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Does in-bed cycling, delivered within 48 hours of mechanical ventilation, reduce the occurrence of delirium in critically ill patients (FRECycl-D): A protocol for a process evaluation.

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Jacqueline.Bennion[1], Mark Hudson[2], Mary Hickson[3], Daniel Martin[4,5], Gita Ramdharry[6], Linda Denehy[7], David McWilliams[8], Bridie Kent[9]

[1]NIHR Doctoral Fellow, Peninsula Medical School, John Bull Building, University of Plymouth, Devon, UK;
[2]Public and Patient Involvement and Engagement Representative;
[3]Professor of Dietetics, School of Health Professions (Faculty of Health), Intercity Place, University of Plymouth, Plymouth, Devon, PL4 6AB UK;
[4]Professor of Perioperative and Intensive Care Medicine, Peninsula Medical School, University of Plymouth, John Bull Building, Derriford, Plymouth, PL6 8BU, UK;
[5]Intensive Care Unit, University Hospitals Plymouth, Plymouth, Devon, UK;
[6]Honorary Associate Professor in Neuromuscular diseases, University College London, Queen Square, Centre for Neuromuscular Diseases, London, WC1N 3BG;
[7]Professor of Physiotherapy, University of Melbourne, Grattan Street, Parkville, Victoria, 3010, Australia;
[8]Professor in Critical Care and Rehabilitation, Centre for Care Excellence, Coventry University, Priory Street, Coventry;
[9]Professor of Leadership in Nursing, School of Nursing and Midwifery (Faculty of Health) InterCityPlace, University of Plymouth, Plymouth, Devon, PL4 6AB

Jacqueline.Bennion : ORCID: https://orcid.org/0000-0001-6047-9277;
Mark Hudson: ORCID: https://orcid.org/0000-0002-5947-2542;
Mary Hickson: ORCID: https://orcid.org/0000-0001-7996-0095;
Daniel Martin: ORCID: https://orcid.org/0000-0001-6220-8235.;
Gita Ramdharry: ORCID: https://orcid.org/0000-0001-9344-0301;
Linda Denehy: ORCID: https://orcid.org/0000-0002-2926-8436;
David McWilliams: ORCID: https://orcid.org/0000-0002-9086-2557;
Bridie Kent: ORCID: https://orcid.org/0000-0001-9550-1913;

Jacqueline.Bennion

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Abstract

Background

Delirium is a severe neuropsychiatric clinical state, presenting as acute cognitive deficits, altered levels of consciousness, inattention and psychotic episodes. Critically ill patients requiring invasive mechanical ventilation (IMV) have the highest risk of developing delirium in the intensive care unit (ICU). Best practice guidelines recommend a bundle of care to prevent delirium in the ICU. This includes early mobilisation interventions. However, these recommendations are based upon preliminary evidence. The FRECycl-D trial is a mixed-methods randomised controlled trial. The trial aims to investigate the feasibility of early (within 48-hours of IMV) in-bed cycling to reduce delirium in the ICU. This process evaluation will assess important implementation outcomes of the FRECycl-D trial.

Methods

A mixed-methods process evaluation of the FRECycl-D trial. Acceptability of the intervention and delirium outcomes will be explored using semi-structured qualitative interviews with trial intervention participants, their relatives and carers. Interviews will be carried out across the course of the 18-month trial recruitment period. The sample size will be guided by data adequacy. Reflexive thematic analysis will be conducted and themes linked to the Theoretical Domains Framework. Fidelity will be assessed at 6,9, and 18 months using descriptive data and integrated with the qualitative interview data.

Conclusion

Evaluation of the implementation outcomes will provide an explanation of the FRECycl-D trial results, highlight key areas for improving outcomes and inform decision makers in the implementation of a larger powered trial.

Attachments

Supplementary file 0...

424KB

Introduction

1 A high proportion (30-50%) of critically ill patients develop delirium following admission to the intensive care unit (ICU), with the highest risk (80%) seen in those requiring invasive mechanical ventilation (IMV) [1,2]. The Diagnostic and Statistical Manual for Mental Disorders 5th edition defines delirium as an acute brain dysfunction manifesting as altered levels of consciousness from near coma to severe agitation, psychotic episodes and inattention [3]. Delirium is a preventive condition, associated with increased mortality, morbidity and poor quality of life [4]. Therefore, the James Lind Alliance has described identifying, monitoring and management of delirium as key priorities for intensive care research [5]. Early mobilisation interventions are recommended in standard care as part of a bundle approach to prevent and manage delirium in the ICU [6]. To support the implementation of early mobilisation interventions into practice, safety criteria specific to in-bed and out-of-bed mobilisation have been published following an expert consensus [7]. These include the consideration of delirium. However, despite more than 2500 publications focused on early mobilisation interventions in the ICU, there is no direct evidence to date investigating the effectiveness of early mobilisation interventions to reduce delirium in critically ill populations [8,9]. Furthermore, several barriers to implementing early mobilisation interventions have been identified including delirium itself [10]. Patients diagnosed with delirium in the ICU reported that early mobilisation is essential to their care because it facilitated their recovery (mind and body) and 'grounded' them back into reality (In-press). Patient and public involvement and engagement (PPIE) representatives reported that in-bed cycling may address the identified barriers (delirium, IMV, sedation, severity of illness) to the implementation of early mobilisation interventions in the ICU. As part of a public advisory group, four previous patients diagnosed with delirium in the ICU and a relative provided valuable expertise into the mixed-methods design of the FRECycl-D trial. A recent systematic review identified that in-bed cycling, as a method of early mobilisation, appears safe and feasible in the ICU to improve physical function, reduce ICU length of stay and duration of IMV without effect on mortality [11]. However, delirium was not included in the outcomes. The FRECycl-D trial aims to investigate the feasibility of early (within 48 hours of IMV) in-bed cycling to reduce delirium in critically ill patients. The Medical Research Council (MRC) guidelines for complex interventions provide a framework for researchers to design, conduct and evaluate trials in consultation with key stakeholders [12]. The guidelines suggest process evaluations are a priority as trial outcomes have been found to be insufficient for implementing evidence into practice [12,13]. Moreover, process evaluations incorporating mixed methods to assess the implementation of feasibility trials have been recommended to develop and evaluate complex interventions [13,14]. The aim of this process evaluation is to assess key implementation outcomes of the FRECycl-D trial.

Objectives

2 Implementation outcomes (acceptability and fidelity) will be evaluated using quantitative data (descriptive statistics, administrative data) from the feasibility trial and qualitative data (interviews, field notes, stakeholder feedback, intervention session observation) [13,15]. Moreover, these data will be assessed alongside the trial implementation strategy (Figure sl). This will provide understanding of change over time, the factors that influenced these changes and trial findings. Evaluation of the implementation outcomes will inform decision makers in considering scaling up to a full definitive trial. The following implementation outcomes will be evaluated:

- Acceptability of the intervention and delirium outcome measures (key stakeholder interviews).
- Fidelity of intervention delivery and delirium outcome measures (descriptive quantitative data at 6, 9, 18-months).

These are further described in detail below.

Methods

3 This mixed-methods process evaluation will evaluate the implementation of the FRECycl-D trial. The design and selected outcomes of the FRECycl-D trial evaluation will be informed by mixed-methods methodology and implementation science theory [13-18]. Descriptive quantitative trial data and in-depth interview data will be linked to the trial findings, assessed and integrated using a convergent approach [14,16]. Interview participants will be selected using a purposive sampling method in consultation with the site research team and professional advisors (e.g., bedside nurse, treating consultant, ICU therapy team member). This method will be used to select intervention participants, their relatives and carers for the qualitative study. The reflexive thematic analysis reporting guidelines (RTARG) will inform the reporting of the qualitative interview data [19]. The MRC guidelines for complex interventions will facilitate the reporting of this process evaluation [12,13]. PPIE will be described using the guidance for reporting involvement of patients and the public (GRIPP2) short form checklist [20]. Due to the complexity of embedded process evaluations, this study will be published separately from the FRECycl-D trial findings.

Setting

4 The FRECycl-D trial will be carried out across three National Health Service (NHS) ICUs in the United Kingdom (UK). ICU-1 is a general-surgical 14 bedded ICU. ICU-2 is a district general hospital with one 14 bedded general-surgical ICU. ICU-3 includes a general-surgical ICU with a total of 19 beds. The quarterly reports for the **Intensive Care National Audit and Research Centre (ICNARC) Case Mix Programme**, were assessed with the FRECycl-D trial eligibility criteria. These data were used to explore the suitability of each

site's participation in the trial. All sites have experience in delivering clinical trials of investigational medicinal products (CTIMP). One site has previous experience in the delivery of a feasibility trial (ICU-1). No sites have had experience delivering non-CTIMP trials. Two sites have had exposure to in-bed cycling with patients following more than four days after ICU admission (ICU-1, ICU-3). One site previously trialled an in-bed cycling device for long-stay patients (>4 days following ICU admission) and opted for a seated cycling device as an adjunct to out of bed mobilisation. Medical records and systems are electronic at two sites and paper-based systems are at one site.

Stakeholder involvement

5 The trial was discussed with site staff to confirm support, site readiness and usual practice of early mobilisation. A logic model will guide implementation, refinement and evaluation of the trial (Figure sII). This will inform the development of the programme theory including description of the context of the FRECycl-D trial and each recruiting site (table sI-sII). The logic model and programme theory will be reviewed and further developed in consultation with key stakeholders across the course of the trial as part of this process evaluation. The primary implementation strategy was informed by PPIE representatives, two EMPRESS trial investigators and collaborators (LD, KM), and the current evidence identifying barriers and facilitators of early mobilisation interventions [21-23]. This will be carried out and further developed based on the theoretical domains framework (TDF) in consultation with the key stakeholders as per expert recommendations and following the researcher's (JB) educational training in implementation sciences, optimising recruitment to randomised controlled trials (RCTs) and qualitative methodology [14]. This will provide a more nuanced and deeper understanding of the mechanisms of change and the impact of these upon trial findings.

Theoretical framework

6 Theoretical underpinning is recommended to optimise learning, development and refinement of trials across contexts [24]. Early mobilisation and delirium monitoring involves input from multidisciplinary teams, engagement from a variety of stakeholders and has been shown to be influenced by environmental and behavioural factors [21,22]. The TDF has been validated for evaluating implementation outcomes relevant to health service users and service providers [25,26]. It comprises 14 theoretical domains (1. knowledge, 2. skills, 3. social/professional role and identity, 4. beliefs about capabilities, 5. optimism, 6. beliefs about consequences, 7. reinforcement, 8. intentions, 9. goals, 10. memory, attention and decision processes, 11. environmental context and resources, 12. social influences, 13. emotion, 14. behavioural regulation) [27]. The TDF has been suggested to compliment implementation of feasibility trials and the development of programme theory as it aims to describe the processes, structures, contexts and behaviours linked to outcomes [24]. The mechanisms of interactions between

implementing the FRECycl-D trial and the relevant context will provide understanding of the extent of the trial outcomes such as, the flexibility and adaptability of the trial findings to other ICUs [14]. The TDF was selected with reference to the current evidence base demonstrating the heterogeneous implementation of early mobilisation interventions and in discussion with two experts who have experience implementing definitive trials of complex interventions (LD, GR). This will inform the theoretical lens for the evaluation of the FRECycl-D trial to understand the important influences, uncertainties and enablers of implementation and the development of the primary implementation strategy.

Description of the trial intervention and delirium outcome measures

7 The intervention and delirium outcome measures have been described according to the template for intervention description and replication (TIDieR) checklist [28]. These details are described further in the FRECycl-D trial protocol [29]. All staff training and delegation of tasks have been listed on the site training and delegation logs.

Intervention and delivery
In-bed cycling will be available to participants randomised to the intervention, five days per week for a maximum of 14 days or until out-of-bed mobilisation commences (whichever comes first). The intervention will be carried out by the chief investigator (CI) or an ICU rehabilitation team member at each site in addition to usual care. A daily safety assessment will be conducted prior to, during and up to 30 minutes after the in-bed cycling intervention [7]. The CI is funded full time for the delivery of the intervention at site ICU-3. An ICU rehabilitation member at site ICU-2 is funded at 0.2 full time equivalent (FTE). The ICU-2 site rehabilitation team comprise a clinical lead physiotherapist, B5 occupational therapist (OT), B5 physical activity specialist and a full-time rotational B6 respiratory physiotherapist. The team are employed part-time and cover ICU and inpatient wards. Therefore, the delivery of the intervention will be co-ordinated alongside the staffing rota. The ICU-1 site voluntarily (i.e., in an unfunded capacity) joined the FRECycl-D trial. The full time and static ICU rehabilitation team includes a B8a advanced practitioner, 2 clinical specialist B7 static physiotherapists, 1 B6 rotational respiratory physiotherapist, 1 B6 rotational physiotherapist, 1 B5 rotational physiotherapist, 2 static OTs B7/B6 and 2 B4 therapy assistants. The team provide cover for inpatient wards where there are staffing pressures. Early in-bed cycling initiated within four days of ICU admission (excluding planned ICU admissions) is unusual in the ICU across the United Kingdom. Usual care of IMV patients includes non-cycling exercise e.g., assisted-limb movement, positioning and respiratory physiotherapy. Currently, the participating sites do not use in-bed cycling within 48 hours of IMV. Usual care is offered at all sites seven days per week. Weekend treatments are limited to respiratory physiotherapy, assisted limb movement and positioning. The activities comprising early mobilisation and usual care were confirmed with the clinical teams at each site prior to site selection.

Delirium outcome measures

The confusion assessment method for the ICU (CAM-ICU) is a valid and sensitive delirium monitoring tool for patients requiring IMV [30]. It is part of standard practice and used twice daily, 7 days per week to diagnose and monitor delirium at the ICU-2 and ICU-3 sites. The outcome measure is embedded in the medical electronic systems. The CAM-ICU is not standard practice at the ICU-1 site. Therefore, the ICU-1 site team have received training to use the CAM-ICU as part of the FRECycl-D trial.

The CAM-ICU-7 is a research tool used to measure severity of delirium [31]. Therefore, all sites have received relevant training. The CAM-ICU-7 will be used once daily 5 days per week.

Data collection

8 Acceptability

Acceptability is defined as 'the perception among implementation stakeholders that a given treatment, service, practice, or innovation is agreeable, palatable, or satisfactory' [15]. Semi-structured interviews will be carried out with the key stakeholders (intervention participants, their relatives and carers). A purposive sample method will be used in consultation with the research team (selection of intervention participants, relatives) and professional advisors at each site (selection of carer participants) to ensure a diverse range of perspectives and experiences (table sIII) [32]. The primary selection criteria are based upon exposure (intervention), delirium outcome measures, participant type (participants in the trial intervention group, their relatives, carers) and site. Secondary criteria include participant demographics (age, ethnicity, biological sex). Following written obtained consent, semi-structured interviews will be carried out across the recruitment period (18 months) of the FRECycl-D trial between July 2024 and January 2026. A variety of methods for interviews (in-person, telephone, virtual) will be offered to participants to optimise accessibility. The method and timings of interviews have been decided upon in consultation with PPIE representatives and senior members of the research team. Data will be transcribed verbatim and member check approval offered to participants prior to anonymising transcripts for data analysis. All data will be stored on a password protected electronic system provided by the University of Plymouth. The sample size will be guided by data adequacy. The interview guide has been co-produced with PPIE representatives to ensure sensitivity of language and relevance of questions for the aim of this study (table sIV-sV). A researcher (JB) and PPIE representative will review the transcribed data to check the accuracy of data. The researcher will take field notes following each interview to ensure reflexivity.

Fidelity

Implementation and theoretical fidelity will be evaluated to understand the training, delivery and receipt of the intervention using quantitative trial data and perspectives of

trial participants, their relatives and carers. Implementation fidelity is defined as 'the degree to which an intervention was implemented as it was prescribed in the original protocol or as it was intended' [15]. This will be measured using descriptive quantitative data at six, nine and 18-months: participants (number/%) who completed the trial intervention and dosage: interventions (number/%) delivered alongside reasons these were not delivered or stopped. Additionally, theoretical fidelity will be described to explore how cohesive the intervention was delivered in practice in relation to how it was originally designed to be delivered [33]. This will importantly outline the adaptability of the intervention in the real-world setting, the effectiveness of the implementation strategy, and the potential impact of these on outcomes. These data will be related to adherence data collected as part of the trial per protocol analysis and integrated with the qualitative interview data to determine the quality of delivery and receipt (intervention and delirium outcomes), participant perspectives and experiences (exposure, responsiveness).

Data analysis

9 Reflexive thematic analysis described by Braun and Clarke (2020) using a constructivist approach will guide the inductive analysis of the interview data [34,35]. These importantly recognise the researcher as part of the research process. This is particularly relevant to the FRECycl-D trial because the CI will implement the intervention at the ICU-3 site, observe site teams delivering the intervention and carry out the implementation strategy in consultation with the key stakeholders (e.g., site teams, research team, professional advisors). Therefore, the CI will be fully emersed in the trial processes, site systems, clinical and research teams to provide an in-depth analysis of findings. Reflexivity in the interpretation of findings will be guided by input from the key stakeholders such as the research team, site teams, PPIE representatives and trial management committees. These data will be gathered using administrative data, field notes, professional meetings (stakeholder meetings, network meetings, clinical staff meetings) and intervention session observation. The themes identified will be linked to the TDF framework to identify key domains to inform the development of the implementation strategy for the future definitive trial. The integration of qualitative and quantitative data will be guided by O'Cathain (2019) and Plano Clark (2019) [14,16]. Data integration will importantly provide an explanation of the trial findings and identify optimal implementation approaches in a real-world setting.

The research team background

10 The inter-professional research team comprise clinical academics and the site clinical research teams with diverse research backgrounds and philosophical stances, as well as a PPIE representative with patient experience in the ICU and previous diagnosis of

delirium. This will importantly facilitate a reflexive approach to the analysis of data collected.

PPIE representatives and professional advisors

11 PPIE representatives with previous experience as patients diagnosed with delirium in the ICU and a relative were consulted on the design of the interview study. One co-produced the interview questions which were reviewed by all advisory group members. PPIE representatives and professional advisors at each site will be consulted on the selection of interview participants. Funding for our PPIE representatives has been costed for within this NIHR Fellowship in accordance with the NIHR guidelines [36]. The integration of PPIE will be informed by professional expertise (GR) with consideration of equality, diversity and inclusion (EDI) to improve the implementation reach of the FRECycl-D trial.

Ethics

12 The FRECycl-D trial including the qualitative interview study has received Research Ethics Committee (REC reference 24/SC/0096), local Research and Development department and Health Research Authority (HRA) approval in accordance with the Declaration of Helsinki [37]. Consent procedures will follow the standard model of consent described in the FRECycl-D trial protocol [29]. This has been prospectively registered on the publicly available **ISRCTN registry (ISRCTN74277350)**.

Dissemination

13 The findings of this process evaluation will be published in a relevant peer-reviewed open-access journal. The plain English summary will be co-produced with PPIE representatives and professional advisors. The dissemination strategy will include publicising results through relevant professional networks, social media networks, industry collaborators and the **ICUsteps charity** support groups.

Strengths and limitations

14 The FRECycl-D trial is a feasibility trial therefore conclusions related to the effectiveness of trial implementation are beyond the scope of this process evaluation. However, the feasibility methodology allows greater flexibility to learn and develop the implementation approach of the trial where this may be limited in trials of effectiveness due to the risk of influencing external validity [15]. Therefore, outcomes will be valuable in improving implementation outcomes to successfully conduct a future definitive trial. Due to the funded time and resources available for this research, the assessment of follow-up outcomes and costs of implementation (intervention delivery, implementation strategy) were not included in this process evaluation.

Conclusion

15 This process evaluation will provide a multi-dimensional understanding of the FRECycl-D trial findings. It will highlight important areas for improvement in the implementation design for the future definitive trial. Moreover, findings will highlight key TDF domains to inform the development of the future trial implementation strategy.

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Professional advisors:
Dr Kay Mitchell, Senior Manager, NIHR Southampton Biomedical Researcher Centre, University of Southampton, ORCID: https://orcid.org/0000-0001-6393-8475
Dr Jamie Murdoch, Reader in Social Science and Health, Population Health Sciences, Kings College London, ORCID: https://orcid.org/0000-0002-9021-3629