such as the Chief Investigator, statistician, project manager, research fellow, and co-applicants. The role of the group is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself.
Project oversight committee	The project oversight committee includes those who oversee the process of assuring the quality of the project management and delivery to reduce risk and improve outcomes.

14. APPENDICES

14.1. Appendix 1: Study Schema

Study Schema	PERMIT Feasibility Study Flowchart



14.2. Appendix 1 Review search strategy

CENTRAL
Date Run: 13/12/2019

ID	Search	Hits
#1	MeSH descriptor: [Intensive Care Units, Pediatric] explode all trees	966
#2	MeSH descriptor: [Intensive Care Units, Neonatal] explode all trees	697
#3	MeSH descriptor: [Critical Illness] explode all trees	1973
#4	MeSH descriptor: [Critical Care] explode all trees	1999
#5	(pediatric icu OR pediatric icuaw OR paediatric icu OR paediatric icuaw):ti,ab,kw	474

#6 ("paediatric intensive care"):ti,ab,kw 855
#7 #1 OR #2 OR #3 OR #4 4509
#8 MeSH descriptor: [Exercise Therapy] explode all trees 12598
#9 MeSH descriptor: [Physical Therapy Modalities] explode all trees23710
#10 MeSH descriptor: [Occupational Therapy] explode all trees 723
#11 MeSH descriptor: [Rehabilitation] explode all trees 33307
#12 ((cycle OR bicycle) NEAR1 ergomet*) 5749
#13 (((rehabilitat* or exercis* or mobili* or ambulat* or physical* or physiotherap*))):ti,ab,kw 217686
#14 ((therap* near/3 (physical or exercise or occupation* or animal or music or nutrition* or psycholog* or vocation*))):ti,ab,kw (Word variations have been searched) 54310
#15 #8 OR #9 OR #10 OR #11 OR #12 #14 34905
#16 #7 AND #15 183

MEDLINE
Database: Ovid MEDLINE(R) and In-Process & Other Non-Indexed Citations <1946 to December 12, 2019
1 exp Pediatrics/ or Paediatric.mp. (106506)
2 Paediatrics.mp. (7305)
3 Pediatric.mp. (276918)
4 1 or 2 or 3 (356323)
5 Intensive Care Units.mp. or exp Intensive Care Units/ (91849)
6 Critical Illness.mp. or exp Critical Illness/ (31374)
7 Critical Care.mp. or exp Critical Care/ (73300)
8 (critical* adj3 (ill* or care*)).tw. (71316)
9 intensive care.tw. (132554)
10 critical care.tw. (25491)
11 icu.ab,ti. (50876)
12 'intensive care'.ab,ti. (132554)
13 (critical* adj3 (ill* or care)).ab,ti. (70706)
14 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 (243400)
15 4 and 14 (23482)
16 Physical Therapy.mp. or exp Physical Therapy/ (48742)
17 Physical Therapy Modalities.mp. or exp Physical Therapy Modalities/ (147898)
18 Exercise Therapy.mp. or exp Exercise Therapy/ or Exercise Movement Techniques/ (50084)
19 Occupational Therapy.mp. or exp Occupational Therapy/ (16730)
20 exp Rehabilitation/ or rehabilitation.mp. (504279)
21 physiotherapy.mp. (18150)
22 Early Ambulation.mp. or exp Early Ambulation/ (3460)
23 Early Mobilization.mp. or Early Mobilization/ (4999)
24 Chest physiotherapy.mp. or exp Chest physiotherapy/ (802)
25 (therap* adj3 (physical* or exercise* or occupation* or respiratory or music or animal)).ab,ti. (50992)
26 ((cycle or bicycle) adj1 ergomet*).ab,ti. (11390)
27 ((bed or 'daily living') adj3 activity).ab,ti. (2394)
28 "physical therapy".ab,ti. (16266)
29 "Physical Therapy Modalities".ab,ti. (134)
30 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 (553008)
31 (Early or earlier or accelerat* or acute or immediate*).mp. (3288276)

32 15 and 30 and 31 (228)

EMBASE
Database: Embase <1974 to 2019 December 12
1 Paediatric.mp. or exp pediatrics/ (189038)
2 Paediatrics.mp. (13444)
3 Pediatric.mp. (433672)
4 1 or 2 or 3 (574894)
5 Intensive Care Units.mp. or exp Intensive Care Units/ (189180)
6 Critical Illness.mp. or exp Critical Illness/ (33862)
7 Critical Care.mp. or exp Critical Care/ (688002)
8 (critical* adj3 (ill* or care*)).tw. (112345)
9 intensive care.tw. (196952)
10 critical care.tw. (44112)
11 icu.ab,ti. (108029)
12 'intensive care'.ab,ti. (196950)
13 (critical* adj3 (ill* or care)).ab,ti. (111501)
14 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 (882921)
15 4 and 14 (65283)
16 exp physiotherapy/ or physiotherapy.mp. (92846)
17 Physical Therapy Modalities.mp. or exp Physical Therapy Modalities/ (82733)
18 exp Exercise Therapy/ or Exercise Movement Techniques/ (74384)
19 Exercise Therapy.mp. or kinesiotherapy/ (31971)
20 Occupational Therapy.mp. or exp Occupational Therapy/ (24294)
21 exp Rehabilitation/ or rehabilitation.mp. (573466)
22 Early Ambulation.mp. or exp Early Ambulation/ or 'ambulation'.ti,ab. (38109)
23 mobilization/ (31007)
24 Chest physiotherapy.mp. or breathing exercise/ (7621)
25 (therap* adj3 (mobilizat* or mobilisat* or rehab* or physical* or exercise* or occupation* or respiratory or music or animal)).ab,ti. (83586)
26 ((cycle or bicycle) adj1 ergomet*).ab,ti. (14656)
27 ((bed or 'daily living') adj3 activity).ab,ti. (3854)
28 Physical Therapy.mp. or "physical therapy".ab,ti. (28243)
29 "Physical Therapy Modalities".ab,ti. (216)
30 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 (744586)
31 (Early or earlier or accelerat*).mp. (2565109)
32 15 and 30 and 31 (485)

CINAHL via EBSCOhost
Search Date: Friday, December 13, 2019
S20 S11 AND S19 6
S19 S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 528,466
S18 TX rehab* OR TX Ambulat* OR TX Exercis* OR TX mobiliz* OR mobilis* OR TX physiotherap* 518,682
S17 (MH “Rehabilitation”) OR (MH “Rehabilitation, Pediatric”) OR (MH “Physical Therapy”) OR (MH “Pediatric Physical Therapy”) 50,773
S16 (MH “Therapeutic Exercise”) 20,895
S15 (MH "Ambulation Therapy (Saba CCC)") OR (MM "Early Ambulation") OR (MH "Exercise Therapy: Ambulation (Iowa NIC)") OR (MH "Ambulation: Walking (Iowa NOC)") 613

S14 (MH "Exercise Therapy: Joint Mobility (Iowa NIC)") OR (MH "Joint Mobilization") 795
S13 MH “Mobility Therapy 534
S12 MH “Ambulation Therapy 1,757
S11 S3 AND S10 28
S10 S4 OR S5 OR S6 OR S7 OR S8 OR S9 140,371
S9 MH “Intensive Care Units, Pediatric” 5,427
S8 TX Critical* ill* or ICU or intensive care or critical care 140,371
S7 MH “Critically Ill Patients” 10,961
S6 MH "intensive care units" 34,582
S5 MH "critical illness" 11,092
S4 MH critical care or intensive care or icu 103,714
S3 S1 OR S2 1,901
S2 "paediatric or pediatric or child or children or infant or adolescent" 116,028
S1 (MH “Child”) OR (MH “Adolescent, Hospitalized”) OR (MH “Adolescence”) OR (MH “Child, Disabled”) OR (MH “Child, Hospitalized”) OR (MH “Child, Medically Fragile”) OR (MH “Child, Preschool”) 532

PEDro
Date of search: 13 Dec. 19
Simple terms

- Pediatric intensive care
- Paediatric intensive care

15. REFERENCES

1. PICANet. Paediatric Intensive Care Audit Network National Report 20014 - 20162016 12th July 2017. Available from: http://www.picanet.org.uk/Audit/Annual-Reporting/PICANet_Annual_Report_2016_Summary.pdf.
2. Ong C, Lee JH, Leow MK, Puthucheary ZA. Functional Outcomes and Physical Impairments in Pediatric Critical Care Survivors: A Scoping Review. Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies. 2016;17(5):e247-59.
3. Manning JC, Redsell SA, Latour JM. Should out of sight mean out of mind? Challenging the role of paediatric intensive care in understanding and supporting children and families following childhood critical illness. Nursing in critical care. 2016;21(5):262-4.
4. Rennick JE, Rashotte J. Psychological outcomes in children following pediatric intensive care unit hospitalization: a systematic review of the research. Journal of child health care : for professionals working with children in the hospital and community. 2009;13(2):128-49.
5. Shudy M, de Almeida ML, Ly S, Landon C, Groft S, Jenkins TL, et al. Impact of pediatric critical illness and injury on families: a systematic literature review. Pediatrics. 2006;118 Suppl 3:S203-18.
6. Rees G, Gledhill J, Garralda ME, Nadel S. Psychiatric outcome following paediatric intensive care unit (PICU) admission: a cohort study. Intensive care medicine. 2004;30(8):1607-14.
7. Colville GA, Pierce CM. Children's self-reported quality of life after intensive care treatment. Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies. 2013;14(2):e85-92.
8. Colville G, Kerry S, Pierce C. Children's factual and delusional memories of intensive care. American journal of respiratory and critical care medicine. 2008;177(9):976-82.
9. Iwashyna TJ, Speelmon EC. Advancing a Third Revolution in Critical Care. American journal of respiratory and critical care medicine. 2016;194(7):782-3.
10. Abdulsatar F, Walker RG, Timmons BW, Choong K. "Wii-Hab" in critically ill children: a pilot trial. Journal of pediatric rehabilitation medicine. 2013;6(4):193-204.
11. Kho ME, Molloy AJ, Clarke FJ, Ajami D, McCaughan M, Obrovac K, et al. TryCYCLE: A Prospective Study of the Safety and Feasibility of Early In-Bed Cycling in Mechanically Ventilated Patients. PloS one. 2016;11(12):e0167561.
12. Walsh TS, Salisbury LG, Boyd J, Ramsay P, Merriweather J, Huby G, et al. A randomised controlled trial evaluating a rehabilitation complex intervention for patients following intensive care discharge: the RECOVER study. BMJ open. 2012;2(4).
13. Cui LR, LaPorte M, Civitello M, Stanger M, Orringer M, Casey F, 3rd, et al. Physical and occupational therapy utilization in a pediatric intensive care unit. Journal of critical care. 2017;40:15-20.
14. Wieczorek B, Ascenzi J, Kim Y, Lenker H, Potter C, Shata NJ, et al. PICU Up!: Impact of a Quality Improvement Intervention to Promote Early Mobilization in Critically Ill Children. Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies. 2016;17(12):e559-e66.
15. Wieczorek B, Burke C, Al-Harbi A, Kudchadkar SR. Early mobilization in the pediatric intensive care unit: a systematic review. Journal of pediatric intensive care. 2015;2015:129-70.
16. Cameron S, Ball I, Cepinskas G, Choong K, Doherty TJ, Ellis CG, et al. Early mobilization in the critical care unit: A review of adult and pediatric literature. Journal of critical care. 2015;30(4):664-72.
17. Needham DM, Korupolu R, Zanni JM, Pradhan P, Colantuoni E, Palmer JB, et al. Early physical medicine and rehabilitation for patients with acute respiratory failure: a quality improvement project. Archives of physical medicine and rehabilitation. 2010;91(4):536-42.
18. Burtin C, Clerckx B, Robbeets C, Ferdinande P, Langer D, Troosters T, et al. Early exercise in critically ill patients enhances short-term functional recovery. Critical care medicine. 2009;37(9):2499-505.
19. Mortamet G, Roumeliotis N, Vinit F, Simonds C, Dupic L, Hubert P. Is there a role for clowns in paediatric intensive care units? Archives of disease in childhood. 2017;102(7):672-5.

20. ENGLAND N. Commissioning Guidance for Rehabilitation NHS England [Online]. 2016 1st Nov 2017. Available from: https://www.england.nhs.uk/wp-content/uploads/2016/04/rehabilitation-comms-guid-16-17.pdf.
21. Calvo-Ayala E, Khan BA, Farber MO, Ely EW, Boustani MA. Interventions to improve the physical function of ICU survivors: a systematic review. Chest. 2013;144(5):1469-80.
22. McWilliams D, Weblin J, Atkins G, Bion J, Williams J, Elliott C, et al. Enhancing rehabilitation of mechanically ventilated patients in the intensive care unit: a quality improvement project. Journal of critical care. 2015;30(1):13-8.
23. Morris PE, Goad A, Thompson C, Taylor K, Harry B, Passmore L, et al. Early intensive care unit mobility therapy in the treatment of acute respiratory failure. Critical care medicine. 2008;36(8):2238-43.
24. Needham DM, Truong AD, Fan E. Technology to enhance physical rehabilitation of critically ill patients. Critical care medicine. 2009;37(10 Suppl):S436-41.
25. Tan T, Brett SJ, Stokes T. Rehabilitation after critical illness: summary of NICE guidance. BMJ (Clinical research ed). 2009;338:b822.
26. Choong K, Koo KK, Clark H, Chu R, Thabane L, Burns KE, et al. Early mobilization in critically ill children: a survey of Canadian practice. Critical care medicine. 2013;41(7):1745-53.
27. Samuel VM, Colville GA, Goodwin S, Ryninks K, Dean S. The Value of Screening Parents for Their Risk of Developing Psychological Symptoms After PICU: A Feasibility Study Evaluating a Pediatric Intensive Care Follow-Up Clinic. Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies. 2015;16(9):808-13.
28. Colville G, Pierce C. Patterns of post-traumatic stress symptoms in families after paediatric intensive care. Intensive care medicine. 2012;38(9):1523-31.
29. Atkins E, Colville G, John M. A 'biopsychosocial' model for recovery: a grounded theory study of families' journeys after a Paediatric Intensive Care Admission. Intensive & critical care nursing. 2012;28(3):133-40.
30. Colville G, Darkins J, Hesketh J, Bennett V, Alcock J, Noyes J. The impact on parents of a child's admission to intensive care: integration of qualitative findings from a cross-sectional study. Intensive & critical care nursing. 2009;25(2):72-9.
31. Williams S, Horrocks IA, Ouvrier RA, Gillis J, Ryan MM. Critical illness polyneuropathy and myopathy in pediatric intensive care: A review. Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies. 2007;8(1):18-22.
32. Department of Health. The Government's mandate to NHS England for 2017-182017.
33. Choong K, Fink EL, Tasker R. Personal Communication with Canadian Critical Care Trials Group members & USA paedatric investigators during PERMIT study development. In: Scholefield, editor. 2017.
34. World Health Organization. International Classification of Functioning, Disability and Health - children and youth version: ICF-CY. 2007.
35. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. BMJ (Clinical research ed). 2008;337.
36. Medical Research Council. A framework for development and evaluation of RCTs for complex interventions to improve health. London; 2000.
37. May CR, Mair F, Finch T, MacFarlane A, Dowrick C, Treweek S, et al. Development of a theory of implementation and integration: Normalization Process Theory. Implementation Science. 2009;4(1):29.
38. Carl M, Tracy F. Implementing, Embedding, and Integrating Practices: An Outline of Normalization Process Theory. Sociology. 2009;43(3):535-54.
39. Cameron S, Ball I, Cepinskas G, Choong K, Doherty TJ, Ellis CG, et al. Early mobilization in the critical care unit: A review of adult and pediatric literature. Journal of Critical Care. 2015;30(4):664-72.
40. Murray E, Treweek S, Pope C, MacFarlane A, Ballini L, Dowrick C, et al. Normalisation process theory: a framework for developing, evaluating and implementing complex interventions. BMC Medicine. 2010;8(1):63.
41. Moore GF, Audrey S, Barker M, Bond L, Bonell C, Hardeman W, et al. Process evaluation of complex interventions: Medical Research Council guidance. BMJ : British Medical Journal. 2015;350.

42. Kneale D, Thomas J, Harris K. Developing and Optimising the Use of Logic Models in Systematic Reviews: Exploring Practice and Good Practice in the Use of Programme Theory in Reviews. PloS one. 2015;10(11):e0142187.
43. Straney L, Clements A, Parslow RC, Pearson G, Shann F, Alexander J, et al. Paediatric index of mortality 3: an updated model for predicting mortality in pediatric intensive care*. Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies. 2013;14(7):673-81.
44. Connolly BA, Mortimore JL, Douiri A, Rose JW, Hart N, Berney SC. Low Levels of Physical Activity During Critical Illness and Weaning: The Evidence-Reality Gap. Journal of intensive care medicine. 2017:885066617716377.
45. Hodgson C, Needham D, Haines K, Bailey M, Ward A, Harrold M, et al. Feasibility and inter-rater reliability of the ICU Mobility Scale. Heart & lung : the journal of critical care. 2014;43(1):19-24.
46. Kanthimathinathan HK, Scholefield BR. Dilemmas in undertaking research in paediatric intensive care. Archives of disease in childhood. 2014.
47. Nadel S, Als LC, Garralda ME. Treatment of Parental Post-Traumatic Stress Disorder After PICU Admission: Who, What, Where, When? Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies. 2015;16(9):877-8.
48. HEALTH DO. Getting the Right Start: The National Service Framework for Children, Young People and Maternity Services- Standards for Hospital Services2003 1st Nov 2017. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/199953/Getting_the_right_start_-_National_Service_Framework_for_Children_Standard_for_Hospital_Services.pdf.
49. Khangura S, Polisena J, Clifford TJ, Farrah K, Kamel C. Rapid review: An emerging approach to evidence synthesis in health technology assessment International Journal of Technology Assessment in Health Care. 2014;30(1):20-7.
50. Haby MM, Chapman E, Clark R, Barreto J, Reveiz L, Lavis JN. What are the best methodologies for rapid reviews of the research evidence for evidence-informed decision making in health policy and practice: a rapid review. Health Research Policy and Systems. 2016;14(1):83.
51. Terwee C, de Vet H, Prinsen C, LB M. Protocol for systematic reviews of measurement properties. 2011.
52. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ (Clinical research ed). 2009;339.
53. Mateen FJ, Oh J, Tergas AI, Bhayani NH, Kamdar BB. Titles versus titles and abstracts for initial screening of articles for systematic reviews. Clinical Epidemiology. 2013;5:89-95.
54. Khangura SD, Karaceper MD, Trakadis Y, Mitchell JJ, Chakraborty P, Tingley K, et al. Scoping review of patient- and family-oriented outcomes and measures for chronic pediatric disease. BMC pediatrics. 2015;15(1):1-9.
55. Terwee CB, Mokkink LB, Knol DL, Ostelo RWJG, Bouter LM, de Vet HCW. Rating the methodological quality in systematic reviews of studies on measurement properties: a scoring system for the COSMIN checklist. Quality of Life Research. 2012;21(4):651-7.
56. Terwee CB, Bot SDM, de Boer MR, van der Windt DAWM, Knol DL, Dekker J, et al. Quality criteria were proposed for measurement properties of health status questionnaires. Journal of Clinical Epidemiology. 2007;60(1):34-42.
57. Sricharoenchai T, Parker AM, Zanni JM, Nelliot A, Dinglas VD, Needham DM. Safety of physical therapy interventions in critically ill patients: a single-center prospective evaluation of 1110 intensive care unit admissions. Journal of critical care. 2014;29(3):395-400.
58. May C, Finch T. Implementing, Embedding, and Integrating Practices: An Outline of Normalization Process Theory. Sociology. 2009;43(3):535-54.
59. Weijer C, Grimshaw JM, Eccles MP, McRae AD, White A, Brehaut JC, et al. The Ottawa Statement on the Ethical Design and Conduct of Cluster Randomized Trials. PLOS Medicine. 2012;9(11):e1001346.