DOCTOR OF PHILOSOPHY

The development of a non-pharmacological intervention for delirium management in critically ill patients

Bannon, Leona

Award date: 2021

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The development of a non-pharmacological intervention for delirium management in critically ill patients

Leona Mary Bannon, BSc (Hons), RN

A thesis submitted for the degree of:

Doctor of Philosophy (PhD)

To the School of Medicine, Dentistry and Biomedical Sciences

Queen’s University Belfast

March 2021
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<th>Meaning</th>
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<tr>
<td>4AT</td>
<td>4 As test</td>
</tr>
<tr>
<td>5W1H</td>
<td>Who, what, when, where, why and how</td>
</tr>
<tr>
<td>6SQUID</td>
<td>6 Steps in quality intervention development</td>
</tr>
<tr>
<td>ABCDE</td>
<td>Awakening and breathing coordination, delirium management and early mobilisation</td>
</tr>
<tr>
<td>ABD</td>
<td>Acute Brain Dysfunction</td>
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<td>ABLE</td>
<td>Age of blood study</td>
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<tr>
<td>ADS</td>
<td>American Delirium Society</td>
</tr>
<tr>
<td>AGREE</td>
<td>Appraisal of guidelines for research and evaluation</td>
</tr>
<tr>
<td>AMED</td>
<td>Allied</td>
</tr>
<tr>
<td>Apache II</td>
<td>Acute physiology and Chronic Health Evaluation</td>
</tr>
<tr>
<td>BEERS criteria</td>
<td>List of potentially inappropriate medications for the elderly</td>
</tr>
<tr>
<td>BLT</td>
<td>Bright light therapy</td>
</tr>
<tr>
<td>BPM</td>
<td>Beats per minute</td>
</tr>
<tr>
<td>BREATHE</td>
<td>Protocolised trial of invasive and non-invasive weaning off ventilation.</td>
</tr>
<tr>
<td>CAM-ICU</td>
<td>Confusion assessment method for the Intensive Care Unit</td>
</tr>
<tr>
<td>CASP</td>
<td>Critical appraisal skills programme</td>
</tr>
<tr>
<td>CERqual</td>
<td>Confidence in the evidence from reviews of qualitative research</td>
</tr>
<tr>
<td>CFIR</td>
<td>Consolidated framework for implementation research</td>
</tr>
<tr>
<td>CI</td>
<td>Chief Investigator</td>
</tr>
<tr>
<td>CICI</td>
<td>The Context and implementation of complex interventions framework</td>
</tr>
<tr>
<td>95% CI</td>
<td>95% Confidence Intervals</td>
</tr>
<tr>
<td>CINAHL</td>
<td>Index of English-language and selected other-language journal articles about nursing, allied health, biomedicine and healthcare.</td>
</tr>
<tr>
<td>CONSORT</td>
<td>Consolidated framework for reporting of trials</td>
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<tr>
<td>CPOT</td>
<td>Critical Care Pain Observation Tool</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report File</td>
</tr>
<tr>
<td>CRP</td>
<td>C-Reactive Protein</td>
</tr>
<tr>
<td>CTD</td>
<td>Cognitive test for delirium</td>
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<tr>
<td>DDS</td>
<td>Delirium detection score</td>
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<tr>
<td>DRS</td>
<td>Delirium rating scale</td>
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<tr>
<td>DMSS</td>
<td>Delirium motor subtyping scale</td>
</tr>
<tr>
<td>DOH</td>
<td>Department of Health</td>
</tr>
<tr>
<td>DSM</td>
<td>Diagnostic and Statistical Manual</td>
</tr>
<tr>
<td>EDA</td>
<td>European Delirium Association</td>
</tr>
<tr>
<td>EBP</td>
<td>Evidence based practice</td>
</tr>
<tr>
<td>EMBASE</td>
<td>a biomedical and pharmacological database of published literature</td>
</tr>
<tr>
<td>EQ-5D</td>
<td>EQ-5D is a standardized instrument developed by the EuroQol Group as a measure of health-related quality of life</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and drug administration</td>
</tr>
<tr>
<td>FES</td>
<td>Functional Electrical Stimulation</td>
</tr>
<tr>
<td>FG</td>
<td>Focus group</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>GCS</td>
<td>Glasgow Coma Scale</td>
</tr>
<tr>
<td>GP</td>
<td>General practitioner</td>
</tr>
</tbody>
</table>
| GRADE        | Grading of recommendation, assessment, development and
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Full Form</th>
</tr>
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<tbody>
<tr>
<td>HR</td>
<td>Heart rate</td>
</tr>
<tr>
<td>HSC</td>
<td>Health and Social Care</td>
</tr>
<tr>
<td>ICDSC</td>
<td>Intensive care delirium screening checklist</td>
</tr>
<tr>
<td>ICH-GCP</td>
<td>International Conference on Harmonisation, good clinical practice</td>
</tr>
<tr>
<td>ICP</td>
<td>Intracranial pressure</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive Care Unit</td>
</tr>
<tr>
<td>IL</td>
<td>Interleukin</td>
</tr>
<tr>
<td>IMC</td>
<td>Information memory concentration</td>
</tr>
<tr>
<td>ISF</td>
<td>Investigator Site File</td>
</tr>
<tr>
<td>IQR</td>
<td>Interquartile range</td>
</tr>
<tr>
<td>MAP</td>
<td>Mean Arterial Pressure</td>
</tr>
<tr>
<td>MDAS</td>
<td>Memorial delirium assessment scale</td>
</tr>
<tr>
<td>MEDLINE</td>
<td>a bibliographic database of life sciences and biomedical information</td>
</tr>
<tr>
<td>MESH</td>
<td>Medical subject heading</td>
</tr>
<tr>
<td>MMS</td>
<td>Manchester Mobility Scale</td>
</tr>
<tr>
<td>MMSE</td>
<td>Mini mental scale examination</td>
</tr>
<tr>
<td>MRC</td>
<td>Medical research council</td>
</tr>
<tr>
<td>mRCT</td>
<td>Meta-register of controlled trials</td>
</tr>
<tr>
<td>NDSS</td>
<td>Nursing Delirium Screening Scale</td>
</tr>
<tr>
<td>NHS</td>
<td>National Health Service</td>
</tr>
<tr>
<td>NICE</td>
<td>National Institute for Clinical Excellence</td>
</tr>
<tr>
<td>NICRN</td>
<td>Northern Ireland Clinical Research Network</td>
</tr>
<tr>
<td>NIHR</td>
<td>National Institute for Health Research</td>
</tr>
<tr>
<td>NOS</td>
<td>Newcastle Ottawa Scale</td>
</tr>
<tr>
<td>NRCTs</td>
<td>Non-randomised controlled trials</td>
</tr>
<tr>
<td>NUDeSC</td>
<td>Nursing delirium screening score</td>
</tr>
<tr>
<td>OR</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>PAD</td>
<td>Pain Agitation and Delirium</td>
</tr>
<tr>
<td>PARiHS</td>
<td>A framework for guiding the implementation of evidence-based practice</td>
</tr>
<tr>
<td>PDSA</td>
<td>Plan Do Study Act</td>
</tr>
<tr>
<td>PI</td>
<td>Principle Investigator</td>
</tr>
<tr>
<td>PRALIMAP</td>
<td>Intervention dose estimation framework</td>
</tr>
<tr>
<td>PIS</td>
<td>Patient Information Sheet</td>
</tr>
<tr>
<td>QI</td>
<td>Quality Improvement</td>
</tr>
<tr>
<td>RASS</td>
<td>Richmond Agitation and sedation score</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised Controlled Trial</td>
</tr>
<tr>
<td>R &amp; D</td>
<td>Research and Development</td>
</tr>
<tr>
<td>RE-AIM</td>
<td>Reach effectiveness adoption implementation maintenance</td>
</tr>
<tr>
<td>REC</td>
<td>Research Ethics Committee</td>
</tr>
<tr>
<td>REST</td>
<td>pRotective vEntilation with veno-venouS lung assisT in respiratory failure</td>
</tr>
<tr>
<td>REVMAN</td>
<td>Review Manager</td>
</tr>
<tr>
<td>RCSQ</td>
<td>Richards Campbell Sleep Questionnaire</td>
</tr>
<tr>
<td>ROB</td>
<td>Risk of bias</td>
</tr>
<tr>
<td>ROC</td>
<td>Receiver Operating Characteristic</td>
</tr>
<tr>
<td>ROM</td>
<td>Range of motion</td>
</tr>
<tr>
<td>RR</td>
<td>Risk Ratio</td>
</tr>
<tr>
<td>RR</td>
<td>Respiratory Rate</td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
</tr>
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</tr>
<tr>
<td>SAT</td>
<td>Spontaneous Awakening Trial</td>
</tr>
<tr>
<td>SBP</td>
<td>Systolic Blood Pressure</td>
</tr>
<tr>
<td>SBT</td>
<td>Spontaneous Breathing Trial</td>
</tr>
<tr>
<td>SCCM</td>
<td>Society of Critical Care Medicine</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>SF-36</td>
<td>36 item short form survey</td>
</tr>
<tr>
<td>SGAs</td>
<td>Second generation antipsychotics</td>
</tr>
<tr>
<td>SMD</td>
<td>Standardised Mean Difference</td>
</tr>
<tr>
<td>SPEACS</td>
<td>Communication training programme</td>
</tr>
<tr>
<td>SPECT</td>
<td>Single photon emission computed tomography</td>
</tr>
<tr>
<td>SOP</td>
<td>Standard Operating Procedures</td>
</tr>
<tr>
<td>SPIRIT</td>
<td>Standard Protocol Items: Recommendations for Interventional Trials</td>
</tr>
<tr>
<td>SQID</td>
<td>Single question in delirium</td>
</tr>
<tr>
<td>TIDieR</td>
<td>Template for Intervention Description and Replication</td>
</tr>
<tr>
<td>TMG</td>
<td>Trial Management Group</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>USA</td>
<td>United States of America</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation</td>
</tr>
</tbody>
</table>
Declaration

I declare this thesis is not one for which a degree has been or will be conferred by any other university or institution. The composition of this thesis is my own work.
Acknowledgements

I would like to acknowledge some of the very many people who have helped me and contributed to the work described herein:

My supervisory team, Professors Bronagh Blackwood, Daniel F McAuley and Mike Clarke for their patience, support and encouragement over the last five years and the opportunities that they have provided me during this time. I would also like to thank my co-author Jennifer McGaughey for all her help and support in being the second reviewer for my systematic review and meta-analysis and qualitative analysis from focus groups.

ICUsteps, a charity that supports survivors of ICU and their families, I would like to give a special mention to Peter Gibb and Mo Peskett for helping to ensure that I had excellent Personal and Public Involvement (PPI), which was essential to the success of this project. I would also like to thank members of ICUsteps who took part in my focus group interviews and provided invaluable feedback on study materials.

British Association of Critical Care Nurses (BACCN), I would like to thank Catherine Plowright and the BACCN national committee for advertising my focus group interviews in their newsletter and on their website.

The clinical team within the Regional Intensive Care Unit; in particular ward manager Rhoda McFarland, Dr Aoibhin Hutchinson, Dr Aveen Goodman and Sister Heather Christie for their support in educating staff about delirium screening in the unit.

I am forever in debt to my research colleagues in the Regional Intensive Care Unit; Justine Quigg, Kathryn Ward and Pauline McElhill, who looked after me so well when I returned to work while still writing my thesis.

Within the Centre for Experimental Medicine, I would like to thank Lydia Emerson for her friendship, support and guidance during the last 5 years. I would also like to thank Emma Cunningham, Suzanne Ringrow, Rejina Verghis, Gerard Quinn, Philip Toner, Marianne Fitzgerald, Ciara O Donnell, Jon Silversides and Andrew Boyle for the advice, laughs and hot chocolate breaks.

International collaborators; I would like to thank Professor Dale Needham and his team at Johns Hopkins, Baltimore, Maryland, USA for facilitating a 4-day visit to their critical care unit, which provided me with an excellent insight into early mobilisation, family participation and environmental interventions for ICU patients. I would also like to thank the delirium experts who participated in my expert panel consensus meeting; Professor EW Ely, Professor T Girard, Professor P Pandharipande, Professor Dale Needham, Dr Thomas Jackson, Dr Emma Cunningham, Dr Daniel Davies, Dr Valerie
Page, Dr Catherine McKenzie, Dr Kieran Rooney, Professor John Devlin, John-Owen Bell and Dr Michelle Balas.

On a personal note, I would like to thank my family and friends, in particular my husband Lorcan, for his unfailing patience and support over the last 5 years. He has done more than his fair share of parenting and housework especially over the last few months and he gives me so much strength. He always champions everything I do and I could not ask for a better partner in life. I would also like to thank my parents, Teresa and Eddie and my parents in-law, Shay and Kathleen for always being there when we needed them to step in while I drafted and re-drafted this thesis. I would also like to thank my beautiful little daughter Helena for her patience, she does not know it yet but she has brought so much joy to me during this time.
A note on the format of the thesis

This thesis contains three published manuscripts, and one peer reviewed ethically approved protocol for a feasibility study. These papers have been inserted in the relevant chapters in an attempt to ensure a rational flow to the thesis. Published manuscripts are incorporated as integrated PDF documents; formatted as per journal specifications, with independent tables, reference lists and page numbers. If applicable, supplementary material is presented at the end of each manuscript. The page numbering flows in sequence through the thesis.
Publications included in this thesis and contributions

This thesis contains three published papers located in chapters 3 and 5 and an ethically approved protocol located in chapter 7. My contribution to each paper, the status of the paper (published/not published) and the bibliographic information, including all authors are as follows;

Chapter 3


Published

Contribution: My contribution to the paper involved: conceptualisation and development of the review protocol, prospective registration of the review, literature search, abstract screening, data extraction, critical appraisal of the literature, drafting of the manuscript, manuscript revision and approval of the final version.


Published

Contribution: My contribution to the paper involved: conceptualisation and development of the review protocol, prospective registration of the review, literature search, abstract screening, data extraction, critical appraisal of the literature, drafting of the manuscript, manuscript revision and approval of the final version. Professor Blackwood was listed as corresponding author on this paper as I was unavailable for personal reasons at the time that the paper was published.

Chapter 5


Published

Contribution: critical appraisal of the literature, conceptualisation and study design, ethics and governance applications, development of focus group interview tools, participant enrolment, data
collection, data analyses and interpretation, drafting of the manuscript and revision of the final version.

Chapter 7


Not published

Contribution: My contribution to the protocol involved: critical appraisal of the literature, conceptualisation and study design, ethics and governance applications, development of a case report form, training manual and study materials, registration with clinical trials registry (trial registration not activated as trial currently on hold), drafting of protocol and revision of final version.
Abstract

Delirium is common in Intensive Care Unit (ICU) patients with incidence up to 74% in the United Kingdom and is associated with increased mortality and morbidity. Multicomponent non-pharmacological interventions are beneficial in the prevention and treatment of delirium in older hospitalised patients however, there is a lack of evidence for their efficacy in critically ill patients. The studies in this thesis investigate which non-pharmacological interventions are effective for the prevention/treatment of delirium in critically ill patients.

The aim of this research project was to develop a non-pharmacological intervention that could be easily delivered by nursing staff in ICU as part of their current role. The objectives were to determine best evidence from experts and stakeholders on what is practical and if one intervention should be used or a package of interventions, define each component of the intervention and how this can be delivered, develop an implementation plan and protocol for a feasibility study and apply for ethical approval. To achieve these objectives, I followed the MRC guidance on the development of complex interventions and the methods are described here in three parts;

(i) Systematic review and meta-analysis: I followed the Cochrane methodology and included qualitative and quantitative studies. This was a novel approach to determine which interventions were effective in reducing the incidence and/or duration of delirium in critically ill patients,

(ii) Consensus meeting of international delirium experts to discuss the results of the systematic review and identify interventions that might work well in a multicomponent design. An expert panel was conducted where experts discussed in-depth a range of interventions that were indicated in a systematic review and meta-analysis to be potentially beneficial.

(iii) Focus group interviews with ICU staff, ICU survivors and their relatives to determine acceptability and feasibility of the interventions for inclusion in a multicomponent intervention. Key stakeholders discussed in depth a prototype for a multicomponent intervention incorporating education, sedation minimisation, physical and occupational therapy and optimisation of the environment.

The DIGNIFY study is the first to develop a multicomponent non-pharmacological intervention for delirium management in critically ill patients following the Medical Research Council (MRC) framework for the development of complex interventions. This novel study recognised the complexities of developing and implementing a non-pharmacological intervention and sought to address these in the intervention design. This was achieved by including expert opinion and stakeholder veto for interventions that were not deemed feasible. The complexities of the ICU environment were also considered and the template for intervention description and replication
(Tidier) framework was used to describe the intervention in its entirety and an implementation plan was devised that considered the ICU context. A thorough analysis of the busy environment, resource and organisation constraints was used to devise an implementation plan that would allow dedicated staff to implement the intervention.

Results from the systematic review of RCTs revealed limited evidence to support non-pharmacological interventions. Results from non-randomised studies were more promising and demonstrated a low-quality signal for improved delirium outcomes associated with education and family participation, sedation minimisation, physical therapy and environmental interventions. Experts felt physical therapy would have to be limited to around the bed mobilisation due to limited resources in UK ICU’s and felt pharmacist buy-in would also be limited with current resources. Staff interviews were largely supportive of the interventions brought forward. ICU survivors and their families placed huge importance on the participation of families, education and communication training or staff. The resultant evidenced based and stakeholder approved intervention incorporated;

1) an education programme for staff to facilitate buy-in from staff and family participation in care
2) an advisory protocol to limit sedatives and improve pain management
3) a physical therapy programme in liaison with the physiotherapy team that was incremental in nature
4) an environmental protocol which focused on structured orientation, communication training and resources, a structured sleep protocol and cognitive stimulation exercises delivered by family members and/or staff.

In summary, this PhD is vital for informing future work in this area due to the extensive work on intervention description using the TIDieR framework and implementation planning including development of a protocol, training manual and implementation strategy. All of this was undertaken in preparation for a single centre feasibility study for which ethical approval has been obtained. This study will be undertaken separate to this PhD thesis and could be taken forward to an RCT.
Chapter 1 Introduction

1.1 Background

“Survival per se is not the ultimate aim of intensive care medicine; rather, the target should be survival with a good quality of life– for patients to be kept alive with no hope of a meaningful life, death can actually be a good outcome” (1).

Critical care medicine has come a long way from tank ventilators and iron lungs. In recent years, intensive care medicine has witnessed many changes. John Louis Vincent outlined some of this progress in his 2013 review, “Critical care – where have we been and where are we going?” in particular the physical and organisational structure of ICUs and enhancements in equipment and technology that have translated to a transformation in patient care (2). With a progressively older population, the demand for critical care services will continue to rise in coming years. Improvements in technology and pharmacology have helped more people to survive critical illness and increased the number needing intensive care, and our challenge now is to provide for an increasing number of survivors with complex needs (3,4). Looking at future projections for critical care need, Needham estimated the number of mechanical ventilated (MV) patients in 2026 by standardising incidence to population projections and calculated there would be an 80% increase from the year 2000 by 2026 in the United States (US) (3). A study by Carson and colleagues also found that as the need for MV increased there were higher rates of impairment and fewer discharges to home (4).

These rates of functional and physical impairment are much higher if the complication of delirium occurs during a period of critical illness. Delirium is a syndrome, characterised by inattention and impaired cognition and it has a particularly high prevalence in critically ill patients (5). There are three subtypes: hypoactive, characterised by fatigue and lethargy; hyperactive, characterised by agitation; and mixed delirium that fluctuates between hyperactive and hypoactive. In addition to increasing the risk of poor outcomes such as increased risk of death, impaired cognition and reduced quality of life, delirium can be an extremely frightening experience for patients who often suffer from vivid hallucinations. Risk factors include age, infection, coma, multi-organ failure, immobility, sedation in particular benzodiazepines and opioids, sleep deprivation and absence of daylight. ICU patients in particular have an elevated risk of developing delirium, as they possess many of these risk factors simultaneously. Internationally, delirium rates range from 25% to 87% with studies of critically ill patients reporting the highest incidence (6, 7).

Delirium has been identified as a top priority for intensive care research (JLA, 2014) (8). There is a need for effective delirium management in critically ill patients and a particular challenge for ICU clinicians is the lack of guidance available on the best strategies for this. To date, no pharmacological
interventions have been shown to reduce incidence and/or duration of delirium, which has resulted in no recommendation for pharmacological therapies in the Society of Critical Care Medicine (SCCM) pain, agitation and delirium guidelines. The SCCM guidelines were published in 2013 \(^{(9)}\) and updated 2018, \(^{(10)}\) after thorough inspection of the evidence and provided only limited recommendations because of the generally poor quality of the evidence available.

The lack of effectiveness shown in studies of pharmacological therapies has forced the spotlight onto non-pharmacological strategies, which have shown promising results in non-ICU populations \(^{(11,12,13)}\).

**Non-pharmacological interventions for delirium management**

In general, Boutron and colleagues (2008) defined non-pharmacological interventions as interventions that include surgery, technical procedures, devices, rehabilitation, psychotherapy, behavioural interventions and complementary and alternative therapies \(^{(14)}\). At present, non-pharmacological interventions for delirium would not include surgery or psychotherapy but could include rehabilitation and complementary and alternative therapies. Essentially, a non-pharmacological intervention is any non-drug treatment or strategy targeting a specific disease or syndrome.

Historically, delirium was seen as an unavoidable consequence of critical illness due to lack of knowledge about the syndrome \(^{(15)}\). Since the late 1990s, there has been a renewed focus on delirium management and in particular on non-pharmacological management of this syndrome. Unfortunately, this focus has been slow to spread to the high-risk critically ill population but studies in other high-risk patient populations (e.g. geriatric, orthopaedic) have had some success evaluating non-pharmacological interventions \(^{(11,12,13)}\).

As a result, the breadth of the current evidence on non-pharmacological interventions for delirium comes from the older, acute medical population. An overview of 24 systematic reviews of comparative studies was carried out by Abrahà and colleagues (2015) \(^{(16)}\) on non-pharmacological interventions to prevent and treat delirium. They concluded that in the older population in medical and surgical wards, multicomponent non-drug interventions were successful for prevention of delirium but not for treatment. The following interventions were common in multicomponent studies that showed beneficial effects on the prevention of delirium; early mobilisation, hydration, nutrition and correcting sensory impairments \(^{(16)}\). Furthermore, the only single interventions that were identified as successful for delirium prevention were risk assessment software targeted at older patients \(^{(17)}\), a patient reorientation protocol \(^{(18)}\) and staff education \(^{(19)}\).
A number of studies evaluating non-pharmacological interventions for delirium in the older population were examined to determine beneficial interventions that might inform the search strategy for my systematic review. Inouye and colleagues found episodes of delirium were 10% in the interventions group compared to 15% in the control group ($p = 0.02$) using their risk targeting strategy (11). Martinez and colleagues (2012) (12) reduced delirium incidence by half with 5.6% incidence in the intervention group and 13.3% in the control group ($p = 0.03$) by introducing a delirium prevention protocol delivered by families. Marcantonio and colleagues (13) achieved an 18% reduction intervention versus control (32% versus 50%) ($p=0.04$) in the incidence of delirium by introducing an early specialist protocol for surgical hip fracture patients with guidelines to reduce potentially deliriogenic medications, control pain, regulate blood pressure, avoid hypoxemia and correct sensory impairment (13). Two studies (11,12) reported issues with contamination where details about the interventions was conveyed by word of mouth to staff in the control group and the authors felt this would explain the lower incidence seen in this study compared to other recent studies of this acutely ill older population. Orientation, pharmacy review, correcting sensory impairment and education of families can be considered beneficial, as these were the common non-pharmacological interventions used in all three studies.

In addition, many studies have incorporated education programmes into their multicomponent interventions to successfully reduce incidence and/or duration of delirium in both older acute medical and orthopaedic patients (19,20,21,22). Milisen and colleagues reported reductions in duration and severity of delirium but no difference in incidence or length of stay in a longitudinal, prospective, before and after study of an education programme for nurses (20). The education component comprised placement of ‘an eye-catching poster’ in the emergency department and trauma units. The poster included; (1) the core symptoms of delirium according to the CAM criteria (2) comparative features and differences between delirium, dementia and depression and (3) the relevance of correct and early recognition of delirium. Tabet and colleagues also had success with an educational package for medical and nursing staff, which demonstrated an almost 10% reduction in point prevalence of delirium in the intervention group (19). Their educational component included a one-hour presentation with group discussion, written management guidelines and follow-up sessions. Research in other patient populations can be informative for ICU clinicians and may be transferrable despite the lack of evidence in the ICU setting but this has not been adequately researched (23).

Although these non-pharmacological strategies have not been adequately tested on critically ill patients, it could be assumed that they might benefit these patients who have a higher risk of developing delirium. Nevertheless, ICU patients are exposed to many more risk factors for delirium.
and therefore the effectiveness of these interventions may not be generalizable and further research into use of these interventions in an ICU population is needed. Inouye and colleagues (2001) estimated intervention costs at approximately US$300 per patient but estimated over US$6000 of savings for every episode prevented, so a successful intervention has the potential to improve outcomes and reduce costs for critical care units.

Moving to an ICU context, despite beneficial results from some single non-pharmacological interventions, such as early mobilisation and reorientation protocols, the evidence does not indicate which interventions are most effective or how to overcome the barriers to their implementation (24, 25, 26).

In keeping with this lack of research evidence, there is limited guidance on non-pharmacological management of delirium in the critically ill population. The PAD guidelines provided a conditional recommendation for non-pharmacological interventions, for example mobilisation (low quality evidence) (9). Furthermore, NICE guidelines on delirium in adults (27) also recommended a number of non-pharmacological interventions to prevent delirium such as ‘ensuring adequate fluid intake, encouraging exercise or range of motion exercise, introducing cognitively stimulating activities and providing appropriate lighting and clear signage. However, the NICE guidelines are largely informed by the studies discussed above for non-ICU patients (older adults, acute medical) (11, 12, 13) whose findings may not be generalizable to the ICU population. In the non-ICU patient populations, multi-component interventions have been successful by focusing on modifiable risk factors. Risk factors and non-pharmacological management of delirium will be discussed further in chapter 2. Studies in the non-ICU population have also had success by incorporating education programmes into their intervention. There has been a lack of similar studies in critical care, but non-randomised studies by Devlin and Gesin and colleagues in ICU both found that education had a positive effect on nurses’ ability to recognise delirium and use validated screening tools (21, 22).

Regarding multicomponent non-pharmacological interventions in the ICU, evidence mainly comes from non-randomised studies (28, 29) and many of the interventions have not been tested in randomised trials. To address this lack of randomised trials of multicomponent non-pharmacological interventions in the ICU, the rationale for this project is to carry out a series of linked research projects to develop a multicomponent intervention that is evidence-based, pragmatic and robust enough to be tested in such a trial. This research will focus on defining the intervention by using the MRC framework for developing complex interventions, through identifying the evidence (systematic review and meta-analysis and expert panel consensus), assessing feasibility and acceptability of the interventions (focus group interviews) and operationalising the intervention in preparation for a
single centre study. When feasibility of the intervention has been determined, the intervention will be evaluated for effectiveness in a randomised trial. Success of a multi-component non-pharmacological intervention is largely dependent on the motivation of the clinical ICU nurses, who deliver these interventions at the bedside. Therefore, achieving buy-in for nursing staff and identifying barriers and facilitators to implementation underpins the pragmatic nature of this study and should increase its chances of success. The focus on developing a pragmatic intervention ensures that evidence can be translated into clinical practice more efficiently.

The NMC Code of Professional Conduct for nurses calls us to ‘prioritise people’ and ‘practice effectively’ and as ICU nurses, we are ideally placed to target risk factors such as disorientation, immobility, sensory and cognitive impairment and sleep deprivation. Through my clinical and research work in ICU, I saw first-hand the devastation that delirium can bring to patients and their families through functional, cognitive and psychological impairment and I recognised the need for further study in this area. I acknowledge that there are many complexities in the study of non-pharmacological therapies for example which to adopt or whether they should be bundled or delivered as single interventions. Of equal importance, introduction of these types of interventions requires buy-in from staff, contextual resources such as adequate staffing in appropriate disciplines (depending on what interventions are being tested) and it requires a comprehensive implementation plan and intervention description. Taking all of this into consideration, a suitable framework is required to ensure that the development of this intervention is moulded to address these complexities.

1.2 Theoretical framework underpinning this thesis

As previously discussed, my proposed intervention is a complex intervention for a number of reasons. Complex interventions are generally defined as interventions that have several different interacting components that work together. However, there are also other factors to consider that may make an intervention complex. These include attitudes of the people who will be delivering the intervention, number of groups targeted, variability of outcomes and degree of flexibility or tailoring of the intervention that is allowed. In the case of this proposed intervention, it requires robust development prior to evaluation to ensure that it is not only evidenced based and effective but that it is also feasible to service providers and users in ensure their buy-in.

In 2000, the Medical Research Council published guidelines for the development and evaluation of complex interventions and these were updated in 2008 from a linear to a more cyclical process. The MRC Framework is an excellent resource for developing and implementing a complex intervention in a complex environment such as ICU and provides many useful suggestions. I have
chosen to use this framework as it is easy to follow and includes many important steps that will serve to identify the contextual factors that will determine the development and successful implementation of the intervention as well as ensuring that my intervention is robust enough to be tested in a randomised controlled trial.

One of the criticisms levelled at the MRC guidelines is that they are lacking in complexity in relation to definition of and context for health services interventions. Kernick\(^{(32)}\) criticised the new MRC guidance for advocating inappropriate methods. He felt the guidance confused complex with complicated and lacked insight into complexity due to its simplification and the absence of complexity theory. However, the authors of the guidance reported that they had considered incorporating complexity theory in the guidance but did not find suitable practical applications of the theory for health interventions. Instead, the guidance favours a pragmatic approach by researchers to allow them to adopt the guidelines to each respective contextual situation\(^{(30)}\). Ensuring that an intervention can be adopted to its respective area or ICU is an important consideration for this project as contextual factors may differ from one ICU to another.

To address all of the above, I chose the following theoretical framework; The Medical Research Council’s framework for the development of a complex intervention (Figure 1) to guide the development of my delirium management strategy. I chose this framework as it is an iterative process that allows for consideration of the many complexities, mentioned above, that a delirium intervention for critically ill patients may present. These complexities include identifying which interventions to include when there is minimal evidence to support in the literature and identifying barriers and facilitators that are essential to ensure translation into practice.

This research is significant because if offers an original contribution to delirium management in critically ill patients, which was developed using the Medical Research Council (MRC) framework for the development of complex interventions. It blends qualitative analysis with quantitative analysis to determine an evidenced-based, pragmatic intervention that is feasible and acceptable to ICU staff, ICU survivors and their families. The completed research yields important implications for clinical practice, education programmes and future research. The use of the MRC framework for the development of complex interventions is in keeping with previous research projects in the ICU that have used this framework\(^{(33, 34)}\).
Figure 1 MRC framework for the development of complex interventions

Although there are many new evaluation methods, for example realistic evaluation and logic modelling, Craig and colleagues encouraged us not to reinvent the bicycle and concluded that any future improvement or revisions to the framework ‘are likely to be within rather than beyond the current framework’ \(^{(35)}\).

The MRC framework and accompanying BMJ paper are widely cited and help researchers to identify the appropriate methodology for development of a complex intervention. The MRC guidelines recommend a systematic approach to the development of complex interventions. The steps to consider are identifying existing evidence, identifying and developing theory and modelling process and outcomes as discussed below;

**Identifying the evidence base**

The MRC guidelines recommend identifying the ‘relevant, existing evidence base, ideally by carrying out a systematic review’ \(^{(30)}\). In accordance with this guidance, I undertook a systematic review and meta-analysis on the effectiveness of non-pharmacological interventions for delirium management in critically ill patients (Chapter 3). As there was limited evidence from Randomised Controlled Trials (RCTs), I included non-randomised studies. I also included qualitative studies to gain insight into barriers and facilitators to the interventions. This novel approach was important to identify interventions that might be included in my intervention.

**Identifying/ developing appropriate theory**

The MRC guidelines recommend developing an awareness of the relevant theory that would influence the success of the intervention, for example, how change can be achieved. They suggest
this can be achieved by familiarising oneself with current evidence and theory or completing ‘interviews with stakeholders’, i.e. those who receive or deliver the intervention[^30]. Therefore, I carried out qualitative investigation including an international delirium expert panel consensus meeting and focus group interviews with ICU staff, ICU survivors and their family members that allowed me to develop theory on the barriers and facilitators prior to implementation of the interventions. (Chapters 4 and 5).

**Modelling process and outcomes**

The framework recommends that developers think about implementation at an early stage in the development of the intervention before embarking on evaluation[^30]. To meet this recommendation, I researched implementation theories and selected theories that provided guidance for the implementation of a complex intervention and used these as a framework for an implementation plan. I used the TIDieR framework to describe how the intervention could be replicated. I also chose efficacy and feasibility outcomes to measure and incorporated these into a study protocol, which received research ethics committee (REC) approval.

**Assessing feasibility and piloting methods**

When the intervention is defined, the next step in the MRC Framework is to assess feasibility of the intervention. Although this actual testing is beyond the scope of this PhD, I have brought together all the information from the series of research project outlined above to design a protocol for a single centre before and after study to test adherence to components of the intervention in clinical practice (Chapter 7). A training manual for training staff on how to deliver the multicomponent intervention was also developed and this would be tested in the feasibility study with qualitative input to evaluate the impact of interventions and difficulties encountered with implementation.

**Evaluating a complex intervention**

Researchers are urged to choose study designs that consider the kind of intervention and specific characteristics of the study[^30]. The single centre feasibility study will determine what needs to be changed before moving to a larger scale trial. Depending on the results of the feasibility study, future plans for evaluation of the multicomponent non-pharmacological intervention involve carrying out a definitive randomised trial in which I would evaluate the effectiveness of the interventions, randomisation procedures, seek to understand processes of follow up and measure efficacy outcomes[^30] (Chapter 8).

**Implementation and beyond**
If the randomised trial had a favourable outcome, then the process would be to roll out the intervention to ICUs around the UK. Future work would also include a process evaluation alongside the main trial to determine if the intervention was delivered as directed, if the implementation plan was sufficient, outline the process through which the outcome were achieved and identify if there were different contextual factors that influenced the intervention in a positive or negative way. My colleagues in the centre for experimental medicine at Queens University Belfast are world leaders in process evaluation.

### 1.3 Aims and objectives

The overall aim of my programme of research for this PhD is to define a non-pharmacological intervention for delirium management in critically ill patients, guided by the MRC framework for developing complex interventions.

The objective of this thesis is to address the following research questions:

1. Which non-pharmacological interventions are effective in reducing the incidence and/or duration of delirium in critically ill patients?

2. On reviewing the evidence for non-pharmacological interventions for delirium management in critically ill patients, what do international multidisciplinary experts believe should be included in an intervention?

3. What are the perceptions of ICU staff about the feasibility of evidenced based non-pharmacological interventions for delirium and barriers and facilitators to their implementation in critically ill patients?

4. What are the perceptions of ICU survivors and their families on the acceptability of non-pharmacological interventions for delirium management and barriers and facilitators to their implementation in critically ill patients?

5. How might I test a non-pharmacological intervention for delirium management in critically ill patients?

### 1.4 Thesis structure

This thesis presents a collection of linked research studies that will inform the intervention and implementation plans; a systematic review to synthesis the evidence, a consensus meeting to design the intervention prototype, interviews with staff, patients and their families to ascertain acceptability of the intervention, the intervention protocol and the study protocol. The thesis is presented in eight chapters. The introductory chapter one provides a brief introduction and
background into delirium as a syndrome and non-pharmacological interventions as a potential management strategy to set the scene. An overview of the theoretical framework is also included to guide the development of the intervention and the rationale for this research project. A note on the format of the thesis is included in the opening sections of this thesis.

Chapter two presents an extensive review of the delirium literature up to January 2021. This addresses the empirical evidence on what we know about delirium to date. It covers the definition of delirium, epidemiology, subtypes, risk factors, pathophysiology, outcomes, identification and current pharmacological and non-pharmacological strategies for the management of the syndrome.

Chapter three presents the systematic review and meta-synthesis for studies evaluating the effectiveness of non-pharmacological interventions for delirium management in critically ill patients. A copy of the protocol and systematic review and meta-analysis as published have been embedded into this chapter to maintain a logical flow to the research process of this thesis. The remainder of the chapter presents the results from a systematic review of non-randomised and qualitative studies; these have not yet been published. I outline the development of the search strategy, eligibility and selection, data extraction, selection of outcome measures, risk of bias assessment and plans for data analysis, and discuss quantitative and qualitative findings and conclusions. These include the implications for development of a non-pharmacological intervention.

Chapter four presents the methods and findings from the expert panel consensus meeting on an evidenced based non-pharmacological delirium management strategy incorporating mobilisation, drug minimization and environmental interventions. The chapter concludes with a depiction of the intervention in its current developmental stage.

Chapter five presents the rationale for choosing focus group interviews, the aims and objectives for focus group interviews and a discussion of how knowledge of the barriers and facilitators to implementation can impact the success of an intervention. As in chapter three, a PDF copy of the published paper has been inserted into this chapter. This chapter includes an introduction to the paper and concludes with a discussion and a table describing what interventions have been deemed feasible (and remained in) and what interventions were not deemed feasible (and are out).

Chapter six presents the multicomponent intervention. It is described and reported using the template for intervention description and replication (TIDIER) guidelines. The chapter also presents plans for implementation of this intervention into an intensive care unit.
Chapter seven presents the study protocol as approved by the ethics committee, this is embedded in the chapter. The chapter also discusses the development of the study materials for a feasibility study.

Chapter eight provides a summary of the key findings of my programme of research for this PhD. Implications for clinical practice and future research are also discussed. While this PhD study has only addressed steps from the MRC framework up to feasibility, this chapter also delineates how the remaining steps will be employed, incorporating feasibility, evaluation and implementation.

1.5 Conclusion
This chapter introduces the study and the potential for non-pharmacological interventions as a management strategy for delirium in critically ill patients. The methods chosen follow the MRC guidance by; (1) identifying an evidence base through a systematic review and meta-analysis, (2) modelling theory through an expert panel consensus meeting and qualitative focus group interviews with ICU staff, ICU survivors and their families, and (3) assessing feasibility by designing an intervention training manual and preparing the protocol and materials for a feasibility study. This thesis is an integral part of a much larger research plan which will include investigating the feasibility of the intervention by measuring adherence to its various components in a feasibility study and if deemed feasible, going on to measure its effectiveness in a definitive randomised trial. The thesis then concludes with a discussion of studies that have been published since the systematic review and meta-analysis that are directly applicable to this research project.

This chapter has introduced the background and context to my research and provided the rationale for undertaking this complex, inter-linked series of studies. It sets the scene for how the rest of this thesis will explore the empirical and theoretical considerations for the development of a complex intervention for delirium management in the ICU. Chapter two will examine the existing empirical literature, identifying gaps in the current knowledge base and expanding the context and rationale for my research.
Chapter 2 Literature Review: Delirium

2.1 Introduction

This chapter provides a broad review of the literature on delirium that sets the scope of the project. It addresses the following key areas; definition of delirium, motoric subtypes and tools to assess subtype, delirium screening tools, epidemiology, risk factors, phenotypes, pathophysiology, outcomes, costs and management of delirium including pharmacological and non-pharmacological. The chapter commences with the definition of delirium and motoric subtypes, which were first identified by Lipowski in 1989 (36) and assessment tools used to identify delirium in patients. The epidemiology section explores the incidence and prevalence of delirium in different patient populations before moving on to describe the risk factors of delirium, which can be modifiable or non-modifiable. Targeting modifiable risk factors is an important part of delirium management. The pathophysiology of delirium remains unknown but several hypotheses are explored in this chapter. The chapter continues by outlining the significant costs for the National Health Service (NHS), the individual and society that are associated with this syndrome and concludes with a discussion of the current evidence and guidelines on management strategies for delirium.

Studies evaluating delirium incidence and duration will be considered together because the steps to prevent and treat delirium are likely to be the same for both approaches.

Search strategies

To inform this literature review, I searched Medline, Embase, CINAHL and the Cochrane library on 20th June 2015 for relevant literature on delirium. I used the keywords delirium, critical care or critical illness or intensive care and outcomes, incidence and prevalence, guidelines, subtypes, management, cost, pathophysiology, screening tools and risk factors. I did not restrict language or year of publication as the delirium literature does not become prominent until the late 1990s and I was interested in the evolution of management strategies for delirium. I also carried out hand searches of relevant journals. I repeated the searches in January 2021 in order to ensure that the literature was up to date and added 27 studies.

Definition of delirium

Critically ill patients have a heightened risk of developing delirium during their ICU and hospital stay. Delirium is characterised by ‘a fluctuating course, shifting attention, disorganised thinking and a changed level of consciousness’ (37). The American Psychiatric Association (APA) released the updated Diagnostic and Statistical Manual of Mental Disorders in 2015 (DSM-5) (5). In summary, the APA define delirium as a disturbance in attention and awareness that develops over a short period of
time and there is evidence in their history that it is the consequence of a pre-existing neurocognitive condition, a medical condition, drugs or toxins (DSM-5). The full DSM 5 criteria are outlined in table 1.

Table 1 DSM-5 Diagnostic criteria for Delirium [taken from the APA DSM-5, 2013 (5). p. 596].

Diagnostic criteria

A. A disturbance in attention (i.e. reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment).

B. The disturbance develops over a short period of time (usually hours to a few days), represents an acute change from baseline attention and awareness and tends to fluctuate in severity during the course of the day.

C. An additional disturbance in cognition (e.g. memory deficit, disorientation, language, visuospatial ability, or perception).

D. The disturbances in Criteria A and C are not better explained by a pre-existing, established or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal such as coma.

E. There is evidence from the history, physical examination, or laboratory findings that the disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal (i.e. due to a drug or abuse or to a medication), or exposure to a toxin, or is due to multiple aetiologies.

This update has subtle differences in criterion A, B, C and E from the previous definition in DSM-IV (38) but the major difference is in the addition of criterion D, which indicates that delirium cannot be diagnosed in the setting of neurological disorder or in a severely comatose patient.

The addition of this criterion is significant for the critical care population and there has been considerable scrutiny of the new DSM-5 diagnostic criteria due to concerns about missed diagnosis of delirium due to criterion D. The inclusion of this criterion might mean that patients with coma or neurocognitive disorders might have their delirium diagnosis overlooked. The European Delirium Association (EDA) and the American Delirium Society (ADS) released a joint statement regarding these changes. They advised ‘an inclusive interpretation of criteria A and D’; and recommended that patients who demonstrate impaired arousal and are unable to participate in cognitive tests should be classified as having inattention to facilitate improved patient safety and effective delirium management (39).
Delirium may serve as a marker of a vulnerable brain, a brain more susceptible to injury \textsuperscript{(40)}. In vulnerable brains, minor insults such as an infection or metabolic imbalance may be enough to instigate delirium \textsuperscript{(41)}. In consideration of the DSM-5 criteria and the fact that there is often a high incidence of delirium in those populations with high brain vulnerability, the advice from the EDA and ADS should be taken into account in these populations to avoid missed diagnosis of delirium \textsuperscript{(40)}. A recent international interdisciplinary delirium expert panel used a modified Delphi process to agree definitions for delirium and encephalopathy. The panel advised using the descriptor ‘subsyndromal delirium’ for acute cognitive changes associated with delirium but not meeting all five of the DSM 5 criteria. They also recommended against the use of the terms acute confusional state, acute brain failure, acute brain dysfunction or altered mental status \textsuperscript{(42)}. These recommendations were approved by ten professional societies. This work ameliorates some of the confusion around definitions of delirium in clinical practice and research.

2.2 Delirium subtypes

As outlined above, there is still some confusion over the definition of delirium. The different subtypes and more recently phenotypes that are recognised in the delirium literature further complicate this. Delirium was first described by Hippocrates in terms of ‘phrenitis’ and ‘lethargus’ some 2,500 years ago but it was not until 1989 that motoric subtypes of delirium were first differentiated by Lipowski as hypoactive and hyperactive, adding the mixed subtype a year later \textsuperscript{(36, 43)}.

Hypoactive subtypes are characterised by fatigue and lethargy, with a possible trajectory towards stupor \textsuperscript{(5)}. Older age is independently associated with hypoactive delirium (adjusted OR 3.0, 95% CI 1.7-5.3) compared to no delirium in a model that adjusted for severity of illness, use of sedatives and mechanical ventilation status \textsuperscript{(44)}. Hypoactive delirium is estimated to occur in 43-64% of critically ill patients \textsuperscript{(44, 45)}. Patients with this subtype have been found to have a higher associated mortality independent of covariates such as comorbidities, age and delirium and dementia severity. This may be due to the delayed detection of this subtype \textsuperscript{(44, 45)}.

Hyperactive subtypes are often characterised by agitation and uncooperative behaviour (American Psychiatric Association, 2013, p 598). Solely hyperactive delirium is the rarest subtype and only occurs in approximately 1-2% of cases of delirium in ICU \textsuperscript{(44, 45)}.

The mixed subtype of delirium is characterised by a fluctuation in motor activity intensity \textsuperscript{(5)}. Estimates for the prevalence of mixed delirium vary widely with Peterson and colleagues identifying approximately 55% prevalence in their study of medical ICU patients while Pandharipande and
colleagues identified much lower prevalence rates of 9% and 6% respectively in surgical and trauma ICU patients\(^\text{44}\). The difference in incidence of this subtype in medical and ICU populations may be explained by the older age and increased frailty in medical patients.

Overall, a knowledge of delirium subtypes can help with the identification of delirium and avoid delirium being confused with depression or other mental health conditions. Correct identification means delirium management strategies can be started promptly without delay.

Studies have used validated psychometric tools to define clinical motor subtypes of delirium\(^\text{47}\). These include the Richmond Agitation and Sedation Scale (RASS)\(^\text{48}\), the revised Delirium Rating Scale (DRS-R98)\(^\text{49}\), Memorial Delirium Assessment Scale (MDAS)\(^\text{50, 51}\), the Delirium Motor Subtyping Scale (DMSS-4)\(^\text{52}\) or clinical criteria such as the Liptzin and Levkoff criteria\(^\text{53}\). Table 2 provides additional information on these subtyping tools for delirium.
### Table 2 Delirium subtyping tools

<table>
<thead>
<tr>
<th>Delirium subtyping tools</th>
<th>Description</th>
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<tbody>
<tr>
<td>Delirium Rating Scale Revised-98</td>
<td>16-item clinician rated scale for judging the severity of delirium and has been validated against other delirium rating scores. It has high interrater reliability and internal consistency scores.</td>
</tr>
<tr>
<td>The abbreviated version of the Delirium motor subtyping scale (DMSS-4)</td>
<td>Developed by Meagher and colleagues and they compared it to the original delirium motor subtype scale and found four features that determined the subtypes and had good similarity with the original DMS. The four features were hyperactive, hypoactive, mixed and non-motor. DMSS-4 also had the further advantage of being more convenient for users.</td>
</tr>
<tr>
<td>The memorial delirium assessment sale (MDAS)</td>
<td>Ten-item four-point clinician rated scale (0-30) used to measure the severity of delirium in medical patients. Shyamsundar and colleagues evaluated the reliability and validity of the MDAS in medical and cardiac ICU patients in India and found it had a sensitivity of 100% and specificity of 95% in non-intubated patients.</td>
</tr>
<tr>
<td>The Richmond Agitation Sedation Scale (RASS)</td>
<td>Measures sedation and agitation levels in critically ill patients. A patient is scored from 4 to -5 on a 10-point scale with four scores for agitation (1, 2, 3, 4), one score for alert and orientated (0) and 5 scores for sedation (-1, -2, -3, -4, -5).</td>
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### 2.3 Assessment of delirium in critically ill patients

Having a reliable definition of delirium and different subtypes paves the way for the development of screening tools to assess for the presence of delirium. In recent times, there have been increased appeals to implement screening programmes in the ICU to identify patients with delirium and adjust care accordingly. Several studies have identified that delirium is significantly under diagnosed with detection rates of approximately 29% for doctors and 35% for nurses in the absence of valid screening tools. The gold standard for diagnosis of delirium is the diagnostic and statistical manual of mental disorders (DSM-5) criteria however, this assessment requires a trained psychiatrist, which may not be feasible in an ICU context.
For critically ill adults, many delirium detection tools have been validated for use in the ICU. The most popular tools are the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC) \(^{6,57}\).

**Confusion assessment method for the ICU (CAM-ICU)**

The CAM-ICU tool has four features; altered mental status or fluctuating course, inattention, altered level of consciousness and disorganised thinking. Features 1 and 2 must be present with either feature 3 or 4 to achieve a delirium positive result. Ely and colleagues designed and tested the CAM-ICU, on 38 patients admitted to the intensive care unit \(^6\). They compared ratings from two research nurses and an intensivist against the ratings of a delirium expert using the criteria for delirium from the DSM (fourth edition). Interrater reliability was high for the two nurses and intensivist and compared well to the reference standard, sensitivities were 95-100% and specificities were 89-93% indicating that CAM-ICU is a reliable and valid tool for delirium screening in the intensive care unit. The tool takes 2-3 minutes to complete and requires only minimal training for staff to administer \(^6\). Ely and colleagues reported that enrolment of 38 patients exceeded sample size estimates for 25 patients to achieve a lower range of 80% for the confidence interval. In addition, further validation studies have been completed and the tool has now been translated into many languages \(^{58-61}\).

**Intensive care delirium screening checklist (ICDSC)**

Bergeron and colleagues created a screening checklist called the intensive care delirium screening checklist (ICDSC) \(^{57}\). This checklist had eight items, largely informed by the DSM criteria, including altered level of consciousness, inattention, disorientation, hallucination or delusion, psychomotor agitation or retardation, inappropriate mood or speech, sleep/wake cycle disturbance and symptom fluctuation. Each item that is assessed as present score one point with a score greater than four indicating a positive delirium score. It can be completed rapidly and with ease by nursing and medical staff \(^{113}\). It has been tested on 93 patients against a psychiatric evaluation. Using ROC analysis, they scored sensitivity at 99% and specificity at 64% indicating that the ICDSC may be a useful tool for identifying patients with delirium in the ICU. The specificity of 64% would indicate that the ICDSC should not be used as a diagnostic tool due to the high false positive rate.

**The Neelon and Champagne (NEECHAM) confusion scale**

The Neelon and Champagne (NEECHAM) confusion scale \(^{62}\) is a 0-30 scale with four categories; no delirium, at risk, mild confusion and moderate to severe confusion. A score of 0-19 was validated against DSM-III criteria \(^{63}\). Immers and colleagues found the NEECHAM confusion scale to have high internal consistency and a moderate interrater reliability, (Cohen’s kappa = 0.60). Sensitivity was
rated as 97% and specificity was rated as 83%. However, this tool is only validated for use on non-intubated ICU patients and requires modification on two items for non-verbal communication so that it can be used in intubated patients [63].

Other tools

A psychometric analysis and systematic review by Gelinas and colleagues identified 36 studies evaluating 5 different delirium assessment tools used in ICU; CAM ICU, Cognitive Test for Delirium (CTD), Delirium detection score (DDS), Intensive Care Delirium Screening Checklist (ICDSC) and Nursing Delirium Screening Scale (NDSS). They judged psychometric properties of CAM-ICU and ICDSC as very good, NDSS as moderate, DDS as low and CTD as very low indicating that CAM-ICU and ICDSC are the most valid and reliable tools for delirium assessment in critically ill patients [64]. Both tools have been used extensively both clinically and in research studies. In a single centre study by Tomasi and colleagues [65] (2012), CAM-ICU did emerge as a superior tool for predicting clinical outcomes. There were less false positives using the CAM-ICU than the ICDSC. However, the false positives using the ICDSC are attributed to including patients with clinical features that mimic delirium such as certain psychiatric diagnoses so psychiatric review should be used in cases where a psychiatric influence is suspected. In a systematic review and meta-analysis of thirteen studies assessing the CAM-ICU and the ICDSC screening tools for diagnosis of delirium, Gusmao-Flores and colleagues [59] (2012) concluded that both tools could be used to efficiently screen for delirium in critically ill patients.

Based on this evidence, the 2018 PAD guidelines recommend that ICU patients are screened regularly for ICU delirium using either the CAM-ICU or the ICDSC [10]. Overall, the CAM-ICU and ICDSC are the most suitable tools for screening for delirium in the ICU. There is a paucity of qualitative evidence on the ease of use of these tools and studies in this area might help clinician’s choose an appropriate tool.

Barriers to screening for delirium

Adherence to screening for delirium remains inconsistent in ICUs with MacSweeney and colleagues finding only 25% (170/681) respondents in their survey had a routine screening program for delirium [66]. Although this survey is now over 10 years old, barriers to implementation of screening programmes for delirium continue to be identified, indicating that screening is not yet established in many ICUs [67]. A review of the literature around barriers and facilitators to implementation of routine screening in ICU indicated that the greatest barrier was ICU culture and lack of engagement; staff deemed delirium an unavoidable part of the critical illness journey. Facilitators were providing
feedback on delirium screening in actual time, multifaceted education incorporating case-based scenarios and interdisciplinary communication at bedside ward rounds and use of official documentation systems (67). This contributed to an overall understanding of the importance and priority that delirium screening should have in the ICU.

2.4 Epidemiology of delirium

After appropriate identification of possible delirium using validated screening tools, the next step towards delirium management is getting a sense of the incidence and prevalence of delirium. Delirium incidence and prevalence can vary widely in different patient populations and hospital wards. Hip fracture patients over 65 years of age have a delirium incidence of 40–56% (68,69). In the general medicine cohort, there is a 15-20% prevalence for delirium at time of admission to the ward and 18% prevalence for patients 65 years and over within 72 hours of admission with a further 2% of incident delirium in the following week (70-72). In the emergency medicine population, prevalence rates are 5-10% (70) while in long-term care, 52.6% of older hospitalised patients experience delirium (73).

The highest incidence and prevalence is seen in critically ill patients. There is a distinct diversity in incidence of delirium with estimates ranging from 25% to 87% in critically ill patients in both UK and international studies (74–78). The basis for this extensive range can be elucidated by differences in screening practices for delirium, under-recognition of the syndrome and variations in ventilation status and severity of illness in different study populations (79–81). ICUs report higher incidences of delirium than the general wards most likely due to patients being exposed to a larger number of risk factors and having more robust screening protocols.

2.5 Risk factors for delirium in critically ill patients

Two systematic reviews, one meta-analyses and a study developing a delirium prediction model identified numerous risk factors that are associated with the development of delirium in critically ill patients (82–85). The literature often describes risk factors as modifiable and less modifiable. A modifiable risk factor is something that you can do something about and a less-modifiable risk factor is something you cannot change although their effect can be controlled or reduced.
Table 3 Risk factors for ICU delirium

<table>
<thead>
<tr>
<th>Modifiable risk factors</th>
<th>Less-modifiable risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedation (in particular benzodiazepines and opioids)</td>
<td>Age</td>
</tr>
<tr>
<td>Transfer to another ward</td>
<td>Dementia or pre-existing cognitive impairment</td>
</tr>
<tr>
<td>Immobility</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Social isolation</td>
<td>Higher Apache 2 score</td>
</tr>
<tr>
<td>Sleep or sensory deprivation</td>
<td>Metabolic acidosis</td>
</tr>
<tr>
<td>Use of physical restraints</td>
<td>Emergency surgery</td>
</tr>
<tr>
<td>Absence of daylight</td>
<td>Elevated urea concentration</td>
</tr>
<tr>
<td>Infection/sepsis</td>
<td>Need for mechanical ventilation</td>
</tr>
</tbody>
</table>
| Knowledge of the risk factors for delirium may provide a potential treatment strategy as there is evidence in the literature that targeting these risk factors can help reduce incidence and duration of delirium. Van den Boogaard and colleagues developed a model called the PREDELIRIC to predict risk of delirium in adult ICU patients. It was validated in five intensive care units in the Netherlands using univariate logistic regression to assess the association between each risk factor and the development of delirium. This model includes 10 risk factors for the development of delirium; age, APACHE II score, admission group, coma, infection, metabolic acidosis, use of sedatives and morphine, urea concentration and urgent admission. This model provides a formula that can be used to calculate delirium risk for patients and to allow healthcare professionals to instigate preventative measures on admission. Many researchers have developed therapies based on their knowledge of risk factors and have successfully reduced delirium incidence and duration using this risk-factor targeting approach. Overall, it seems logical that intervening to alleviate or prevent risk factors could have an impact on the pathogenesis of delirium for example, improving sleep (targeting sleep deprivation) or reducing the amount of sedative drugs (targeting polypharmacy).

2.6 Delirium Phenotypes

Girard and colleagues identified phenotypes, observable physical characteristics, associated with clinical risk factors for delirium; sepsis, hypoxia, sedation exposure and metabolic (renal or hepatic) dysfunction. In a multicentre, prospective cohort study of 1,040 adult medical surgical ICU patients with respiratory failure, shock or both, they found that phenotypes often occur simultaneously i.e. one patient may exhibit delirium associated with sepsis and hypoxia. Delirium associated with sedation exposure was the most common accounting for 63% delirium days and
longer duration of sedative associated delirium. Hypoxic, septic and unclassified delirium were associated with worse cognitive function at 12 months but no association existed for delirium related to metabolic dysfunction. In the future, there may be opportunities to target these different phenotypes with different management strategies. Knowledge about the mechanisms that cause delirium in relation to different phenotypes could lead us to effective management strategies.

2.7 Pathophysiology of delirium
The pathophysiology of delirium has not been fully elucidated however; many mechanisms have been hypothesised. The following theories provide plausible explanations for how delirium may occur.

1) It has been hypothesised that reduced cerebral blood flow and hypoxia causes widespread brain dysfunction. This theory might also explain the long-term cognitive impairment that is often associated with delirium. Several studies describe a reduction in blood flow or ischaemic injury in multiple areas of the brain during or after acute delirious episodes. Hypoxic ischaemic injury was noted in the hippocampus, pons and striatum of 6 out of 7 participants who were delirious prior to death and had a brain autopsy carried out within 24 hours of their death. This was a small study that did not look at the brains of non-delirious patients. In addition, hypoxic injury to the hippocampus and other parts of the brain could be explained by the facts that 6 out of 7 patients suffered from ARDS and septic shock. Another study in general medical patient found frontal or parietal cerebral perfusion abnormalities on single photon emission computed tomography (SPECT) scans of delirious patients. Yokota and colleagues used xenon enhanced computed tomography to measure the regional cerebral blood flow (rCBF) of patients both during delirium and after resolution. They found that rCBF was reduced during delirium and resolved afterwards implying cerebral hypoperfusion is implicit in the pathogenesis of delirium. All studies have inherent weaknesses; The Fong and Yokota studies only included hypoactive patients for feasibility of scanning and they were all small studies (with 22, 7 and 10 participants respectively). These results could indicate that cerebral hypoxia and impaired cerebral blood flow may be involved in the development of delirium in critically ill patients however larger studies are needed to confirm these findings.

2) Another theory for the pathogenesis of delirium is neuroinflammation. Gunther and colleagues explored the hypothesis that delirium presents when sepsis causes central nervous system dysfunction and damage to the brain via inflammatory mediators infiltrating a damaged blood brain barrier and travelling into the brain inducing endothelial damage and increased permeability. This inflammatory response seen in critical illness causes numerous injuries to the brain including
damage to the vascular system, ischaemia, neuroinflammation and apoptosis\(^{(91)}\). Increased levels of interleukin (IL)-6, IL-8, C-reactive protein and procalcitonin, that are produced in response to inflammation, have also been investigated and found to be associated with delirium development\(^{(92} - 95\)). An exploratory non-randomised study of 100 ICU patients found IL-8 was associated with delirium in inflamed patients (with systematic inflammatory response syndrome [SIRS]) while anti-inflammatory cytokines IL-10 and AP1 -42/40 were associated with delirium in non-inflamed (without SIRS) patients\(^{(92)}\). A study of 87 patients found high baseline inflammatory biomarkers (procalcitonin and CRP) correlate to less delirium/coma free days providing further evidence to support the hypothesis of inflammation having a role in the pathogenesis of delirium\(^{(93)}\). A study of 187 patients found IL-6 and IL-8 levels were significantly above the threshold level in patients with delirium versus patients without delirium. Again, this supports the hypothesis that inflammation is implicated in delirium pathogenesis\(^{(94)}\). Finally, statin use was associated with lower CRP levels and delirium free days, which supports the hypothesis of neuroinflammation in delirium\(^{(95)}\). Many of these studies were non-randomised in nature and included small sample sizes so they would need to be repeated with larger sample sizes to allow for controlling for other potential covariates.

3) The third theory is the hypothesis that neurotransmitter imbalances are implicated in delirium pathogenesis. Hshieh and colleagues undertook a detailed review of the impact of cholinergic deficiencies in the pathogenesis of delirium. They postulated that impairments in global metabolism, cytokine interaction and neurotransmitters interact to induce central cholinergic deficits\(^{(96)}\). One study, identified in the review, found there was increased severity of delirium symptoms in older patient using anticholinergic drugs even after adjusting for total number of non-anticholinergic medications (drugs that do not have anticholinergic properties), dementia, baseline delirium severity and length of follow up\(^{(97)}\). In addition to cholinergic deficiencies, an excess of monoamines including dopamine, norepinephrine and serotonin are also implicated in the development of delirium\(^{(98)}\). The role of neurotransmitter imbalances, including cholinergic deficiencies and dopamine excess requires further exploration however, the evidence suggests that their interactions play a crucial role in the presentation of delirium.

A common final pathway for delirium is hypothesised regardless of the aetiology. This pathway is impaired neuronal network connectivity and it is hypothesised that an underlying predisposition and exposure to an acute stressor may contribute to a failure in the function of connectivity in neural networks with significant implication for normal brain function\(^{(99)}\). Functional MRI (fMRI) and EEG changes have also confirmed network changes during delirium that support this hypothesis\(^{(100)}\).
In summary, the theories described above are potential mechanisms for the development of delirium and this list is not exhaustive. The strength of the evidence for these theories is weak as the evidence is often from small studies that had many confounding factors such as sepsis or other disease processes. There are many inconsistencies with these hypotheses. For example, although studies have shown a link between cholinergic deficiency and delirium severity, studies of cholinesterase inhibitors have failed to show effect in prevention or treatment of delirium. In addition, antipsychotic drugs, which often work by blocking D2 dopamine receptors, have been studied in many trials. No trial has shown any evidence of their effect on preventing or treating delirium, which weakens the hyperdopaminergic theories. Furthermore, although many studies indicate inflammation in the pathogenesis of delirium, studies involving treatment with statins did not show improved delirium outcomes. Delirium is multifactorial and there may be many different pathophysiologic pathways at play in different parts of the brain. These require further investigation with larger trials and more consistent assessment of delirium before we can truly explain the pathogenesis of this syndrome. Knowledge of the mechanisms involved in the development of delirium could help us understand and potentially prevent the negative outcomes associated with this syndrome.

2.8 Outcomes associated with delirium in critically ill patients

Heightened emphasis on the importance of delirium in critically ill patients has resulted from the realisation that this syndrome is associated with serious negatives outcomes which can be short term (during ICU and hospital stay) or long term (after hospital discharge). These include increased mortality and morbidity and cognitive and functional decline. Furthermore, the longer a patient experiences delirium, the higher their risk of these negative outcomes. The research focus on identifying the mechanisms and finding therapies to prevent and treat delirium is motivated by a commitment to minimising these negative outcomes.

A number of prospective cohort studies identified a link between delirium and in-hospital mortality \(^{(77, 102-106)}\) however evidence from cohort studies can be considered weak. Post-ICU follow-up studies have examined long term effects of critical illness and found that delirium is an independent risk factor for a three times higher likelihood of death at 6 months even after adjusting for covariates such as severity of illness, coma and use of sedatives \(^{(106, 107)}\). This picture was further expanded by Pisani et al (2009) \(^{(108)}\), who found that the number of days of delirium in ICU was significantly associated with time to death within one year after admission (HR 1.10) after adjusting for age, severity of illness, baseline cognitive and functional decline, comorbid conditions and use of psychoactive medications \(^{(108)}\). When patients with delirium were compared with control patients...
without delirium, mortality was higher for patients with delirium during their ICU admission (RR 2.19, 95 % CI 1.78-2.70, P < 0.001) \(^{109}\).

Associations found between delirium and mortality in cohort studies are considered weak, as there may be many other factors at play that are not adequately controlled for in prospective cohort studies. Recent studies debate the link between delirium and increased mortality \(^{110, 111}\). Klouwenberg and colleagues used a marginal structural model analysis that allowed them to adjust for confounding factors by development of disease severity and found that the association with mortality was not detected after adjustment using this method \(^{110}\). In their prospective longitudinal cohort study, Shehabi and colleagues also concluded that the association between delirium and mortality might not be significant after adjustment for sedation intensity \(^{111}\). Although many studies linking delirium to higher mortality have tried to control for severity of illness, there may have been residual confounding that was not accounted for. Some studies used multivariate analysis in an attempt to control for potential confounding factors but still found that delirium was an independent predictor for mortality \(^{104, 105}\). Currently, although there is an association between delirium and risk of mortality, there is insufficient evidence to demonstrate a causal relationship. Future studies should be sufficiently powered to assess mortality in delirious versus non-delirious patients.

Studies have also reported associations between delirium and other clinical outcomes. Development of delirium in ICU was associated with an extended length of MV, ICU and hospital stay \(^{9, 76, 77, 102}\). Each additional day spent in delirium caused a 20% increased risk of a prolonged hospitalisation which can be interpreted as over ten extra days in hospital \(^{107}\). In a systematic review and meta-analysis (n = 42) of outcomes of delirium in critically ill patients, mean length of ICU stay was approximately 1 day longer for patients with delirium (SMD 1.38, 95% CI 0.99-1.79, p < 0.001). Hospital length of stay was also longer (SMD 0.97, 95% CI 0.61 – 1.33, P = <0.001) and mean duration of mechanical ventilation was almost two days longer in patients with delirium (SMD 1.79, 0.31-3.27, p < 0.001) \(^{109}\). This result was significant even after adjusting for variables such as age, number of females and APACHE II scores \(^{109}\).

Furthermore, delirium in critical illness is an independent predictor of a ten-fold higher likelihood of cognitive impairment at one year \(^{101}\). Girard and colleagues found that at three and 12 months, 79% and 71% (n = 126) respectively had significant cognitive impairment (62% and 36% of these were severely impaired). They used nine tests measuring seven domains of cognition to assess long-term cognitive function. After adjusting for age, education, pre-existing cognitive function, severity of illness, severe sepsis and use of sedative medications in the ICU, duration of delirium was found to
be an independent predictor of worse cognitive performance \cite{101}. Up to 60% of patients that survived critical illness had serious cognitive dysfunction for months to years after their ICU stay limiting quality of life, increasing health care costs and care needs \cite{101}. Pandharipande and colleagues also noted that a longer duration of delirium was associated with worse global cognition and executive function scores at 3 and twelve months using the repeatable battery for the assessment of neuropsychological status (RBANS) and trail making test, part B \cite{74}.

Studies showed that an episode of delirium led to a significant acceleration of cognitive decline in patients with dementia \cite{112,113}. The information memory concentration (IMC) subtest of the Blessed Dementia Rating Scale scores range from zero to 37, with higher scores indicating impairment \cite{114}. The rate of deterioration in scores on the information memory concentration (IMC) was three fold higher in patients with delirium compared to those without delirium \cite{112}. Goldberg and colleagues also found a link between delirium and long term cognitive decline in a meta-analysis of 23 studies with an estimated effect size (Hedges g) of 0.45 (95% CI, 0.34 – 0.57, p = 0.001) \cite{115}. Fong noted that a significant acceleration in the slope of cognitive decline occurs following an episode of delirium. Among patients who developed delirium, the average decline at baseline for performance on the IMC was 2.5 points per year, but after another episodes of delirium there was a further decline of 4.9 points per year, p = 0.001 \cite{112}. That is almost double the average decline. It is important to note that this study did not include ICU patients but focused specifically on patients with Alzheimer’s disease. A criticism of the other studies would be that they excluded patients with severe dementia however they did make efforts to include patients with less severe cognitive impairment who they felt could return to independent living. Both studies used the short Informant Questionnaire on Cognitive Decline in the Elderly (IQcode) short form to identify pre-existing cognitive impairment \cite{74,101}.

Delirium was shown to be a significant predictor of an inability to carry out activities of daily living (ADLs), at both hospital discharge and three-month follow up \cite{116}. The consequences of delirium increase costs for the National Health Service (NHS) and more importantly can result in persistent cognitive deficiencies such as dementia \cite{74,117}. Furthermore, Brummel and colleagues found that after adjusting for covariates, longer duration of delirium was independently associated with worse ADL and motor-sensory function (measured using the motor/sensory factors section of the awareness questionnaire comparing arm/leg movement, eyesight, coordination and hearing to pre-illness function) \cite{118}. Altman and colleagues (2018) also reported an association between duration of delirium and post discharge sleep disturbances \cite{119}. This 122 patient non-randomised cohort study also reported a trend towards worsening functional disability up to one-year post discharge.
In a large prospective, multicentre cohort study of 821 medical/surgical ICU patients, Jackson and colleagues found that up to 25% of patients had poor mental health and functional disabilities at 3- and 12-months post discharge but this was not consistently associated with delirium status\(^{(120)}\). Other studies have also failed to find an association between delirium and development of mental health problems\(^{(121, 122)}\).

Overall, the physical and psychological effects associated with delirium have been clearly elucidated in the literature and it is important that these are addressed. In terms of determining causality in relation to delirium and the association with negative outcomes in observational studies, a lot of the evidence is derived from observational studies. In order to draw any conclusions on causality from observational data, the Bradford Hill Criteria\(^{(123)}\) could be considered. In terms of determining causality in relation to delirium and the association with negative outcomes, much of the evidence is derived from observational studies. One way to assess this is to use the Bradford Hill Criteria\(^{(123)}\) for causality. These criteria use nine principles to guide the assessment of association: strength, causality, specificity, temporality, biological gradient, plausibility, coherence, experiment and analogy. In relation to delirium research, there is a strong association between the development of delirium and increased mortality and morbidity, which is consistent across studies. However, specificity is unlikely to be met as delirium is a syndrome and is linked to many different outcomes and patients in critical care have a complex mixture of factors that might impact on their outcomes. Regarding temporal sequence, many studies have demonstrated that negative outcomes such as cognitive impairment follow an episode of delirium. As delirium aetiology is multifactorial, criteria relating to biological gradient, biologic rationale and analogous evidence criteria are unlikely to be met, and in terms of coherence, there are several theories about the pathophysiology of this syndrome but this research is still in its infancy. There is also a lack of experimental evidence since this would probably need to come from animal models and the literature cites a lack of such studies\(^{(124)}\). In summary, the use of the Bradford Hill Criteria highlight the methodological limitations in determining causation for delirium and other health outcomes. There are many gaps in the knowledge and a potential for confounding or undetected causes to have an impact such that a conclusion about causation cannot be made at present. This means that the extent to which delirium indicates an impending decline in physical and cognitive function and how it effects the subsequent trajectory downwards are uncertain. Further research is required to elucidate the full impact of delirium on cognitive and functional outcomes.

2.9 Costs associated with delirium

In addition to the human costs of delirium, there is a significant financial burden associated with the syndrome also. The average overall cost for staff and treatment per ICU day ranged from €1168 to
€2025 in a study by Tan and colleagues at seven ICUs in four European countries; Germany, Netherlands, Italy and the United Kingdom (125). There is a deficiency of studies evaluating cost of delirium in ICU specifically but one North American study uncovered that delirium translated to a 1.3- and 1.4-fold increase in ICU and total hospital costs respectively (95). When considering that increased length of ICU stay is one of the outcomes associated with delirium, costs can quickly escalate without appropriate management strategies.

Pharmacological interventions are especially costly and non-pharmacological interventions such as early mobilisation, staff education, noise reduction and orientation may present a more cost-effective alternative for the NHS. Valsilevskis and colleagues used data from the BRAIN-ICU study to estimate the association between Acute Brain Dysfunction (ABD) (defined as delirium or coma) by estimating mean cost over a 30-day period using a three-part model that incorporated a) a time-varying Cox model to measure daily hazard of death, b.) a Poisson model with a log link to estimate costs for intervals when patients died, and c) a Poisson model with a log link to estimate costs for intervals for patients who survived. Costs of $18000 ($600 per day) were revealed for persistent daily delirium calculated using this model (126). The Milibrant study mainly attributed costs to increased length of stay. Valsilevskis identified professional, bed expenses and dialysis as the first major costs followed by pharmacy and treatment associated with complications such as aspiration. Through the use of a comprehensive modelling technique, Valsilevskis also showed that incidence of early mortality disguised the true cost of delirium.

An economic analysis by Agus and colleagues on statins (which were not deemed effective and therefore not cost effective) identified methodological difficulties to economic evaluations in critical care such as outliers (patients with excessive costs due to prolonged length of stay) and patients lost to follow up (127). These findings may be important to address in future cost analysis studies.

In an attempt to calculate the cost benefit of a delirium prevention strategy in the ICU, Lee and colleagues calculated the difference between total costs in a usual care group versus a prevention care group. The delirium prevention strategy incorporated (1) neuropsychiatric consultation (2) medication according to consultation (3) avoidance of medication at night (4) regulation of light at night (5) orientation and (6) regular evaluation of mental status. They calculated a net benefit of US$5539.60 per patient post liver transplantation using the delirium prevention strategy (128). The prevalence difference between groups was not significant however, the rate of complications was lower in the intervention group, which may have influenced savings. The authors also reported that nurses were not adequately trained to identify other delirium subtypes, such as hypoactive delirium, so prevalence rates may actually have been higher.
Overall, costs associated with delirium in the ICU continue to climb in relation to increased length of stay and associated complications of delirium so it is imperative that we take steps to counteract this.

2.10 Management of delirium

The severe physical, psychological and financial impacts associated with delirium are a major driver for ensuring there are effective management strategies in place. The first line treatment for delirium management should be to identify and treat the suspected cause. Surveys of sedation use in mechanically ventilated patients indicate a culture of maintaining deep sedation to facilitate patient care. Shehabi and colleagues found that increases in sedation intensity of one point translated to an almost 30% increase in risk of death at 180 days and a 25% increase to subsequent development of delirium. Sedation intensity was measured by calculating a sedation index that was the sum of negative RASS divided by the total number of assessments.

Clinicians often turn to clinical practice guidelines for the appropriate management strategies for patient care in the ICU. The next section will provide an overview of the evidence for pharmacological and non-pharmacological management of delirium and clinical practice guidelines from a range of countries.

2.10.1 Pharmacological management of delirium

The longer the patient experiences delirium in ICU, the worse the consequences; so removal or reversal of the underlying cause of delirium is the top priority for successful management of the condition.

The FDA have not approved any medication for the prevention or treatment of delirium. A survey by MacSweeney and colleagues of 681 UK ICU clinicians with a 52% response rate (681/1308) highlighted that hyperactive delirium was treated with haloperidol in 95% of cases whereas only 25% of hypoactive delirium was treated with haloperidol despite limited evidence. Another survey of 250 critical care pharmacists in the US found haloperidol was used in 87% of cases while second generation antipsychotics such as quetiapine and olanzapine were used 59% and 26% respectively.

To date, there has been limited success with pharmacological therapies, results are inconsistent and therapies can be expensive. An umbrella review of 378 reviews found no evidence for pharmacological interventions for prevention or management of delirium due to a lack of evidence or poor quality of evidence.
A focused review by Hsieh and colleagues (2013) \cite{131} asking ‘can intensive care delirium be prevented or reduced?’ concluded that there was limited evidence on the most favourable approach to pharmacologic and multicomponent non-pharmacologic strategies to prevent the onset and reduce the duration of delirium.

No single pharmacologic intervention to prevent or treat delirium has been consistently able to improve survival or hospital length of stay \cite{132-139}. As a result, PAD guidelines cannot recommend a pharmacological treatment for delirium \cite{10}.

The following is an overview of the classes of drugs often prescribed to treat delirium in the ICU;

**Antipsychotics**

Antipsychotics target neurotransmitter imbalances and the most common drug used for the treatment of delirium in ICU is a first-generation antipsychotic known as haloperidol. The mechanism of action of first-generation antipsychotics involves postsynaptic blockade of DA D2 receptors whereas second generation antipsychotics (SGAs) action involves postsynaptic effects at serotonin 5-HT2A and DA D2 sites \cite{140}. There are some promising findings with SGAs from small trials such as shorter time to first resolution of delirium with quetiapine versus placebo \cite{141-143}. A systematic review of four studies reported that antipsychotics may reduce the duration of delirium but concluded that there was insufficient evidence to support this as studies had small sample sizes and methodological problems \cite{144}. A systematic review by Serafim and colleagues found one study that showed shorter time to resolution of delirium with quetiapine versus placebo however this was a small study (n = 34) that failed to show any impact on important outcomes \cite{145}. A more recent systematic review and meta-analysis of 19 studies investigated antipsychotics for prevention and treatment of delirium in hospitalized adults including ICU patients. They found no association between antipsychotic use and improvements in duration or severity of delirium, hospital or ICU stay or mortality \cite{146}. Systematic reviews continually report small sample sizes and methodological problems indicating that there is a need for much larger, better-designed RCTs of antipsychotics for treatment and prevention of delirium. Results from the MIND-USA trial were published in December 2018 and provided further clarification on the role of antipsychotics in the management of delirium in ICU \cite{147}. Girard and colleagues found there was no difference in delirium/coma free days between groups treated with haloperidol, ziprasidone or placebo in their large 1183 patient trial. This was further validated by the REDUCE RCT; a large 3 group randomised, double blind placebo controlled multicenter trial of 1789 patients conducted over 21 ICUs examined 1mg haloperidol TDS, 2mg TDS and placebo. The trial reported no statistical difference in mortality or 15 secondary outcomes including delirium incidence (33.3% for 2mg Haloperidol vs 33% for placebo, proportion difference
[0.4 (95% CI -4.6 to 5.4)] and delirium/coma free days [26 (17-28) vs 26 (19-28), proportion difference 0.0 (0 – 0)]. In addition, there was no significant difference in adverse event rates (2 (0.3%) for 2mg Haloperidol vs 1 (0.1%) for placebo) reported in both groups. The AID-ICU trial is ongoing and seeks to enrol 1000 critically ill patients to investigate the benefits and harms of haloperidol; (NCT03392376) Outcomes are expected April 2021 [149]. In March 2019, NICE removed the recommendation for olanzapine for the treatment of people who are distressed or at risk to themselves or others [27].

**Cholinesterase inhibitors**

Cholinesterase inhibitors also target neurotransmitter imbalances associated with the development of delirium. Cholinesterase inhibitors for example donepezil and rivastigmine suppress the enzymatic breakdown of acetylcholine [150] and have been investigated as a potential therapy to address the acetylcholine deficiency theory for pathogenesis of delirium. A Cochrane systematic review of one trial of 15 patients found no evidence to support the use of cholinesterase inhibitors for delirium (Donepezil versus placebo) [151]. Quality of the evidence was very low. Furthermore, a study by van Eijk and colleagues evaluating rivastigmine as an adjunct to haloperidol was stopped prematurely due to increased mortality in the rivastigmine group and as a result, this would not be recommended for delirium management in ICU [152]. More studies are needed to assess the impact of cholinesterase inhibitors on delirium outcomes.

**Alpha 2 agonists**

Alpha 2 agonists minimise respiratory suppression, hemodynamic fluctuations and are believed to have neuroprotective properties through release of glutamine [150]. These are hypothesised to target many causes of delirium including neurotransmitter imbalances and inflammation. Dexmedetomidine is often favoured as it has a much stronger profile than clonidine however it is significantly more expensive. A systematic review of eight RCTs evaluating clonidine for sedative use in critically ill patients found insufficient evidence to support its routine use in critically ill mechanically ventilated patients although they reported insufficient data to report on the incidence of delirium [153]. Dexmedetomidine decreases norepinephrine release and restricts sympathetic activity in the CNS [154]. A Cochrane systematic review of 12 RCTs evaluating interventions for preventing ICU delirium found that two studies of dexmedetomidine (versus lorazepam and versus haloperidol), had positive effects on delirium outcomes [155]. The quality of the evidence for delirium outcome was graded moderate. A systematic review of pharmacologic prevention and treatment of delirium identified four studies where dexmedetomidine reduced delirium duration when compared to benzodiazepines however, it is difficult to decipher if the reduction was associated with the
addition of dexmedetomidine or the removal of benzodiazepines. A GRADE assessment for quality of evidence was not undertaken in this systematic review. Larger, more robust trials are needed to confirm these findings and caution should be used for hypotensive and bradycardia risk with dexmedetomidine. A large 4,000 patient investigation (SPICE III) into early sedation using dexmedetomidine revealed no difference in mortality but reported more delirium/coma free days in the dexmedetomidine group (median 24 (11-26) vs 23 (10-26) days). The MENDS II study included 422 patients randomised to dexmedetomidine (0.2 micrograms/kg/hr) or propofol (5-50 micrograms/kg/min) for sedation in mechanically ventilated patients with sepsis and doses were adjusted according to RASS. They reported no significant difference in primary outcome, number of days alive without delirium or coma (adjusted median 10.7 in dexmedetomidine group vs 10.8 days in propofol group, OR 0.96 (95% CI 0.74-1.26). In addition, a two-centre, 100 patient study of dexmedetomidine versus placebo, a greater proportion of patients in the intervention group remained delirium free during their ICU stay versus the placebo group and there was no difference reported in adverse event reporting between groups.

The National Institute for Health Research (NIHR) has funded a randomised controlled phase 3 pragmatic trial (A2B trial) measuring the effect of alpha 2 agonists (Clonidine or dexmedetomidine) versus standard care on outcomes after critical illness such as time to successful extubation and delirium incidence and duration (NCT036538321). Outcomes are expected July 2021.

Melatonin

It is hypothesised that melatonin may be effective in preventing delirium. It would seem rational that improving sleep might have an impact on preventing delirium by targeting sleep deprivation, a known risk factor for delirium. However, there is insufficient evidence to support its’ use for prevention of delirium at this time and larger trials are required to support this hypothesis especially in the critically ill population.

Statins

The hypothesised mechanism of action for statins is that they target inflammation. Studies in animal models indicated that statins might have a role to play in modifying delirium and coma in the ICU. This role involves targeting pathways of inflammation and microglial activation, which are fundamental aspects in the pathogenesis of delirium. Morandi and colleagues hypothesise that statins may re-direct microglial activation and initiate an anti-inflammatory phenotype. A systematic review and meta-analysis of six studies (mainly non-randomised) in critically ill and cardiac surgery patients found no benefit with statins for the prevention of delirium. The grades of
recommendation, assessment, development and evaluation score showed moderate quality of evidence.

The aetiology of delirium is multifactorial and this may mean that pharmacological therapies may not be effective for all types of delirium and there may need to be a personalised medicine approach to delirium management. In the meantime, further investigation into delirium endotypes and larger, more robust randomised controlled trials of pharmacological therapies are needed.

2.10.2 Non-pharmacological management of delirium

Non-pharmacological management means aiming to prevent or treat delirium using non-drug interventions such as cognitive stimulation, early mobility, hydration, pain control and orientation. Systematic Reviews in non-ICU populations have found non-pharmacological interventions to be associated with improved delirium outcomes. An umbrella review of 34 systematic reviews was undertaken by Abraha and colleagues (16). The review found that multicomponent non-pharmacological interventions were effective in reducing delirium incidence in surgical wards (RR 0.71, 95% CI 0.59-0.86) and medical wards (RR 0.65, 95% CI 0.49-0.86). As a result, it recommended multicomponent non-pharmacological interventions such as early rehabilitation, hydration, nutrition, pain control, regulation of bladder and bowel function for prevention of delirium in older patients mainly in medical or geriatric wards. They provided additional recommendations for staff education to prevent delirium in low risk; older patients in medical wards; re-orientation protocols for surgical patients in ICU; and software supporting medication review for nursing home patients.

A meta-analysis carried out by Hshieh and colleagues (164) on multicomponent interventions for delirium in the older population, found that when they stratified by study type, multicomponent non-pharmacological delirium interventions lowered the odds of delirium by 44% (relative risk, 0.56; 95% CI, 0.42-0.76). Interventions included orientation, early mobility, hearing, sleep wake cycle preservation, vision and hydration (encouraging fluids and assisting with feeding). The Hospital Elder Life Program (HELP) was developed as a result. This is an evidenced based program that helps prevent delirium and functional decline in older patients and to date it has been rolled out to 200 sites across 32 states in America and 11 countries throughout the world (165).

There is a lack of evidence on the efficacy of multi-component interventions in ICU but there are some encouraging results from several single intervention studies (24-26). Exercise can improve cardiac and respiratory function and can reduce the need for sedatives (166). Unfortunately, it remains unclear which dose of exercise is effective in improving outcomes for critically ill patients (167). Other ICU studies examined reducing noise at night and orientating and cognitively stimulating patients during their ICU stay also lowered incidence of delirium although these results were mainly from
non-randomised studies \(^{18,37}\). These interventions are believed to be effective as they engage the patient and directly target known risk factors such as disorientation and immobility. They are relatively simple and cheap to deliver and as a result, they could potentially be pragmatic therapies to deliver in ICU with limited risk. Combining some of these interventions into a multicomponent bundle of interventions could increase the chances of reducing incidence and/or duration of delirium.

Success of multi-component non-pharmacological interventions ultimately depends on the capacity of the clinical ICU nurses to deliver these interventions at the bedside \(^{168}\). Overall, the data on the use of non-pharmacological interventions for delirium in ICU is limited and it is unclear which interventions are effective in improving delirium outcomes and which interventions work best together for critically ill patients. A systematic review and meta-analysis of quantitative and qualitative studies are required to determine the effectiveness of existing interventions. Of equal importance, investigation into the barriers and facilitators and other contextual factors that influence the success of an intervention is required.

2.10.3 Delirium guidelines

Several guidelines have been published on how delirium should be managed in hospital and intensive care unit settings. These include; National institute for Clinical Excellence (NICE) delirium guidelines (NICE, 2014) \(^{27}\); Society of Critical Care Medicine Pain, agitation and Delirium (PAD) guidelines \(^{10}\); Clinical practice guidelines for the management of delirium in older patients in Australia \(^{169}\); Canadian national guidelines for the assessment and treatment of delirium \(^{170}\) and the department of veterans affairs delirium: screening, prevention and diagnosis \(^{171}\).

These guidelines included graded recommendations based on the strength of the evidence for targeting known risk factors for delirium, mobilisation, staff education and music therapy, orientation, provision of hearing and visual tools, encouraging/assisting with intake to avoid dehydration, educational interventions, prevention and early detection of post-operative complications, creating safe environment, limiting bed moves, medication review, pain control, use of interpreters and other communication aids, family/carer involvement and sleep promotion \(^{27,169-171}\).

A systematic literature search by Bush and colleagues identified 12 delirium guideline summary papers and 3 evaluation papers from 2008 to 2013 \(^{171}\). Using the appraisal of guidelines for research and evaluation (AGREE II) tool, the NICE delirium guideline was rated the highest quality across five of the six domains; scope and purpose, stakeholder involvement, rigour of development, clarity of presentation and applicability. Interestingly, the previous ICU PAD guidelines \(^{9}\) were rated highest
for editorial independence and was the only tool that was approved by all four reviewers, without any modifications. The reviewers put significant importance on the fact that these guidelines did not issue recommendation where there was insufficient evidence. A rating has not yet been applied to the 2018 update of the PAD guidelines \(^{10}\).

The PAD guidelines were released by the Society of Critical Care Medicine in 2018, an update on the previous version \(^{10}\). They recommended early mobilisation for adult ICU patients to reduce the incidence and/or duration of delirium (continuous recommendation, low quality evidence) and suggested dexmedetomidine should be used in cases where agitation is impeding weaning from ventilation (conditional recommendation, low quality of evidence \(^{10}\)). The group recommended using a multicomponent, non-pharmacologic intervention that targeted modifiable risk factors such as enhancing cognition, improving sleep, mobility, hearing and vision) (conditional recommendation, low quality of evidence). In addition, the group recommended against the use of haloperidol, atypical antipsychotics or statins for delirium treatment (conditional recommendation, low quality of evidence) or delirium prevention (conditional recommendation, very low to low quality of evidence) \(^{10}\). These guidelines provide an excellent summary of the current level of evidence supporting interventions for delirium management. In addition, they highlighted the difficulties in providing recommendations for delirium management due to lack of evidence or low-quality evidence.

2.11 Conclusion

In summary, this chapter has provided an overview of the important elements associated with delirium. It is essential to have a knowledge of the definition, subtypes, assessment tools, epidemiology, risk factors and phenotypes, pathophysiology, outcomes, costs and management of delirium to understand the rationale around management strategies, in particular non-pharmacological interventions. Knowledge about each of these components can help the reader to understand the complexities that exist in relation to the development of a management strategy for delirium. ICU patients have a greater risk of developing delirium in comparison to other hospital populations reinforcing the importance of addressing delirium in this population. Tools for assessing and measuring delirium are many, but these assessments are infrequently performed and staff are largely unaware of their importance. When delirium is diagnosed, treatment and management are largely broad and diverse with poor quality evidence to guide clinicians thus it is essential that the evidence is examined in order to provide recommendations. The prevailing message from the studies discussed in this review is that there is a need for larger, better-designed trials of pharmacological and non-pharmacological interventions that include controls to reduce bias.
Despite limited evidence supporting therapies for the management of delirium, the strongest evidence suggests non-pharmacological interventions may have a role in the management. However, there are many complexities to be considered in the development of a non-pharmacological intervention for critically ill patients. Firstly, there is a need for an analysis of non-pharmacological interventions for delirium management in critically ill patients to determine which interventions or combination of interventions are most effective. Secondly, these interventions are complex and quantitative data will not elucidate the factors that determine the success of the intervention therefore an analysis of qualitative data is required. Thirdly, feasibility and acceptability need to be determined to ensure buy-in from stakeholders. Fourthly, due to complexities around implementation of these types of interventions, the interventions need to be clearly described in addition to a robust implementation plan that illustrates how the intervention can be introduced and integrated into clinical practice. Finally, the proposed intervention needs to be tested in a feasibility study to determine compliance in the clinical area and prepare for future evaluation.
Chapter 3 Identifying the evidence: Systematic reviews and meta-analysis results

3.1 Introduction

This chapter is concerned with the empirical evidence on the effectiveness of non-pharmacological interventions for delirium management in critically ill patients. The section of the MRC guidance that is described in this chapter is ‘identifying the evidence base’. To adhere to the recommendations laid out in the MRC framework, I undertook a mixed methods systematic review and meta-analysis. In order to identify the evidence base, I undertook a broad search of all relevant literature including RCTs, non-randomised studies and qualitative studies to ensure a systematic approach to data collection that reduces bias and improves the quality of the data \(^{(172)}\). In addition, meta-analysis of outcomes from the RCTs was completed in an attempt to increase the power and precision of estimates of treatment effect \(^{(173)}\).

This chapter presents the methods (published in the protocol paper included below) followed by the systematic review and meta-analysis paper (published and included below) followed by the unpublished results of non-randomised and qualitative studies. In combination with chapter 4 and chapter 5, this systematic review and meta-analysis was used to inform the empirical component for development of the intervention, which is the focus of this thesis.

The results from the RCTs only were published in Intensive Care Medicine \(^{(172)}\) on the request of the editor and the publication has been embedded in the chapter below in the most logical position. This should allow the reader to engage with the natural research process.

These systematic reviews and meta-analysis were conducted to assess the level of evidence at a point in time to inform a prototype intervention to present to delirium experts. As a result, the searches have not been updated to the current date. However, I have conducted regular searches of PubMed to ensure that I am up to date with the literature on delirium and this update has been included in chapter 8.

The systematic review was registered on Prospero \(^{(174)}\) prior to commencement and the protocol was published a priori \(^{(175)}\). The published protocol is embedded in the text below. This outlines the methods utilised in this component of the study.
3.2 Methods

The published protocol paper included below outlines the methods that were used to complete a systematic review including randomised, non-randomised and qualitative studies. To avoid duplication, the supplementary materials referenced in this both papers are only included in the protocol paper. The additional search strategies are included in Appendix A.
Systematic review protocol paper (Published 2016)

PROTOCOL

Impact of non-pharmacological interventions on prevention and treatment of delirium in critically ill patients: protocol for a systematic review of quantitative and qualitative research

Leona Bannon¹, Jennifer McGaughy², Mike Clarke³, Daniel Francis McAuley¹ and Bronagh Blackwood¹

Abstract

Background: Critically ill patients have an increased risk of developing delirium during their intensive care stay. To date, pharmacological interventions have not been shown to be effective for delirium management, but non-pharmacological interventions have shown some promise. The aim of this systematic review is to identify effective non-pharmacological interventions for reducing the incidence or the duration of delirium in critically ill patients.

Methods: We will search MEDLINE, EMBASE, CINAHL, Web of Science, AMED, psycINFO and the Cochrane Library. We will include studies of critically ill adults and children. We will include randomised trials and controlled trials which measure the effectiveness of one or more non-pharmacological interventions in reducing incidence or duration of delirium in critically ill patients. We will also include qualitative studies that provide an insight into patients and their families’ experiences of delirium and non-pharmacological interventions. Two independent reviewers will assess studies for eligibility, extract data and appraise quality. We will conduct meta-analyses if possible or present results narratively. Qualitative studies will also be reviewed by two independent reviewers, and a specially designed quality assessment tool incorporating the CASP framework and the POPAY framework will be used to assess quality.

Discussion: Although non-pharmacological interventions have been studied in populations outside of intensive care units and multicomponent interventions have successfully reduced incidence and duration of delirium, no systematic review of non-pharmacological interventions specifically targeting delirium in critically ill patients have been undertaken to date. This systematic review will provide evidence for the development of a multicomponent intervention for delirium management of critically ill patients that can be tested in a subsequent multicentre randomised trial.

Systematic review registration: PROSPERO CRD42015015625

Keywords: Delirium, ICU syndrome, Critical illness, Intensive care unit, Non-pharmacological interventions

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Background
Description of the condition
Survivors of critical illness frequently experience ‘malfunction of the cognitive processes in the brain’, known as delirium [1]. The American Psychiatric Association [2] defines delirium as ‘a global disturbance of consciousness characterised by fluctuating mental status, inattention, and disorganised thinking’ which develops over a short period of time and tends to fluctuate throughout the course of the day (p. 127). Delirium is not a disease but a syndrome with a wide spectrum of possible aetiologies [3]. Critically ill patients have an increased risk of developing delirium during their hospital stay. This often results from sepsis and disturbances in inflammation and coagulation pathways leading to microvascular thrombosis [3]. In addition, critical illness disrupts circadian rhythm and sleep patterns and along with sedatives such as benzodiazepines that are commonly used to treat delirium in septic patients, can impair immunity and contribute to delirium [1, 4].

The incidence of delirium is difficult to determine. In the United Kingdom (UK), studies find a 65% incidence of delirium in mechanically ventilated intensive care unit (ICU) patients [5] and international studies have demonstrated incidence from 25 to 87% in critically ill patients [6–9]. In a recent point prevalence survey of nine ICUs in the UK, the incidence of delirium was 29% in adult ICU patients. This study also confirmed that delirium screening practices in the UK remain inconsistent, which may account for the low incidence rates found [10]. Other reasons for a broad range in incidence figures could be differences in incidence in subspecialty ICUs, populations with variable severity of illness and under-recognition of the syndrome [11, 12].

Delirium is potentially modifiable depending on the individual patients’ circumstances. In recent years, the need to introduce validated screening programmes in the ICU has been recognised [13]. In the absence of a valid screening tool, delirium can go unnoticed in up to 70% of patients [12, 14]. The gold standard for diagnosis of delirium is the DSM-IV criteria applied by a trained psychiatrist, but this method is often not feasible in the hospital setting as psychiatric services are not available around the clock. As a result, multiple delirium detection tools have been developed and validated against DSM-IV criteria for use in the ICU. The Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC) are the most commonly used tools [6, 15]. The cardinal feature of delirium, inattention [2], is included in both CAM-ICU and ICDSC tools.

Delirium screening and awareness of the associated risk factors are mutually dependent for the successful management of delirium. Van den Boogaard [16] recently developed a delirium prediction model for intensive care patients based on ten risk factors including age, Apache II score, admission group, coma, infection, metabolic acidosis, use of sedatives and morphine, urea concentration and urgent admission. Many of these risk factors are irreversible, but others, such as use of sedatives and morphine, could potentially be modified.

Risk factors for delirium can be divided into three categories, acute illness, host factors including age or chronic health problems and iatrogenic or environmental factors [17]. The iatrogenic or environmental factors include immobilisation, sensory deprivation, sleep deprivation and social isolation [17–24]. Sleep deprivation can be caused by high levels of background noise, absence of natural light, patient care activities, mechanical ventilation, medication, pain, anxiety and stress [25, 26]. These factors have been found to disrupt normal sleep-wake cycles causing sleep and increasing the risk of delirium [25]. Disrupted sleep in the ICU has been identified as a modifiable precipitating risk factor for delirium [13, 19].

In addition to sleep disruption, mechanically ventilated patients often experience prolonged bed rest and heavy sedation during their ICU stay and this can lead to complications such as ICU weakness or delirium [20]. The introduction of physical and occupational therapy in the earliest days of critical illness has been shown to prevent sedative-related immobility and reduce incidence of delirium [22].

Patients often wake in ICU in unfamiliar surroundings with no recollection of the previous days or even weeks, and this can be extremely confusing for them. Staff need to focus on helping patients adjust to their new environment with regular communication. Education and orientation programmes have shown benefit for delirium management in ICU by increasing awareness of the condition and helping staff cater for patients psychological needs [27]. Targeting these risk factors might help manage the negative outcomes that are associated with delirium.

Patients who experience delirium during critical illness can experience short (during ICU and hospital stay) and long-term (after hospital discharge) sequelae. Studies have shown that short-term outcomes for patients who develop delirium while in ICU are associated with prolonged duration of mechanical ventilation, ICU admission and hospital stay [7, 16, 28, 29]. Evidence suggests that for every extra day patients test positive for delirium, it increases the risk of a prolonged hospital stay by 20% [8]. Similarly, Sahlul et al. [30] in their systematic review and meta-analysis of outcomes of delirium in critically ill patients found that patients with delirium had an increased mean length of stay (approximately 1 day longer) and increased mean duration of mechanical ventilation (almost 2 days longer than patients without delirium), even after
adjusting for variables such as age, sex and Apache II scores. Prolonged duration of delirium increases the risk of these negative consequences [31, 32]. Several studies have also identified a link between delirium and in-hospital mortality [5, 12, 16, 26, 28, 33, 34]. These findings suggest that an increased duration of mechanical ventilation, ICU admission and hospital stay often contribute to long-term negative outcomes such as increased mortality and morbidity.

Some critically ill patients have been followed up to 1-year post ICU to study long-term effects of critical illness. These studies found that delirium is an independent risk factor for a threefold higher likelihood of death within 6 months of critical illness even after adjusting for covariates such as severity of illness, coma and use of sedatives [35, 36]. Pisani et al. [23] found that the number of positive delirium days in ICU was significantly associated with time to death in the year following critical illness. Delirium in critical illness can also predict a tenfold higher likelihood of cognitive impairment at 1 year [31]. Studies show that up to six out of every ten patients that survive critical illness struggle with significant cognitive impairment for months to years after their critical illness has resolved. This has significant implications on their quality of life and health care costs and leads to institutionalisation [31]. In addition, delirium is a significant predictor of functional decline and inability to carry out activities of daily living, at both hospital discharge and 3-month follow-up [37]. These negative outcomes incur increased costs and more importantly result in long-term persistent cognitive deficits such as dementia [32, 38] which can significantly impact on a patient's ability to return to their normal lives.

A longer duration of delirium in ICU is associated with worse outcomes, so removal or reversal of the underlying cause of delirium remains a top priority for successful management of the condition [2]. There has been limited success with pharmacological therapies, results are inconsistent and therapies can be expensive [38]. This lack of evidence on pharmacological therapies for prevention and treatment of delirium is highlighted in the 2013 pain, agitation and delirium (PAD) guidelines of the American College of Critical Care Medicine [13]. Prophylactic antipsychotics and dexmedetomidine have been shown to reduce the prevalence of delirium in critically ill patients. However, no single pharmacologic intervention to prevent or treat delirium has been routinely able to improve mortality rates or hospital length of stay [4, 34, 39–45].

The American College of Critical Care Medicine's pain, agitation and delirium guidelines recommend non-pharmacological interventions such as early mobilisation [13]. Recently published NICE guidelines [46] recommend a number of non-pharmacological interventions to prevent delirium such as ensuring adequate fluid intake, encouraging exercise or range of motion exercise, introducing cognitively stimulating activities and providing appropriate lighting and clear signage. However, it is worth noting these recommendations are based largely on studies in non-ICU patients (older adults, acute medical) [47–49]. Although this strategy has not been tested on critically ill patients, these non-pharmacological interventions might also benefit ICU patients, but these patients are exposed to many more risk factors for delirium and therefore the proven effectiveness of these interventions in other patients may not be generalizable to them. Therefore, further research into the use of these interventions in an ICU population is needed.

**Description of the intervention**

A non-pharmacological intervention is any non-drug intervention. Research in other patient populations is informative for ICU clinicians despite the lack of direct evidence from the ICU setting [49]. Interventions are aimed at targeting risk factors associated with delirium in ICU such as immobilisation, sensory deprivation, sleep deprivation and social isolation and aimed to reduce incidence and/or severity of delirium in critically ill patients. Interventions are not limited to but may include earplugs, eye masks, noise control strategies, pharmacy medication review, music therapy, physical therapy, cognitively stimulating activities, family presence, bright light therapy, education and orientation programmes.

**How the intervention might work**

It is hypothesised that a multicomponent non-pharmacological intervention may reduce incidence and severity of delirium by targeting known risk factors such as sensory deprivation, sleep deprivation and immobilisation in critically ill patients. In other patient populations, multicomponent interventions have been successful by targeting modifiable risk factors. For example, Inouye et al., [47] investigated a risk factor targeted protocol for prevention of delirium in an acutely ill elderly population. The protocol targeted sleep deprivation, disorientation, immobility, dehydration and visual and hearing impairments. It successfully achieved a 40% risk reduction in incidence of delirium in the intervention group. Martinez et al., [48] halved delirium incidence in an acute hospital setting by introducing a delirium prevention protocol delivered by families. Family members were educated about the signs and symptoms of delirium, orientation with familiar objects and photographs and providing hearing aids and eyeglasses. Similarly, Marcantonio et al., [49] achieved an 18% absolute reduction in the incidence of delirium by introducing a protocol which involved a geriatric consultation early in the surgical hip fracture patient’s admission. The protocol aimed to reduce potentially delirigenic
medications, provide adequate pain relief, control blood pressure, prevent hypoxemia and ensure presence of hearing aids and eyeglasses if needed.

Some single intervention studies of non-pharmacological interventions have also shown promise in the ICU setting, including early mobilisation, earplugs and orientation programmes for patients [22, 26, 27].

Why is it important to do this review?
Delirium has a high prevalence in ICU and is associated with serious negative outcomes and increased costs. Each delirium incident increases ICU costs 1.3-fold and hospital costs 1.4-fold [38]. Pharmacological interventions are costly and have not shown significant benefit for delirium prevention to date whereas non-pharmacological interventions such as physical therapy, ear plugs and orientation are likely to be less expensive and have shown promise in delirium management in ICU [22, 26, 27]. Additionally, a recently published Cochrane Review on non-pharmacological interventions for sleep promotion in critically ill patients found that the use of earplugs and/or eye masks may have beneficial effects on sleep and delirium incidence but recommended further research due to the poor quality of the studies [50]. There is a growing need and interest in non-pharmacological interventions, and a systematic review of the literature specifically addressing delirium in critically ill patients would help guide ICU staff in delirium management [51, 52]. In addition to providing guidance for staff, the findings would be useful for developing an intervention for future evaluation. This systematic review is both unique and important for two major reasons. First, it will summarise the current evidence and provide an effect estimation for non-pharmacological interventions for delirium targeted at critically ill patients. Secondly, it will synthesise qualitative data from staff, ICU survivors and families’ views on interventions to inform the development and acceptability of non-pharmacological interventions. An understanding of these factors is important for determining the success of the interventions. These interventions are complex, and quantitative studies often do not provide details on factors that can influence the success of the interventions such as workload or implementation process. However, a knowledge of these factors could help ensure the development of a successful intervention.

Review question
What are the effects of the 11 non-pharmacological interventions named below*, (which could feasibly be delivered within the current roles of the multidisciplinary team in intensive care), on delirium prevention and treatment in Intensive Care units?

* (1) earplugs, (2) noise reduction, (3) eye masks, (4) lighting control, (5) education, (6) orientation, (7) cognitive therapy, (8) bright light therapy, (9) music therapy, (10) physical therapy or exercise and (11) pharmacy protocol or review.

Sub-questions
1. What are ICU survivors and their family members perceptions of non-pharmacological interventions for delirium in ICU?
2. What are clinical staff’s perceptions on acceptability and sustainability of non-pharmacological interventions for delirium in ICU?

Methods
This protocol was written in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) checklist (Additional file 1) [53].

Types of studies
We will include both quantitative and qualitative studies. The quantitative studies will include clinical trials (randomised trials and other clinical controlled trials including controlled before/after studies and interrupted time series) that evaluate non-pharmacological interventions for reducing incidence and duration of delirium for critically ill patients regardless of age. We will exclude cohort studies, case studies and reports.

The qualitative studies will include studies that use observation, interviews and focus groups that are grounded in phenomenology, ethnography, grounded theory, action research and descriptive research.

Types of participants
Critically ill patients in the intensive or high dependency unit requiring vasopressors, oxygen therapy, invasive or non-invasive ventilation will be eligible for this review. Both adult and paediatric participants will be included in this review although these will be analysed separately.

We will exclude studies of interventions delivered after ICU/high dependency unit (HDU) discharge.

In qualitative studies, the types of participants will be ICU survivors, their families and clinical staff from the ICU environment who have experience caring for patients with delirium.

Types of intervention(s) and comparators for quantitative studies
We will include studies of non-pharmacological interventions that could be reasonably undertaken by clinicians in the UK NHS, including but not limited to earplugs, noise reduction strategies, eye masks, lighting control, education, orientation, cognitive therapy, bright light therapy, medication review, music therapy and physical therapy. Interventions can include behavioural, cognitive, psychological and
physical training interventions. Studies may examine one or a combination of interventions. We will include studies that compare non-pharmacological interventions with either different non-pharmacological interventions, pharmacological interventions (sedatives and antipsychotics) or with no delirium targeted intervention.

We will exclude studies that require trained professionals to deliver the intervention such as acupuncturists or massage therapists that could not reasonably be delivered within the current roles of the multidisciplinary team in ICU.

Types of outcome measures for quantitative studies

1. Primary outcomes

The primary outcome is the incidence and/or duration of delirium. Delirium must be measured by any delirium screening tool that has been validated against DSM-IV criteria for delirium [2] such as the Confusion Assessment Method for the ICU (CAM-ICU), the Intensive Care Delirium Screening Checklist (ICDSC) or the Neelon and Champagne Confusion Scale (Necham).

2. Secondary outcomes

- any adverse event reported by the authors
- mortality as reported by the authors
- subjective sleep quality (measures) as reported by participants to authors
- cognitive function (measures) as reported by the authors
- quality of life measured by a validated tool

Qualitative phenomena of interest

The perception and experiences of ICU survivors, their families and ICU clinical staff are the main qualitative phenomena of interest. As each group has unique perceptions and experiences, the phenomenon of interest will vary. Non-pharmacological interventions are complex, and there are several factors that can influence the success of these interventions in ICU. For clinical staff, their perception of the acceptability and sustainability of non-pharmacological interventions for delirium would include phenomenon related to user friendliness and impact on workload, and their views on how the interventions and process of implementation worked and did not work as applicable are the phenomena of interest. For ICU survivors, the phenomena of interest are memories of non-pharmacological interventions, their views on value and worth of these interventions, views on how they impacted their ICU delirium and views on overall acceptability of these interventions. For families, the phenomena of interest are their degree of involvement with non-pharmacological interventions, i.e. were they involved in education on delirium or orientating their relatives, satisfaction regarding their involvement, their views on how the interventions worked and their satisfaction and views on acceptability and value of the interventions. A deep understanding of these factors is crucial for interpreting the study findings. Quantitative studies do not provide information on how these factors can influence the success of the interventions however, a knowledge of these factors could help decipher the reasons why an intervention was or was not successful.

Search strategy

We will search the Cochrane library, MEDLINE (via OVID SP 1966 to present) (Additional file 2), EMBASE (via OVID SP, 1974 to present), CINAHL (via EBSCO, 1981 to present), PsycINFO, (via OVIDSP 1967 to present), AMED (Allied and Complementary Medicine Database) (via EBSCO host, 1985 to present) and ISI Web of Science (1950 to present). Additional information will be sought from searches of grey literature databases (Opengrey) and NHS databases (NHS Evidence and NICE Guidelines).

Various synonyms for delirium will be searched to include ICU syndrome, acute encephalopathy, cognitive failure, acute brain syndrome, acute confusional state, reversible dementia, ICU psychosis, altered mental state, pseudosenility, toxic encephalopathy, septic encephalopathy, transient organic brain syndrome and acute brain failure. Synonyms for non-pharmacological interventions will include earplugs or ear protective devices, eye masks, relaxation therapy, cognitively stimulating activities, sound masking, orientation programmes, education, bright light therapy, sleep promotion, noise reduction or control, lighting control, therapeutic touch, family presence, exercise or physical therapy, music, behavioural or cognitive therapy, medication review and pharmacological services or protocol or guidelines. Synonyms for critical illness will include critically ill, intensive or critical care and intensive care or critical care unit.

We will attempt to identify ongoing and closed but unpublished studies by searching the major clinical trials registries such as the metaRegister of Controlled Trials (mRCT) (www isrct n.com/page/mrc t), ClinicalTrials.gov (https://clinical tri als.gov/) and the World Health Organisation (WHO) International Clinical Trials Registry Platform (ICTRP) (http://apps.who.int/trialsearch/). We will also search the reference lists of any identified RCTs and contact primary authors for missing or additional data.

Selection of studies

One authors (LB) will examine the titles retrieved and exclude any titles that are irrelevant. Two authors (LB, JMeG) will independently examine the abstracts identified from the search. We will retrieve and evaluate the full text of potentially relevant studies. Two authors
(LB, JMcG) will independently assess their eligibility according to the review's eligibility criteria and resolve any disagreements by discussion. A third author (BB) will settle any disagreements. Where appropriate, LB will contact study authors by telephone or email to clarify study eligibility. We will record reasons for study exclusion in the table 'Characteristics of excluded studies'.

Data extraction
Data extraction will be independently undertaken by two authors (LB, JMcG).

The data extraction form will be divided into sections to include randomised studies, non-randomised/observational studies and qualitative studies. Data will be extracted from each quantitative study using a data extraction form which will include general study information, study characteristics, participant's characteristics, intervention and settings, complications and outcome data/results. Data will be extracted from each qualitative study on study setting, population, phenomena of interest, study design, methods, finding and comments.

Assessment of risk of bias in included quantitative studies
All included studies will be assessed for internal validity and risk of bias using domain-based evaluation as described in the Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0, chapter 8 [54]. The Cochrane risk of bias form will be used to evaluate each included study. Each study will be assessed as low, high or uncertain risk for the adequacy of sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other bias. Two authors will critically appraise included studies using this tool (LB, JMcG). The Newcastle Ottawa Scale [55] will be used to assess risk of bias in non-randomised studies such as controlled before and after studies and intermittent time series studies.

Qualitative studies
For qualitative studies, quality assessment will be judged using a tool adapted from the Critical Appraisal Skills Programme (CASP) [56] framework and Popay [57] framework for critical appraisal of qualitative studies and previously used in Jordan et al., [58] (included in Additional file 3). Using this approach, studies were defined as high, moderate or low quality studies as follows; high: criteria was clearly applied and described or communicated from primary author; moderate: criteria not reported clearly and unable to communicate with primary author and finally, low: criteria not applied or applied inappropriately.

Data analysis—quantitative studies

Measures of treatment effect
We will use changes in scores from validated delirium screening tools, such as CAM-ICU (Confusion Assessment Method for the Intensive Care Unit), NEECHAM and CHAMpagne confusion scale (NEECHAM) or ICDSC (Intensive Care Delirium Screening Checklist) to evaluate intervention effect. In the event that change scores are not available, we will use final value data.

Effect measures for dichotomous outcomes
Where possible, the treatment effect for dichotomous outcomes will be expressed as a risk ratio (RR) with 95 % confidence intervals (CIs).

Effect measures for continuous outcomes
The treatment effect for continuous outcomes will be displayed as a mean difference with 95 % CI. Where continuous outcomes are measured using difference scales, the treatment effect will be expressed as a standardised mean difference (SMD) with 95 % CI if the results of studies are combined.

Effect measures for ordinal outcomes and measurement scales
If performing meta-analysis, we will analyse longer ordinal scales as continuous data and we will combine adjacent categories and make them into dichotomous data for shorter ordinal scales. Where ordinal scales are summarised using methods for dichotomous data, we will use risk ratios, odds ratios or risk difference to describe the intervention effect. When ordinal scales are summarised using methods for continuous data, we will calculate mean difference or standardised mean difference to estimate the intervention effect.

Unit of analysis issues
When alternative measurement scales are used, we will contact the study authors to obtain their participant level data and try to convert the results to standardised units. If a study with more than two intervention groups is included in meta-analysis, we will try to combine relevant groups to create a single pairwise comparison. For cluster randomised trials, we will use the appropriate unit of analysis.

Dealing with missing data
Wherever possible, we will contact the original authors to request missing data. If more than 20 % of the data are missing from a study, we will exclude the study from the meta-analysis and perform an available case analysis on remaining studies. If possible, we will estimate missing statistics (such as standard error or confidence intervals).
Assessment of heterogeneity
We will assess heterogeneity of each trial and the intervention effects by compiling ad examining forest plots. We will first explore clinical heterogeneity by assessing clinical and methodological characteristics of the included studies (for example trial design and quality, participant's characteristics, intervention or outcome measurements). We will only attempt to incorporate data into a meta-analysis if there is negligible clinical heterogeneity among the selected studies.

We will use chi² test ($P < 0.1$, significant heterogeneity) to assess statistical heterogeneity [54]. If the chi² test is significant, we will use the $I^2$ statistic to measure inconsistency across the studies. $I^2$ greater than 50 % indicates significant heterogeneity. We will use a fixed-effect model if the studies are homogenous.

Assessment of reporting biases
We will attempt to obtain and include data from unpublished trials through grey literature searches to reduce the risk of publication bias. We will use funnel plot analysis to assess publication bias when there are greater than ten studies included in the meta-analysis. In interpreting funnel plots, we will explore other reasons for asymmetry such as selection bias, methodological quality and heterogeneity; artefactual and chance.

Subgroup analysis and investigation of heterogeneity
If sufficient studies are available, we will perform separate analysis on paediatric patients, patients receiving mechanical ventilation versus no mechanical ventilation and studies of interventions aimed at prevention or treatment of delirium.

Sensitivity analysis
We will test how robust the evidence is by performing sensitivity analysis according to the risk of bias arising from sequence generation and allocation concealment (adequate or unclear or inadequate). We will compare fixed-effect model results to random-effects model results. If necessary, we will undertake sensitivity analysis to examine the effects of excluding study subgroups.

Summary of findings tables
For quantitative studies, we will use the principles of the GRADE system [59] to assess the quality of the body of evidence associated with specific outcomes reported in the trials. We will include the following outcomes: incidence of delirium, duration of delirium, mortality, quality of life, adverse events and cognitive outcomes in our review and generate a summary of findings (SoF) table using the GRADE software.

Data synthesis for qualitative studies
A thematic synthesis approach will be undertaken [60]. Coding and thematic development will be conducted manually in three rigorous stages. In the first stage, two reviewers (LB, JMCG) will independently code and arrange the data into themes that involves a continual process of attributing codes to small sections of meaning within the text, moving back and forward across studies and constantly comparing data and codes. In the second stage, the reviewers will work collaboratively, to group codes into logical and meaningful clusters analytical themes relating to the aims of the review will be developed. These will deliver evidence-based recommendations for patient-centred interventions that consider the needs of staff and patients. The third stage will involve assessment of the Confidence in the Evidence from Reviews of Qualitative research (CERQual) [61] which will be used to provide an assessment of confidence for individual review findings from qualitative evidence synthesis; the themes will be summarised in the form of a qualitative findings table. This table is similar to the 'Summary of findings' tables used in Cochrane reviews of effectiveness. The four components of the CERQual are the methodological limitations of the qualitative studies contributing to a review finding, the relevance to the review question of the studies contributing to a review finding, the coherence of the review finding and the adequacy of data supporting a review finding. There are four levels for assessment of confidence high, moderate, low and very low [61]. High confidence indicates a high likelihood that the review finding is a reasonable representation of the phenomena of interest, moderate confidence indicates it is likely that the review is a reasonable representation of the phenomenon of interest, low confidence indicates it is possible that the review finding is a reasonable representation of the phenomenon of interest and very low confidence indicates that it is not clear whether the review finding is a reasonable representation of the phenomenon of interest [61].

Discussion
This systematic review will synthesise research evidence on the effect of non-pharmacological interventions in all critically ill patients. To our knowledge, this synthesis has not been carried out in the ICU population. Non-pharmacological interventions have been studied in populations outside of intensive care units, and multi-component interventions have successfully reduced incidence and duration of delirium. The NICE guidelines [46] are largely based on studies of non-pharmacological intervention in non-ICU populations [47–49]. Since the publication of these studies, interest in non-pharmacological interventions has increased significantly. This systematic review is important as it provides an
update on non-pharmacological interventions for delirium targeted at critically ill patients, and it is also unique as it will provide qualitative data on ICU staff, ICU survivors and their families’ views on interventions to inform the development of the multicomponent bundle.

Registration
This systematic review has been registered with PROSPERO, an international prospective register of systematic reviews (http://www.crd.york.ac.uk/prospERO/display_record.asp?ID=CRD42015016625).

Additional files

Additional file 1: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 checklist. Recommended items to address in a PR protocol. (PDF 147 KB)

Additional file 2: MEDLINE search strategy. A list of the keywords used in the MEDLINE search strategy to identify papers for assessment for systematic review. (DOCX 13 KB)

Additional file 3: Data extraction form. Data extraction form with section for randomised controlled trials, observational studies and qualitative studies to assess quality and risk of bias. (DOCX 73 KB)

Abbreviations

Competing interests
LB has attended study days sponsored by Orion pharmaceuticals.

Authors’ contributions
LB and DM conceived the idea for this review. LB drafted the protocol under the supervision of BB, DM, JMAC and MC. All authors read and approved the final manuscript. Neither the funding body, sponsor nor institution had any involvement in the development of this protocol.

Acknowledgements
We thank Patricia Watt and Richard Falle, subject librarians at Queen’s University Belfast Medical Library, and the Belfast Health and Social Care Trust. This work is being conducted as part of a Doctoral Research Fellowship awarded to LB, funded by the Public Health Agency in Northern Ireland, Research and Development Division.

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Received: 22 November 2015 Accepted: 25 April 2016

Published online: 04 May 2016

References
3.3 Results

3.3.1 RCTs

From this point forward, the results of the systematic review are presented in three parts (1) results from the RCTs (published in Intensive Care Medicine (ICM)); (2) results from the non-randomised studies; and (3) results from the qualitative studies. It was my intention to publish the review of all studies together, however ICM preferred to publish the RCT results only.
The effectiveness of non-pharmacological interventions in reducing the incidence and duration of delirium in critically ill patients: a systematic review and meta-analysis

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Abstract

Purpose: To evaluate the effect of non-pharmacological interventions versus standard care on incidence and duration of delirium in critically ill patients.

Methods: We searched electronic and grey literature for randomised clinical trials up to March 2018. Two reviewers independently screened, selected and extracted data. Meta-analysis was undertaken using random effects modelling.

Results: We identified 15 trials (2812 participants). Eleven trials reported incidence of delirium. Pooled data from four trials of bright light therapy showed no significant effect between groups (n = 829 participants, RR 0.45, 99% CI 0.10–2.13, P = 0.19, very low quality evidence). Seven trials of various individual interventions also failed to report any significant effects. A total of eight trials reported duration of delirium. Pooled data from two trials of multicomponent physical therapy showed no significant effect [n = 404 participants, MD (days) = 0.65, 99% CI = 2.73 to 1.44, P = 0.42, low quality of evidence]. Four trials of various individual interventions also reported no significant effects. A trial of family voice reorientation showed a beneficial effect [n = 30, MD (days) = −1.30, 99% CI = −2.41 to −0.19, P = 0.003, very low quality evidence].

Conclusions: Current evidence does not support the use of non-pharmacological interventions in reducing incidence and duration of delirium in critically ill patients. Future research should consider well-designed and well-described multicomponent interventions and include adequately defined outcome measures.

Keywords: Critical care, Delirium, Meta-analysis, Non-pharmacological interventions, Systematic review
Introduction

Although delirium is not specific to intensive care units (ICU), Page and colleagues reported an incidence of 45% in a general ICU population including ventilated and non-ventilated patients; however, incidence is reportedly much higher (up to 80%) in mechanically ventilated critically ill patients [1, 2]. Delirium is also associated with an increased mortality, and patients with delirium in ICU are three times more likely to die in the first 6 months after critical illness [2]. Studies of ICU survivors report that up to 60% will have deterioration in their cognitive processes comparable to mild dementia or moderate traumatic brain injury [3, 4]. A recent study reported that these levels of cognitive impairment reduce over time with 40% impaired at 3 months and 24% impaired at 6 months [5]. Additionally, delirium is associated with significantly increased healthcare costs, longer duration of mechanical ventilation, longer ICU stay and long-term psychological problems [6–9].

Findings from surveys conducted in the UK and the USA, in addition to a large 13-country cohort study report that delirium is often managed with haloperidol as a first-choice treatment despite a lack of evidence for its efficacy [10–15]. Guidelines from the Society of Critical Care Medicine found moderate evidence to support non-pharmacological interventions such as early mobility; however, there is still confusion about whether or not non-pharmacological interventions are effective in improving delirium outcomes [16]. As opposed to implementing single interventions, multicomponent strategies have been purported to target several risk factors for delirium simultaneously. A systematic review of 21 studies reported that using six or more interventions simultaneously has greater potential to improve clinical outcomes [17]. Furthermore, multicomponent interventions may have efficacious effects even without full compliance. In implementing a multicomponent bundle, Barnes-Daly and colleagues reported that a 10% increase in total bundle compliance translated to a 2% increase in delirium- and coma-free days; and a 10% increase with partial compliance translated to a 15% increase in delirium- and coma-free days [18].

Studies in non-ICU populations have shown associations between use of non-pharmacological interventions and reductions in delirium incidence [19–21]. Currently there is no clear indication to guide practice on use of non-pharmacological interventions for critically ill patients who have greater risk factors for delirium.

The aim of this review was to evaluate the effectiveness of non-pharmacological interventions compared to standard care or other non-pharmacological or pharmacological interventions on the incidence and duration of delirium and other clinical outcomes in critically ill patients.

Methods

The protocol was prospectively registered with PROSPERO (CRD42015016625) and published [22]. This paper focuses on findings from the randomised clinical trials (RCTs). We used Cochrane review methodology in protocol development and review conduct. The review is reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [23].

Search strategy

Using synonyms for delirium non-pharmacological interventions and critical care, we searched MEDLINE, EMBASE, CINAHL, all seven databases of the Web of Science, PsycINFO, AMED and the Cochrane library up to March 2018 for potentially eligible studies with no restrictions on language or year of publication. We searched OpenGrey (http://www.opengrey.eu/), NHS evidence (https://www.evidence.nhs.uk/) and reference lists of included studies. Ongoing and unpublished trials were identified from metaRegister of Controlled Trials (http://www.controlled-trials.com/mrct/), ClinicalTrials.gov (http://clinicaltrials.gov) and the World Health Organisation International Clinical Trials Registry Platform (http://apps.who.int/trialsearch). The search strategies for each database are detailed in Supplementary Appendix A.

Inclusion and exclusion criteria

We included RCTs of critically ill patients that evaluated the effectiveness of non-pharmacological interventions targeted at prevention or treatment or both compared to usual care (no intervention), different non-pharmacological interventions or pharmacological interventions for reducing the incidence and duration of delirium. Critically ill patients were defined as patients being nursed in an intensive care or high dependence unit of any specialty including cardiac, medical, surgical, neurosurgical, mixed or cancer units following elective or emergency admission. Trials focusing on post-ICU care, requiring specialist staff or equipment and non-randomised studies were excluded.

Selection of studies, data extraction and quality assessment

Two authors (LB, JMcG) independently searched titles and abstracts for eligibility. The same authors reviewed full texts, performed data extraction and assessed trial risk of bias using the Cochrane risk of bias tool [24]. Data extracted included study characteristics, participants’
characteristics, intervention and settings, adverse events, risk of bias and outcome data/results. Where necessary, we made attempts to contact study authors for missing data. The data extraction form is presented in Supplementary Appendix B.

Outcome measures
Primary outcomes were (a) incidence of delirium and (b) duration of delirium. Secondary outcomes were ICU and hospital mortality, sleep quality, cognitive function, adverse events and quality of life measured by a validated tool. We included all outcome measures reported by the authors.

Analysis
Data were analysed in Review Manager Version 5.3 software [25]. We calculated the difference in means, standard deviation and 95% confidence intervals (CIs) for continuous outcomes. Where necessary, we estimated mean and standard deviation from median and interquartile ranges using a standard approach [26]. For dichotomous data, we described treatment effects using risk ratios (RR) and 95% CIs. Meta-analyses were performed if outcomes from two or more studies with similar interventions were available. We used random-effects models to calculate pooled estimates.

We evaluated clinical heterogeneity by qualitative assessment of study and intervention differences. Statistical heterogeneity was evaluated using the Chi-square test ($P<0.1$, significant heterogeneity) and $I^2$ statistic ($I^2>50\%$, significant heterogeneity).

We planned to undertake subgroup analyses on paediatric patients, patients receiving mechanical ventilation versus no mechanical ventilation and studies of interventions aimed at prevention or treatment of delirium, but there were insufficient subgroups to do this. We undertook sensitivity analyses on (a) studies judged as having high risk of bias for sequence generation and allocation concealment and (b) random versus fixed effects models.

Outcome data not suitable for meta-analysis are presented in Table 1 or the text. The quality of the evidence was rated using Grades of Recommendation, Assessment, Development and Evaluation (GRADE) for incidence and duration of delirium, intensive care and hospital mortality, health-related quality of life and adverse events [27].

Results
Of the retrieved 7230 citations, 15 trials including 2812 adult participants were included (Fig. 1) [28–42]. No paediatric trials were found.

Trials were conducted in ICU patient populations including medical [33, 35–37, 42], surgical [28, 29, 31, 41] and mixed medical and surgical [30, 32, 34, 38–40]. There were five multicentred [33, 37, 38, 40, 42] and ten single-centred trials [28–32, 34–36, 39, 41]. Sample sizes ranged from 15 to 734 participants. Trials were conducted in the USA [33, 35, 37, 40], Japan [28, 29], Italy [36], Canada [38], Belgium [32], Netherlands [30], Chile [34], UK [41], Turkey [42], Thailand [31] and Korea [39].

Interventions included physical [35] and psychological occupational therapy; bright light therapy [28–31]; range of motion exercises [42]; earplugs [32]; multicomponent orientation and cognitive stimulation protocol [36]; multicomponent occupational therapy including positioning, cognitive training, relative involvement [34]; a mirrors intervention [41]; multicomponent targeting risk factors for delirium [39]; protocolised weaning and daily sedation interruption [38]; reorientation using family voice [40]; and paired awakening and breathing [37]. We found no trials comparing one intervention against another or a non-pharmacological against a pharmacological intervention. Usual care was either unreported or reported variably among ICUs and generally determined by the medical team in charge. Usual care groups did not mandate any pharmacological treatments for delirium; however, these were administered as directed by the medical team.

All 15 trials evaluated delirium: 11 reported incidence of delirium [28–32, 34, 36, 38, 39, 41, 42] and eight reported duration of delirium in days [30, 33–35, 37, 40–42]; nine reported delirium as a primary outcome [29–32, 34, 36, 39–41], three as a secondary outcome [33, 37, 38] and three did not specify [28, 35, 42]. Trials screened for delirium using the CAM tool [34], CAM-ICU tool [30, 31, 33, 35–37, 39–42], ICDSC [38] or Neecham tool [28, 29, 32]. Five studies clearly specified that interventions were targeted at prevention of delirium in the title or abstract of the paper [28, 32, 39, 40, 42]; 10 studies did not clearly specify if interventions were targeted at prevention or treatment of delirium. Follow-up periods were either not reported [31, 36, 40] or reported at 5 days [38, 29, 32], 12 weeks [41], ICU discharge [42], hospital discharge [34, 38], 28-day follow-up [30, 33, 39], 6 months [35] and 1-year follow-up [37].

A table of included study characteristics are in Supplementary Appendix C and excluded and unclassified studies are presented in Supplementary Appendices D and E.

Methodological quality and risk of bias
The risk of bias within studies is presented in Supplementary Appendix F. Blinding of participants and personnel was not possible in all trials because of the nature of the interventions being tested. In eight trials, blinding of outcome assessors was not undertaken [29, 38] or was unclear [28, 36, 37, 39, 40, 42]. Furthermore, there was unclear random sequence generation and allocation.
Table 1  Summary of findings: non-pharmacological interventions for reducing delirium versus usual care/no intervention

<table>
<thead>
<tr>
<th>Patient or population: Critically ill adult patients</th>
<th>Setting: Critical care</th>
<th>Intervention: Various interventions highlighted under each outcome</th>
<th>Comparison: Standard care or no intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcomes</td>
<td>Assumed risk, usual care</td>
<td>Corresponding risk, intervention</td>
<td>Relative effect (99% CI)</td>
</tr>
<tr>
<td>Incidence of delirium</td>
<td></td>
<td></td>
<td>RR 0.45 (0.30 to 0.67)</td>
</tr>
<tr>
<td>(a) Bright light therapy [28–31] 335 per 1000</td>
<td>Anticipated absolute effects* (99% CI) 151 per 1000 (47–492)</td>
<td></td>
<td>RR 0.45 (0.30 to 0.67)</td>
</tr>
<tr>
<td>(b) Multicomponent intensive occupational therapy [34]</td>
<td>10/65</td>
<td>2/65</td>
<td>RR 0.15 (0.02 to 1.03)</td>
</tr>
<tr>
<td>(c) Earplugs [32]</td>
<td>18/67</td>
<td>14/69</td>
<td>RR 1.05 (0.32 to 3.54)</td>
</tr>
<tr>
<td>(d) Multicomponent (orientation and cognitive stimula-</td>
<td>6/31</td>
<td>3/17</td>
<td>RR 0.91 (0.18 to 4.73)</td>
</tr>
<tr>
<td>(e) Protocolised sedation [38]</td>
<td>113/209</td>
<td>113/214</td>
<td>RR 0.98 (0.77 to 1.23)</td>
</tr>
<tr>
<td>(f) Multicomponent (risk factor targeting) [39]</td>
<td>21/63</td>
<td>12/60</td>
<td>RR 0.60 (0.27 to 1.35)</td>
</tr>
<tr>
<td>(g) Structured mirrors [41]</td>
<td>177/108</td>
<td>20/115</td>
<td>RR 1.10 (0.51 to 2.40)</td>
</tr>
<tr>
<td>(h) Range of motion exercises [42]</td>
<td>10/47</td>
<td>4/47</td>
<td>RR 0.40 (0.10 to 1.67)</td>
</tr>
</tbody>
</table>
### Table 1 (continued)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Assumed risk, usual care</th>
<th>Corresponding risk, intervention</th>
<th>Relative effect (99% CI)</th>
<th>No. of participants analysed (studies)</th>
<th>Certainty of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Duration of delirium (days)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) Multicomponent physical therapy [33, 35]</td>
<td><strong>Mean duration 0</strong></td>
<td>Anticipated absolute effects*</td>
<td>MD = 0.65 (−2.73 to 1.44)</td>
<td>404 (2 RCTs)</td>
<td>++OOO</td>
<td>Low&lt;sup&gt;2&lt;/sup&gt; Defined as number of hospital days with delirium [33]</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>(99% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean duration 0.65 lower (2.24 lower to 0.04 higher)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(b) Multicomponent intensive occupational therapy [34]</td>
<td>2.34 (1.34)</td>
<td>1.83 (1.87)</td>
<td>MD = 0.17 (−0.91 to 0.57)</td>
<td>130 (1 RCT)</td>
<td>++OOO</td>
<td>Very low&lt;sup&gt;b&lt;/sup&gt; Defined as number of days CAM scores were positive or negative for delirium [33]</td>
</tr>
<tr>
<td>(c) Awakening and breathing [37]</td>
<td>2.67 (4.01)</td>
<td>2.33 (3.7)</td>
<td>MD = 0.34 (−1.43 to 0.75)</td>
<td>335 (1 RCT)</td>
<td>++OOO</td>
<td>Very low&lt;sup&gt;b&lt;/sup&gt; Defined as number of days in the study period (28 days) during which patients were CAM-ICU positive and not comatose</td>
</tr>
<tr>
<td>(d) Bright light therapy [36]</td>
<td>3.23 (2.97)</td>
<td>2.66 (2.97)</td>
<td>MD = 0.34 (−0.84 to 0.16)</td>
<td>734 (1 RCT)</td>
<td>++OOO</td>
<td>Very low&lt;sup&gt;b&lt;/sup&gt; Duration measured in hours, method unclear</td>
</tr>
<tr>
<td>(e) Structured mirrors [41]</td>
<td>4.5 (3.83)</td>
<td>4.5 (3.11)</td>
<td>MD 0.00 (−1.21 to 1.21)</td>
<td>223 (1 RCT)</td>
<td>++OOO</td>
<td>Very low&lt;sup&gt;b&lt;/sup&gt; Defined as ICU days with delirium</td>
</tr>
<tr>
<td>(f) Family voice orientation [40]</td>
<td>1.28 (0.48)</td>
<td>0.30 (1.28)</td>
<td>MD = 1.30 (−2.41 to −0.19)</td>
<td>20 (1 RCT)</td>
<td>++OOO</td>
<td>Very low&lt;sup&gt;b&lt;/sup&gt; Mean days of delirium where at least one assessment indicated that CAM-ICU criteria were met (positive result on the study day)</td>
</tr>
<tr>
<td>(g) Range of motion [42]</td>
<td>51.25 (32.94)</td>
<td>44.25 (44.07)</td>
<td>MD 7.00 (−24.41 to 38.41)</td>
<td>94 (1 RCT)</td>
<td>++OOO</td>
<td>Very low&lt;sup&gt;b&lt;/sup&gt; Duration measured in hours, method unclear</td>
</tr>
<tr>
<td><strong>Hospital mortality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) Multicomponent risk factors [39]</td>
<td>3.63</td>
<td>4.60</td>
<td>RR 0.32 (0.08 to 1.31)</td>
<td>123 (1 RCT)</td>
<td>++OOO</td>
<td>Very low&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>(b) Protocolised sedation [38]</td>
<td>63/209</td>
<td>63/214</td>
<td>RR 0.98 (0.66 to 1.43)</td>
<td>423 (1 RCT)</td>
<td>++OOO</td>
<td>Very low&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>(c) Physical rehabilitation [33]</td>
<td>14/55</td>
<td>9/49</td>
<td>RR 0.72 (0.27 to 1.92)</td>
<td>104 (1 RCT)</td>
<td>++OOO</td>
<td>Very low&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
### Table 1 (continued)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Assumed risk, usual care</th>
<th>Corresponding risk, intervention</th>
<th>Relative effect (99% CI)</th>
<th>No. of participants analysed (studies)</th>
<th>Certainty of the evidence (GRADE)</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>Bright light therapy [30]</td>
<td>68/360</td>
<td>64/354</td>
<td>RR 0.96 (0.64 to 1.44)</td>
<td>734 (1 RCT)</td>
<td>++/++  Very low</td>
<td>SF-36 physical functioning and mental health scale scores not significantly different for rehabilitation intervention at discharge, 2, 4 and 6 months [33]. The EQ-5D Visual Analogue Scale and Index at 12 weeks were not significantly different for a structured mirrors intervention [41].</td>
</tr>
<tr>
<td>Quality of life</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>523 (2 RCT)</td>
<td>++/++  Very low</td>
<td>Protocolised sedation intervention, increase in self-examination in intervention group 19% difference, 95% CI: 0.6 to 1.18 [33]. Early physical and occupational therapy intervention, 24h rehabilitation intervention sessions: one accidental radial artery line removal, ventilator dysynchrony in 4% of intervention group [35]. Standardised rehabilitation intervention reported a similar number of adverse events in both groups [37].</td>
</tr>
<tr>
<td>Adverse events</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>739 (3 RCT)</td>
<td>++/++  Very low</td>
<td>Explanations</td>
</tr>
</tbody>
</table>

CI confidence interval, RR risk ratio, MD mean difference
GRADE Working Group grades of evidence

- **High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate certainty:** We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Low certainty:** Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
- **Very low certainty:** We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

Explanations:

- Downgraded for high risk of bias in one study [29], Indirectness due to small sample sizes [28, 29] and imprecision from wide CI [28, 29, 31].
- Downgraded for severe inconsistency and imprecision.
- Downgraded for inconsistency due to unexplained heterogeneity [7 statistic = 77% [33, 35], imprecision due to too few events [36] and indirectness due to variability in interventions and outcome measures [33, 35].

*The risk in the intervention group and its 95% confidence interval is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
concealment [29, 42], incomplete outcome data and selective reporting [36], and potential for other bias due to limited information in the paper [29] and in translation [36].

**Primary outcome: incidence of delirium**

Eleven trials [28–32, 34, 36, 38, 39, 41, 42] including 2016 participants reported incidence of delirium as an outcome for seven different interventions, but the relatively small number of participants available for each intervention provide little statistical power to detect either beneficial or harmful effects. There was significant clinical heterogeneity due to the variety of interventions. Incidence of delirium ranged from 20% to 62% in the included studies.
Pooled data from four trials of bright light therapy versus no bright light therapy [28–31] did not show any significant effect on incidence of delirium with substantial heterogeneity (n = 829, pooled RR 0.45, 99% CI 0.10–2.13, P = 0.19; I² 69%, P = 0.02) (Fig. 2). Using GRADE summary of evidence the quality of evidence was very low, downgraded for indirectness, high risk of bias and imprecision.

Sensitivity analyses showed no significant change in the effect (RR 0.44, 99% CI 0.07–2.96, P = 0.27) when one trial with unclear risk of bias was removed [29], and with using a fixed effects model (RR 1.03, 99% CI 0.80–1.33, P = 0.74).

Seven trials of earplugs [32], occupational therapy [34], multicomponent orientation and cognitive stimulation [36], protocolised sedation with daily sedation interruption [38], multicomponent targeting risk factors [39], structured mirrors [41] and range of motion exercises [42] reported no significant effects (Table 1).

**Primary outcome: duration of delirium**

Eight trials [30, 33–35, 37, 40–42] including 161 participants evaluated seven different interventions and reported duration of delirium. Five trials reported more than one measure for this outcome. Duration of delirium ranged from 1 h to 4 days in the included studies.

Six trials reported number of days with delirium [33–35, 37, 40, 41] and two reported number of hours [30, 42]. We pooled data from two trials of similar interventions (physical therapy) [33, 35] that showed no significant effect on number of days with delirium (n = 404, pooled MD (days) – 0.65, 99% CI –2.73 to 1.44, P = 0.42; I² 77%, P = 0.04) (Fig. 3). Using GRADE the quality of evidence was low, downgraded for indirectness and imprecision.

We did not pool data from the remaining trials as the interventions were all different. One trial evaluating family voice reorientation showed a favourable effect (n = 20, MD (days) – 1.30, 99% CI –2.41 to –0.19, P = 0.003) [40], and the remaining five trials reported no significant effects on number of days with delirium [34, 37, 41] or number of hours with delirium [30, 42] (Table 1).

Three trials reported the percentage of time spent delirious. A trial of physical and occupational therapy reported a significantly reduced proportion of delirium days/100 patient days (control 57% versus intervention 33%, P = 0.02) [33]. A trial of intensive occupational therapy reported significantly reduced proportion of delirium days/100 patient days (control 8.2% versus intervention 1%, P < 0.001) [33]. A trial of standardised rehabilitation therapy reported no significant difference in delirium days/100 patient days (control median 0, IQR 0–9.1) versus intervention (median 0, IQR 0–12.5, P = 0.71) [35].

Two trials reported delirium-free days. A trial of bright light therapy reported no significant effect (median 27, IQR 16–28) versus control (median 26, IQR 17–28, P = 0.29) [30]. A trial of family voice reorientation reported a significant difference (P = 0.04) between groups of family voice (mean 1.9, SD 0.99), unknown

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**Fig. 2.** Forest plot for incidence of delirium in bright light therapy versus standard care trial. Taguchi measured incidence within ICU; other studies did not report the endpoint.

**Fig. 3.** Forest plot for duration of delirium (days) in physical rehabilitation versus standard care trials. Morris measured within ICU duration; Schweickert measured within hospital duration.
voice (mean 1.6, SD 1.07) and control (mean 1.6, SD 1.13) [40].

Secondary outcomes
Hospital mortality
Hospital mortality was reported in four trials [30, 33, 38, 39]. A trial of a multicomponent intervention targeting risk factors reported a significantly reduced risk of mortality compared to usual care (n = 123, RR 0.32, 99% CI 0.08–1.31, P = 0.04) [39]. There were no significant differences in mortality reported by the other three trials: protocolised sedation with daily interruption (n = 423, RR 0.98, 99% CI 0.66–1.43, P = 0.87) [38], physical rehabilitation during sedation interruption (n = 104, RR 0.72, 95% CI 0.27–1.92, P = 0.39) [33] and bright light therapy (n = 714, RR 0.96, 99% CI 0.64–1.44, P = 0.78) [30].

Sleep quality
A trial of earplugs using a self-report sleep questionnaire reported a significant improvement in sleep quality after the first night in the intervention group (data not reported, P = 0.04) [32]. A trial of bright light therapy used a night-time movement count measured by accelerometer as a surrogate measure of sleep quality [28]. The researchers reported no significant differences in hourly movement counts to day 3 and a significantly lower count in the intervention group on day 4 (1750 vs 400 at 2 a.m.; 1500 vs 600 at 4 a.m.; 2100 vs 1100 at 6 a.m.; and 2600 vs 1600 at 7 a.m.; P < 0.05) [28].

Cognitive function
Two trials measured cognitive function with the Mini Mental Scale Assessment (MMSE, range 0–30, greater than 24 = normal) [34, 35]. One trial evaluated an occupational therapy protocol and reported a significantly higher MMSE at discharge in the intervention group (median [IQR], intervention 28 [25, 29] versus control 26 [24, 28], P = 0.04) [34] whereas a study of rehabilitation therapy reported no significant effect at hospital discharge and 2, 4 and 6 months with all means and 95% CI above score 24 [35].

Quality of life
Two trials measured quality of life as a study outcome [35, 41]. A trial of standardised rehabilitation reported no significant differences in the mean (95% CI) for SF-36 physical functioning at 2 months (1.2, –1.8 to 4.3), 4 months (2.3, –0.9 to 5.5) and 6 months (3.4, –0.02 to 7.0); or mental health summary scores at 2 months (0.1, –3.5 to 3.7), 4 months (0.2, –3.2 to 3.6) and 6 months (2.4, –1.2 to 6.0) [35]. A trial of a mirrors intervention found no significant differences in the EQ-5D visual analogue scale at 12 weeks [mean (SD), 73 (19) versus 77 (15); P = 0.127] and EQ-5D index scores [0.87 (0.13) versus 0.87 (0.13), P = 0.95] [41].

Adverse events
Three trials evaluated adverse events [33, 35, 37]. A spontaneous awakening and breathing versus standard care trial reported a significantly increased percentage of self-extubation in the intervention group (n = 16 versus 6, 6% difference, 95% CI 0.6–11.8, P = 0.03) [37]. However, there were no significant differences in numbers requiring reintubation after self-extubation. In a study of early physical and occupational therapy there was one event in 498 therapy sessions of desaturation to 80%, one episode of radial arterial line removal, and therapy was discontinued in 4% of all cases because of perceived ventilator asynchrony in the intervention group [32]. In a study of standardised rehabilitation adverse events were similar in both groups [35].

Additional analyses
We used our findings to calculate the required information size to test a hypothesis that non-pharmacological treatment compared to usual care reduces the incidence of delirium. On the basis of a 20% relative risk reduction, a baseline risk of delirium in the control group of 45%, two-tailed alpha of 0.05 and power of 90%, we calculated this to be 645 patients per arm.

Discussion
We included 15 studies that evaluated the effectiveness of non-pharmacological interventions compared to usual care or other non-pharmacological or pharmacological interventions on the incidence and duration of delirium, hospital mortality, sleep quality, cognitive function, quality of life or adverse events in critically ill adult patients. No paediatric studies were included. Study interventions and outcomes were highly variable and as a result data from many studies could not be pooled. Pooling of data from a small number of studies showed that the implementation of single interventions, such as bright light therapy, or multicomponent physical therapy has no significant effect on the incidence (very low certainty of evidence; four studies) or duration of delirium (low certainty of evidence; two studies) in critically ill adult patients.

From 12 non-pharmacological intervention studies measuring incidence or duration of delirium, nine interventions showed no effect. Comparisons across studies were limited as a result of heterogeneity in terms of interventions delivered (type, number of components, duration, intensity); outcomes reported (specific measurement variable; analysis metric; aggregation method; time points); and patient populations. Only three trials of three different interventions reported a positive effect
on delirium primary outcomes, but as a result of heterogeneity limitations they provide low quality evidence. A pilot study of a multicomponent intensive occupational therapy intervention delivered twice per day for 40 min each session reported a significantly reduced incidence of delirium in addition to a lower proportion of time delirious and a beneficial effect on cognitive functioning [34]. An incremental physical therapy intervention delivered daily during sedation holds reported a beneficial effect on duration of delirium in days; however, the effect disappeared when the findings were pooled in a meta-analysis [33]. Consistent with other systematic reviews [43, 44], the beneficial effect of one bright light therapy trial on incidence of delirium also disappeared when study outcomes were pooled. A discovery was the lack of a positive effect on delirium outcomes for multicomponent risk factor interventions targeting orientation and cognitive stimulation [36, 39] as these strategies have been effective in other patient populations [19, 20]. Interventions may need to be more personalised to their respective population i.e. medical, surgical or cardiac. Some studies recruited small numbers without appropriate sample size calculation, which may have influenced the power to detect an effect on delirium outcomes. There is insufficient evidence to support single or multicomponent non-pharmacological interventions. However, as delirium has multiple causes, interventions with multicomponent interventions may present a more credible opportunity to target several risk factors simultaneously and further work in this field is ongoing. Indeed, a new multifaceted approach targeting factors to minimise delirium was proposed (eCASH: Early implementation of Comfort and Analgesia using minimum Sedation and Human care), but it has yet to be evaluated in a randomised clinical trial [45].

Additional beneficial patient outcomes were reported for four non-pharmacological interventions including improved sleep quality (earplugs [32] and bright light therapy [28]), physical health at 6 months (standard rehabilitation [40]) and hospital mortality (multicomponent intervention [39]). However, these were small studies and the quality of evidence to support these benefits is very low. The majority of outcomes were measured within the ICU stay except for cognitive function (range discharge to 6 months) and quality of life (range 2–6 months).

The strengths of our review were the high quality systematic review Cochrane methodology used to screen, extract data and assess quality independently by two reviewers and the comprehensive search strategy developed with two independent medical librarians.

We acknowledge that there were important limitations in the studies included in this systematic review. There was considerable heterogeneity in the types of interventions studied, how they were delivered, and the outcome measures. Duration of delirium was reported in a variety of ways and this presented difficulties for presentation of data and grading findings in a meaningful way. This underscores the important need for a core outcome measurement set for future trials, which is currently in development [46]. Many included trials were single centred, included a range of patient populations such as postoperative and cardiac surgery patients or patients with lower severity of illness and where standard care was reported it was variable, limiting generalisability of findings. There was large variation in the interventions studied, including duration of time and intensity of delivery, generating further challenges to drawing strong conclusions from the data.

Inter-professional research into prevention, treatment and management of patients with ICU-acquired delirium has grown considerably over the last 10 years, and a recent review has outlined a proposed research agenda for the next 10 years [47]. Adding to this following our review, we recommend that future clinical trials into non-pharmacological interventions should focus on defined patient populations that would most benefit from patient-centred interventions. The sample size calculation which our systematic review has informed should help trial design. Investigators should clearly and fully describe their interventions, methods and required resources using the template for intervention description and replication (TIDieR) checklist and guide [48].

To overcome the considerable outcome variation that we found, outcomes and their measures should be clearly defined and investigators should use the delirium core outcome set when this becomes available [46]. Additionally, investigators should consider incorporating a process evaluation alongside multicomponent complex trials to identify the barriers and facilitators to successful implementation and sustainability of non-pharmacological interventions [49].

Although pharmacological management of delirium was not the focus of this systematic review, atypical antipsychotics could be considered for short-term use for agitated patients with hyperactive delirium and alpha-2 agonists such as dexmedetomidine may be effective for delirium management but should be used with caution for patients at risk of hypotension or bradycardia [50, 51]. Results of pending trials may provide better evidence to support the use of some of these agents [52].

**Conclusion**

There is low to very low quality evidence to suggest that single or multicomponent non-pharmacological interventions are effective in reducing the incidence and duration of delirium in critically ill patients. As delirium has multiple
causes, multicomponent interventions may be useful in targeting several of these simultaneously. Further robust research may likely change our confidence in the findings. Future research should focus on patient populations with high risk factors for delirium, the feasibility of multicomponent interventions, and should clearly describe interventions and outcome measures.

Differences between the protocol and the review
We amended the search strategy to identify more relevant information related to non-pharmacological interventions. As we had two primary outcomes and five secondary outcomes, we applied a more conservative 99% confidence interval instead of 95%. We were unable to conduct subgroup analyses as studies did not always report if the intervention was targeting prevention or treatment, or if the sample received mechanical ventilation. Additionally we found no paediatric trials.

Electronic supplementary material
The online version of this article (https://doi.org/10.1007/s00134-018-5452-2) contains supplementary material, which is available to authorized users.

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Acknowledgements
The authors acknowledge Mrs Patricia Watt, Mrs Brenda Allen and Mr Richard Falls from Queen’s University Belfast medical library for their invaluable help in developing a search strategy and locating full text of manuscripts. The authors also thank E. Alvarez, R. Simons, L. Denesy, P. Black and C. Smith for providing additional information on their studies. This work was funded by a Doctoral Fellowship Award to LB by the Northern Ireland Health and Social Care research and development division. Funding was provided by Public Health Agency (Grant no. EAT/509/2014).

Compliance with ethical standards

Conflicts of interest
The lead author (LB) has been paid an honorarium for a presentation on non-pharmacological interventions for delirium management in critically ill patients by Otsna Pharmaceuticals. Other authors report no conflict of interest.

Received: 31 May 2018 Accepted: 3 November 2018
Published online: 30 November 2018

References
10
Appendix A. Medline search strategy

1. Delirium
2. ICU syndrome
3. Cognitive failure
4. Acute brain syndrome
5. Acute confusional state
6. Reversible dementia
7. ICU psychosis
8. Altered mental state
9. Pseudosenility
10. Toxic encephalopathy
11. Septic encephalopathy
12. Transient organic brain syndrome
13. Acute brain failure
14. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. Critically ill patients
16. Critical* and Ill*
17. Intensive care
18. Critical care
19. Intensive or critical and unit*
20. 15 or 16 or 17 or 18 or 19
21. Earplugs or ear protective devices
22. Eyemasks
23. Relaxation
24. Cogni*
25. Sound masking
26. Orientat*
27. Education or Educat*
28. Bright light therapy
29. Sleep and (promot* or help* or support* or initiat*)
30. Noise and (reduct* or control)
31. Lighting and (reduct* or control)
32. Therapeutic touch
33. Famil*
34. Sedat*
35. Exercise*
36. Music or complementary or alternative or cognitive or behaviour or physical (and therap*)
37. Pharmac* and (services or protocol or guidelines or interventions)
38. 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37
39. 14 and 20 and 38
## Appendix B

**Study selection, Quality Assessment & Data Extraction Form**

**Name of author extracting data:**

**Date form completed:**

### Study ID

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</thead>
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<tr>
<td>(Family name of first author and year of publication and letter if more than one year, e.g. Bannon2015a)</td>
<td></td>
</tr>
<tr>
<td>Are there other articles of same? (Yes, No, Unclear. If Yes, write study IDs)</td>
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### Study Eligibility

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<th>(please circle)</th>
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</tr>
</thead>
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<tr>
<td>1. Can this study be considered a randomised controlled trial or controlled trial including controlled before and after and intermittent time series? or 3. Is this a qualitative study? (please complete qualitative section below)</td>
<td>Yes, Unclear, No</td>
<td></td>
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<table>
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<th>Types of participants</th>
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<th>Yes, Unclear, No</th>
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<td>1. Were the participants’ critically ill patients (defined as patients cared for in critical care and intubated and ventilated or receiving oxygen therapy or vasopressors) or relatives of critically ill patients or clinical staff caring for critically ill patients?</td>
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<td>Can the intervention be considered non-pharmacological and can it be delivered within the current roles of the usual multidisciplinary team in ICU without the need for specialist staff? Or</td>
<td>Yes, Unclear, No</td>
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</table>
Is this a qualitative study that examines lived experiences of delirium or an intervention?

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<tr>
<td>1. Incidence of delirium or</td>
<td></td>
</tr>
<tr>
<td>2. Duration of delirium or</td>
<td></td>
</tr>
<tr>
<td>3. Qualitative insights into non-pharmacological intervention for delirium management in the critically ill</td>
<td></td>
</tr>
</tbody>
</table>

Conclusion:
Do not proceed if any of the previous answers are ‘No’.

- [ ] Included
- [ ] Excluded and listed in excluded table
- [ ] More information needed before inclusion decision (specify)

Please complete the next section for randomised trials, please see below for observational or qualitative research sections.

**Randomised controlled studies**

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<td>Delirium screening tool used</td>
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<td></td>
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<tr>
<td>Intervention</td>
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<td>--------------</td>
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<tr>
<td>Describe intervention, who delivered it? How was it delivered? Duration of treatment? How many times per day?</td>
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<tr>
<td>Allocation concealment</td>
<td>Was allocation adequately concealed?</td>
<td>□ Yes</td>
</tr>
<tr>
<td>Blinding (participants,</td>
<td>Was knowledge of the allocation intervention adequately prevented during the study?</td>
<td>□ Yes</td>
</tr>
<tr>
<td>Selective outcome reporting</td>
<td>Are reports of the study free of suggestion of selective outcome reporting?</td>
<td>□ Yes</td>
</tr>
<tr>
<td>Other sources of bias. Study</td>
<td>Free from other bias?</td>
<td>□ Yes</td>
</tr>
</tbody>
</table>
### Appendix C. Summary table of characteristics of included studies

<table>
<thead>
<tr>
<th>Author and publication year</th>
<th>Methods</th>
<th>Participants</th>
<th>Summary of intervention tried</th>
<th>Summary of usual care</th>
<th>Key outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alvarez 2017</strong>&lt;sup&gt;116&lt;/sup&gt; South America</td>
<td>RCT</td>
<td>Setting: ICU of the University of Chile Clinical Hospital - Bed size: not described.</td>
<td>n = 140&lt;br&gt;Exclusion: Age &gt; 60 years&lt;br&gt;Spend &gt; 24 hrs in ICU, admitted for monitoring acute or chronic disease&lt;br&gt;Exclusion: Previous cognitive impairment, severe communication disorder, delirium positive prior to the intervention, need for invasive MV</td>
<td>Multicomponent: a) Polymorphosal stimulation, b) positioning, c) cognitive stimulation, d) Training on basic everyday life activities e) Motor stimulation of the superior limbs and f) participation of the relatives. Performed twice a day for a period of 5 days for 40 mins.</td>
<td>Reorientation, early mobilisation, correction of sensorial deficit (use of technical help: lenses, audiophones), environmental management, diminishing drugs with anticholinergic potential and minimising the use of benzodiazepines.</td>
</tr>
<tr>
<td><strong>Finotto 2006</strong>&lt;sup&gt;118&lt;/sup&gt; Italian</td>
<td>RCT</td>
<td>Setting: Cardiology unit in Guastalla, bed size: not provided.</td>
<td>n = 48&lt;br&gt;Exclusion: Age &gt; 65 yrs, alert and orientated, family present 3 times/day, reads a daily newspaper&lt;br&gt;Exclusion: Ps with delirium at admission, medical diagnosis of cognitive impairment or psychiatric disorders</td>
<td>Multicomponent: Orientation &amp; cognitive stimulation with therapeutic touch, correct sensory deficits, reduce noise, facilitate family participation and education about delirium.</td>
<td>Translation of article, Limited detail of comparator supplied.</td>
</tr>
<tr>
<td><strong>Girard 2008</strong>&lt;sup&gt;120&lt;/sup&gt; USA</td>
<td>RCT</td>
<td>Setting: Four large medical centres in Nashville, Chicago &amp; Philadelphia, bed size: not described.</td>
<td>n = 336&lt;br&gt;Exclusion: Adults &gt; 14yrs, required MV &gt; 12hrs (receiving full MV &amp; those being weaned)</td>
<td>Multicomponent: Paired Spontaneous Awakening trial and Spontaneous breathing trial protocols.</td>
<td>Patient targeted sedation and an Spontaneous Breathing Trial protocol.</td>
</tr>
<tr>
<td><strong>Giraud 2016</strong>&lt;sup&gt;104&lt;/sup&gt; UK</td>
<td>Pilot time cluster RCT</td>
<td>Setting: 32 bed cardiac ICU</td>
<td>n = 233&lt;br&gt;Exclusion: Age &gt; 70 years, admitted to ICU after elective or urgent cardiac surgery over a 32 week period.&lt;br&gt;Exclusion: Mobility to obtain consent, care pathway anticipating admission elsewhere than to ICU following surgery, severe visual impairment impeding ability to recognise self in mirror, physical or communication barriers likely to impede effective administration of study procedures, severe mental disability likely to impede assessment of delirium and history of psychiatric illness previously requiring hospitalisation.</td>
<td>Multicomponent: Structured mirrors protocol. (1) Patient coached in use of mirror as reorienting tool and for supporting self-awareness. (2) Mirror used to aid explanation about procedures to patient and awareness of objects/events in patients personal space, patient coached in use of mirror as communication tool for asking about what is happening to going on around them. (3) Patient coached in using the mirror to obtain visual feedback to support hand eye coordination and allow self care. Patient coached in using visual feedback to understand body and limbs positions, monitor limb trajectories, trunk control, posture and balance, and promote earlier mobilisation.</td>
<td>Patients allocated to the usual care group received the current standard post surgical ICU care which includes no prescriptions around the use of mirrors but there were no restrictions imposed on using their own mirrors as would occur in routine practice.</td>
</tr>
<tr>
<td><strong>Karadas 2016</strong>&lt;sup&gt;117&lt;/sup&gt; Turkey</td>
<td>RCT</td>
<td>Setting:</td>
<td>n = 94&lt;br&gt;Exclusion:</td>
<td>Single intervention: ROM exercises once a day until discharge, Passive assisted active or active ROM exercises</td>
<td>Daily CAM-ICU assessment, RASS assessment and routine clinical procedures.</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Setting</td>
<td>Inclusion Criteria</td>
<td>Exclusion Criteria</td>
<td>Intervention</td>
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<tr>
<td>Mehta 2012 (Canada &amp; USA)</td>
<td>RCT</td>
<td>16 tertiary care medical and surgical ICUs. Specific bed size of ICUs not provided.</td>
<td>(n = 430)</td>
<td>Pts expected to remain MV &gt; 48hrs with continuous sedation and/or opioid infusion.</td>
<td>Multicomponent: Protocolized sedation plus daily interruption.</td>
</tr>
<tr>
<td>Moon 2015 (Korea)</td>
<td>RCT</td>
<td>Setting: 1049 bed general hospital with a 105 bedded ICU under department of internal medicine and surgery.</td>
<td>(n = 134)</td>
<td>Age &gt; 70yrs, ability to understand study purpose and/or provide consent independently or via a caregiver or proxy, hospitalisation for &gt; 48 hrs in ICU</td>
<td>Multicomponent: Delirium risk monitoring and screening, cognitive assessment and orientation, environmental intervention and providing comfortable physical environment. Targeting risk factors such as malnutrition, infection, pain, presence of urinary catheter, fluid and electrolyte imbalance, immobility and sleep deprivation.</td>
</tr>
<tr>
<td>Morris 2016 (USA)</td>
<td>RCT</td>
<td>Setting: Single centre MICU. Bed size not described.</td>
<td>(n = 300)</td>
<td>Admission to MICU, adult &gt;18 yrs, MV via ET tube or noninvasive ventilation mask, PaO2/FiO2 ratio &lt; 200</td>
<td>Multicomponent: Standardised rehabilitation therapy. Protocol contained 3 exercise types (passive range of motion, physical therapy and progressive resistance exercises), which was administered by a rehab team for a total of 8 separate sessions every day of hospitalisation for 7 days per week.</td>
</tr>
<tr>
<td>Munro 2017 (USA)</td>
<td>RCT</td>
<td>Setting: 5 ICUs (Medical ICU, Cardiothoracic ICU).</td>
<td>(n = 30)</td>
<td>Single intervention: (1) family member voice recorded re-orientation</td>
<td>No voice recorded messages</td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Design</td>
<td>Setting</td>
<td>Sample Size</td>
<td>Inclusion Criteria</td>
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<tr>
<td>Ono 2011</td>
<td>Japan</td>
<td>RCT</td>
<td>Setting: Osaka University Hospital</td>
<td>(n = 26)</td>
<td>Adults aged &gt; 18 years, within 24 hrs of ICU admission</td>
</tr>
<tr>
<td>Pothisarajorn 2016</td>
<td>Thailand</td>
<td>Single blind RCT</td>
<td>Setting: Surgical ICU in Bangkok. Bed size not described.</td>
<td>(n = 62)</td>
<td>Single blind RCT</td>
</tr>
<tr>
<td>Schweickert 2009</td>
<td>USA</td>
<td>RCT</td>
<td>Setting: 2 medical centers (University of Chicago and University of Iowa). Specific bed details not provided. One centre was a medical ICU.</td>
<td>(n = 104)</td>
<td>Adults ≥ 18 yrs, MV &lt; 72h but expected to continue another 24h</td>
</tr>
<tr>
<td>Simons 2016</td>
<td>Netherlands</td>
<td>RCT</td>
<td>Setting: teaching hospital, 36 bed mixed medical/surgical ICU.</td>
<td>(n = 734)</td>
<td>Adult &gt;18 years, &gt;24 hours ICU stay, could be assessed for delirium.</td>
</tr>
<tr>
<td>Taguchi 2007</td>
<td>Japan</td>
<td>RCT</td>
<td>Setting: Osaka University Hospital Bed size of unit not described.</td>
<td>(n = 15)</td>
<td>Inclusion: Middle-aged or aged patients who were operated on for oesophageal cancer between July and December 2003 capable of communication in Japanese.</td>
</tr>
<tr>
<td>Study</td>
<td>Reason for exclusion</td>
<td></td>
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</tr>
</tbody>
</table>
11. Figuero-Ramos, 2010, "The effect of a sedation wake-up trial and a spontaneous breathing trial on the occurrence of delirium and perception of sleep in critically ill patients, University of California, San Francisco.

Abstract only. Contacted author — no reply.


Abstract only. Contacted author – not published.


Review


Abstract/ poster only. Email author – no plans to publish.


Secondary analysis.


Case series


Protocol only, not trial.


Secondary analysis.


Subgroup analysis.


Case series


- Non-CT

---


Review


Editorial


Suspended.


Pharmacological


Description of GI project, not a trial


Post only, for Balas ABCDE


Post only.


Review


Descriptive study of Intervention arm Schweertek study.


Post ICU
### Appendix E: Table of unclassified and ongoing studies

<table>
<thead>
<tr>
<th>Study Reference</th>
<th>Title or Description</th>
<th>Status</th>
<th>Updates/Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Small C.</td>
<td>&quot;Restorative virtual environments for rehabilitation: does virtual nature therapy enhance sleep on the ICU, SIRC763077347.&quot;</td>
<td>Update from author- April 2018. Study completed and analysis and writing up in progress.</td>
<td></td>
</tr>
<tr>
<td>3. Risco, B.</td>
<td>&quot;Quality improving program in surgical intensive care unit&quot;, NCT02199262</td>
<td>Completed. No results posted on clinicaltrials.gov for this study.</td>
<td></td>
</tr>
<tr>
<td>5. Gehlbach, B.</td>
<td>&quot;Improving the sleep and circadian rhythms of mechanically ventilated patients, NCT01284140.</td>
<td>Completed. Last update Feb 2018. Results not yet submitted to clinicaltrials.gov.</td>
<td></td>
</tr>
<tr>
<td>8. Grams, 2013, &quot;Evaluating the feasibility and effectiveness of a delirium prevention bundle&quot;, critical care Medicine, 41 (2), Suppl 1, A106.</td>
<td>Completed and published but raw data incidence of delirium not reported. Contacted author but busy schedule at present, will send data at later date.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13. Effects of patient-directed interactive music therapy on sleep, delirium and melatonin levels in critically ill elderly patients. NCT03156205</td>
<td>Completed. No results or contact details available on clinicaltrials.org.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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15. Leung et al. Study of sleep and delirium in the ICU. Contacted author. Received response: Study not yet funded or started.


Appendix F: Risk of bias graph: review authors’ judgements about each risk of bias item for each included study
3.3.2 Non-randomised study results

The search was conducted up to March 2018. Nineteen studies including 6792 participants fulfilled the eligibility criteria and were included in the systematic review\textsuperscript{(18, 28, 29, 177-192)}. Search results are shown in PRISMA diagram\textsuperscript{(176)} (Figure 2).
Figure 2 PRISMA diagram for non-randomised studies
Characteristics of non-randomised studies

Nineteen non-randomised studies were included in this review; characteristics are summarised in Table 4. Eighteen were controlled before and after studies and one was a comparative time series study in which non-pharmacological interventions were compared with standard care. Sample sizes ranged from 16 to 1214. The proportion of country representation is presented in Figure 3 with the majority of studies being carried out in the USA (50%).

![Country Representation](image)

Figure 3 Country representation in included studies n, %

Eighteen studies were single centre and one study was a multicentre study. Studies were conducted in five different ICU specialty types (Figure 4). Fifteen non-randomised studies used the Confusion Assessment Method for the ICU, four studies used the Intensive Care Delirium Screening checklist, as validated screening tools for delirium (Figure 5).
Overall, 15 non-randomised studies evaluated multicomponent interventions, nine of these studies showed a multicomponent intervention was associated with reduced incidence and/or duration of
Four studies evaluated single non-pharmacological interventions, two of these studies were associated with reduced incidence and/or duration of delirium associated with functional electrical stimulation cycling and an extended visiting policy in the ICU. The interventions evaluated ranged from protocols aimed at reducing sedation, studies with a mobility intervention included, studies that included orientation, studies that included sleep interventions, interventions that included family participation.
<table>
<thead>
<tr>
<th>Author</th>
<th>Methods</th>
<th>Patient characteristics</th>
<th>Intervention</th>
<th>Key outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dale et al, 2014</td>
<td>Single centre controlled before/after cohort study, USA</td>
<td>(n= 1483)</td>
<td>Updated sedation protocol</td>
<td>Incidence of delirium</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Baseline:</td>
<td>- regular pain and agitation score documentation</td>
<td>Duration of delirium</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Age: Mean 48.1 (SD 18.7)</td>
<td>- assessment of delirium</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Male: 69.4%</td>
<td>- protocolised de-escalation of sedative meds</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- ISS: mean 29.4 (SD 15.5)</td>
<td>- pairing of spontaneous awakening and breathing tests</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>USA</td>
<td>- lowering sedation goal on RASS</td>
<td></td>
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<td></td>
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<td>- offering adjunct pain meds</td>
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<td>- assessing and treating pain before admin of sedatives</td>
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<td></td>
<td>- avoidance of benzodiazepines</td>
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<td></td>
<td>Delirium protocol</td>
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<td></td>
<td>- Limit deliriogenic medications</td>
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<td></td>
<td>- Daily SATs and SBTs</td>
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<td></td>
<td>- Suggestions for treatment of delirium based on age, type of delirium and presence of TBI</td>
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<td></td>
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<td></td>
<td>- Sleep protocol</td>
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<td></td>
<td>- Verilux lights</td>
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<td></td>
<td></td>
<td></td>
<td>- 90-minute quiet periods daily with relaxing music</td>
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<td></td>
<td></td>
<td></td>
<td>- staff trained to provide massage</td>
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<td></td>
<td></td>
<td>Post-intervention</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>- Male 53</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>- Age: med/IQR: 67 (64, 69)</td>
<td></td>
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</tr>
<tr>
<td>Bryczkowski et al, 2014</td>
<td>Before and after study, USA</td>
<td>(n = 123)</td>
<td></td>
<td>Incidence of delirium</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Baseline:</td>
<td></td>
<td>Mortality SICU</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Male: 63%</td>
<td></td>
<td>Received Seroquel for agitation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Age: med/IQR: 66 (63, 69)</td>
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<td>- &gt;65: 37%</td>
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<td>- Trauma: 44%</td>
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<td>- ISS: mean 15</td>
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<td>Post-intervention</td>
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<td></td>
<td>- Male 53</td>
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<td></td>
<td></td>
<td>- Age: med/IQR: 67 (64, 69)</td>
<td></td>
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<tr>
<td>Author</td>
<td>Methods</td>
<td>Patient characteristics</td>
<td>Intervention</td>
<td>Key outcomes</td>
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<td>-----------------</td>
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<td>-------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Balas 2014</td>
<td>Prospective cohort</td>
<td>(n= 170)</td>
<td>therapy training for families</td>
<td>Incidence of delirium</td>
</tr>
<tr>
<td></td>
<td>baseline study</td>
<td></td>
<td>- daily rounds to provide delirium education to family members and alert</td>
<td>duration of delirium</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>patients</td>
<td>% of ICU days spent delirious</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>education pamphlet for families and encouraged to participate in feeding,</td>
<td>28 day mortality</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>massaging and reorienting</td>
<td>hospital mortality</td>
</tr>
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<td></td>
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<td></td>
<td>ABCDE protocol</td>
<td>ICU mortality</td>
</tr>
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<td></td>
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<td>Daily SATs and SBTs</td>
<td>safety outcomes</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Delirium assessment and management protocol</td>
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<td></td>
<td></td>
<td>Early mobilisation protocol</td>
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<td></td>
<td></td>
<td>USA</td>
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<td>Baseline:&lt;</td>
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<td>- Age: mean 59.2 (SD 16.1)</td>
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<td>- Male: 54.1%</td>
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<td></td>
<td>- APACHE II score med, IQR 23.5 (17-29)</td>
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<td>Post-intervention</td>
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<td>- Age: mean 55.6 (SD 14.9)</td>
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<td>- Male: 57.3%</td>
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<td></td>
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<td></td>
<td>- APACHE II score: med/IQR 21 (16-28)</td>
<td></td>
</tr>
<tr>
<td>Skrobik 2014</td>
<td>Prospective pre/post</td>
<td>(n= 1214)</td>
<td>- Routine orientation</td>
<td>incidence of delirium</td>
</tr>
<tr>
<td></td>
<td>study</td>
<td></td>
<td>Patients given a choice of music or sedation to alleviate anxiety</td>
<td>subsyndromal delirium</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Protocol incorporating co-analgesia with paracetamol and NSAIDs and</td>
<td>no delirium ICDSC 0</td>
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<tr>
<td></td>
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<td></td>
<td>titrated administration of meds based on self-reported NRS</td>
<td>Antipsychotics administered</td>
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<td></td>
<td>Canada</td>
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<td>Baseline:&lt;</td>
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<td></td>
<td>- Age med 66</td>
<td></td>
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<td></td>
<td>- Male 58.4%</td>
<td></td>
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<td></td>
<td>- Apache II score: mean/SD 17.1 (8.5)</td>
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<td>Post-intervention</td>
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<td></td>
<td></td>
<td>- Age: med 66</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>- Male: 59%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Apache II score: mean/SD 18.1 (7.9)</td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Methods</td>
<td>Patient characteristics</td>
<td>Intervention</td>
<td>Key outcomes</td>
</tr>
<tr>
<td>-----------------</td>
<td>------------------------------------------</td>
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<td>--------------------------------------------------------</td>
<td>----------------------------------------</td>
</tr>
<tr>
<td>Rivosecchi 2015</td>
<td>Prospective pre-post quality improvement project.</td>
<td>(n = 483)</td>
<td>MMORE protocol</td>
<td>- MICU LoS spend in a delirious state i.e. total hours delirious divided by total LoS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Baseline:</td>
<td>Mobility</td>
<td>- incidence of delirium</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Age median 59 (48-70)</td>
<td>Music therapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Apache2 score: 15(11-20)*</td>
<td>Opening and closing blinds</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- % receiving MV: 53.9%</td>
<td>Reorientation and cognitive stimulation</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Male: 53.6%</td>
<td>Eye and Ear protocol</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post-intervention group:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Age median 59 (4-67)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>- Apache2 score 17 (12-24)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- % receiving MV: 51%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Male: 51.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black 2010</td>
<td>Comparative time series design.</td>
<td>(n = 170)</td>
<td>- Staff education</td>
<td>- incidence of delirium</td>
</tr>
<tr>
<td>(183)</td>
<td></td>
<td>Control group</td>
<td>- Training staff to educate families</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Age 18-87</td>
<td>- Reorientation</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- &gt;60: 61 (74%)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td>Intervention group</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>- Age 19-89</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- &gt;60: 64 (74%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kamdar 2013</td>
<td>Non-randomised pre/post design.</td>
<td>(n = 300)</td>
<td>Sleep protocol</td>
<td>- delirium/coma free days</td>
</tr>
<tr>
<td>(184)</td>
<td></td>
<td>Baseline:</td>
<td>- Reduce noise and light</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Age: med/IQR 54 (43-63)</td>
<td>- Choice of earplugs and eye masks and relaxing music</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Male: 46%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Received MV: 63.9%</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Post-intervention</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Age: 54 (44-66)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Methods</td>
<td>Patient characteristics</td>
<td>Intervention</td>
<td>Key outcomes</td>
</tr>
<tr>
<td>-------------</td>
<td>----------------------------------------------</td>
<td>-------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>Colombo 2012</td>
<td>Two-stage prospective non-randomised study</td>
<td>- Male: 47.7%</td>
<td>- Reorientation strategy 5W1H</td>
<td>- Incidence of delirium</td>
</tr>
<tr>
<td></td>
<td>(n = 214)</td>
<td>- Caucasian 46.1%</td>
<td>- Environmental, acoustic and visual stimulation</td>
<td>- Duration of delirium</td>
</tr>
<tr>
<td></td>
<td>Italy.</td>
<td>- Received MV: 46.6%</td>
<td>- ICU light and noise reduction at night</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Paper states no significant difference in patient characteristics between groups</td>
<td>- Pharmacological advice to treat agitation with haloperidol or olanzapine</td>
<td></td>
</tr>
<tr>
<td>Parry 2014</td>
<td>Case-matched control study.</td>
<td>(n = 16)</td>
<td>- Functional electrical stimulation cycling</td>
<td>- Delirium incidence</td>
</tr>
<tr>
<td>(185)</td>
<td>Melbourne, Australia.</td>
<td></td>
<td></td>
<td>- Duration of delirium</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Control:</strong></td>
<td></td>
<td>- Mortality</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Age: mean 60.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Male: 50%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Khan 2014</td>
<td>Pre/post implementation study design</td>
<td>- Apache 2 score: mean 20.3</td>
<td>- Daily paired SATs and SBTs</td>
<td>- Incidence of delirium</td>
</tr>
<tr>
<td>(187)</td>
<td>USA</td>
<td></td>
<td></td>
<td>- In-hospital mortality</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Baseline:</strong></td>
<td></td>
<td>- Prevalence of delirium</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Age: mean 55.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Male: 53%</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td><strong>Post-Intervention:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Methods</td>
<td>Patient characteristics</td>
<td>Intervention</td>
<td>Key outcomes</td>
</tr>
<tr>
<td>-----------------</td>
<td>------------------------------</td>
<td>--------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------</td>
<td>--------------------------------------</td>
</tr>
<tr>
<td>Patel 2014</td>
<td>Before and after study</td>
<td>Male: 44.1% (n=341)</td>
<td>Reduce noise</td>
<td>-sleep quality</td>
</tr>
<tr>
<td>(28)</td>
<td></td>
<td><strong>Baseline:</strong> Age: mean 60</td>
<td>Dim lights</td>
<td>-incidence if delirium</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Male: 51%</td>
<td>Group care procedures</td>
<td>-duration of delirium</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Post:</strong> Age: mean 60.6</td>
<td>Complete care procedures before 2300</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Male: 53%</td>
<td>Orientate</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Apache 2 score: med/IQR 15.0 (7.6)</td>
<td>Review meds</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Post:</strong> Age: mean 60.6</td>
<td>Set sedation target</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Male: 53%</td>
<td>Assess suitability for SAT &amp; SBT</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Apache 2 score: med/IQR 14.7 (6)</td>
<td>Hourly pain scores</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Baseline:</strong> Age: 60</td>
<td>Early mobilisation where possible</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Male: 51%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Apache 2 score: 15.0 (7.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Needham 2010</td>
<td>Prospective before/after QI</td>
<td>(n = 57)</td>
<td>1. Modifying the standardized MICU admission orders to change the default activity level from “bed rest” to “as tolerated.”</td>
<td>-Duration of delirium</td>
</tr>
<tr>
<td>(177)</td>
<td>project</td>
<td><strong>Baseline:</strong> Age: med 50</td>
<td>2. Encouraging a change in sedation practice from use of continuous intravenous infusions of benzodiazepines and narcotics to “as needed” bolus doses.21,22</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Age: med 50</td>
<td>3. Establishing and disseminating simple guidelines for PT and OT consultation.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Male: 30%</td>
<td>4. Developing safety-related guidelines (developed from the existing literature12) regarding when patients were considered eligible for PM&amp;R-related consultation, which</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>- Apache: med 26</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Post-intervention</strong> Age: med 53</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Male: 30%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Apache: med 27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Methods</td>
<td>Patient characteristics</td>
<td>Intervention</td>
<td>Key outcomes</td>
</tr>
<tr>
<td>--------</td>
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<td>--------------</td>
</tr>
<tr>
<td>Lee 2012 (178)</td>
<td>Untreated control group design with pre-test and post-test</td>
<td>(n = 28)</td>
<td>included (a) were not comatose (i.e., Richmond Agitation-Sedation Score 2 or below), (b) required only moderate ventilatory support (i.e., positive end-expiratory pressure 10cmH2O and fraction of inspired oxygen 0.6), and (c) had no increase in the dose of any vasopressor infusion (used for management of hypotension/shock) for at least 2 hours.</td>
<td>- Incidence of delirium</td>
</tr>
<tr>
<td>Hager 2014 (188)</td>
<td>Prospective QI project with retrospective</td>
<td>(n = 202)</td>
<td>Sedation protocol that targets RASS score 0 and follows an algorithm to reduce sedatives.</td>
<td>- Incidence of delirium</td>
</tr>
</tbody>
</table>

Baseline:
- Age: med 48
<table>
<thead>
<tr>
<th>Author</th>
<th>Methods</th>
<th>Patient characteristics</th>
<th>Intervention</th>
<th>Key outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lizza 2017</td>
<td>Prospective quasi experimental pilot study</td>
<td>(n = 17)</td>
<td>Enhanced daily clinical pharmacist assessment. 3 x daily assessments by pharmacist and recommendations for dosing adjustments of analgesic and sedative infusions based on a standardised, nursing driven sedation algorithm.</td>
<td>Incidence of delirium - Duration of delirium - Hospital mortality</td>
</tr>
<tr>
<td>Martinez 2017</td>
<td>Before and after non-randomised study</td>
<td>(n = 287)</td>
<td>Physio and early mobility Daily reorientation Prevention of sensory deprivation Drug reviews Pain control Sleep hygiene Environmental stimulation</td>
<td>Incidence of delirium - Duration of delirium -- ICU mortality</td>
</tr>
<tr>
<td>Author</td>
<td>Methods</td>
<td>Patient characteristics</td>
<td>Intervention</td>
<td>Key outcomes</td>
</tr>
<tr>
<td>-----------------</td>
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<td>--------------------------------------------------</td>
<td>------------------------------------------------------------------------------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td>Rosa 2017</td>
<td>Controlled before and after</td>
<td>Post-intervention:</td>
<td>Monitoring of urinary and rectal function</td>
<td></td>
</tr>
<tr>
<td></td>
<td>study</td>
<td>(n = 227)</td>
<td>Avoidance of restraints</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post-intervention:</td>
<td>Family participation</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(n = 286)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>van de Pol 2017</td>
<td>Interrupted time series analysis</td>
<td>Post-intervention:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(n = 421)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zhang 2017</td>
<td>Prospective before and after</td>
<td>Pre-intervention:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>study</td>
<td>Pre-intervention:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- MV: n/% 30 (50%)

Post-intervention:
(n = 227)
- Age: mean/SD 63.5 (18.4)
- Sex F: n/% 103(45%)
- SOFA score: med/IQR 3 (1-5)
- Dementia: n/% 17 (8%)
- MV-: n/% 116 (51.1%)

Baseline:
- Age: Mean/SD 62.4 (20.6)
- Sex M: n/% 72 (51.6)

Baseline:
- Age: Mean/SD 60.5 (18.6)
- Sex M: n/% 72 (49.6)

Pre-intervention:
- Age: med/IQR 68 (60, 75)
- Sex M: n/% 119 (56%)

Post-intervention:
- Age: med/ IQR 69 (62, 76)
- Sex M: n/% 122 (58%)

Pre-intervention:
- Age:63.45 (9.26)

- Incidence of delirium
- Duration of delirium
- ICU mortality
- Incidence of delirium
- Hospital mortality
- Subjective sleep quality
- Incidence of delirium
- Duration of delirium
- in hospital mortality
<table>
<thead>
<tr>
<th>Author</th>
<th>Methods</th>
<th>Patient characteristics</th>
<th>Intervention</th>
<th>Key outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>Cardiac ICU after</td>
<td>- Sex M: n/% 110 (80.29)</td>
<td>- more family visits</td>
<td>- Subjective sleep quality</td>
</tr>
<tr>
<td>CABG</td>
<td>Post-intervention:</td>
<td>- Age: mean/SD 63.09 (8.49)</td>
<td>- less care related interruptions</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Sex M: n/% 110 (78.01)</td>
<td>- optimising comfort – room temperature, mattress, personal hygiene at 8pm</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>- monitoring sleeping difficulties</td>
<td></td>
</tr>
</tbody>
</table>

**Footnote:** MV = Mechanical ventilation, ISS = Injury Severity Score, SAPS = Simplified Acute Physiology score, OR = odds ratio, RCSQ = Richards Campbell Sleep Questionnaire, QI = quality improvement, APACHE II score = Acute Physiology and Chronic Health Evaluation II, MICU = Medical intensive care unit, ALI = Acute Lung Injury, ICDSC = Intensive Care Delirium Screening Checklist, CCI = Charlson co-morbidity index
**Methodological quality and risk of bias**

There was low risk of bias in eight studies, moderate risk of bias in 10 studies and unclear risk of bias in one study \(^{178}\) as I was unable to obtain a complete translation and only had data available from the abstract and findings sections. I attempted to contact the authors but did not receive a reply. Results are presented in Table 5.

Unfortunately, I was unable to obtain a full translation of the Lee and Colleagues (2012) study \(^{178}\) so the ICU specialty is unknown.
### Table 5 Risk of bias non-randomised studies, Newcastle Ottawa Scale

<table>
<thead>
<tr>
<th>Study</th>
<th>Selection 1 2 3 4</th>
<th>Comparability 5 6</th>
<th>Outcome 7 8 9</th>
<th>Total stars</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dale et al, 2014 179</td>
<td>★★★★</td>
<td>★</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>Bryczkowski et al, 2014 180</td>
<td>★★★★</td>
<td>★</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Balas et al, 2014 181</td>
<td>★★★</td>
<td>★★</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Skrobik et al, 2010 181</td>
<td>★★★</td>
<td>★★</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Rivosecchi et al, 2016 29</td>
<td>★★★★</td>
<td>★</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>Black et al, 2010 183</td>
<td>★★★★</td>
<td>★★</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>Kamdar et al, 2013 184</td>
<td>★★★</td>
<td>★★</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>Colombo et al, 2012 18</td>
<td>★★★★</td>
<td>★★</td>
<td></td>
<td>7</td>
</tr>
<tr>
<td>Parry et al, 2014 185</td>
<td>★★★</td>
<td>★★</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>Khan et al, 2014 187</td>
<td>★★</td>
<td>★★</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>Patel et al, 2014 28</td>
<td>★★★</td>
<td>★★</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>Needham et al, 2010 177</td>
<td>★★★★</td>
<td>★★</td>
<td></td>
<td>7</td>
</tr>
<tr>
<td>Lee et al, 2012 178</td>
<td>★★</td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Hager et al, 2013 188</td>
<td>★★★★</td>
<td>★★</td>
<td></td>
<td>7</td>
</tr>
<tr>
<td>Martinez et al, 2017 192</td>
<td>★★★★</td>
<td>★★</td>
<td>★★</td>
<td>9</td>
</tr>
<tr>
<td>Zhang et al, 2017 191</td>
<td>★★★★</td>
<td>★★</td>
<td>★★</td>
<td>8</td>
</tr>
<tr>
<td>Rosa et al, 2017 189</td>
<td>★★★★</td>
<td>★★</td>
<td>★★</td>
<td>8</td>
</tr>
<tr>
<td>van del Pol et al, 2017 186</td>
<td>★★★★</td>
<td>★★</td>
<td>★★</td>
<td>9</td>
</tr>
<tr>
<td>Lizza et al, 2017 190</td>
<td>★★★★</td>
<td>★★</td>
<td>★★</td>
<td>8</td>
</tr>
</tbody>
</table>

**Note:** A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability i.e. maximum no of stars 9.

**Scoring:** 1-3 = high risk of bias, 4-6 = medium risk of bias, 7-9 = low risk of bias.

### Outcomes

**Incidence of delirium**

Incidence of delirium was reported in sixteen non-randomised studies. In pooled analysis of 16 trials, non-pharmacological interventions versus usual or standard care were associated with a reduced incidence of delirium (n = 4235, pooled RR 0.69, 95% CI 0.58-0.83, I² = 70%, p = <0.0001) (Figure 6). I assigned the quality of the evidence as low according to GRADE criteria due to downgrading for serious inconsistency and risk of bias. Ten studies found that a non-pharmacological intervention was associated with a reduced incidence of delirium. These were the awakening, breathing coordination, delirium management and early mobilisation [Balas 2014 181], family participation in psychological care and orientation [Bryczkowski 2014 180], an orientation protocol [Colombo 2012 18], a sleep protocol [Kamdar 2013 184], interventions targeting risk factors for delirium [Patel 2014 28, Rivosecchi 2015 29,

Figure 6 Incidence of delirium
Duration of delirium (days)

Seven trials reported this outcome. Five reported as median and interquartile ranges \cite{180, 181, 185, 189, 190} and two as mean and standard deviation \cite{28, 189}. Median and interquartile values were converted to mean and standard deviation as previously described. Five studies reported that non-pharmacological interventions were associated with reduced duration of delirium in days (n = 1305, pooled SMD -0.79, 95% CI -1.33 - -0.25, \(I^2 = 94\%\), \(p = 0.004\)). I assigned the quality of the evidence as very low according to GRADE criteria due to serious inconsistency and risk of bias. The studies associated with reduced duration of delirium evaluated the following interventions; awakening, breathing coordination, delirium management and early mobility protocol \cite{181}, a multicomponent protocol incorporating sleep enhancement, education and pharmacological recommendation \cite{180}, risk factor targeting protocols \cite{28, 192} and an extended visiting policy \cite{189}.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Std. Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bañas 2014</td>
<td>2.33</td>
<td>2.01</td>
<td>150</td>
<td>3.33</td>
<td>3.7</td>
<td>146</td>
<td>16.2%</td>
<td>-0.34 [-0.57, -0.11]</td>
</tr>
<tr>
<td>Brzozowski 2014</td>
<td>3</td>
<td>2.5</td>
<td>30</td>
<td>6</td>
<td>4.8</td>
<td>27</td>
<td>14.5%</td>
<td>-0.62 [-1.33, -0.30]</td>
</tr>
<tr>
<td>Lizza 2017</td>
<td>1.33</td>
<td>2.86</td>
<td>6</td>
<td>1.75</td>
<td>1.91</td>
<td>11</td>
<td>10.6%</td>
<td>-0.18 [-1.17, 0.82]</td>
</tr>
<tr>
<td>Martínez 2017</td>
<td>3.5</td>
<td>2.9</td>
<td>227</td>
<td>5.6</td>
<td>6.8</td>
<td>60</td>
<td>15.9%</td>
<td>-0.52 [-0.81, -0.23]</td>
</tr>
<tr>
<td>Parry 2014</td>
<td>7.03</td>
<td>7.74</td>
<td>8</td>
<td>8</td>
<td>1</td>
<td>8</td>
<td>10.7%</td>
<td>-0.08 [-1.06, 0.90]</td>
</tr>
<tr>
<td>Pauš 2014</td>
<td>1.2</td>
<td>0.8</td>
<td>171</td>
<td>3.4</td>
<td>1.4</td>
<td>187</td>
<td>16.1%</td>
<td>-1.87 [-2.23, -1.10]</td>
</tr>
<tr>
<td>Rosa 2017</td>
<td>1.5</td>
<td>0.75</td>
<td>145</td>
<td>3.87</td>
<td>2.25</td>
<td>141</td>
<td>16.1%</td>
<td>-1.30 [-1.55, -1.04]</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>745</td>
<td></td>
<td></td>
<td>560</td>
<td>100.0%</td>
<td>-0.79 [-1.33, -0.25]</td>
</tr>
</tbody>
</table>

Figure 7 Forest plot; Duration of delirium (days)

Duration of delirium as a proportion of time delirious in the ICU was also provided and is reported in table 6. Three studies were associated with a lower percentage of days with delirium in ICU; these interventions were multicomponent sedation and analgesia protocol \cite{179}, ABCDE risk factor targeting protocol \cite{181} and multicomponent sedation reduction and early mobilisation risk factor targeting protocol \cite{177}. The intervention arm in the Hager study was associated with a higher percentage of days delirious than in the control arm \cite{188}.
### Table 6 Percentage of days delirious in ICU (non-randomised studies)

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention description</th>
<th>Control</th>
<th>Intervention</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dale et al, 2014 (179)</td>
<td>Updated sedation protocol</td>
<td>172 (25.1%)</td>
<td>455 (21.2%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Needham et al, 2010 (177)</td>
<td>Sedation reduction and early mobilisation</td>
<td>107 (36)</td>
<td>125 (28%)*</td>
<td>0.003</td>
</tr>
<tr>
<td>Hager et al, 2014 (188)</td>
<td>Sedation protocol</td>
<td>20 (0.40)</td>
<td>38 (0.60)</td>
<td>0.010</td>
</tr>
<tr>
<td>Balas et al, 2012 (181)</td>
<td>Awakening and breathing coordination, delirium management and early mobilisation.</td>
<td>50 (30-64.3)</td>
<td>33.3 (18.8-50)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

**ICU mortality**

ICU mortality was reported in seven studies. Results are presented in figure 8. None of the interventions were associated with reduced ICU mortality (n = 1714, pooled RR 0.72, 95% CI 0.52 - 0.99, I² = 0%, p = 0.05). This was not statistically significant suggesting there is no ICU mortality benefit associated with non-pharmacological interventions versus usual or standard care.

**Hospital mortality**

Hospital mortality was reported in seven non-randomised studies. Results for five studies are presented below in figure 9. Two studies that measured hospital mortality could not be included in the forest plot as I was unable to work out risk ratio with the data that was provided. Khan and colleagues (187) reported the percentage of mortality in each group (pre 19.5% and post 19.6%, p = 0.97). Despite contacting the authors, I was unable to obtain the raw data for Dale and colleagues (179) study, which reported the odds ratio (OR) for hospital mortality (OR 1.18, 95% CI 0.80-1.76, p
Pooled analysis for the other five studies found an association between non-pharmacological interventions and reduced hospital mortality versus usual or standard care (n = 1297, pooled RR 0.72, 95% CI’s 0.53, 0.97, I² = 8%, p = 0.03).

I assigned the quality of the evidence as low according to GRADE criteria due to serious inconsistency and risk of bias. Out of the seven studies included, one study of awakening, breathing coordination, delirium management and early mobilisation was associated with reduced hospital mortality (181).

Figure 9 Forest plot; Hospital mortality
Sleep quality

Sleep quality was reported in three non-randomised studies. Three studies used the Richards Campbell Sleep Questionnaire (RCSQ) as a measurement of sleep quality (28, 184, 186). Results are available in table 7. Lee and colleagues measured sleep quality reported by the patient, daytime sleepiness reported by patients and level of sleep quality assessed by nursing staff (178). They found overall mean sleep quality in the control versus intervention groups 5.27 (SD 1.40) vs 5.85 (SD 1.56), p = 0.363, significant differences were detected in sleep quality reported by patients 4.27 (SD 2.43) vs 6.46 (SD 1.56), p = 0.009 and levels of sleep quality assessed by nursing staff 3.93 (SD 1.53) vs 6.46 (SD 2.30), p = 0.004. Overall, only one study reported improved sleep efficiency scores associated with a sleep hygiene checklist (28).

Table 7 Sleep quality RCSQ- Sleep efficiency index for non-randomised studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention description</th>
<th>Pre-intervention Mean/ SD</th>
<th>Post-intervention Mean/ SD</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patel et al, 2014</td>
<td>Protocol targeting risk factors for delirium versus standard care</td>
<td>60.8 (3.5)</td>
<td>75.9 (2.24)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Kamdar et al, 2013</td>
<td>Sleep protocol versus standard care</td>
<td>54.5 (27.1)</td>
<td>53.2 (27.3)</td>
<td>0.46</td>
</tr>
<tr>
<td>Van de Pol et al, 2017</td>
<td>Nocturnal sound reduction versus standard care (no sound reduction policy)</td>
<td>54.1 (3.87)</td>
<td>58.7 (7.5)</td>
<td>p = 0.85</td>
</tr>
</tbody>
</table>

Cognitive function

Cognitive function was reported in a before and after study of a sleep protocol by Kamdar and colleagues (2013) (184). They utilised neurocognitive tests including the digit span and trail making tests A & B to measure cognition. There were no significant differences between groups. The digit span total score in baseline group versus sleep QI group was 12 (IQR 10-14) versus 13 (IQR 10-14), p = 0.60. The trail making A test was 52 (IQR 38-94) versus 44 (IQR 36-70), p = 0.50 and trail making B test was 180 (IQR 99-180) versus 146 (IQR 69-180), p = 0.19 for baseline group versus sleep QI group.

Adverse events

Adverse events were reported in three non-randomised studies. Four minor events involving tube removal were reported by Needham and colleagues (2010) (177) in their trial of reduced sedation and improved mobilisation. Balas and colleagues (181) observed no adverse events in their study of spontaneous awakening and breathing tests and early mobilisation. Parry and colleagues (185)
reported one minor adverse event in the intervention group where there was a desaturation to 86% and an increase in 0.2 Fio2 for one hour in their study of functional electrical stimulation cycling (185).

**Summary of evidence**

A summary of evidence table was conducted for non-randomised studies and can be found in table 8 below. The quality of the evidence was downgraded for risk of bias and inconsistency.
### Table 8 Summary of findings table for non-randomised studies

Experimental compared to usual care for non-pharmacological interventions in Critically ill patients

**Patient or population:** Delirium in Critically ill patients  
**Setting:** Hospital  
**Intervention:** Experimental  
**Comparison:** Usual care

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No of participants (studies)</th>
<th>Follow up</th>
<th>Certainty of the evidence (GRADE)</th>
<th>Relative effect (95% CI)</th>
<th>Anticipated absolute effects</th>
<th>Risk with control</th>
<th>Risk difference with Experimental</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of delirium</td>
<td>4235 (16 non-randomised studies)</td>
<td></td>
<td>⨁◯◯◯ LOW a,b,c</td>
<td>RR 0.69 (0.58 to 0.83)</td>
<td>368 per 1,000</td>
<td>99 fewer per 1,000 (121 fewer to 74 fewer)</td>
<td></td>
</tr>
<tr>
<td>ICU mortality</td>
<td>1714 (7 non-randomised studies)</td>
<td></td>
<td>⨁◯◯◯ LOW a,c</td>
<td>RR 0.72 (0.52 to 0.99)</td>
<td>102 per 1,000</td>
<td>29 fewer per 1,000 (49 fewer to 2 fewer)</td>
<td></td>
</tr>
<tr>
<td>Hospital mortality</td>
<td>1297 (5 non-randomised studies)</td>
<td></td>
<td>⨁◯◯◯ LOW a,c</td>
<td>RR 0.72 (0.53 to 0.97)</td>
<td>146 per 1,000</td>
<td>42 fewer per 1,000 (69 fewer to 9 fewer)</td>
<td></td>
</tr>
<tr>
<td>Duration of delirium, days</td>
<td>1305 (7 non-randomised studies)</td>
<td></td>
<td>⨁◯◯◯ VERY LOW a,c</td>
<td>-</td>
<td>-</td>
<td>SMD 0.79 lower (-1.33 lower to 0.25 lower)</td>
<td></td>
</tr>
</tbody>
</table>

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).  
CI: Confidence interval; RR: Risk ratio; SMD: Standardised mean difference

**GRADE Working Group grades of evidence**

**High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect  
**Moderate certainty:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different  
**Low certainty:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect  
**Very low certainty:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

**Explanations**

a. Downgraded for risk of bias as non-randomised studies  
b. Downgraded for risk of bias as unable to obtain full translation in one study (178)  
c. Downgraded for indirectness due to heterogeneity between interventions in included studies
3.3.3 Qualitative studies results

The search strategy yielded a total of 25 citations of qualitative research, from which 12 were subjected to screening by two authors and seven articles were included in the qualitative synthesis (193-199). Figure 10 shows the PRISMA search results for qualitative studies (176).

Figure 10 PRISMA diagram for Qualitative studies
Study characteristics

The qualitative studies were conducted in four different countries and published between the years 2014 and 2016. Two studies were conducted in the USA (196, 199), Spain (194, 197) and Canada (193, 198) and one study was conducted in Sweden (196). Two studies were multicentre with 4-5 ICUs included (195, 199) and five studies were single centre (193, 195 - 198). Studies used a range of methods; focus group interviews (194, 197), semi-structured interviews (193, 195, 196), questionnaires (198) and a multiple methods approach including survey, observation and interviews (199). Sample sizes ranged from 10-81 participants. Full table of characteristics for qualitative studies can be found in table 9.
<table>
<thead>
<tr>
<th>Author</th>
<th>Methods</th>
<th>Setting and participants</th>
<th>Key objectives/ aims</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carrothers et al, 2013</td>
<td>- Document review</td>
<td>- 4 x ICUs (2 x urban, 2 x community hospitals)</td>
<td>- To identify which contextual factors facilitate/ hinder the implementation of the awakening, breathing, coordination, delirium and early mobility (ABCDE) bundle for guidance in future studies</td>
</tr>
<tr>
<td></td>
<td>- Site visits (interviews and observation)</td>
<td>USA n = 81</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Online contextual factors survey</td>
<td>7-36 participants per site.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- self reported process and outcome data</td>
<td>Profession:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>76% registered nurses</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>7% physicians</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>11% ancillary staff (Respiratory therapists, physical/ occupational therapists)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4% QI staff or management</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4% physician assistant/ nurse practitioner</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Experience:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>82% &gt; 6 years experiences in current profession</td>
<td></td>
</tr>
<tr>
<td>Eakin et al, 2015</td>
<td>- Semi structured interviews</td>
<td>Setting: Johns Hopkins MICU, Baltimore, USA</td>
<td>- to describe a multidisciplinary team perspective regarding how to implement and sustain an early rehabilitation program</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Participants: n = 20</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clinical discipline:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rehab services 30%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Physician 25%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nurses 25%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Program coordinator 10%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Physician assistant 5%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>RT 5%</td>
<td></td>
</tr>
<tr>
<td>Engwall et al, 2015</td>
<td>Part II: semi-structured Interviews</td>
<td>Setting: Sweden.</td>
<td>The aim was to describe patients experiences of an ICU room equipped with a cycled lighting environment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Participants:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Part II: n = 19 interviews</td>
<td></td>
</tr>
<tr>
<td>Cachon-Perez</td>
<td>- Semi-structured focus</td>
<td>Setting: Spain</td>
<td>To describe factors that constitute non-pharmacological</td>
</tr>
<tr>
<td>Author</td>
<td>Methods</td>
<td>Setting and participants</td>
<td>Key objectives/ aims</td>
</tr>
<tr>
<td>-------------------------</td>
<td>------------------------------</td>
<td>------------------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>et al, 2014</td>
<td>group interviews</td>
<td>Participants: n = 16</td>
<td>measures for treatment of ACS.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 Focus groups- 6, 5, 5</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Spain</td>
<td></td>
</tr>
<tr>
<td>Palacios-cefia et al, 2016</td>
<td>Focus groups interviews</td>
<td>Setting: 5 ICUs located In 4 hospital in Madrid, Spain</td>
<td>The aim of this study was to explore the experiences of doctors and nurses caring for patients with delirium in the intensive care unit (ICU) and to describe the process of delirium management</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Participants: n = 38.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Profession: 19 doctors</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>19 nurses.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sex: 22 women and 16 men.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age: 39 (Mean age)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Years of experience: 12.15 years (mean)</td>
<td></td>
</tr>
<tr>
<td>Whitehorne et al, 2015</td>
<td>Semi-structured individual</td>
<td>Setting: Canada</td>
<td>What is the lived experience of the ICU for patients who have experienced delirium?</td>
</tr>
<tr>
<td></td>
<td>interviews</td>
<td>Participants: n = 10</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sex: Male 7, female 3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age: 46-70</td>
<td></td>
</tr>
<tr>
<td>Rose et al, 2015</td>
<td>Questionnaire</td>
<td>Setting: Canada</td>
<td>Primary aim to evaluate ICU clinicians' perspectives regarding the use of protocolized sedation alone and protocolized sedation plus DI while managing patients enrolled in the SLEAP trial. Secondary objective was to compare perspectives of nurses and physicians.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Participants: n = 58</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>MDs 165 (54%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>RNs 139 (46%)</td>
<td></td>
</tr>
</tbody>
</table>
Quality appraisal

Using the POPAY CASP quality appraisal tool\(^{(200)}\), I assessed quality of the included qualitative articles (Table 10). Seven studies scored seven or more indicating low risk of bias.
<table>
<thead>
<tr>
<th>Quality Appraisal Questions</th>
<th>Carrothers</th>
<th>Eakin</th>
<th>Engwall</th>
<th>Cachon-Perez</th>
<th>Palacios-cefia</th>
<th>Whitehorne</th>
<th>Rose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Was there a clear statement of the aims of the research?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>2. Is a qualitative methodology appropriate?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>3. Was the research design process appropriate to address the aims of the research?</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>4. Was the recruitment strategy appropriate to the aims of the research?</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>5. Is there a clear and detailed statement of findings? (How ‘rich’ are the findings in</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
</tr>
<tr>
<td>terms of their detail and conceptual / theoretical development?)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Is there clear evidence of steps taken to enhance the validity and reliability of study</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>process / findings?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Is there evidence of consideration of the risk of bias in the production of findings</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
</tr>
<tr>
<td>(i.e. from a qualitative position - a reflexive concern with the researcher’s</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>standpoint)?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Is there evidence of analysis and interpretation of the</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
findings at a conceptual and theoretical level?

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>Yes</th>
<th>No</th>
<th>No</th>
<th>Yes</th>
<th>Yes</th>
<th>Yes</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>9. Is there evidence of consideration of the generalisability of study findings, that is, how they are related to broader theoretical concerns and/or other empirical contexts?</td>
<td>7/9</td>
<td>9/9</td>
<td>8/9</td>
<td>7/9</td>
<td>9/9</td>
<td>8/9</td>
<td>7/9</td>
<td>7/9</td>
</tr>
</tbody>
</table>

Final results
CERQual summary statements from synthesis of qualitative findings are reported in table 11.
Based on CERQual assessment, the findings range from low to moderate confidence. The main reasons for downgrading the methodological limitations was a minor risk of researcher bias in interpretation of results and minor to moderate concerns about relevance, coherence and adequacy due to lack of generalisability of results (review findings generated from small number of studies) and thin data from a small number of countries.
Perspective: ICU staff, ICU survivors’ perspectives on delirium and non-pharmacological interventions

Included interventions: ABCDE protocol, early rehabilitation, cycled lighting environment, protocolised sedation.

**Objective:** To synthesise qualitative data on the acceptability of non-pharmacological interventions for delirium management

<table>
<thead>
<tr>
<th>Review findings</th>
<th>Studies contributing to the review finding</th>
<th>Assessment of methodological limitations</th>
<th>Assessment of relevance</th>
<th>Assessment of coherence</th>
<th>Assessment of Adequacy</th>
<th>Overall CERQual assessment of confidence</th>
<th>Explanation of judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU staff perceptions about acceptability and feasibility of non-pharmacological interventions</td>
<td>Early mobilisation protocols were difficult to follow due to lack of personnel and equipment. Interventions for orientation, communication, family participation in care and sleep improvement were user friendly. [194, 195, 197], 3 studies had minor methodological limitations.</td>
<td>Minor concerns about relevance (studies of ICU staff perspectives on interventions from 2 different countries; Spain and Canada).</td>
<td>Minor concerns about coherence (data reasonably consistent across studies)</td>
<td>Moderate concerns about adequacy (3 studies that offer thin data)</td>
<td>Low confidence</td>
<td>The finding was graded as low confidence due to minor concerns about methodological limitations and relevance and moderate concerns about coherence and adequacy.</td>
<td></td>
</tr>
</tbody>
</table>
Reducing sedation and implementing early rehabilitation were associated with an increase in workload (194, 198). Two studies with minor methodological limitations showed moderate concerns about relevance (Partial relevance only 2 settings; Spain and Canada). Minor concern about coherence (data reasonably consistent across studies). Moderate concerns about adequacy (2 studies offer thin data). Low confidence. The finding was graded low confidence due to minor concerns about methodological limitations and coherence and moderate concerns about relevance and adequacy.

Effective leadership and teamwork, training and education and creating a safe environment were facilitators to implementing non-pharmacological interventions while lack of infrastructural, environmental and organisational resources were the greatest barriers. Two studies had minor methodological limitations. Minor concerns about relevance (studies of ICU staff from 4 different settings, USA, Spain, Sweden). Minor concern about coherence (data reasonably consistent across studies). Minor concerns about adequacy (5 studies offer rich data). Moderate confidence. The finding was graded moderate confidence due to minor concerns about methodological limitations, relevance, coherence and adequacy.

**ICU survivors' perceptions of delirium and acceptability of non-pharmacological interventions**

| Memories of disorientation and feeling unsafe caused great distress. ICUs lacked adequate orientation, sleep promotion and communication | 2 studies had minor methodological limitations | Moderate concerns about relevance (Partial relevance as studies from) | Minor concern about coherence (data reasonably consistent) | Moderate concerns about adequacy (2 studies offer thin data) | Low confidence | The finding was graded low confidence due to minor concerns about methodological limitations, coherence, and moderate concerns about relevance and adequacy. |
|---|---|---|---|---|---|---|---|

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strategies. Communicating, providing information, staff and family presence and support were deemed valuable. 

| 2 studies had minor methodological limitations | Moderate concerns about relevance (partial relevance as only from 2 settings; Canada and Spain) | Minor concern about coherence (data reasonably consistent across studies) | Moderate concerns about adequacy (2 studies offer thin data) | Low confidence | The finding was graded low confidence due to minor concerns about methodological limitations and coherence and moderate concerns about relevance and adequacy. |
Results of synthesis

As outlined in the protocol, a data synthesis was carried out on qualitative studies to identify information from;

- ICU staff on user friendliness of interventions, impact on workload and how interventions worked or did not work (i.e. barriers and facilitators);
- ICU survivors on how the interventions affected their delirium and their views on their acceptability;
- Families of ICU survivors to get their views on the level of involvement they had with interventions and their satisfaction with this.

ICU staff views on user friendliness of interventions, impact on workload and how interventions worked or did not work (i.e. barriers and facilitators)

User friendliness of interventions

User friendliness of interventions is not directly discussed in any of the eligible studies however one study referred to the lack of personnel, equipment and organisation for the delivery of early mobilisation, which would certainly impact the user friendliness of this intervention and is something that needs to be considered in the development of an intervention \(^{(195)}\).

Impact on workload

The impact on workload was evaluated in two studies \(^{(195, 198)}\). One study focused on reducing sedation and implementing early rehabilitation and this was associated with increased workload \(^{(195)}\). Early rehabilitation was perceived as time consuming with ‘time management’ identified as one of the ‘biggest struggles’ \(^{(195)}\). Another study of sedation protocol with daily interruption found the intervention was associated with a significant increase in workload \(^{(198)}\). This increased workload might be offset against the significant increase in workload associated with looking after a delirious patient if the intervention was proven to be effective. The workload of potential interventions must be taken into consideration prior to their implementation and measured against their potential effectiveness. Workload may be an important element to measure in subsequent RCT and this will have an impact on implementation planning.

How interventions worked or did not work

In relation to how interventions worked and did not work, three facilitators and two barriers to implementation of non-pharmacological interventions for delirium management in critically ill
patients were identified. I categorised the facilitators to implementation of non-pharmacological interventions incorporated in these studies to identify organisational, staff and environmental needs that might support the development of a future implementation plan.

**Facilitators to implementation of different non-pharmacological interventions**

*Effective leadership, structures, QI culture and teamwork: organisational factors that facilitate implementation of non-pharmacological interventions for delirium management.*

The need for support from the organisation in terms of funding from administration for quality improvement programmes, dedicated rehabilitation staff, communication within the multidisciplinary team and changing the culture to focus on quality improvement were identified as important for the successful implementation of non-pharmacological interventions by ICU staff in two studies (195, 199).

Teamwork, communication and discipline champions for delirium helped create a supportive environment according to one study (192) and strong leadership predicted higher success in another study (196). In two studies, buy-in from staff was reported as essential for successful implementation with rehabilitation staff reporting that without buy-in from ‘‘nurses and physicians and respiratory, it is not gonna happen’’ (195, 199). Good leadership ensures that plans to enhance buy-in from staff can be considered at the early stages of implementation planning.

The use of structures such as sedation protocols were effective in improving staff behaviour regarding delirium management. Eakin and colleagues noted that during a study on an early rehabilitation program in the ICU, staff were decreasing sedation and assessing for delirium in addition to getting patients out of bed meaning that the staff recognised that they could deliver early mobilisation more effectively this way (195).

A culture of quality improvement was identified as extremely important for the success of multicomponent interventions. One study reported that the two ICUs in their study that achieved more successful implementation of bundle elements were identified as the ICUs that already had a culture of quality improvement (199).

Therefore, the data from these two qualitative studies indicate that from the early stages of project planning for implementation of a delirium management bundle, a strong leader should be identified to lead the project and build a culture of QI and teamwork within the organisation prior to initiating the implementation process.
Empowering staff through training and education: the importance of including superusers and consistent approaches to delirium management

Educating the staff on the goals of rehabilitation was an important facilitator for its implementation because it may help staff to understand how early rehabilitation can target the negative impacts of critical illness and in particular, delirium \(^{(195)}\). Teaching was reported to enhance motivation in staff in two studies and including education as a continuous process with ongoing hands-on support from champions/super users can empower staff to deliver delirium management strategies such as pain, agitation and delirium (PAD) protocols and early rehabilitation \(^{(195,199)}\). Lack of education is recognised as a barrier to implementation of delirium management strategies \(^{(199)}\). Palacios-Cefia et al. and colleagues reported that staff felt delirium management was not straightforward versus other medical conditions like shock that have clear guidelines to follow and there was an overreliance on pharmacological therapies due to inadequate education \(^{(194)}\).

Interestingly, one study examined different educational approaches for example on the job training, and train the trainer however it still remains unclear which educational approach is superior \(^{(199)}\) and this is something that needs additional research. Without a clear strategy, a combination of techniques may be the most effective to meet different educational needs and learning styles.

Overall, education and training on delirium aetiology, epidemiology, outcomes and management strategies can enable staff to tackle the ambiguity that exists around delirium management strategies (for example, pharmacological use despite lack of evidence) while hands on support with rehabilitation manoeuvres can help inspire confidence in practitioners.

Environmental factors: Creating an environment that facilitates staff and family presence, a healthy sleep-wake cycle, orientation and communication to enhance a feeling of safety

The role of family in the intensive care unit was identified as an important adjunct for the delivery of non-pharmacological interventions such as communication and orientation in two studies \(^{(193,197)}\). Simply by being present, families were able to assist with communication and orientation of the patient \(^{(197)}\). Staff felt that the expansion of visiting hours was crucial to allow families to visit and play a role in their relative’s care \(^{(197)}\).

Creating a feeling of safety for patients was identified in two studies as important for delirium management. Families can play a role in creating a safe environment for patients by maintaining familiarity with one patient reporting that ‘holding a cross that a spouse had given them contributed to feeling of safety’ \(^{(193)}\). Huge emphasis was placed on communication for enhancing a feeling of safety in particular when staff ‘explained what they were doing step by step’ \(^{(194)}\).
In general, an environment that promotes staff presence and family involvement in care enhanced a feeling of safety for patients and was a facilitator to orientation and communication.

**Barriers to implementation of non-pharmacological interventions for delirium:**

*Lack of resources: infrastructural, environmental and organisational.*

Poorly resourced ICU environments may be complicit in the development of delirium\(^{(194,197)}\). These include lack of natural and diurnal light, noise reduction and sleep protocols.

A lack of infrastructure in terms of equipment was identified as a barrier to implementation of non-pharmacological interventions such as rehabilitation. The most common barrier in one study was the lack of resources for early mobility in the ICU\(^{(199)}\). In fact, in that study, success with implementation of early mobility was only achieved in the site where required resources were provided by ICU leadership\(^{(199)}\).

In terms of a lack of environmental resources, many units have limited natural light available and this is a barrier to delirium management and regulation of the circadian rhythm. Lack of natural light resulted in difficulty maintaining a sleep-wake cycle\(^{(197)}\). Some units reported having access to only one window and lack of natural light was associated with stress. Nurses advocated the need for a sleep protocol and a reduction in non-essential care at night to aid sleep\(^{(197)}\). Noise can be a barrier for sleep protocols and one study reported that staff can ‘forget that the patients have to sleep’\(^{(195,198)}\). Noise was reported to contribute to an ‘aggressive, hostile’ environment. Noise was a barrier for sleep with staff conversation recognised as a major cause of noise\(^{(193)}\).

In relation to a lack of organisational resources, poor organisation of care and lack of organisational support regarding development of protocols and pathways for delirium was identified as a barrier. In two studies, staff reported that there was inconsistency in delirium management in ICUs with no guidelines for medical management of delirium, inconsistencies in treatment and no anti-delirium protocols to follow\(^{(194,197)}\). Lack of consistency in approaches, lack of guidance in the form of protocolised care pathways, standardised therapeutic tools and references for drug management can prevent staff from delivering the best-evidenced based care. Poor organisation of care for example waking patients for non-essential care was one of the major barriers to successful compliance with sleep protocols\(^{(193)}\).

Staff perception of delirium as being problematic, belief that delirium only occurred in the elderly and doctors’ perceptions of delirium management as non-urgent speaks to the lack of education in organisations, which presents barriers to successful implementation of interventions. Staff perceived delirium as non-urgent and difficult to manage\(^{(194)}\). There were misconceptions about delirium
occurring only in elderly and staff reported insufficient training on delirium. Staff reported that delirium management felt ‘beyond our intellectual management’.

Knowledge about lack of resources can help a unit plan for and cost the introduction of a new intervention prior to the implementation phase.

**Safety concerns**

Another barrier identified in two studies was safety concerns in particular in relation to sedation protocols and early mobilisation. Sedation protocols often mandate a reduction of sedative levels, depending on a safety check, over a longer period. Regarding sedation interruption, a staff survey elucidated concerns about respiratory compromise, which were significantly greater in the registered nurse group compared to medical staff, and agitation, pain and discomfort, device removal, cardiac instability and long-term psychologic consequences. In another study, concerns about early rehabilitation were expressed with staff feeling ‘nervous about losing tubes, patients self-extubating and causing more harm than good’ and being hesitant about deciding when patients were ready for rehab.

Overall, if these interventions were successful in reducing delirium, these concerns may be offset against the elevated risk of removal of devices that occurs during a delirious episode. If implementing these interventions, it would be important to develop safety criteria and education programmes so that staff could mitigate for any potential harm and this would involve planning in the early stages of implementation.

**ICU survivors’ views on how the interventions affected their delirium and their views on acceptability**

Only two of the qualitative studies identified using my search criteria included ICU survivors and family members in their sample. One study examined patients’ experiences of ICU and a second study evaluated a particular light intervention.

**Memories of ICU delirium and non-pharmacological interventions**

In the qualitative studies identified, there was very limited information on patients’ experiences of non-pharmacological interventions. However, patients in one study did comment on a lack of communication and orientation. Patients reported that their inability to communicate meant they felt a disconnection with staff and this intensified stress and anxiety in the ICU.

Patients reported feeling disorientated and fearful and often did not realise where they were and found it difficult to make sense out of ‘unexplained experiences’ (delirium hallucinations).
fear contributed to a need for constant attention\textsuperscript{(194)}. One patient reported that orientation was inadequate as he recalled being able to name the hospital but, in his mind, it was the name of the boat he was stranded on\textsuperscript{(193)}.

Overall, there is limited data from one study to suggest communication and orientation interventions may be helpful for patients in the ICU for delirium management.

*Views on acceptability, value and worth and how interventions impacted their delirium*

ICU survivors in one study placed high value on interventions from staff for coping with delirium for example communicating, providing information, therapeutic touch, being present and providing support\textsuperscript{(193)}.

Due to poor memory recall of their ICU experiences, survivors provided very limited information on how interventions impacted their delirium but rather suggested interventions that they felt had a positive impact on their wellbeing.

*Families of ICU survivors’ views on the level of involvement they had with interventions and their satisfaction with this.*

No articles that provided qualitative information on families of ICU survivors’ experiences with non-pharmacological interventions were identified using my search strategy however, staff provided some limited data on the involvement of families of ICU patients. Data is synthesised below.

*Degree of involvement*

Feedback from staff indicated that involving family in care could have a positive effect on patients care and prevention of delirium. Staff felt there was good collaboration with families and they helped orientate patients and they felt visiting should be flexible\textsuperscript{(197)}. However, this was a small study but this could also be investigated further in focus group interviews.

*Satisfaction regarding involvement with non-pharmacological interventions*

No information was identified on the satisfaction of ICU survivors’ families regarding their involvement with non-pharmacological interventions for delirium in the studies identified.

*Views on acceptability and value*

No information was identified on the views of ICU survivors’ families regarding acceptability and value of non-pharmacological interventions for delirium in the studies identified.

*Summary*
Knowledge of the factors discussed above that impact on the implementation of non-pharmacological interventions can help shape education programmes for delirium in ICU and are crucial factors to be taken into consideration in the development, planning and testing of a multicomponent intervention. Awareness of these factors will ensure I have the knowledge to incorporate facilitators into my intervention development and identify solutions to counteract the barriers to ensure it is a sustainable intervention. These findings are important as I move forward into the next stage of my research, which involves assessing feasibility and acceptability of different non-pharmacological interventions. This information can help shape the questions that are asked in the focus group interviews to decipher which interventions tend to increase workload substantially and which interventions are less time-consuming assessing overall feasibility.
3.4 Discussion

Summary of findings

Although guidelines for pain, agitation and delirium recommend non-pharmacological interventions such as mobilisation, these are not widely implemented in ICUs [10]. In addition to a lack of clarity on the effectiveness of interventions, complexities further complicate the process of implementation. These reviews sought to evaluate which interventions were effective compared to usual care or other interventions in reducing the incidence and/or duration of delirium in critically ill patients. In addition, I wanted to identify barriers and facilitators to their implementation in order to determine why implementation often fails and what measures I should consider to counteract this failure.

The findings from the systematic review and meta-analysis of RCTs on the effectiveness of non-pharmacological interventions on delirium incidence and duration reported limited evidence to support the use of non-pharmacological intervention for delirium management. The quality of the evidence for RCTs was deemed low to moderate on GRADE assessment downgraded due to indirectness, high risk of bias and imprecision.

As these types of interventions are generally difficult to test in an RCT, I also included non-randomised studies. The quality of the evidence for non-randomised studies was downgraded for risk of bias and indirectness however, findings indicate an association between non-pharmacological interventions and reduced incidence and/or duration of delirium in critically ill patients. Evaluating the non-randomised studies separately allowed me to identify interventions that may have promising effects and could be studied further.

From the evidence reviewed, studies of multi-component non-pharmacological interventions are more likely to find an association with reduced incidence or duration of delirium in critically ill patients. It may be hypothesised that this is because they target many risk factors for delirium simultaneously. However, the relative effectiveness of the single components within these bundles is uncertain. I was unable to explore individual components of multi-component interventions and decipher why single components that do not have an effect on their own can be effective as part of a multi-component intervention.

Non-randomised studies have often been excluded from meta-analysis due to the increased risk of bias associated with absence of randomisation and double-blind process. I made the decision to pool analysis on non-randomised studies based on findings from Shrier and colleagues, 2007 that showed that estimates of effect sizes were comparable in
of cases comparing RCTs to non-randomised studies (202). Based on their findings, they recommended that non-randomised studies should not be excluded from meta-analysis a priori. My review of non-randomised studies found that education, sedation minimization, physical and occupational therapy and environmental interventions were associated with reduced incidence and/or duration of delirium in critically ill patients and improvements in other secondary outcomes such as sleep quality, cognitive function and hospital mortality.

In my published systematic review of RCTs, significant clinical and statistical heterogeneity meant it was difficult to compare studies in meta-analyses and only six studies were deemed suitable for two separate meta-analyses (24,26,203-206).

The pooled analysis showed that bright light therapy (BLT) was not effective as a single intervention in reducing incidence of delirium similar to other reviews which failed to show improvement in delirium outcomes with BLT (16,17). A second pooled analysis indicated that physical therapy was not effective in reducing the duration of delirium.

In comparison to my reviews, the wider published literature reports similar difficulties with heterogeneity of interventions and outcomes. Regarding the effectiveness of multicomponent non-pharmacological interventions for management of delirium in geriatric, acute medical and ICU populations many studies make recommendations for non-pharmacological interventions based largely on non-randomised data (12,16,168,207). In contrast to my reviews, Collinsworth and Rivosecchi’s reviews reported that multifaceted interventions including physical therapy might be associated with reduced duration of delirium in ICU however, analysis was not pooled for this outcome in either review (168,207).

Many studies had short follow up periods so I was unable to assess the effect of interventions on long-term outcomes. Rivosecchi’s systematic review included 17 studies (4 RCTs, 13 non-randomised) was carried out in the US (168) and reported a 24.7% mean reduction in incidence of delirium in studies of non-pharmacological interventions. Out of 17 studies, only two studies did not show benefits for delirium incidence, duration and/or severity with the introduction of non-pharmacological interventions. The review supported the inclusion of education, reorientation with cognitive stimulation and early mobility for delirium management. It included evidence from ICU and non-ICU populations. In an SR of eight studies that included outcome measures for delirium (three RCTs, five controlled clinical trials), Collinsworth reports evidence that non-pharmacological interventions may improve patient outcomes including incidence and duration of delirium (207). In comparison with my review, this review included only ICU populations however, it did not assess single
interventions but focused on multifaceted approaches that included two or more interventions. In addition, this review included a further six studies that focused on implementation strategies (five studies) and cost-effectiveness (one study) (207). The qualitative data in my review provided additional information on how non-pharmacological interventions may be implemented and delivered in critical care. Organisations and groups planning trials should consider these recommendations when implementing complex interventions in the ICU and ensure there is sufficient education and training to achieve buy-in from staff. Analogous to my qualitative review, Collinsworth and colleagues identified a need for ongoing education to address resistance to change from clinical staff and lack of awareness of the benefits of implementing care bundles for delirium (207). Their review recognised the need for cultural change in ICUs to support the acceptance of contemporary evidenced based care practices. There appears to be a role for families to enhance the care of the ICU patient concerning cognitive stimulation and orientation in particular. This could be facilitated in the organisation by expansion of visiting hours. For the success of early rehabilitation programmes, additional funding and support from the organisation for dedicated rehabilitation staff and equipment may be helpful. When planning and building new intensive care unit facilities, access to natural light should also be considered.

Overall, due to limited, low quality evidence from both RCTs and non-randomised studies, it is very difficult to offer any recommendations for a combination of non-pharmacological interventions. There were large variations in the interventions studied and outcomes measured, which makes it difficult to draw any strong conclusions from the data. This heterogeneity emphasises the need for standardisation of critical care study outcomes for future trials. Louise Rose and colleagues (208,209) have developed a core outcome set specifically for delirium trials but the publication is not yet available. This may be particularly helpful for trials studying sedation minimisation. Delirium incidence often increases during periods of sedation minimisation as it is no longer masked by the sedative. Therefore, a core outcome might direct me to the most appropriate outcome to use. Further research should focus on; (1) which combinations of interventions are more effective in improving delirium management in ICUs, (2) identifying the barriers and facilitators to implementation and sustainability of non-pharmacological interventions.

Strengths and limitations
The strengths of this review were the high-quality systematic review methodology used, the comprehensive search strategy developed with two independent medical librarians and the inclusion of qualitative studies that provided valuable data on the barriers and facilitators of implementation of this strategy to aid development of the intervention. In addition, I contacted experts in the field to ensure I had included all relevant studies, no language or time restrictions were applied to reduce bias, and a minimum of two independent investigators screened the studies, extracted data and assessed for quality and risk of bias.

I acknowledge that there were important limitations in this systematic review. I was unable to obtain sufficient data on mechanical ventilation status for a subgroup analysis and I was unable to obtain a full text translation of the Korean paper \(^{178}\). As a result, I could not adequately assess quality, risk of bias or assess the validity of the questionnaire used, as the methods were not available. The inclusion of non-randomised studies could be considered as introducing a further element of bias due to absence of randomisation however, most studies made attempts to control for confounding. Combining results from trials of non-pharmacological interventions can be difficult in terms of heterogeneity of populations, interventions and delirium outcome measures. A Delirium Core Outcome Set (DelCORs) has only recently become available and, when used, should help address the variability in outcome measures and allow the clinician to better compare effects across trials \(^{206}\). Combining interventions & populations will always be trickier. It has been common to combine trials with interventions into domains for analysis (e.g. environmental, sedation minimisation, early mobilisation). However, until more studies with similar populations & interventions become available, clinicians should assess generalisability of results to their practice.

### 3.5 Conclusion

A systematic review and meta-analysis of randomised controlled trials did not provide sufficient evidence to support the use of non-pharmacological interventions for delirium management in critically ill patients. There is some evidence from non-randomised studies to suggest that interventions such as education, sedation minimization, physical and occupational therapy and environmental interventions may be associated with a reduced incidence and duration of delirium.
Further research into the feasibility of multicomponent interventions in clinical practice is needed and trials to test their impact on clinical outcomes such as mortality and cognitive and functional status post ICU should be considered.

Adhering to the MRC guidance on the development of complex intervention, the next step was to take this evidence forward to an international, multidisciplinary delirium expert panel and use the qualitative evidence to help us formulate the implementation plan and questions for the focus group interviews.

Implications for clinical practice and future research will be discussed in chapter 8.

Chapter 4 will explore the opinions of an international multidisciplinary delirium expert group on the evidence from the systematic review.
Chapter 4 Identifying the evidence: Expert panel consensus

4.1 Introduction

The systematic review findings highlighted that there was limited scientific evidence from randomised controlled trials to support the use of non-pharmacological interventions for delirium in critically ill patients however there were promising results from trials of physical and occupational therapy and family voice reorientation, which require further study. Evaluating the limited evidence from the systematic review of non-randomised studies, sedation minimisation, mobilisation, sleep promotion, orientation and cognitive stimulation, extended visiting policy and multicomponent intervention combining a number of these interventions together were associated with improved delirium outcomes. It is hypothesised that targeting multiple risk factors for delirium simultaneously might have a cumulative effect on delirium outcomes. To provide a mechanism to assist with translating the findings into a usable, practical intervention, I utilised a consensus meeting of experts. Clinical research and systematic reviews are important for the synthesis of evidence on a given topic however, they are not sufficient to ensure that this evidence is translated into practice (210). Taking the evidence to experts for discussion enhances links between research evidence, research aims and actual practice decisions and the synthesis of these elements allows for development of true evidence-based healthcare (210).

Consensus methods are recommended as a way to manage conflicting scientific evidence (211). Where insufficient evidence or low-quality evidence exists, there are two options; ask the most qualified person to make the decision or ask a group for example, requesting opinions and experiences of a group of expert delirium researchers and clinicians to develop a non-pharmacological intervention for delirium (212).

My expert panel comprised participants who were selected based on their clinical or academic excellence in delirium. They were asked to participate in a discussion on non-pharmacological interventions for delirium, in one round, in person or using telephone conferencing services. The aim of this consensus group was to evaluate the level of agreement between experts or lay people on what interventions should be included in a multicomponent intervention. Using a group consensus method ensured that I had a wide range of direct knowledge and experience. I asked experts to analyse the evidence and provide insight into the implementation of the evidence into the practice setting. In addition to obtaining data on what might work in the intervention, I was also able to evaluate anything that might impact on adoption of the evidence and plan for translating
evidence into practice. This process also allowed me to formulate questions that might be useful for the next stage— focus group interviews with ICU staff, survivors and families who might be delivering/receiving the interventions.

This chapter follows the guidance from the MRC on development of complex interventions and identifying and developing theory by exploring the aforementioned theory with a group of delirium experts [30]. The chapter outlines the aims and objectives, methods, results, discussion and conclusion of the expert panel consensus meeting. The methods will outline the planning and execution of the meeting and the results will describe the discussion and overall group consensus on which interventions would work well as part of a multicomponent non-pharmacological intervention. The chapter concludes with a description of the interventions going forward for testing in focus group interviews.

**Aims & objectives**

The aim of the consensus meeting was to gain a group consensus on non-pharmacological interventions to include in a multicomponent non-pharmacological intervention bundle.

The objectives were:

- To review systematic review findings
- To discuss efficacy, feasibility and delivery of interventions
- To achieve consensus on what interventions should be included in the multicomponent bundle

**4.2 Methods**

**Expert panel participants**

A purposive sample was used to recruit panel participants. Patton [213] described purposive sampling as a method of seeking information rich cases; that is, choosing people for their expertise.

Together with the research team, I identified a purposeful sample of multidisciplinary international experts in delirium management based on publication record and recommendations from researchers in the field. I contacted eighteen experts via email to request their participation in a two-hour expert panel consensus meeting in person or via teleconferencing facilities. After a satisfactory number of positive responses were received, I did not seek any further contact details for experts. Agreement to participate was taken as
verbal consent. Participants agreed to be audiotaped and their participation is acknowledged in this thesis.

**Format of the consensus meeting**

The consensus meeting was held face to face and via teleconferencing facilities in a meeting room at the Excel London during the Intensive Care Society State of the Art meeting on 8th December 2015. Expert panellists were presented with the findings from the systematic review and meta-analysis on the effectiveness of non-pharmacological interventions for delirium management in critically ill patients via a PowerPoint presentation by the facilitator LB who has experience and training in facilitating group interviews (Appendix B). The meeting lasted two hours and was moderated by a supervisor (DMA). The moderators (DMA) role was to chair the meeting, pose questions around the findings to initiate discussion and sum up the overall agreement on interventions. Consensus was agreed when each intervention was discussed by all participants, views were summed up by the moderator and no further divergent opinions were expressed. The consensus meeting was audio recorded and transcribed verbatim.

In a PowerPoint presentation, results from RCTs and non-randomised studies were broadly divided into 4 categories for the purpose of the meeting; mobilisation, drug management, environmental interventions and multifactorial interventions. Results from qualitative studies were not presented at this meeting as final analysis had not yet been completed. After presenting findings from each category, the moderator asked specific questions to stimulate the discussion and allow group members to participate. Each category was discussed at length, the moderator summed up the perceived consensus on the topic until agreement was achieved among members.

A summary of the meeting and consensus agreement was drawn up and emailed to each of the expert panel consensus group members for review to re-validate consensus and ensure everyone was in agreement with what was agreed upon in the meeting.

**Data Analysis**

The discussions were audiotaped and transcribed verbatim by the facilitator, LB and checked by the moderator, DMA. The transcripts were examined in detail to determine key points in the discussion and consensus on each individual category that was discussed.

The qualitative analysis method used was content analysis. This is a popular qualitative research technique and is described as a flexible method for analysing text data from
qualitative interviews\textsuperscript{214, 215}. As a research method, content analysis is considered systematic and objective and allows researchers to describe and quantify phenomena\textsuperscript{216}. Using this approach allows the researcher to analyse and condense text into smaller categories.\textsuperscript{215} For the purpose of the expert panel consensus meeting, content analysis was chosen as an appropriate method for data analysis as it was considered a simple and candid method which allowed for investigation and grouping of the opinions of experts on the interventions studied.

4.3 Results

Setting and participants

Participants and their characteristics are presented in Table 12.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>9 (69 %)</td>
</tr>
<tr>
<td>Female</td>
<td>4 (31 %)</td>
</tr>
<tr>
<td><strong>Nationality</strong></td>
<td></td>
</tr>
<tr>
<td>Irish</td>
<td>1 (8 %)</td>
</tr>
<tr>
<td>British</td>
<td>6 (46 %)</td>
</tr>
<tr>
<td>American</td>
<td>5 (38 %)</td>
</tr>
<tr>
<td>Canadian</td>
<td>1 (8 %)</td>
</tr>
<tr>
<td><strong>Discipline</strong></td>
<td></td>
</tr>
<tr>
<td>Nursing- ICU</td>
<td>2 (15.5 %)</td>
</tr>
<tr>
<td>Medical- ICU</td>
<td>6 (46 %)</td>
</tr>
<tr>
<td>Medical- geriatrics</td>
<td>3 (23 %)</td>
</tr>
<tr>
<td>Pharmacy</td>
<td>2 (15.5 %)</td>
</tr>
</tbody>
</table>

Names and affiliations are available in Table 13.
Table 13 Participants expertise and affiliations

<table>
<thead>
<tr>
<th>Name</th>
<th>Affiliation</th>
<th>Role/Job</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Daniel F McAuley</td>
<td>Queen’s University Belfast</td>
<td>Moderator</td>
</tr>
<tr>
<td>Ms Leona Bannon</td>
<td>Queen’s University Belfast</td>
<td>Facilitator</td>
</tr>
<tr>
<td>Professor Wes Ely</td>
<td>Vanderbilt University, USA</td>
<td>Professor of Medicine.</td>
</tr>
<tr>
<td>Professor Dale Needham</td>
<td>Johns Hopkins University, USA</td>
<td>Professor of Medicine.</td>
</tr>
<tr>
<td>Dr Kieron Rooney</td>
<td>Bristol Royal Infirmary</td>
<td>Consultant in critical care.</td>
</tr>
<tr>
<td>Mr John Owen Bell manager</td>
<td>Bristol Royal Infirmary</td>
<td>Senior critical care nurse.</td>
</tr>
<tr>
<td>Dr Valerie Page</td>
<td>Watford general hospital</td>
<td>Consultant/researcher in.</td>
</tr>
<tr>
<td>Dr Emma Cunningham Consultant</td>
<td>Queen’s University Belfast</td>
<td>Academic Clinical Lecturer,</td>
</tr>
<tr>
<td>Professor Timothy Girard</td>
<td>Vanderbilt University.</td>
<td>Assistant Professor of.</td>
</tr>
<tr>
<td>Dr Thomas Jackson Medicine</td>
<td>University of Birmingham</td>
<td>Clinical scientist in Geriatric</td>
</tr>
<tr>
<td>Dr Daniel Davis Medicine</td>
<td>University College London</td>
<td>Fellow/ Consultant in Geriatric</td>
</tr>
<tr>
<td>Dr Catherine McKenzie critical care.</td>
<td>Guys and St Thomas’ trust</td>
<td>Consultant pharmacist in.</td>
</tr>
<tr>
<td>Dr Michelle Balas</td>
<td>Ohio State University, USA</td>
<td>Associate Professor, Nursing.</td>
</tr>
<tr>
<td>Professor John Devlin scientist.</td>
<td>Northeastern University, USA</td>
<td>Geriatrician and clinical.</td>
</tr>
<tr>
<td>Prof Pratik Pandharipande surgery</td>
<td>Vanderbilt University, USA.</td>
<td>Professor of Anaesthesiology/</td>
</tr>
</tbody>
</table>

Synthesis of interventions

Based on a discussion with the research team about the studies identified in the systematic reviews, 19 interventions were divided into four sections to be presented in the PPT presentation; mobilisation, drug management, environmental interventions and multifactorial (these were a combination of interventions from the previous three categories) (Appendix B). The participants also provided advice about generalisability of the interventions, methodological considerations for the future RCT of the interventions and future plans for involvement in the study.

The expert panel discussed efficacy, feasibility and deliverability of three studies that evaluated a mobilisation intervention.

(a) Mobilisation
The results for summary evidence on primary outcome for the following three studies of mobilisation interventions were presented to the expert panel consensus meeting:

**Table 14 Results from mobilisation studies**

<table>
<thead>
<tr>
<th>Author</th>
<th>Study type</th>
<th>Study size</th>
<th>Intervention</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schweickert et al, 2013</td>
<td>RCT</td>
<td>104</td>
<td>Early mobilisation during periods of daily interruption of sedation versus.</td>
<td>Intervention group had shorter days of delirium (median 2 days versus 4 days, SMD -1.66 (-3.20, -0.12), p = 0.02).</td>
</tr>
<tr>
<td>Needham et al, 2010</td>
<td>Non-randomised B &amp; A study</td>
<td>57</td>
<td>MDT weaning of deep sedation and new consultation guidelines and additional staff for physical and occupational therapy.</td>
<td>Patients in the post intervention group had more days alert without delirium [MICU days alert (30% versus 67%, p &lt; .001) and not delirious (21% versus 53%, p = 0.003). Delirium reported out of total MICU patient days and mean and SD not reported.</td>
</tr>
<tr>
<td>Parry et al, 2014</td>
<td>Non-randomised pilot case-match study</td>
<td>16</td>
<td>Functional electrical stimulation cycling</td>
<td>Intervention group had lower incidence and shorter duration of delirium [incidence (87% versus 25%, RR 0.29 (0.08, 0.98) and duration (6 days versus 0 days, SMD -0.47 (-5.88, 4.94), no p value reported]</td>
</tr>
</tbody>
</table>

The discussion considered the efficacy and feasibility of mobilisation interventions, the dose of mobilisation, operation of mobilisation and a threshold level of achievement.

**Efficacy and feasibility**

The discussion around functional electrical stimulation was that there was insufficient evidence to show efficacy from one small study from a mechanistic viewpoint. From a
practical viewpoint, participants felt FES was perceived as an impressive gadget but it is expensive, requires many accessories and it has a significant impact on workload. For those reasons, participants felt it made mobilisation too complicated. Participants agreed that there may be a niche patient group who are only able for passive ROM who might benefit for FES cycling such as sedated or brain injured patients and this could potentially be tested in a subgroup with the major study later. For early mobilisation, they felt that the benefit came from actively engaging the patient and the consensus on passive ROM exercises was that it might not be enough to engage the patient.

**Dose of mobilisation**

Regarding dose, participants were unclear at what level the benefit occurs. They acknowledged that early mobilisation research was relatively immature. Participants believed it was unclear what dose of mobilisation corresponds to a reduction in delirium but felt we should be grading mobility using a scale such as the ICU mobility scale *(217)*. Participants acknowledged that there was a synergistic relationship between reducing sedation and mobilisation and recognised that non-pharmacological interventions were difficult to deliver if large amounts of sedation were being used. The group agreed there were three things to consider when mobilising the patient to achieve a reduction in delirium (1) the input (2) the interaction and (3) the mobility outcome and felt we should measure the healthcare outcome (what staff were required), physical outcome (what level of mobility achieved) and delirium outcome (how much delirium recorded). The panel acknowledged difficulties trying to prescribe a dose as they found different patients were at different stages of rehabilitation and suggested that this might need to be personalised.

The consensus was that mobility should be progressive and hierarchical and for every level of sedation score. If a patient receives a Richmond Agitation Sedation Score (RASS) of -1 which indicates drowsiness, the recommendation would be to commence dangling at the edge of the bed, transferring to chair or walking. There should be a target goal to achieve (for example sitting) but also aim for the maximum progress for that patient on that day (for example if they can stand aim for standing). The group agreed that I should investigate in focus groups if achieving a minimum standard is feasible.

**Operation of mobilisation**
Regarding delivery, experts expressed that if nurses, family members and nursing assistants delivered rehabilitation then it could be delivered more often. This would need to be delivered in consultation with and under the guidance of the physiotherapy team.

\textit{(b) Drug management protocol}

Four studies were presented in table 15;
Table 15 Results from drug management protocol studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Study type</th>
<th>Study size</th>
<th>Intervention</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khan et al, 2013</td>
<td>RCT</td>
<td>60</td>
<td>Clinical decision support system.</td>
<td>No differences in incidence of delirium (27% versus 29%, RR 0.89 (0.40, 1.99), p = 0.85).</td>
</tr>
<tr>
<td>Mehta et al, 2012</td>
<td>RCT</td>
<td>430</td>
<td>Daily sedation interruption with or without a sedation protocol</td>
<td>No difference in delirium rates between groups, Incidence (53.3% vs 54.1%, RR 0.98, (0.82, 1.17), p = 0.83).</td>
</tr>
<tr>
<td>Nassar-Junior et al, 2014</td>
<td>RCT</td>
<td>60</td>
<td>Daily sedation interruption versus intermittent sedation</td>
<td>No significant difference in incidence of delirium (30% versus 40%, RR 1.33 (0.66, 2.69) p = 0.47)</td>
</tr>
<tr>
<td>Skrobik et al, 2010</td>
<td>Observation pre/post</td>
<td>1214</td>
<td>Protocolised management of analgesia, sedation and delirium.</td>
<td>Delirium rates were similar in pre and post groups (34.7% versus 34.2%, RR 0.99 (0.83, 1.17) p = 0.9) while subsyndromal delirium was significantly reduced (33% versus 24.6%, p = 0.009)</td>
</tr>
</tbody>
</table>

The discussion included non-pharmacological status, efficacy and feasibility and operation of a drug management protocol.

**Non-pharmacological status**

The panel debated whether stopping sedation could be considered non-pharmacological and participants concluded that interventions that seek to reduce drug exposure are non-pharmacological. The panel suggested that this component of the intervention should be called a sedation withdrawal component rather than a drug management component.

**Efficacy and feasibility**
The inclusion of a drug management/sedation withdrawal component was considered of utmost importance despite lack of evidence to support this in the literature. Participants felt it was important to point out that by simply including a sedation withdrawal mechanism to the bundle may mean more delirium is detected as it is no longer disguised by sedation. However, they felt this issue of confounding of results could be addressed by careful selection of outcome measurements i.e., avoiding using overall prevalence or number of days without delirium.

**Operation of a sedation withdrawal protocol**

Most participants did not have fixed opinions about how sedation withdrawal was achieved as long as it was achieved but suggested two prominent approaches; aiming for light sedation or no sedation (sedation breaks).

Participants also agreed that there was anecdotal evidence in their professional opinion to support the inclusion of optimisation of pain management prior to administration of sedation and they recommended continuation of pain medication during sedation breaks if needed. The participants felt there could be a role for a pharmacist to play in removing sedation and debated the use of the BEERS or STOPPSTART criteria (Criteria used to ensure medication review in older patients) \(^{(220, 221)}\) or a clinical pharmacist rounding with the team who can discuss benefit and lower doses if possible. The participants concluded that a pharmacist reviewing drugs on the ward during a ward round for example was more beneficial than an external review (away from the clinical area), which might fail to influence change.

**What to take forward to focus groups**

The panel agreed that a sedation withdrawal protocol was important whether this would be a sedation break or a guideline to aim for light sedation. There may be a role for a pharmacist but this should be explored further in focus group interviews with staff.

Participants also recommended to investigate in focus groups why nurses do not reduce sedation and identify barriers and facilitators.

**Environmental interventions and multifactorial studies**

Twelve studies were presented to the expert panel were (seen in table 16;
### Table 16: Results from environmental and multifactoral studies presented to expert panel

<table>
<thead>
<tr>
<th>Author</th>
<th>Study type</th>
<th>Study size</th>
<th>Intervention</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ono et al, 2007</td>
<td>RCT</td>
<td>22</td>
<td>Bright Light Therapy (BLT)</td>
<td>No significant difference in delirium between groups (intervention 1/10 versus control 5/12, RR 0.24 (0.03,1.73), p value not provided)</td>
</tr>
<tr>
<td>Taguchi et al, 2012</td>
<td>RCT</td>
<td>11</td>
<td>Bright light therapy</td>
<td>No significant difference in delirium incidence (intervention 16% versus control 40%, RR 0.42 (0.05, 3.36), p = 0.42)</td>
</tr>
<tr>
<td>Van Rompaey, 2012</td>
<td>RCT</td>
<td>136</td>
<td>Earplugs</td>
<td>No significant difference in delirium incidence (intervention 19% versus control 20%, RR 1.05 (0.53, 2.06), no p value provided)</td>
</tr>
<tr>
<td>Colombo et al, 2012</td>
<td>Non-randomised pre/post study</td>
<td>214</td>
<td>A reorientation protocol</td>
<td>Significant difference in delirium incidence in phase II (22% versus 35%, RR 0.63 (0.44,0.91), p = 0.020)</td>
</tr>
<tr>
<td>Kamdar et al, 2012</td>
<td>Non-randomised pre/post</td>
<td>300</td>
<td>Sleep protocol</td>
<td>Reduced incidence of delirium in the intervention group (49% versus 69%, RR 0.71 (0.58, 0.87), p = 0.02); shorter duration of delirium (43 vs 48, p = 0.003)</td>
</tr>
<tr>
<td>Black et al, 2010</td>
<td>Comparative time series</td>
<td>170</td>
<td>Nurse facilitated family participation in psychological care.</td>
<td>The intervention did not reduce delirium (control 77% versus 29%, RR 0.41, 0.25, 0.60), p value &lt; 0.05). Despite big differences in delirium incidence between intervention and control, the authors use a Bonferroni adjustment to control for the use of multiple t tests therefore a higher value of significance of p &lt; 0.001 was used</td>
</tr>
<tr>
<td>Moon et al, 2015</td>
<td>RCT</td>
<td>123</td>
<td>Delirium prevention protocol targeting</td>
<td>No significant difference in episodes of delirium (intervention 20% versus control 33%, RR 0.60, 0.05, 0.88), p value not provided)</td>
</tr>
<tr>
<td>Author</td>
<td>Study type</td>
<td>Study size</td>
<td>Intervention</td>
<td>Result</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>----------------------</td>
<td>------------</td>
<td>-------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Rivosecchi et al, 2016 168</td>
<td>Non-randomised</td>
<td>483</td>
<td>malnutrition, dehydration, sleep deprivation, immobility, polypharmacy, hypoxia, pain, infection and disorientation.</td>
<td>0.32, 1.11, p = 0.10)</td>
</tr>
<tr>
<td>Balas 181</td>
<td>Non-randomised pre/post</td>
<td>296</td>
<td>Non-pharmacological delirium protocol targeting sleep deprivation, cognitive impairment, disorientation and staff education.</td>
<td>Significantly less delirium in the intervention group (control 15.7% versus intervention 9.4%, RR 0.61 (0.37, 0.98), p= 0.04) and less time spent delirious (control 16.1% versus 9.6%, p &lt; .001)</td>
</tr>
<tr>
<td>Bryczkowski et al, 2015 180</td>
<td>Non-randomised pre/post study</td>
<td>123</td>
<td>Multicomponent Awakening, Breathing Coordination, Delirium management and Early mobility protocol (ABCDE)</td>
<td>Reduced incidence of delirium associated with the intervention (pre 62.3% versus post 48.7%, RR 0.78 (0.63, 0.96), p 0.02). Duration of delirium in days was also reduced but this was not statistically significant (pre 3 vs post 2, SMD -1.00 (-1.68, -0.32), p = 0.52) and percentage of ICU days spent delirious was reduced (pre 50 versus post 33.3, p = 0.003)</td>
</tr>
<tr>
<td>Dale et al, 2014 170</td>
<td>Non-randomised</td>
<td>1483</td>
<td>Multicomponent analgesia,</td>
<td>Incidence of delirium was significantly higher in the</td>
</tr>
<tr>
<td>Author</td>
<td>Study type</td>
<td>Study size</td>
<td>Intervention</td>
<td>Result</td>
</tr>
<tr>
<td>------------------</td>
<td>-----------------------</td>
<td>------------</td>
<td>------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Khan et al, 2014</td>
<td>Non-randomised pre/post study</td>
<td>702</td>
<td>Multicomponent: Daily paired spontaneous awakening and breathing trials</td>
<td>Post intervention group (10.7% versus 22.6%). The authors believe that the standard care of deep sedation most likely led to less delirium being detected in the pre-intervention group (Dale et al, 2014)</td>
</tr>
<tr>
<td>Patel et al, 2014</td>
<td>Non-randomised</td>
<td>341</td>
<td>Multicomponent delirium prevention protocol targeting sleep deprivation, pain, immobility, disorientation, and polypharmacy.</td>
<td>Incidence of delirium was lower in the post intervention group (33% vs 14% pre vs post, RR 0.43, 0.28, 0.65), p &lt; 0.001) and less time spent in delirium 3.4 (1.4 days) vs 1.2 (0.9) days, SMD -2.2 (-2.45, -1.95), p = 0.021).</td>
</tr>
</tbody>
</table>

**Efficacy and feasibility**

Environmental interventions were deemed easy to use without a need for additional resources and effective especially sleep promotion. The panel commented that there was evidence to show that sleep interventions can reduce delirium, but not necessarily improve sleep, and they suggested that researchers might need to reconsider how sleep is measured in the ICU, as current measurements are very subjective. The ‘this is me’ tool (a one-page document with information about the patient that can aid communication) was considered feasible and participants felt a further benefit of this tool was that it reinforced that the patient is a person and not a disease. This tool was included as part of the orientation materials along with the 5W1H.

There were mixed opinions on the feasibility of family participation as the panel wondered what carers could do in ICU but overall, they agreed that it was feasible to have carers participate in some aspects of care as long as they were under direct supervision of the
bedside nurse. Participants discussed music therapy in the ICU and felt it was important but it should be patient selected music. Although participants perceived earplugs and eye masks to be helpful, they noticed in clinical practice that they could induce anxiety for some patients.

**Operation of environmental interventions**

Participants agreed on the inclusion of the ‘This is me’ tool which could be adapted from the Alzheimer’s Society but felt it should be visible and prescriptive so everyone knows what it is being used for and education should be provided. Participants felt patients’ daytime naps should not be encouraged as it disrupts night-time sleep. Although not directly identified in the studies discussed, participants discussed the importance of helping patients to communicate their symptoms and experiences and felt using SPEACS 2 training (online communication training for staff) and materials might be helpful for staff and patients (223). For flexible or open visiting hours to be effective, participants felt leaflets and guidelines to set rules for enforcement were needed.

**What to take forward to focus group interviews from environmental interventions**

Participants felt bright lights or lux lights were an expensive intervention with no signal of efficacy but agreed I should ask staff opinions on feasibility. ‘This is me’ and sleep interventions were considered favourably. Overall, the consensus was that patients should be given the choice of sleeping with earplugs/eye masks or earphones with patient selected music. Participants felt open or flexible visiting was very feasible and should be discussed in focus group interviews.

**Discussion of other suggestions**

Four additional other suggestions were given by the participants;

(a) The intervention should be simple and easy to remember

(b) missing studies, participants suggested one RCT and one quality improvement project (224, 188) that might be eligible for inclusion in the review; these were subsequently screened for suitability and added to the systematic review

(c) Interventions should be applicable to a broad population.

(d) Plans for future research should involve completion of feasibility study to test if there is adherence to the interventions and following this, a definitive RCT to test efficacy of the interventions.
The intervention was circulated to the expert panel group electronically prior to the next step, focus group interviews. Table 17 below is a summary of the consensus on interventions that should be presented in focus group interviews for feedback on feasibility and acceptability in clinical practice.
Table 17 Outcome: Expert panel consensus on inclusion of interventions going forward to be tested for feasibility in focus group interviews.

<table>
<thead>
<tr>
<th>Interventions to be include in bundle</th>
<th>Interventions that were not deemed feasible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early mobilisation that is progressive and hierarchical for every level of sedation score (RASS or SAS)</td>
<td>Functional electrical stimulation cycling [excluded as expensive and significantly increases workload with limited proven efficacy]</td>
</tr>
<tr>
<td>Sedation withdrawal – aiming for light sedation or no sedation.</td>
<td>Passive Range of Motion (PROM) exercises [excluded as experts believed benefit from early mobilisation is from engaging the patient]</td>
</tr>
<tr>
<td>Pain management- pain relief should be offered prior to offering sedation.</td>
<td>External pharmacist review [excluded as experts believed there would be more benefit if pharmacist was physically present for discussion on a ward round]</td>
</tr>
<tr>
<td>Pharmacist rounding on the ward round</td>
<td>Bright light therapy [experts believe insufficient evidence for bright light therapy]</td>
</tr>
<tr>
<td>Sleep interventions</td>
<td></td>
</tr>
<tr>
<td>Orientation, cognitive and sensory stimulation, ‘this is me (document that displays vital information about the patient for example likes and dislikes, preferred names) with education for families on how to complete</td>
<td></td>
</tr>
<tr>
<td>Family participation with direct supervision</td>
<td></td>
</tr>
<tr>
<td>Music therapy- earphone for patient selected music</td>
<td></td>
</tr>
<tr>
<td>An offer of earplugs and/or eye mask for sleeping</td>
<td></td>
</tr>
<tr>
<td>Open or flexible visiting</td>
<td></td>
</tr>
<tr>
<td>Communication training for staff for example SPEACS</td>
<td></td>
</tr>
<tr>
<td>* No evidence for communication training from studies presented but panel consensus for including some communication training</td>
<td></td>
</tr>
</tbody>
</table>
4.4 Discussion

Participants provided advice on a range of interventions that were indicated in the systematic review and meta-analysis as beneficial for delirium management. The strengths of this expert panel consensus meeting were the inclusion of participants from a wide range of disciplines including nursing, medical (geriatrics and critical care), and pharmacy with valued clinical and research experience in the delirium field. However, a limitation of this study was the absence of allied health professionals including physiotherapy experts to provide expert advice on early mobilisation. A further limitation was the absence of ICU survivor and family input due to last minute unavailability. I plan to address this by aiming to recruit ICU survivors and their families and physiotherapists, occupational therapists, and clinical psychologists in the focus group interviews to gain further insight into feasibility from their perspective. Communication training was recommended based on anecdotal evidence as research on this concept is in its infancy and experts believed this could be beneficial to include in the multicomponent intervention.

A criticism of using an expert panel consensus approach is that it is not entirely inclusive. I acknowledge that broadening group participation may have achieved greater inclusivity of other professions and views. An alternative would have been to choose a Delphi method, with broader reach, participation and blinded consensus. This part of the study was limited by time and resource in this respect. Nevertheless, the expert panel, albeit a limited purposeful sample, provided a greater depth of discussion that would not have been achieved in a Delphi study.

A further limitation is that the group brainstorming technique may have introduced bias, for example, including participants in the expert panel who had published together and who had more positive views for particular interventions. I attempted to address this limitation by using a moderator to encourage critical objectivity and ensure every voice was heard in obtaining group consensus.

4.5 Conclusion

The overall consensus from the expert panel was that the interventions as depicted in Table 18 below should be presented in focus group interviews with ICU staff, ICU survivors and their families to determine feasibility and acceptability of the interventions. This intervention incorporates an incremental mobility programme (evidence from one RCT and four non-randomised studies\(^{24, 28, 168, 177, 181}\)), sedation withdrawal component (evidence from four non-randomised studies\(^{28, 177, 179, 181}\)), and environmental interventions for sleep...
(evidence from five non-randomised studies \(^{(18, 28, 29, 180, 184)}\)), orientation (evidence from five non-randomised studies \(^{(18, 28, 29, 177, 183)}\)), communication (expert opinion), family education (evidence from three non-randomised studies \(^{(29, 177, 183)}\)) and flexible visiting (evidence from one non-randomised study \(^{(183)}\)) and cognitive and multisensorial stimulation (evidence from two non-randomised studies \(^{(18, 29)}\)).

Building on the recommendations and guidance provided in the MRC framework about developing theory, chapter 5 will describe the background, methods and results for focus groups interviews with ICU staff and ICU survivors and their relatives respectively.
Table 18 Bundle to be tested for feasibility in focus group interviews with staff based on evidence and expert opinion

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Description</th>
<th>Evidence from;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mobilisation</td>
<td>- A protocol that advises an incremental increase in daily mobilisation based on safety criteria.</td>
<td>Schweickert, 2013; Needham, 2010; Balas, 2013; Rivosecchi, 2016; Patel, 2014.</td>
</tr>
<tr>
<td></td>
<td>Pharmacist rounding with medical team and discussing deliriogenic drugs</td>
<td>Expert opinion.</td>
</tr>
<tr>
<td>Orientation including this is me board</td>
<td></td>
<td>Colombo, 2013; Bryczkowski, 2014; Patel, 2014; Black 2011; Rivosecchi 2015.</td>
</tr>
<tr>
<td>Communication training using SPEACS 2</td>
<td></td>
<td>Expert opinion.</td>
</tr>
<tr>
<td>Flexible visiting</td>
<td></td>
<td>Black, 2011.</td>
</tr>
<tr>
<td>Education on how to use ‘this is me’ orientation and cognitive stimulation materials &amp; under supervision of nursing staff, families to participate in-patient care i.e. orientation, communication, cognitive stimulation.</td>
<td>Black, 2011; Rivosecchi 2015; Bryczkowski, 2014.</td>
<td></td>
</tr>
</tbody>
</table>
Chapter 5 Focus group interviews with PPI and ICU staff

5.1 Introduction

Chapter 4 focused on the progression of the research as the results from the systematic review and meta-analysis were presented at an expert panel consensus meeting and the intervention was modified accordingly. The next step was to present the modified intervention for feedback from ICU staff, survivors and their families. Engagement of those who will deliver and receive care is paramount if interventions are to be evaluated as being acceptable, feasible and practical.

This chapter describes focus group interviews with ICU staff, ICU survivors and their families to determine the feasibility and acceptability of 11 proposed non-pharmacological interventions. These interventions were associated with a reduction in incidence and/or duration of delirium in critically ill patients from evidence gathered in a systematic review and meta-analysis. In addition, a panel of international delirium experts believed these interventions were promising non-pharmacological therapies for delirium management.

This chapter commences with an introduction, aims, and objectives for the focus group interviews. The published paper titled ‘Designing a nurse-delivered delirium bundle: What intensive care unit staff, survivors, and their families think?’ has been embedded in this chapter in PDF format in the most logical position in the thesis to allow for the presentation of information in chronological order for the reader. The chapter continues by providing additional information on methods, ethical considerations and study details that were not provided in the published paper due to word count restrictions. The chapter concludes with a discussion of the findings and a summary of how the intervention has been modified following stakeholder review.

Aims and objectives

The overall aim of the focus group interviews with ICU staff and ICU survivors and families was to assess feasibility of a multicomponent non-pharmacological intervention for delirium management in critically ill patients from the perspective of those who deliver and receive care in the intensive care unit.

The objectives for the focus group interviews were to present the multicomponent intervention to participants and to:
- determine perceptions of the feasibility and acceptability of a multicomponent intervention for delirium management in critically ill patients.

- gather data to support implementation

- identify barriers and facilitators to implementation of interventions.

### 5.2 Methods and results

**Focus group interviews paper (published 2018)**

The following paper presents the background, methods and results from focus group interviews with ICU staff, survivors and families. Additional information that was not included in the paper is available at the end of this chapter.
Research paper

Designing a nurse-delivered delirium bundle: What intensive care unit staff, survivors, and their families think?

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Article history:
Received 26 October 2017
Received in revised form 31 January 2018
Accepted 4 February 2018

Keywords:
Delirium
Focus groups
Non-pharmacological
Perceptions

ABSTRACT

Background: Implementation of quality improvement interventions can be enhanced by exploring the perspectives of those who will deliver and receive them. We designed a non-pharmacological bundle for delirium management for a feasibility trial, and we sought to obtain the views of intensive care unit (ICU) staff, survivors, and families on the barriers and facilitators to its implementation.

Objective: The objective of this study is to determine the barriers and facilitators to a multicomponent bundle for delirium management in critically ill patients comprising (1) education and family participation, (2) sedation minimisation and pain, agitation, and delirium protocol, (3) early mobilisation, and (4) environmental interventions for sleep, orientation, communication, and cognitive stimulation.

Methods: Nine focus group interviews were conducted with ICU staff (n = 68) in 12 UK ICUs. Three focus group interviews were conducted with ICU survivors (n = 12) and their family members (n = 2). Interviews were digitally recorded, transcribed, and thematically analysed using the Braun and Clarke framework.

Results: Overall, staff, survivors, and their families agreed the bundle was acceptable. Facilitating factors for delivering the bundle were staff and relatives’ education about potential benefits and encouraging family presence. Facilitating factors for sedation minimisation were evening ward rounds, using non-verbal pain scores, and targeting sedation scores. Barriers identified by staff were inadequate resources, poor education, relatives’ anxiety, safety concerns, and ICU culture. Concerns were raised about patient confidentiality when displaying orientation materials and managing resources for early mobility. Survivors cited that flexible visiting and re-establishing normality were important factors; and staff workload, lack of awareness, and poor communication were factors that needed to be considered before implementation.

Conclusion: Generally, the bundle was deemed acceptable and deliverable. However, like any complex intervention, component adaptations will be required depending on resources available to the ICU; in particular, involvement of pharmacists in the ward round and physiotherapists in mobilising intubated patients.

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1. Introduction

Critically ill patients have an increased risk of developing delirium during their intensive care stay. Delirium is a common and devastating syndrome characterised by inattention and associated with increased mortality and morbidity.1-3 Pharmacological

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https://doi.org/10.1016/j.aucc.2018.02.007

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Please cite this article in press as: Bannon L, et al., Designing a nurse-delivered delirium bundle: What intensive care unit staff, survivors, and their families think?, Australian Critical Care (2018), https://doi.org/10.1016/j.aucc.2018.02.007

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therapies remain the popular choice for delirium management in the United Kingdom (UK) intensive care units (ICUs) despite the publication of recent studies and guidelines that indicate that there is insufficient evidence to support their use.\textsuperscript{15} A multi-component non-pharmacological intervention may reduce incidence and severity of delirium by targeting known risk factors such as sensory deprivation, sleep deprivation, and immobilisation in critically ill patients. Non-pharmacological interventions for delirium management have been effective in non-ICU populations but whether they are effective for critically ill patients has not been adequately researched.\textsuperscript{27}

We conducted a systematic review of studies evaluating non-pharmacological interventions for delirium management in critically ill patients to determine which interventions were most effective for reducing the incidence and/or duration of delirium.\textsuperscript{19} Findings indicated a number of effective interventions, some that could be delivered singly or in combination.\textsuperscript{15,26,27} These findings were presented to a panel of international, multidisciplinary delirium experts for agreement at the 2016 Intensive Care Society State of the Art meeting in London. Following discussion with the panel, a delirium bundle based on best evidence was designed to be tested in a feasibility study. The bundle comprised four components: (1) education and family participation; (2) sedation minimisation and pain, agitation, and delirium protocol; (3) early mobilisation; and (4) environmental interventions.

Translating knowledge to practice for healthcare professionals can be more successful if it is informed by an assessment of the barriers and facilitators.\textsuperscript{28} Therefore, the aim of this study was to elicit the perspectives of ICU staff, survivors, and families about the barriers and facilitators to delivering and receiving this delirium bundle that would inform design, delivery, and implementation.

2. Methods and materials

2.1. Research approach

The research approach was guided by the Medical Research Council framework for the development of complex interventions\textsuperscript{21} and a systematic review of key factors affecting intervention implementation.\textsuperscript{22} This approach enabled us to examine deliverability and acceptability of the components in the bundle using focus group interviews. We elicited the perspectives of ICU staff, survivors, and their families using focus group interviews conducted between July and September 2016.

Semi-structured questions in the interview guide were framed around the key findings from Durlak and DuPre’s systematic review\textsuperscript{22} (see appendix 1 for interview schedule). The study was approved by an National Health Service (NHS) research ethics committee (OREC/16/EM/0028). The standards for reporting qualitative research were applied.\textsuperscript{29}

2.2. Setting

Staff interviews took place in 12 NHS adult general ICUs in England, Scotland, Wales, and Northern Ireland. We used a sampling matrix to ensure inclusion of units from all four devolved nations of the UK and staff with a range of experience from less than 1 year to more than 10 years. ICUs ranged in size from seven beds to 52 beds with a range of specialities including medical, surgical, trauma, and burns. Interviews with ICU survivors and their families were conducted face-to-face at ICUsteps group meetings in England and Northern Ireland and online using Skype technology with each participant in their own home.\textsuperscript{30}

2.3. Participant recruitment

ICU staff who were members of the British Association of Critical Care Nurses (BACCN), the professional organisation for critical care nurses in the UK that has representation in the majority of UK ICUs, were recruited. The ethos of the association promotes engagement in research for patient benefit, which is why I chose this method. Approval was granted by BACCN to post a study advertisement on the website and in the newsletter. Interested members discussed potential participation with staff in their ICUs, received approval from the ICU managers, and recruited staff to attend focus group interviews. Interviews took place in a hospital or university meeting room.

Inclusion criterion was staff with more than 6 months experience working in critical care, and purposeful sampling method was encouraged to ensure a range of professions and experience within the focus group.\textsuperscript{31} ICU survivors and families were recruited from ICUsteps, a charity that supports survivors of critical illness and their families. Approval was received by ICUsteps to circulate study information via the ICUsteps newsletter and website: potential participants then contacted an investigator (LB) directly. Inclusion criterion was that ICU survivors had to have been cared for in ICU for more than 48 h.

2.4. Data collection

Focus groups interviews were approximately 60–90 min in length and conducted by LB with experience in critical care nursing and research. The interview was preceded by a PowerPoint presentation of the multicomponent delirium bundle to initiate the discussion. Interviews were recorded using a W5-831 Digital Voice Recorder (Olympus Imaging Corp, Tokyo, Japan) and transcribed verbatim by an independent transcriber. Interviews continued until data saturation was obtained which was judged by no new data arising in the interviews.\textsuperscript{32}

2.5. Data analysis

The transcripts were reviewed by the interviewer (LB) and compared with the voice recordings and the handwritten notes taken during discussions to reduce the risk of errors and missing information. The corrected transcripts were thematically analysed using the Braun and Clarke thematic analysis framework to identify barriers and facilitators to the multicomponent bundle.\textsuperscript{33}

<table>
<thead>
<tr>
<th>Variable</th>
<th>Characteristics, n (%)</th>
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</thead>
<tbody>
<tr>
<td>Sex, n (%)</td>
<td>Male 13 (31%)</td>
</tr>
<tr>
<td></td>
<td>Female 55 (69%)</td>
</tr>
<tr>
<td>Years employed in critical care setting, n (%)</td>
<td>Up to 5 years 16 (33.9%)</td>
</tr>
<tr>
<td></td>
<td>5–10 years 19 (28%)</td>
</tr>
<tr>
<td></td>
<td>10 years or more 33 (48.5%)</td>
</tr>
<tr>
<td>Profession, n (%)</td>
<td>Nurse 44 (40%)</td>
</tr>
<tr>
<td></td>
<td>Doctor 8 (12%)</td>
</tr>
<tr>
<td></td>
<td>Physiotherapist 7 (10%)</td>
</tr>
<tr>
<td></td>
<td>Pharmacist 3 (4%)</td>
</tr>
<tr>
<td></td>
<td>Clinical psychologist 2 (3%)</td>
</tr>
<tr>
<td></td>
<td>Critical care scientist 2 (3%)</td>
</tr>
<tr>
<td></td>
<td>Nursing assistant 1 (1%)</td>
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<tr>
<td></td>
<td>Occupational therapist 1 (1%)</td>
</tr>
</tbody>
</table>

Table 1. Characteristics of staff participants (n = 68).

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To enhance confirmability of the results, a random sample of 15% of the transcripts were independently analysed by a second investigator (JMG). Interpretations were discussed until consensus was reached to reduce the influence of personal characteristics on interpretation and bias.

3. Results

Results are presented separately for (1) staff and (2) survivors and family members outlining generic (to the interventions as a whole) and specific (for each component of the intervention) barriers and facilitators to delivery and acceptability of the bundle. Quotes from transcripts have been used to support the themes arising for each participant group.

Twelve focus group interviews were conducted, nine involved staff (n = 68) and three involving ICU survivors (n = 12) and family members (n = 2). Tables 1 and 2 present a summary of participant characteristics.

3.1. ICU staff perceptions of the multicomponent bundle

3.1.1. Acceptability of the intervention

Staff from all focus groups felt that this multicomponent intervention comprising education, sedation minimisation, early physical therapy, and environmental interventions was feasible and acceptable to implement for delirium management in critically ill patients. Concerns were expressed about the feasibility of involvement of pharmacists in the ward round and early physical activity of mechanically ventilated patients without an improvement in current staffing levels.

"I think there's lots of elements that we are already working on and we can definitely do some things better." [FG3, ICU nurse, M]

"There are limitations; chairs and staff, coordinating time." [FG11, ICU nurse, F: speaking about early physical activity]

3.1.2. There were two generic factors that staff perceived would facilitate their use of this bundle

1. Family presence was perceived as creating a sense of familiarity and safety for patients. Staff felt that families were an underutilised resource in ICU and could be used to assist with communication, orientation, personalising music selection, and personal care if appropriate training and support was available. Family presence could be encouraged by facilitating more flexible visiting hours.

"I've seen people who I thought were tipping into delirium actually end it in a much shorter period because of the presence of familiarity and safety around them." [FG8, Clinical Psychologist, F]

2. Education for staff about delirium in ICU was deemed important for challenging existing cultures of deep sedation and excessive noise at night and would improve staff engagement with the delivery of the interventions. They suggested that education programs should include some formal feedback from patients about their experiences in the ICU. Additionally, staff reported that education for relatives might help address their anxiety although timing in the patient's illness trajectory would be crucial to enable retention of information.

Specifically focusing on individual components of the bundle, factors that would facilitate the orientation and communication component were use of picture boards and phototags. Factors that would facilitate the sedation minimisation component, particularly for less experienced staff, were protocols, guidelines, targeted sedation, non-verbal pain scores, and identifying suitable patients for a sedation break in an evening ward round on the previous day. Use of a Richmond Agitation Sedation Score (RASS) for monitoring sedation scores is a standard practice in ICU; however, targeting a specific score, for example, 0 alert and orientated, is not a part of this practice, but participants believed that this helped reduce the amount of sedation administered overall. The use of a pain tool such as Critical Care Pain Observation Tool (CPOT) for non-verbal patients is not standard practice; however, staff participants reported that the use of this tool facilitated sedation minimisation by avoiding the need for higher sedation due to better controlled pain. Staff reported that communication training and availability of tools would be useful to help meet patients' pain and care needs.

3.1.3. There were five generic barriers perceived by staff as barriers to successful delivery of the bundle

1. Staff cited limited resources, in terms of personnel, equipment, and space, which could be further exacerbated by the need to facilitate staff breaks and lengthy patient transfers out of ICU. A busy workload was a barrier to the delivery of the bundle. Caring for a critically unstable patient could negatively influence the care of other patients under their supervision, and interventions like sedation interruptions or extubation might be delayed. Staff reported that assessments were completed but not formally documented because of lack of time. Staff felt that there was a role for support staff such as nursing auxiliaries and volunteers to sit with patients when they are agitated to reduce staff workload. Damaged or missing seating and equipment blocking corridors were additional barriers to early mobilisation.

2. Lack of in-service education about the effects of sedation and the negative impact of delirium were cited as barriers. Interviewed staff reported having a poor knowledge of delirium management policies and a general perception among staff that sedated patients lacked awareness of noise and care activities. The majority of staff interviewed were not aware of recommendations for non-verbal pain scores and daily screening for delirium, and compliance with delirium screening was poor across all of the ICUs included in this study.

"Does it matter, if someone is heavily sedated and they come to do that, are they aware to a certain level?" [FG12, Physiotherapist, M; speaking about washing patient in the middle of the night]

"There is a tendency for staff to leave radios on in sedated patients' rooms." [FG11, Nurse, F]

3. Anxious relatives often created a barrier to the delivery of interventions in two ways; they asked excessive questions that increased staff workload and created a chaotic environment for patients. Staff felt that this was due to fear and lack of control, and they discussed how flexible visiting (can visit at any time

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Characteristics of ICU survivors and relatives (n = 14).</th>
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<tr>
<td>Variable</td>
<td>Characteristics, n (%)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>9 (64%)</td>
</tr>
<tr>
<td>Female</td>
<td>5 (36%)</td>
</tr>
<tr>
<td>ICU team member status</td>
<td></td>
</tr>
<tr>
<td>ICU survivor</td>
<td>12 (86%)</td>
</tr>
<tr>
<td>ICU survivor's relative</td>
<td>2 (14%)</td>
</tr>
<tr>
<td>ICU — intensive care unit.</td>
<td></td>
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</tbody>
</table>
but advised to avoid busy times or night time) rather than open visiting (open 24 h) could be beneficial to patients and families as they needed permission to go home and often felt guilty for leaving.

4. Patient safety concerns especially during busy times were felt to be a barrier to the delivery of the bundle. Staff reported using higher doses of sedation to maintain patient safety especially when covering for staff breaks, transfers, or patient care. Additionally, they reported that weaning patients off sedation was often delayed as it was easier to get patient care activities, administration of medications, and documentation completed when looking after a sedated patient.

5. A further barrier cited was a difference in cultural perceptions. Staff discussed how families in other countries provided food and personal care for patients, and they felt this culture shift had not occurred in the UK. Historically, deep sedation was required for the management of an intubated and ventilated patient in the ICU, and as a result, a culture of deep sedation emerged which often meant there was a reluctance to mobilise these patients for fear of dislodging their endotracheal (ET) tubes.

“I think if they’ve got the mask or they have got a [tracheostomy], you slightly do push them further than you would if they had an ET tube.” [FGC, ICU nurse, F]

In relation to barriers regarding specific components, staff felt the whiteboard might raise concerns about confidentiality by displaying patients’ information, especially in small ICUs where this information was more readily seen. Regarding early mobilisation, physiotherapists felt they might be restricted by competing priorities; chest physiotherapy was often seen as a priority over early mobilisation, which might restrict their time to deliver this intervention.

3.2. ICU survivors and their families’ perceptions of the multicomponent bundle

3.2.1. There were two generic factors that survivors and their relatives perceived would facilitate their use of this bundle

1. Re-establishing normality was seen as a facilitator to the delivery of a multicomponent intervention. Survivors reported that they felt being able to mobilise out of bed, listen to music, and get their hair washed gave them a sense of normality and improvement, and this helped them engage with the interventions as they perceived them as beneficial.

“But I think just as importantly, getting out of bed, you’re actually thinking, great, I’m out of ICU in the next couple of days.” [FG10, ICU survivor, M]

2. Flexible visiting for relatives was a facilitator to communication, family participation, orientation, and early mobilisation. Relatives reported that a flexible visiting policy could allow them to assist with care, orientation, mobilising, choosing music for loved ones, and bringing in communication materials. Flexible visiting also allowed relatives to manage visiting more effectively so everyone was not arriving at the same time and tiring the patient.

Specifically focusing on individual components of the bundle, providing an escape from the loud, hostile environment by using earplugs, music, and headphones were perceived as helping to facilitate sleep and relaxation for survivors. Importantly, survivors and their relatives felt it was essential to give patients the choice of using these devices as they may not suit everybody. Additionally, relatives welcomed the communication bundle and made useful suggestions such as having a dedicated box with communication materials that was easily accessible to staff and relatives.

3.2.2. There were three generic factors that survivors and their relatives perceived as barriers to the delivery of this bundle

1. Relatives felt that low staff numbers could be a barrier to the delivery of the bundle as staff may not have the time required to deliver the interventions on top of a busy workload.

2. ICU survivors perceived that staff lacked awareness and understanding about patients’ experiences under sedation and were not aware that patients were often privy to their personal conversations. Survivors also felt staff did not understand their difficulties retaining information and, as a result, their need for constant reorientation. Relatives suspected this lack of awareness might contribute to staff not engaging with the bundle.

“They would come next to your bed and speak to one another but they wouldn’t engage the patient.” [FG 10, ICU survivors, F]

3. Intubation and upper limb weakness can restrict a patients’ ability to communicate in ICU. Difficulty communicating was perceived as a barrier to participation in many components of the bundle as survivors felt physically unable to participate or quickly became frustrated if staff could not understand them.

One participant reported that there was “no way to communicate because [he] couldn’t even move a finger and even if [he] could, there wasn’t a fingerboard.” [FG10, ICU survivor, M]. Survivors and relatives considered whiteboards helpful for communication and orientation, and when questioned, they had no confidentiality concerns.

In relation to barriers concerning specific components, fear was a barrier to family participation as relatives were cautious that they might cause harm or damage to the patient. Regarding early mobilisation, survivors felt that limb weakness or limited their ability to participate. Survivors reported significant muscle wastage during their ICU stay and many were shocked at the speed at which muscle strength deteriorated. They felt they needed to rely heavily on staff to support them and help them back into bed.

4. Discussion

This study found that a multicomponent delirium bundle was acceptable to survivors and families and feasible to deliver in the ICU by staff with the exception of pharmacy involvement on the ward round and early mobilisation of patients with endotracheal tubes. The most important facilitators perceived by staff for delivering the intervention were the provision of additional supportive staff, increased family engagement, and presence and more in-service education about sedation and its effects. Indeed, all participant groups recognised family presence as a facilitator and lack of education and awareness, lack of staff, and communication as barriers.

Studies have reported high levels of anxiety, depression, and post-traumatic stress disorder in family members of ICU patients. Family members’ anxiety can be reduced by providing the knowledge and tools for them to participate in care giving. A survey by Garrouset-Orges et al (2010) found that 96% of families’ favoured participation in care and educating family members to assist in delivery of interventions would help relieve some of the burden for staff. In our study, groups suggested ways in which
families could participate such as assisting with orientation, communication, and aspects of personal care. To ensure effective implementation of the bundle in practice, additional organisational resources would be required. There is a need to address staff support in the ICU to deliver early mobility to all patients and during delivery of sedation interruption (SI) especially for agitated patients. Surprisingly, staff reported that sedated patients were often treated differently to awake patients, and staff believed there was a lack of knowledge about levels of awareness amongst sedated patients. Gesin et al. (2012) found that an education program on delirium improved nurses’ knowledge of delirium and their understanding about why it is important to recognise delirium; therefore, a similar delirium education program for staff would address knowledge deficits that exist and help change the culture of excessive noise and deep sedation. A consensus meeting in 2014 outlined safety considerations that should be reviewed before mobilisation of adult, mechanically ventilated patients, and these should be incorporated into a protocol with a non-verbal pain tool and a daily care plan with an area for the evening ward round to plan sedation breaks for the next day. Improving communication was a major priority for all participant groups, and therefore, training is required, and provision of appropriate tools shown to improve communication between nurses and patients in ICU will need to be considered in the bundle. These are simple patient-centred realistic facilitators that could enhance delirium management in the ICU with no additional organisational cost.

Interestingly, ICU staff and survivors had divergent views on the confidentiality of whiteboards with information displayed about the patient to enhance communication. Staff felt that this could be a confidentiality issue; while in contrast, survivors had no concerns about the information being displayed and felt it would be very useful. Therefore, the whiteboard component would need to be considered for individual ICUs, and staff may need to contemplate local adaptations to ensure privacy of this information.

The available literature on barriers and facilitators to non-pharmacological bundles is limited. A study of implementation of the awakening and breathing coordination, delirium monitoring, and early mobility bundle (ABCD) reported similar findings to our study with education identified as an important facilitator and knowledge deficits, workload concerns, and lack of communication reported as common barriers. In contrast to our study, this study identified the strength and quality of the evidence base for the bundle as a facilitator, and this was not highlighted in our interviews. In addition, the importance of family presence as a facilitator was agreed in all participant groups and has been emphasised previously in other studies.

4.1. Strengths and limitations of the study

A strength of this study was that we recruited ICU survivors and their families from different geographical locations in the UK and represented a range of admission types with good experience of the interventions discussed. Tape-recording the interviews, multiple coding during analysis, and co-author checks also enhanced the rigour of this study.

A limitation of this study was that high levels of sedation, disorientation, and confusion during the survivor’s ICU stay might have diminished patients’ memories and views of pain, agitation, and delirium management. Participants self-selected for this study, and this may have resulted in a biased sample, as participants with particularly strong opinions may be more likely to have volunteered. There were inherent difficulties in recruiting ICU survivors and in particular, their family members to participate in this study likely due to the burden of supporting the recovery and cognitive and functional impairments that present as part of the typical illness trajectory post ICU. This is not unusual in ICU research and has previously been reported as very challenging.

5. Conclusion

This bundle of non-pharmacological interventions may present a useful and relatively inexpensive approach to delirium management in critically ill patients. The four components are deemed feasible and acceptable to staff, ICU survivors, and their families. However, like any complex intervention, there will need to be adaptations made depending on the resources available to the particular ICU, especially regarding pharmacy involvement on the ward round and early mobilisation of patients with endotracheal tubes. This approach is paramount to defining an intervention and has helped shape this bundle, which is now being taken forward to test in a feasibility study.

Authors’ contributions

LB collected data, analysed the data, interpreted the data, and wrote the manuscript. JM analysed and interpreted 15% of the transcripts. BB, DM, and MC advised on data analysis and BB and JM provided critical input into the manuscript writing and completion. All authors approved the final version of the paper and are entitled to authorship as listed authors.

Acknowledgements

The authors would like to acknowledge ICUstepe and the BACCN for advertising focus groups and Heather Baid, Julie Highfield, Lynda Purdy, Manav Bhavani, Andrew Ward, Katharine Thomas, Heidi Dawson, Melanie Gager, and Deborah Dawson for volunteering to be the ICU contacts and identifying staff for interviews. This work is supported by a Doctoral Fellowship Award to LB by the Northern Ireland Health and Social Care research and development division (EAT/5092/14).

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jaacc.2018.02.007.

References

5.3 Additional information

Data analysis

The following section contains additional information about the methods chosen for analysis of the focus group interviews, attempts to reduce bias and ethical considerations for the interviews that were not included in the paper due to word count limitations.

Thematic analysis is a qualitative method that is used to identify, analyse and report patterns or themes within the data (225). I choose thematic analysis as a data analysis method for my focus group interviews as it provided more structure for me as a novice researcher and allowed me to consider the context in which the data was collected. While I recognise the disadvantages to using a thematic analysis approach including lack of explicit definition and procedures (225, 226) and risk of lacking consistency and coherence in thematic development (227). I attempted to overcome this by having a second researcher independently analyse the transcripts using the thematic analysis technique. There is significant overlap between content analysis and thematic analysis however I feel thematic analysis was a superior method to meet the needs of my research due to the flexibility and adaptability of the approach. As noted in the literature, it is also useful for comparing perspectives between groups and can be useful for summarising a large amount of evidence and producing a clear report (225, 227, 228).

In addition to using the thematic analysis approach to analyse transcripts. I also applied additional measures to make the methods more explicit as detailed here. To ensure validity of qualitative research, it was important to consider ways to enhance validity while conducting my research. Guba and Lincoln (1985) identified criteria for credibility, transferability, dependability and confirmability to ensure the trustworthiness of qualitative research (229).

I strengthened credibility in my study by summing up the consensus on interventions at the end of each section while conducting my focus group interviews to ensure there were no differences between participants views’ and my depiction of their views as advised by Tobin & Begley (229). Credibility can also be operationalised by using researcher and data collection triangulation techniques or prolonged engagement or observation (229).

I used a sampling matrix to ensure participants represented a range of geographical locations and a range of experience thus enhancing the generalisability of results. I also
described the setting in detail to enable the reader to judge whether findings can be transferred to their setting \(^{(229)}\).

To ensure dependability of the data, I have clearly documented the research process and the themes have been presented clearly with associated quotes as recommended by Tobin & Begley, 2004 and Guba & Lincoln, 1985 \(^{(229,230)}\).

Finally, to enhance confirmability of the results in this study, a random sample of 15% of the transcripts were independently analysed by a second investigator (JMG). Interpretations were discussed until consensus was reached to reduce the influence of personal characteristics on interpretation and bias. Confirmability is involved with deciding if the findings can be clearly linked to the data and encouraging the researcher to delineate how their conclusions and interpretations were achieved \(^{(230)}\).

Ensuring the trustworthiness of data was a major priority of this component of the study as well as ensuring the safety of the participants. The next section details the potential ethical issues that I considered prior to carrying out the research.

**Ethical considerations**

The following ethical considerations were reviewed prior to undertaking the study.

*Data management.*

The data collected during the focus group interviews was only shared as themes. Information was anonymised so it could not be attributed to any specific person. The recordings and transcripts were stored in a locked cabinet in the PhD room at the Wellcome Wolfson Building at Queen’s University Belfast (QUB) in adherence with QUB policy. Audiotapes were destroyed after use and transcribed data were backed up on the University server. Records will be kept for five years in accordance with guidelines and the Chief Investigator will have the ultimate responsibility regarding archiving.

*Confidentiality.*

Confidentiality of information was upheld at all times. Measures were taken to ensure that participants could not be identified from their comments and participants were encouraged not to share the issues discussed outside of the focus groups. These measures included a coding system whereby the Focus group number, gender of the participant and profession were displayed beside each quote to ensure the participant could not be identified.
Emotional distress

There was a possibility that some of the ICU survivors and their families could become distressed as they recalled traumatic events associated with their ICU stay however, this did not occur in my focus group interviews. In my experience of working as an ICU nurse and a committee member at the ICUsteps NI meetings, it was not likely to occur however, I was prepared to use my interpersonal skills to counsel these participants and provide support taking them into a private room if necessary, away from the group meeting. I was also prepared to encourage them to visit their General Practitioner (GP) for further help and advice.

Further study details

The study was sponsored by Queens University Belfast [Appendix C]. As discussed in the published paper, this research received favourable ethical opinion from the proportionate Review Sub-Committee of the East-Midlands-Nottingham Research Ethics Committee on 10 May 2016 16/EM/0208. [Appendix D]. Participants provided verbal and written consent prior to commencement of the focus group interviews. A copy of the protocol (Appendix E) patient information sheets (Appendices F and G) and consent forms (Appendices H and I) can be found in the appendices.

5.4 Discussion and conclusion

This bundle of non-pharmacological interventions may present a useful and relatively inexpensive approach to delirium management in critically ill patients. The four components were deemed feasible and acceptable to staff, ICU survivors and their families. However, like any complex intervention there will need to be adaptations made depending on the resources available to the particular ICU, especially regarding pharmacy involvement on the ward round and early mobilisation of patients with endotracheal tubes. In light of feedback from focus group interviews with staff additional components were added; education of staff, daily meetings with family to encourage orientation, family participation and cognitive stimulation. In addition, focus groups with ICU survivors and their family members provided useful information that was added to the intervention manual and education booklet about communication aids, legal rights etc. (Appendices J and K). ICU survivors and family members also suggested that to aid communication, there should be a dedicated box for materials and this should include picture boards and wide grip markers.
This approach was paramount to defining an intervention and has helped shape this bundle, which will be tested in a feasibility study. As a result of feedback from the focus group participants, the following components will not be included in the final intervention; pharmacy involvement on the ward round (not feasible without additional resources), early mobilisation of patients with endotracheal tubes (not feasible without additional resources). The final agreed intervention is detailed in the next chapter.
Chapter 6 Implementation

6.1 Introduction

Historically, implementation research failed to acknowledge the theoretical underpinnings of implementation and this may explain why evidenced-based interventions have failed to be translated into clinical practice \(^{(231)}\). In this research, the theoretical underpinnings of searching the literature and gaining feedback from staff, family and experts was essential to understanding implementation needs for the intervention.

The earlier chapters in this thesis have outlined a series of research studies that were used to define a complex intervention for delirium management in critically ill patients. Chapter Five delineated the methodology and results from focus group interviews with intensive care unit (ICU) staff, ICU survivors and their families. The findings from these interviews were used to modify my intervention, drawing on the perceptions of key care users and providers about feasibility of components of the intervention.

This chapter begins with an introduction to the field of implementation science before providing a thorough description of the intervention using the Template for Intervention Description and Replication (TIDieR) framework as a guide. Using this framework should help to ensure that the intervention will be implemented in the same manner by all users, with no confusion about who, what, when, where, how and why the intervention is delivered.

This chapter also provides an overview of important constructs of implementation science that could have potential implications for the success of this intervention in practice. A thorough insight into conceptual elements associated with the clinical environment may help me to develop a strong implementation plan. Understanding how staff members embrace change and respond to situations is integral to the success of this study and may help ensure that the evidence it generates is translated into practice.

Background

Implementation science is still in its infancy and there has been slow progress in linking it to evidenced-based practice \(^{(232)}\). Theories used to inform implementation science date back at least as far as the early 1960s \(^{(233)}\) and the Journal of Implementation Science was founded in 2006. However, given that it can take 17 years for Evidenced Based Practice (EBP) to be incorporated into healthcare \(^{(234)}\), improvements are needed to speed up this process. This is particularly challenging for the ICU setting because it is more difficult to achieve effective
implementation of guidelines or interventions in the ICU than in other clinical areas\textsuperscript{(235)}. Klein and colleagues observed that people who make ‘high stakes decisions’ in ‘highly complex environments’ react based on previous experience of analysing current stimuli and categorising the situation rather than applying any new actions or behaviours\textsuperscript{(236)}. Bassi and colleagues felt that this might explain why implementation of guidelines was poor in ICU\textsuperscript{(231)}. They suggested developing processes based on available evidence, but also specific to the needs of the unit or setting, to implement the intervention. Sinuff and colleagues observed that ICU staff are trained to respond quickly to alarms and changes in parameters and suggested that this should be taken into consideration when attempting to achieve a behavioural change in staff\textsuperscript{(237)}. From an education point of view, this information might be useful to inform the development of simulated scenarios to help staff develop experience working with a new intervention or idea before implementation into clinical practice.

While components of my intervention are evidenced based, the intervention bundle requires further testing. In addition, this bundle has many components and it will involve very complex implementation planning so it is essential that I choose an implementation framework that addresses the complex needs of this bundle.

Learning about what works and what does not work when implementing change can provide insight into implementation success. As I discuss later, culture can have a huge influence on whether an intervention or new idea will be adopted successfully in a given setting. Andre and Sjovoid compared work culture in a hospital unit that successfully implemented change with that in a unit that was unsuccessful in implementing change\textsuperscript{(238)}. They found that work culture was different in the successful unit in comparison to the unsuccessful unit in relation to the number of positive qualities. The successful unit had high scores for seven qualities: task orientation, caring, criticism, loyalty, acceptance, engagement and empathy and low scores for negative qualities such as resignation. The unsuccessful unit had high levels of self-sacrifice and resignation that were deemed as negative qualities and associated with a work culture of complaining, low confidence, passive behaviour and dissatisfaction. Using the Systematizing Person-Group Relations method, they found that a work environment that prioritises goal achievement and task orientation is better set up for implementing change\textsuperscript{(238)}. So how can I recreate the positive culture seen in the successful unit? Andre and Sjovoid suggest that promoting user input in the changes, promoting discussion and allowing staff to express opinions and having structured decision support in the implementation process is beneficial in creating a positive change culture. While considering the implementation of a complex intervention in
a complex environment, it is important to be appropriately prepared and aware of potential challenges. The first step in the implementation plan is ensuring there is a clear and concise description of the intervention and how it can be replicated. To achieve this goal, I have used the Template for Intervention Description and Replication (TIDieR) as detailed in the next section.

Template for Intervention Description and Replication (TIDieR)

I used a checklist to describe and define the multicomponent intervention to ensure a complete and accurate description of the interventions. Using this approach will allow future replication of protocols, interpretation of outcome results and investigation of dose response effects so that researchers achieve buy-in from fellow clinicians in translating evidence into practice. A review of intervention description of non-pharmacological interventions found that elements of the intervention were missing in 41 out of 80 studies in publications and even after contacting authors, treatment information was still missing for 19 studies\(^{(239)}\). A similar review of intervention description in 58 trials detailing 76 interventions for exercise training in peripheral vascular disease found none of the trials sufficiently described the interventions in a way that would enable replication\(^{(240)}\). This is concerning as it has a negative impact on the ability of clinicians to use the interventions correctly.

The quality improvement (QI) literature is awash with methodologies used to describe how QI interventions were applied in the clinical setting for example Plan-Do-Study-Act (PDSA), Lean, sigma, total quality management and continuous quality management\(^{(241)}\). Popular QI frameworks like the 6SQUiD advocate clarifying how an intervention will be delivered\(^{(242)}\) however, these methodologies often lack the structure required for applying complex interventions to the clinical setting for example targeting different risk factors simultaneously and maintaining engagement from staff throughout.

In direct response to the poor quality of intervention description in publications, an international group of experts and stakeholders developed the Template for Intervention Description and Replication (TIDieR) checklist and guide. This 12-item checklist contains explicit information about the delivery of all elements of the intervention in a format that supports the teaching of staff, as outlined below\(^{(243)}\). In the absence of a complete, sufficiently detailed description of an intervention, clinicians cannot reliably translate evidence into practice for interventions that have been shown to be effective and researchers cannot replicate or expand on the findings\(^{(244)}\). The TIDieR template can be
used as an extension for the CONSORT 2010 and SPIRIT guidelines (Equator network) in the report of the findings of a trial, but I have used it here to describe the intervention in advance of the trial (hence the non-applicability of some of the items at this time). An intervention manual will be provided to all staff during the training process (Appendix J).

6.2 Template for intervention description and replication (TIDieR)

The following template outlines the intervention guide and how it should be delivered.

**Intervention description using template for intervention description and replication (TIDieR)**

**Item 1. Brief name: Provide the name or a phrase that describes the intervention**

Development of Delirium non-pharmacological interventions in critically ill patients: a Feasibility study (DIGNIFY) multicomponent intervention

**Item 2. Why: Describe any rationale, theory, or goal of the elements essential to the intervention**

The theory for the development of this intervention was informed by MRC framework for the development of complex interventions. I conducted a systematic review of studies evaluating non-pharmacological interventions for delirium management in critically ill patients to determine which interventions were most effective for reducing the incidence and/or duration of delirium, based on a published protocol. Findings indicated a number of potentially effective interventions, some of which could be delivered singly or in combination. These findings were presented to a panel of international, multidisciplinary delirium experts at the 2016 Intensive Care Society State of the Art meeting in London, UK. Following discussion with the panel, a delirium bundle based on best evidence was designed to be tested in a feasibility study. The research team then used the following criteria to decide which interventions would be included in the bundle;

1. Interventions that have a positive effect on delirium incidence and/or delirium in randomised trials

2. Interventions that show benefit in non-randomised studies on delirium outcomes but have not been tested in randomised trials

3. Interventions identified by the expert panel
4. Interventions identified as feasible to deliver by staff, ICU survivors and their families in focus group interviews.

The theory is that interventions combined together to target multiple risk factors for delirium simultaneously work best with 6 or more complementary components \(^{(245)}\).
## Rationale

### Table 19 Strength of evidence for the bundle

<table>
<thead>
<tr>
<th>Elements</th>
<th>Strength of evidence from Systematic review</th>
<th>Acceptability by staff, family and experts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Education</td>
<td>Very low quality (4 non-randomised studies found beneficial results for delirium management by including education as part of a multicomponent intervention)</td>
<td>Deemed essential by staff and family.</td>
</tr>
<tr>
<td>PAD protocol</td>
<td>Low quality (4 non-randomised studies found beneficial results for delirium management when a PAD protocol was included)</td>
<td>Deemed important by staff.</td>
</tr>
<tr>
<td>Sedation minimisation</td>
<td>Low quality (4 non-randomised studies found beneficial results for delirium management when sedation minimisation was included)</td>
<td>Deemed of high importance to experts. Staff also agreed this should be included.</td>
</tr>
<tr>
<td>Physical and occupational therapy</td>
<td>Low quality (Two RCTs (one a pilot study) and five non-randomised studies showed a positive delirium outcome when physical and occupational therapy were included).</td>
<td>Deemed important by experts, staff and ICU survivors but concern raised about level of mobility that was feasible.</td>
</tr>
<tr>
<td>Sleep protocol</td>
<td>Low quality (Six non-randomised studies that included a sleep protocol found beneficial results regarding delirium management). Experts agreed to include.</td>
<td>Deemed important by experts, staff, ICU survivors and family and easy to deliver.</td>
</tr>
<tr>
<td>Orientation</td>
<td>Low quality (Five non-randomised studies found beneficial results for delirium management when an orientation protocol was included). Experts agreed to include.</td>
<td>Deemed important by experts, staff, ICU survivors and family and easy to deliver.</td>
</tr>
<tr>
<td>Communication</td>
<td>No evidence to support communication identified in SR.</td>
<td>Suggested by expert panel and deemed acceptable by staff and family. Family reported that this was an important component.</td>
</tr>
<tr>
<td>Cognitive stimulation</td>
<td>Low quality evidence (One small pilot RCT and two non-randomised studies found beneficial results for delirium management when cognitive stimulation was included)</td>
<td>Deemed important by experts, staff, ICU survivors and family and easy to deliver.</td>
</tr>
</tbody>
</table>
Although quality of the evidence is considered low or very low for the above interventions, I have used multiple methodologies to ensure the development of a robust intervention. I also plan to contribute further to the evidence by testing this in a feasibility study and subsequently in an RCT. There is insufficient evidence of effect rather than evidence of no effect. This study provides an opportunity to test interventions that provided a signal to benefit and that experts in delirium, patients, family and staff have endorsed as potentially effective. Therefore, I am using all methods available under the guidance of the MRC framework to enhance the evidence base for this intervention.

The rationale for proposed action of the interventions is that they target known risk factors for delirium; education and family participation (targets disorientation, impaired cognition and ensures management is activated in a timely manner by increasing awareness), sedation withdrawal (targets polypharmacy), effective pain relief (targets polypharmacy by allowing a reduction in sedative drugs), mobilisation protocol (targets immobility), sleep protocol (targets sleep deprivation), orientation (targets disorientation), communication (targets impaired cognition, disorientation) and cognitive stimulation (targets impaired cognition).

The goal of each component is as follows;

**Education and family participation**

The goal is to;

1. educate staff about delirium to enable engagement with delivery of the interventions (i.e. teaching staff that preventing or reducing delirium can have a significant impact on physical and cognitive function after ICU)

2. educate staff on how to provide education to family members for orientation of patients and assistance with aspects of care under direct supervision.

**Sedation minimization and PAD protocol**

The goal is to provide a protocol for nurses to follow to enable them to provide adequate pain management to patients while aiming for lighter levels of sedation.

**Early physical and occupational therapy**
The goal is to provide a protocol for nurses in collaboration with physiotherapists to follow to enable them to deliver optimal physical and occupational therapy to patients based on their ability and level of awareness.

*Environmental interventions for sleep, orientation, communication and cognitive stimulation*

The goal is to improve sleep by using a checklist, ensure patients are regularly orientated to their surroundings using a standardised approach and ‘this is me’ tool, use tools to improve communication and provide standardised exercises to ensure regular cognitive stimulation of the patient.

**Item 3. What (materials):** Describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in training of intervention providers. Provide information on where the materials can be accessed (for example, online appendix, URL)

*Education and family participation:*

Material required for;

**Staff training:** Laptop computer, PowerPoint presentation on delirium for staff and training on how to deliver family education and encourage family participation.

Intervention booklet outlining how to deliver the intervention (Appendix J). DIGNIFY poster (Appendix L).

**Family education:** Relative education booklet (Appendix K) outlining information about the unit, explaining what delirium is and what family members can do to help under direct supervision and other information that may be helpful for patients’ family members while their relative is incapacitated.

**Sedation minimisation and PAD protocol:**

Materials required: Intervention booklet, protocol for sedation minimisation, Laminated protocol pages with information on safety criteria and fail criteria for Spontaneous Awakening Trial (SAT). Full details on safety criteria are available on pages 3 and 4 of the intervention booklet.

*Early physiotherapy and occupational therapy:*

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Materials required: Intervention booklet outlining how to deliver each component of the intervention (pages 4 and 5), Resistance bands (1 package per patient), dumbbell 1kg. Arjo Sara Stedy (mobilisation device used to assist patients from sitting to standing - this product is in ward stock in most ICU’s).

Environmental interventions

(a) Sleep checklist to promote sleep

Materials required: one page checklist (laminated and kept at each bedscape) (Appendix M).

(b) Orientation:

Materials required Booklet: White board (to display ‘this is me’ information on the wall at the bedscape). A page with information on how to complete the ‘this is me’ board (Appendix N) [a one page document with information about the patient to aid communication with staff]. One page orientation checklist (laminated), clock and calendar.

(c) Communication:

Materials required: Tablets to access communication training for staff for e-learning module SPEACS 2 (http://nucleus.con.ohio-state.edu/media/speacs2/speacs.htm) and the following communication materials will be required: large grip markers (1 per patient), wipeable picture boards (A3 size or larger, one per bedscape), 1 box or trolley for storage.

(d) Cognitive stimulation:

Materials required: Cognitive stimulation booklet (Appendix O), answers booklet with information about the cognitive exercises, calculator (1 per bedscape), plasticine (1 tube per patient), Digiflex (an instrument to build strength in hands, one per patient), resistance bands (1 pack per patient) and dumbbells (1 kg size).

Item 4. What (procedures): Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities

The health technology being assessed is a multicomponent intervention non-pharmacological intervention for delirium management in critically ill patient incorporating education and family participation, sedation minimisation and pain, agitation and delirium (PAD), early physical and occupational therapy and environmental interventions.

1. Education and family participation:
The bedside nurse will firstly receive training on how to deliver this component of the intervention for ICU delirium champions. The bedside nurse will be instructed to give the family an education booklet [Appendix K] as soon as the patient is stabilised after admission and informed consent has been given. The bedside nurse will also provide the family with instructions on how to orientate the patient and this will be encouraged whenever they are visiting.

2. Sedation minimisation and PAD protocol:

The bedside nurse will assess safety criteria for sedation breaks daily.

The following suitability criteria will be assessed:

(a) Is the patient receiving a sedative infusion for active seizures or alcohol withdrawal?

(b) Is the patient receiving escalating sedative doses due to on-going agitation?

(c) Is the patient receiving neuromuscular blockade?

(d) Does the patient have evidence of active myocardial ischaemia in the previous 24 hours?

(e) Does the patient have evidence of increased intracranial pressure?

Patients who pass the screen undergo an SAT; all sedatives and analgesics used for sedation are interrupted. Analgesics needed for active pain are continued. Patients are monitored by staff for up to 4 hours or more for presence of failure criteria. Patients pass the SAT if they tolerated sedative interruption for at least 4 hours, and if they fail the SAT sedatives are restarted at half the previous dose and then titrated to achieve patient comfort.

Failure criteria:

i. Active seizures

ii. Alcohol withdrawal

iii. Neuromuscular blockade

iv. Evidence of increased ICP

v. Evidence of active myocardial ischemia in the previous 24 hours

vi. Sustained anxiety
vii. Pain

viii. RR > 35 bpm for at least 5 minutes

ix. Acute cardiac dysthymias

x. Two or more of the following, bradycardia, tachycardia, use of accessory muscles, abdominal paradox, diaphoresis or marked dyspnoea).

PAD protocol

The bedside nurse will also assess pain score [Numerical Rating Scale (NRS) (247) 0-10 with a score of 10 indicating worse possible pain and a score of 0 indicating no pain], sedation-agitation score (RASS), and delirium score (Intensive Care Delirium Screening Checklist ICDSC) (48,57).

3. Early physical and occupational therapy:

The physiotherapist or bedside nurse will assess safety criteria for physical rehabilitation using these criteria:

(a) Does the patient have a raised ICP?

(b) Does the patient have an active GI blood loss?

(c) Does the patient have an acute myocardial ischaemia?

(d) Does the patient have continuing procedures for example intermittent dialysis?

(e) Is the patient agitated and did they need increased sedative administration in the previous 30 min?

(f) Does the patient have an unsecure airway?

(g) Is the patient distressed? (evidenced by non-verbal cues or gestures)

(h) Is the patient being physically combative?

(i) Is there a new arrhythmia?

(j) Is there a concern for myocardial ischemia?

(k) Is there a concern for airway integrity?

If the answer to any of these questions is ‘yes’, the patient fails the safety screen, no early mobilisation should be performed and the patient should be reassessed the following day.
Unresponsive patients undertake passive range of motion exercises. Therapy will be delivered by a physical therapist or a nurse in consultation with a physiotherapist and coordinated with daily interruption of sedation. Once patient interaction is achieved, sessions progress to active range of motion exercises, bed mobility, sitting/ balance, transfer training and finally pre-gait exercises and walking as tolerated. Progression of activities will be dependent on patient tolerance and stability. Therapy intervention continues on a daily basis throughout the patient’s hospital stay until he or she returns to a previous level of function or is discharged.

Early mobilisation will be discontinued if the patient has;

1. MAP < 65 mmHg or more than 110 mmHg
2. SBP > 200 mmHg
3. HR < 40 bpm or > 130 bpm
4. RR < 5 BPM OR > 40 BPM
5. Pulse oximetry < 88%

Positioning

Daily discussion between physiotherapist and nurse regarding devices for a comfortable position, as well as support elements used for the prevention of pressure ulcers, decreased range of motion and foot drop.

Activities of daily living

The ICU staff nurse or physiotherapist will encourage relatives to support the patient with grooming, dressing and personal care activities to foster independence.

4. Environmental

(a) Sleep checklist.

Daytime interventions:

• In the morning from 7am, the nurse will raise the blinds/ open curtains/ turn on lights. Staff will also discourage long period of napping throughout the day.

Night-time interventions:
- After 11pm, the nurse will dim lights, turn off televisions, reduce alarm volumes where applicable, offer soft music, earplugs and eye masks to patients who are alert and ensure patients are warm and pain free. Sedated patients may like music as well and this should be discussed with close family members.

(b) Orientation

(i) Verbal and written Information on ‘This is me’ boards should be given to family by the bedside nurse as soon as patient is admitted to ICU and stabilised so they can complete the board. The bedside nurse will provide the family with a template for the ‘This is me’ sheet and instructions on how to complete this. A relative will then complete the patient’s preferred names, likes and dislikes and the board will be displayed in the patient room. (Appendix N).

(ii) A clock and calendar with date and time will be displayed at the bed space in the patient’s view.

(iii) Staff and relatives will use the reorientation strategy (information was provided to families in the education booklet). Staff will be encouraged to call the patient by their first name as often as possible and to give them information about the ward, hospital, illness progression, length of stay and recent clinical findings, date and time and family details.

Reorientation strategy to be delivered by medical, nursing and multidisciplinary staff at each interaction with the patient

- Who you are?

- What happened to them?

- When it happened?

- Where they are?

- Why it happened?

- How it happened?

(c) Communication

Staff will be encouraged to undertake an e-learning communication module (SPEACS 2) and provided with communication tools (e.g. picture boards). They will also encourage
families to use the communication tools when they are trying to communicate with the family.

(d) Cognitive stimulation

(i) If the patient has a RASS score of -1 to +1, nurses or family members will do exercises with the patient to activate mental functions. These are grouped into the following areas: alertness, visual perception, memory, calculus, problem solving, praxis, and language aiming for 15 minutes twice a day. Each patient will be given a booklet for cognitive exercises. The number of minutes achieved will be recorded.

(ii) Families will be encouraged to bring in eye glasses and hearing aids if these are needed by the patient. This information will be detailed on the white board.

Item 5. Who provided: For each category of intervention provider (for example, psychologist, nursing assistant), describe their expertise, background and any specific training given

1. Education and family participation:

Initially local delirium champions (Staff nurses with at least 6 months working in ICU with a special interest in delirium) will deliver education to all regular nursing staff working in the ICU and provide them with the knowledge and skills required to educate families of critically ill patients to participate in the patient’s care through orientation, communication and cognitive stimulation.

2. Sedation minimization and Pain, agitation and delirium protocol (PAD):

ICU medical and nursing staff will be provided with education on the protocol by local delirium champions (how to assess pain, agitation and delirium). An SBT can be undertaken by an appropriately qualified member of clinical staff who has previously been involved in this aspect of clinical practice following safety criteria, this may include medical and nursing staff and will be conducted according to unit policy.

3. Early physical activity and occupational therapy

This will be delivered by the bedside nurse and physiotherapist allocated to the patient. They will have received training on the protocol from local delirium champions.

4. Environmental
(a) Sleep. Delivered by ICU bedside nurse. Other MDT members (medical staff, porters, domestic staff, physiotherapy, radiographers) will also be asked to respect elements of this bundle by keeping noise levels and lights down at night time. This will be enforced by the bedside nurse with signage displayed on all external doors.

* Pagers to silent
* Night mode on machines
* Soft shoes
* Fix noisy trolleys

**Quiet Hospitals Help Healing**

**Help Us Keep The Noise Down**

Figure 11 MDT education poster for noise reduction

(b) Orientation. Delivered by bedside nurse and other disciplines looking after the patient (doctors, physiotherapists, dieticians etc., staff and patients’ relatives.

(c) Communication. Training will be delivered by an e-learning module and a communication box will be available in ICU for bedside nurses and patients relatives to access.

(d) Cognitive stimulation: Delivered by ICU bedside nurse and/or the patient’s relatives under the supervision of ICU bedside staff nurse (Appendix O).

Item 6. How: Describe the modes of delivery (such as face-to-face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group

The active training period will involve a multi-faceted approach involving education for all clinical staff involved in delirium management of critically ill patients. Face to face group training will be delivered by the local delirium champions via a PowerPoint presentation and scenario-based workshops using the intervention materials and sample scenarios (3 hours). This training will be repeated yearly or as required (for example when new staff commence employment in the unit or compliance with protocol reduces). Additional implementation and sustainability tools will include posters and reminders (These will be embedded into the electronic charting system). The one-hour communication e-learning module will be available via a URL on a Health and Social Care Trust computer. This training
will be a one-off training session. Staff will print a certificate once this has been completed and this will be recorded.

**Item 7. Where:** Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features

The interventions will be delivered at the bedside in the intensive care unit. The presentations and workshops will be delivered in the seminar room.

**Item 8. When and how much:** Describe the number of times the intervention was delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity or dose

- **Staff & relative education**
  
  Once off with updates as required for staff.

  On admission and daily reminders for relatives.

- **Sedation protocol**
  
  Once daily

- **Mobilisation**
  
  Once daily

- **Environmental**

  - **Sleep** – twice a day- morning and night-time
  
  - **Orientation**- several times a day (with patient interactions)
  
  - **Communication**- several times a day (with patient interactions)
  
  - **Cognitive stimulation** twice day for 20 minutes

**Item 9. Tailoring:** If the intervention was planned to be personalised, titrated or adapted, then describe what, why, when, and how

The protocol can be tailored to facilitate available ICU resources for example; if there are sufficient physiotherapy staff then mobilisation of patients with endotracheal tubes can occur and if there is sufficient pharmacy cover then they can attend rounds with the clinical team and suggest less deliriogenic drug alternatives for patients at risk of delirium.
Item 10. Modifications: If the intervention was modified during the course of the study, describe the changes (what, why, when, and how)

Not applicable at this time.

Item 11. How well (planned): If intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity

Fidelity should be monitored and adherence measured in the following ways:

1. Completion of a compliance checklist by the ICU bedside nurse (Appendix P)

2. Questionnaire completed by ICU staff involved in the delivery of the intervention to complete after the post-implementation phase to determine;

   (i) Reasons for non-adherence to the intervention

   (ii) Feasibility of individual components of the intervention

   (iii) Perceived effectiveness of the intervention

   (iv) Perceived barriers to delivery of the interventions

   (v) Perceived facilitators to delivery of the interventions

Item 12: How well (actual): If intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned

Not applicable at this time.

6.3 Implementation planning

Implementation ‘refers to what a program consists of when it is delivered in a particular setting’ (248). Few studies provide information on implementation of interventions and most studies do not relate implementation strategies to outcomes (249 – 251). Several elements need to be considered for successful implementation of the intervention and these should be formally assessed to ensure its internal and external validity.

Durlak and DuPre identified eight aspects of implementation that they consider important for implementation of interventions; fidelity, dosage, quality, participant responsiveness, program differentiation, monitoring of control/comparison conditions, program reach and adaptation. In particular, they noted that assessment of fidelity and dosage were associated with better outcomes (252).
In this chapter, I focus on the elements that are most pertinent to the success of implementation of a multicomponent non-pharmacological intervention for delirium management in critically ill patients. My aim is to identify a framework that raises awareness of potential influences on my implementation strategy, facilitates in depth analysis of important processes to follow and outcomes to consider and provides a prescriptive process to guide the implementation plan. As there is currently a large amount of evidence published on constructs to consider for implementation of interventions, the use of a framework may be helpful to avoid confusion and mould the implementation process.

Implementation science increasingly relies on the use of theoretical approaches to determine the reasons why an intervention does or does not work \[^{231}\]. Nilsen and colleagues divided these approaches into five categories; process models, determinant frameworks, classic theories, implementation theories and evaluation frameworks \[^{231}\]. For the purpose of my research, I am going to focus on process models, classic theories and implementation theories as these are more pertinent to the needs of my research. As evaluation is beyond the scope of this project, evaluation frameworks will not be discussed in this section. I start with a brief overview of the four categories of theoretical approaches to implementation science and then discuss my reasons for choosing the model I am using to implement the DIGNIFY bundle.

**Process models**

The aim of process models is to direct the process of translating research evidence into practice by explicitly describing each stage including implementation \[^{231}\].

An example of a process model is the model developed by Pronovost and colleagues, which combines clear methods for translation of knowledge into practice into a model for wider dissemination \[^{252}\]. There is significant overlap with this model and the framework that was utilised in this project for the development of this complex intervention. The model has four steps; summarise the evidence, identify local barriers to implementation, measure performance, ensure all patients receive the intervention and implement the four P is; engage, educate, execute and evaluate. This is depicted in figure 12 below. The first three steps are very similar to the MRC model for the development of complex interventions in summarising the evidence and identifying barriers. Although the success of this QI model was not formally assessed, Pronovost and colleagues hypothesised that the use of ‘tragic
real stories’, valid evidence measures and results, social support and local ownership were instrumental to its success\(^\text{252}\).  

![Figure 12 Pronovost model for translating evidence into practice.](image)

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This model is applicable to the implementation of interventions in critical care and has been used in a study of early physical activity and rehabilitation with positive results\(^\text{177}\).

I feel that the Pronovost model for translating evidence into practice is an excellent model and I would consider using this model for the DIGNIFY study as it is simple to follow and provides a methodical process for implementation that can be easily taught to others. This model may provide a plausible link between development of an intervention and implementation that is a simple to follow however, I would have concerns that it may lack the prescriptiveness required to meet the complex needs of my project and generalisability for future implementation plans.
Determinant frameworks

Determinant frameworks identify individual determinants that act as barriers or facilitators to achieving implementation outcomes \(^{(231)}\). Their aim is to identify the influences of implementation outcomes. Examples of this framework would include The Context and Implementation of Complex Interventions (CICI) framework and the PARiHS framework for guiding the implementation of evidence-based practice \(^{(253,254)}\). As a huge proportion of my work under the guidance of a development framework has allowed for the exploration of determinants then I feel these frameworks do not meet the needs of this project i.e. setting a plan in process that will clearly outline how I will implement and engage staff in delivering this intervention. These frameworks overlap with the MRC framework and do not have enough focus on how to develop an implementation plan or the steps to consider before you implement an intervention.

Classic theories

Classic theories developed from social sciences can be used to provide insight into important aspects of implementation in health care \(^{(231)}\). One such example is Rogers theory of diffusion, which outlines five categories of innovators to indicate how innovation is adopted; innovators, early adopters, early majority, late majority and laggards. Innovators are usually happy to take risks and are usually the first to start acting on a new idea. Early adopters tend to be respected in their social system and are respectful of their peers. The early majority are deliberators who will not adopt an idea until more senior people have accepted it and it has been proved successful. On the other hand, the late majority tend to be sceptical. They doubt the success of an intervention but are eventually convinced by peers. Finally, laggards are ruled by tradition and are often unwilling to accept new ideas or interventions even after they have become commonplace \(^{(233)}\).

Identifying categories of innovators is useful when considering how to engage staff in the implementation process however, this is only one element of the implementation plan and fails to consider other potential influences.

Implementation theories

Implementation theories are developed from infancy by implementation researchers or modified from current theories to provide insight into aspects of implementation \(^{(233)}\). An example would be normalisation process theory, which focuses on the ways to embed and sustain interventions in practice and sheds light on why some interventions become part of
normal practice while others do not \(^{(255)}\). Normalisation process theory is another excellent option that suits the needs of my research project to identify a way to plan the introduction of a complex intervention that needs embedded into normal practice.

Another example of an implementation framework is the Consolidated Framework for advancing Implementation Research (CFIR), which provides structure for approaching implementation of a complex intervention. It is composed of five domains; intervention characteristics, outer setting, inner setting, characteristics of the individuals involved and the process of implementation \(^{(232)}\). This framework guides the individual through all the different influences on implementation of an intervention to the development of an in-depth process plan for implementation.

Although the CFIR framework is lengthy, it is extremely thorough and provides an excellent guide for identifying potential influential factors for implementation in any organisation. I believe this framework could meet the needs of the DIGNIFY study as my intervention is highly complex and needs this level of structure to formulate an implementation plan.

6.4 Discussion

Preparing an implementation plan is an important step before the introduction of a new, complex intervention. My examination of the literature on implementation science identified a number of conceptual theories and frameworks that might be useful when seeking to ensure successful implementation and sustainability of a complex intervention in practice. I have reviewed these frameworks in this chapter and described concepts that are important to implementation science.

Use of theoretical frameworks for implementation have increased in recent years, but researchers are not necessarily using all the elements of the frameworks. Not all elements are applicable for every study but researchers need to be explicit about what elements of the framework they have used and give their reasons for selecting specific dimensions and for not selecting others.

After in-depth exploration of the published frameworks discussed above, I chose to use the consolidation framework for implementation research (CFIR) to forge out a plan for the implementation of my complex intervention \(^{(232)}\). This plan can be found in appendix Q. I chose this framework as it originated in health services research. The framework is straightforward, simple to follow and can be explained simply which enhances generalisability. The CFIR enables the researcher to identify all potential influential factors
separate to those directly involved. In addition, use of this model allow explicit understanding of potential influences on change and guides exploration of change processes and contextual factors for success or failure. The CFIR constructs for the DIGNIFY study are available in Appendix Q. Use of this framework guides planning, tailoring, implementation, strategy and evaluation and therefore the inclusion of additional models for evaluation are not necessary.

Normalisation process theory is an excellent theory for the implementation of complex interventions in a healthcare setting however I choose the CFIR framework as I felt it was more prescriptive and could be used a guide by any critical care unit to ensure that all eventualities were considered prior to the implementation of a complex intervention.

Using the CFIR framework has allowed me to identify external and internal influences on the success of a multicomponent intervention. The framework provides a structure to help identify these individual influences that feeds into a process plan. In relation to my research study, the plan included engaging management and staff through early planning meetings, presentation and blended learning approaches including on-line learning and face-to-face workshops. In addition, my plan included recruiting opinion leaders from all disciplines who were highly respected by their peers, a persuasive leader who would chair discussions and ensure feedback was acted upon, external change agents (outside delirium experts coming to speak as well as patient representatives). The execution plan included training as previously mentioned and development of an intervention booklet outlining how the intervention should be delivered and additional resources on safety criteria to guide delivery of the interventions. In regards to reflecting and evaluating my plan included weekly meetings with opinion leaders to act upon informal feedback from staff and plans for post implementation interviews.

In addition to identifying important constructs to be considered using my chosen framework, a systematic review by Trogrlic and colleagues examined the success of implementation strategies for complex interventions. The group found that four studies that showed a reduction in delirium used all or some of the following strategies; 100% used educational meetings and patient mediated interventions, 75% used local consensus, outreach and distribution of educational materials, 50% used opinion leaders, reminders and provider orientated interventions and 20% used peer review, structural interventions, audit/ feedback and tailored interventions. This evidence guided me to incorporate educational meetings, local consensus, development of educational materials such as
One particular strength of the non-pharmacological intervention developed in this programme of research is the robust methodology used to define it. This included a systematic review and meta-analysis to determine which interventions were effective in reducing incidence and/or duration of delirium in critically ill patients and qualitative interviews with key researchers, clinicians, service providers and users; as presented in earlier chapters. Another strength is the use of an explicit framework in this chapter to describe the intervention in detail to ensure consistent delivery of each component.

However, it is also important to acknowledge some limitations of the intervention. These include the lack of robust randomised trials of non-pharmacological interventions. Although my systematic review and meta-analysis did identify relevant randomised trials, the majority of studies that found non-pharmacological interventions to be associated with improved delirium outcomes were non-randomised studies and may have failed to account for all potential confounding factors.

In addition, it could be argued that standard of care interventions (sedation withdrawal or mobilisation) should not be included in a delirium bundle for a trial as they should already be delivered to all patients. Although recommended in PADIS guidelines, there is evidence that non-pharmacological interventions such as mobilisation, sedation withdrawal and environmental interventions are not consistently implemented in ICUs\(^ {245}\). If the extent of mobilisation requires physiotherapist involvement this may add to cost depending on ICU resources however in many ICUs mobilisation can also be delivered by nursing staff. It can be argued that by focusing only on those interventions that are not considered standard of care, compliance with the overall bundle may be improved. However, if standard of care is not consistently implemented, this may result in confounding. For example if some ICUs use a sedation withdrawal protocol as standard of care and others do not this may impact on rates of delirium. The outcome might be a direct result of using less sedation rather than being related to the actual interventions being studied. Therefore, it makes sense to include sedation and mobilisation in the intervention.

The TIDieR framework was chosen to describe the intervention, but the format and length of this framework may make it difficult to publish in some journals and the full framework may need to be included in supplementary material or made available on a website. Finally,
there may be additional implementation science constructs that are pertinent to the success of multicomponent interventions for delirium in critically ill patients, which have not been identified or discussed in this chapter.

6.5 Conclusion

A thorough knowledge of potential barriers and facilitators to implementation is helpful for planning. However, the list is never exhaustive and it is always important to be vigilant in the early stages of implementation of a new intervention and acknowledge any context specific issues that might arise and deal with them promptly. Using a structured framework like the CFIR is a good defence against failed implementation plans. Further exploration is required on the best ways to manage change and achieve buy-in from staff in the ICU environment.

There are important elements to consider when planning the implementation of a complex intervention. The availability of frameworks for intervention description are sparse and I chose the TIDIER framework because it explicitly describes components of the intervention, providing sufficient information to facilitate the transfer of knowledge into practice and facilitate training on this complex intervention. Consideration and reporting of constructs such as context, fidelity and dose enhances internal and external validity of the interventions. While the monitoring of implementation progress will help ensure that any unanticipated influences are identified early and dealt with effectively.

The full implementation plan is available in Appendix Q
Chapter 7 Protocol for Feasibility Study

7.1 Introduction

Previous chapters (3, 4 and 5) outlined the steps that were undertaken to define the multicomponent intervention using evidence from a systematic review and meta-analysis. The intervention was then refined based on the opinion of international delirium experts, ICU staff, ICU survivors and their families. The previous chapter (chapter 6) also provided a definition of the intervention using the template for intervention description and replication (TIDIER) document to provide a clear and concise explanation of what the intervention components entail, who will deliver the intervention and where, when, why and how the intervention will be delivered in clinical practice.

In accordance with the MRC guidelines for feasibility/ piloting in the development of a complex intervention, this chapter presents the ethics approved study protocol for a feasibility study (inserted in PDF format in this chapter). The aim of this feasibility study is to determine if a multicomponent intervention for delirium management in critically ill patients is feasible to deliver in the clinical setting. The rationale for choosing a before and after non-randomised study design for the feasibility study was because the intervention is complex with multiple components. The feasibility study would allow me to determine what worked, what did not work, was there compliance with each component and if not, why? The rationale is discussed further in the protocol. In addition, this design is ideal for testing feasibility outcomes like adherence to completion of tools that will be used to collect outcome measures in the subsequent RCT trial and functionality of the case report file (CRF), training manual and protocols.

Feasibility studies ‘are studies designed to build the foundation for the planned intervention study’ (256). In order to carry out this feasibility study, the barriers and facilitators to implementation of these interventions that were identified in the systematic review and the focus group interviews have been addressed. A robust training manual for staff and an education programme to include family participation and training has been developed (Appendix J).

The protocol was peer reviewed by Dr Jon Silversides (Consultant Anaesthetist and Researcher in Intensive Care Medicine) and Dr Jennifer McGaughey (Nurse Lecturer and Researcher in Intensive care) and submitted to a research ethics committee where it received favourable opinion (Appendix R). Both researchers were chosen due to their clinical expertise and experience of research trials of critically ill patients.
The aim of the feasibility study is to determine if there is adherence to components of the intervention and completion of outcome measures and to identify any barriers and facilitators to the delivery of the interventions in practice.

This chapter has been structured with an introduction and a final version of the ethically approved protocol has been embedded to ensure a logical flow to this chapter. The chapter concludes with a discussion and conclusion section.
Using a delirium non-pharmacological bundle in critically ill patients: a feasibility study

**DIGNIFY**

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<th>Queen's University Belfast</th>
</tr>
</thead>
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<td>IRAS code 243189</td>
</tr>
<tr>
<td>Version Number / Date:</td>
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<tr>
<td>Research Ethics Committee (REC) Reference Number</td>
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</tr>
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<td>Funder reference number:</td>
<td>EAT/ 5092/14</td>
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<td>List of Amendments to Date:</td>
<td></td>
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<tr>
<td>Chief Investigator:</td>
<td>Professor Bronagh Blackwood, Wellcome-Wolfson Institute for Experimental Medicine, Queen's University of Belfast, Welcome Wolfson Building, 97 Lisburn Road, Belfast, BT9 7BL</td>
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**PROTOCOL AUTHORISATION**

<table>
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<th>Full Protocol Title:</th>
<th>Delirium non-pharmacological interventions for critically ill patients: a feasibility study (DIGNIFY)</th>
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<tr>
<td>Protocol Amendments:</td>
<td></td>
</tr>
</tbody>
</table>
A review of the protocol has been completed and is understood and approved by the following:

_____________________________  ________________________________

_____________________________  ________________________________

Bronagh Blackwood  Signature  01 /  03 /  2018
Chief Investigator Name  Date
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# Abbreviations

## List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation / Acronym</th>
<th>Full Wording</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>Adverse event</td>
</tr>
<tr>
<td>APACHE</td>
<td>Acute Physiology and Chronic Health Evaluation</td>
</tr>
<tr>
<td>AR</td>
<td>Adverse reaction</td>
</tr>
<tr>
<td>BHSCT</td>
<td>Belfast Health and Social Care Trust</td>
</tr>
<tr>
<td>CI</td>
<td>Chief investigator</td>
</tr>
<tr>
<td>CRF</td>
<td>Case report form</td>
</tr>
<tr>
<td>CV</td>
<td>Curriculum vitae</td>
</tr>
<tr>
<td>DoH</td>
<td>Department of Health</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>HRA</td>
<td>Health Research Authority</td>
</tr>
<tr>
<td>ICDSC</td>
<td>Intensive Care Delirium Screening Checklist</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonisation</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive care unit</td>
</tr>
<tr>
<td>IRAS</td>
<td>Integrated Research Application Service</td>
</tr>
<tr>
<td>ISF</td>
<td>Investigator site file</td>
</tr>
<tr>
<td>Main REC</td>
<td>Main Research Ethics Committee providing ethical approval for the study</td>
</tr>
<tr>
<td>MMS</td>
<td>Manchester Mobility Scale</td>
</tr>
<tr>
<td>NHS</td>
<td>National Health Service</td>
</tr>
<tr>
<td>NICTU</td>
<td>Northern Ireland Clinical Trials Unit</td>
</tr>
<tr>
<td>NIHR</td>
<td>National Institute for Health Research</td>
</tr>
<tr>
<td>NRES</td>
<td>National Research Ethics Service</td>
</tr>
<tr>
<td>PC</td>
<td>Personal Consultee</td>
</tr>
<tr>
<td>PI</td>
<td>Principal investigator</td>
</tr>
<tr>
<td>PMG</td>
<td>Project Management Group</td>
</tr>
<tr>
<td>QUB</td>
<td>Queen's University Belfast</td>
</tr>
<tr>
<td>RAD</td>
<td>Research and Development</td>
</tr>
<tr>
<td>RASS</td>
<td>Richmond Agitation Sedation Score</td>
</tr>
<tr>
<td>REC</td>
<td>Research Ethics Committee</td>
</tr>
<tr>
<td>RCSQ</td>
<td>Richards Campbell Sleep Questionnaire</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious adverse event</td>
</tr>
<tr>
<td>SCCM</td>
<td>Society of Critical Care Medicine</td>
</tr>
<tr>
<td>SDV</td>
<td>Source data verification</td>
</tr>
<tr>
<td>SMF</td>
<td>Study master file</td>
</tr>
<tr>
<td>SOP</td>
<td>Standard operating procedure</td>
</tr>
<tr>
<td>SSCC</td>
<td>Study Steering Committee</td>
</tr>
<tr>
<td>TiMeR</td>
<td>Template for Intervention Description and Replication</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
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</table>
LAY SUMMARY

Delirium can be described as a change in a person’s attention and awareness which develops over a short period of time. Patients in the Intensive Care Unit (ICU) have a high risk of developing delirium due to the severity of their illness. In the ICU, delirium is associated with high risk of death and long-term damage to brain function, but the amount of research directed at the subject has not matched this burden that it brings to patients, their families and the health service.

Traditionally, many delirium studies have focused on drug treatments but we don’t know if a group of non-drug interventions might be more beneficial for trying to both prevent and treat delirium in the ICU. We developed such a bundle by first of all doing a complete review of the research that has been published on non-drug interventions for delirium in ICU. A group of delirium experts then helped us to decide how to make best use of our findings. We also involved ICU staff, who would be delivering the interventions in the ICU, as well as patients who had been cared for in ICU and their families. This involvement took the form of meetings of groups of 4-12 people who discussed specific issues relating to the project. This allowed us to decide if the non-drug interventions described in the literature are practical and acceptable to ICU staff, ICU survivors and their families.

By combining the findings from the review, expert panel and discussion groups we were able to decide on what should be in the bundle. We will now test this in a pilot study, which will take place over six months in a 25-bed Intensive Care and High Dependency Unit.
**STUDY SUMMARY**

<table>
<thead>
<tr>
<th>Study Design:</th>
<th>Prospective before and after feasibility study</th>
</tr>
</thead>
</table>
| Study Aims and Objectives: | Trial aims and objectives: The aim of this study is to determine if it is feasible to deliver a multicomponent non-pharmacological intervention for delirium management.  
Objective 1: To determine adherence rates to the interventions  
Objective 2: To evaluate the adherence to completing the assessment tools i.e. RASS, ICDSC, Manchester Mobility scale.  
Objective 3: To determine barriers and facilitators to the delivery of a multicomponent intervention for delirium management in ICU. |
| Study Intervention: | A multicomponent non-pharmacological protocol-based intervention incorporating education, sedation minimization, early physical and occupational therapy and environmental interventions. |
| Comparator | Standard care. |
| Primary Outcome: | The number of days in which staff followed the protocol out of the total number of days studied. |
| Secondary Outcomes: | 1) Sleep quality as measured by Richards Campbell Sleep Questionnaire (RCSQ).  
2) Incidence and duration of delirium, as measured by the Intensive Care Delirium Screening Checklist.  
3) Mobility score measured by the Manchester mobility scale  
4) Sedation score measured by Richmond Agitation Sedation Score (RASS).  
5) Safety and tolerability as assessed by the occurrence of adverse events. |
| Study Setting: | A 25-bed Intensive Care Unit (ICU) in Belfast Health and Social Care Trust. |
| Study Population: | Adult patients admitted to a critical care unit and fulfilling eligibility criteria for the study. |
| Sample Size: | As this is a feasibility study, a formal sample size calculation has not been done. |
| Study Duration: | 6 months. |
# STUDY TEAM

| Chief Investigator: | Professor Bronagh Blackwood  
| Chair in Critical Care,  
| Welcome-Wolfson Institute  
| Centre for Experimental Medicine  
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| | Professor Daniel F McAuley  
| Professor of Intensive Care Medicine and Consultant Intensivist in Critical Care  
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| | Professor Mike Clarke  
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| Trial Statistician: | Biostatistician (to be named)  
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| Royal Hospitals  
| Grosvenor Road, Belfast, BT12 6BA |
| Study Sponsor: | Queen's University Belfast  
| Mr Stephen Liggett  
| Research Governance Manager  
| Research and Enterprise Directorate  
| 83 University Road, Belfast, BT7 1HF |
BACKGROUND & RATIONALE

Background information

Delirium is a common devastating clinical syndrome typically characterised by inattention and impaired cognition that fluctuates throughout the course of the day (1). Delirium is associated with increased mortality, increased length of mechanical ventilation, increased length of hospital and intensive care unit (ICU) stay, increased costs and long term cognitive and functional problems (2-4,5). It has a prevalence of 30-85% in critically ill patients (6,7). The high incidence, mortality, long-term consequences and high economic costs mean that delirium is an important healthcare problem (8). The exact mechanisms of action are unknown but it is hypothesized that neurotransmitter imbalance or neuroinflammation may play a role (9). Several risk factors are associated with the development of delirium in the ICU (10,11). These include predisposing factors such as age, cognitive, hearing and visual impairment. Precipitating factors are disturbed laboratory blood values, surgical interventions, drugs and having multiple comorbidities. A validated prediction model (E-PRE-DELIRIC) identifies ten predictors of delirium (12). This model provides ICU clinicians with the opportunity to identify patients likely to develop delirium during their ICU admission and allows early delirium prevention interventions to be applied. The high incidence and mortality and morbidity associated with delirium mean it is an extremely important healthcare problem.

Rationale for the study

We conducted a systematic review of studies evaluating non-pharmacological interventions for delirium management in critically ill patients to determine which interventions were most effective for reducing the incidence and/or duration of delirium (13). Findings indicated a number of effective interventions, some that could be delivered singly or in combination (14-20). These findings were presented to a panel of international, multidisciplinary delirium experts for agreement at the 2016 Intensive Care Society State of the Art meeting in London, UK. Following discussion with the panel, a delirium bundle based on best evidence was designed to be tested in a feasibility study.

The Template for Intervention Description and Replication (TIDier) framework was used to define the intervention (21). We set the following criteria a priori to decide which interventions would be included in the bundle;

1. Interventions that have a positive effect on delirium incidence and/or duration in randomised trials
2. Interventions that show benefit in observational studies on delirium outcomes but have not been tested in randomised trials
3. Interventions identified by the expert panel
4. Interventions identified as feasible to deliver by staff, ICU survivors and their families in focus group interviews.

Rationale for the intervention

The intervention being assessed is a multicomponent non-pharmacological intervention incorporating education and family participation, sedation minimization, early physical and occupational therapy, patient, staff and relative education, orientation, communication and sleep promotion.

There is evidence from other patient populations that non-pharmacological interventions may have a role in reducing the incidence and/or duration of delirium (22-24). When combined together to target multiple risk factors for delirium simultaneously, there is evidence that
multicomponent interventions work best with six or more complementary components (25). Standard care for delirium management in ICU is inconsistent, with many ICUs using pharmacological treatment despite limited evidence (23).

Guidelines from the Society of Critical Care Medicine (SCCM) and the National Institute of Health and Care Excellence (NICE) provide recommendations for non-pharmacological interventions such as early mobilisation and sedation minimization (27, 28). Our systematic review found that early physical and occupational therapy, sedation minimization, education, orientation and cognitive stimulation and sleep promotion may be helpful for delirium management in the critically ill population (14-20). It is unclear if a multicomponent non-pharmacological intervention is feasible to deliver in critically ill patients therefore we plan to test this strategy to determine compliance and identify barriers and facilitators. Our intervention was defined using the TIDieR framework and the manual will be available to staff when the intervention training commences (21).

**Description of the intervention**

<table>
<thead>
<tr>
<th>Multicomponent intervention</th>
<th>Frequency</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Education</strong> for staff on how to teach family members to orientate their loved ones in the ICU and assist with personal care activities. Daily meeting with families to encourage family participation.</td>
<td>Prior to implementation and weekly updates</td>
<td>Daily</td>
</tr>
<tr>
<td><strong>Sedation minimisation</strong></td>
<td>Daily</td>
<td>1-2hours</td>
</tr>
<tr>
<td>A protocol that mandates a daily sedation interruption based on safety criteria. This is standard practice in many UK ICUs.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Physical therapy</strong></td>
<td>Daily</td>
<td>30 minutes</td>
</tr>
<tr>
<td>Progressive from range of motion exercises to sitting, standing and walking based on safety criteria. Variations of this are standard practice in many UK ICUs.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Environmental interventions</strong></td>
<td>Daily</td>
<td>10pm – 6am</td>
</tr>
<tr>
<td>- Sleep checklist to promote sleep</td>
<td>Daily</td>
<td>Variable</td>
</tr>
<tr>
<td>- Orientation to time/ place/ person</td>
<td>Daily</td>
<td>Variable</td>
</tr>
<tr>
<td>- Communication training (non-verbal)</td>
<td>Daily</td>
<td>30 mins (2 x 15 mins)</td>
</tr>
<tr>
<td>- Cognitive and multisensorial stimulation</td>
<td>Daily</td>
<td></td>
</tr>
</tbody>
</table>
STUDY AIMS AND OBJECTIVES:

Study Aim

The aim of this study is to test the feasibility of delivering a multicomponent non-pharmacological intervention comprising education and family participation, sedation minimization and Pain, Agitation and Delirium (PAD), early mobilisation and environmental interventions for delirium management in critically ill patients. This will be tested in a before and after feasibility study.

Study Objectives

Process feasibility outcomes

- To determine adherence rates to all components of the intervention by staff/relatives
- To determine the barriers/facilitators to delivery of the interventions

Study feasibility outcomes

- To determine recruitment and retention rates for patients
- To evaluate the feasibility of completing the data collection tools i.e. RASS, ICDSC, Manchester Mobility scale.
- To measure delirium incidence using the ICDSC tool daily to assist sample size calculation for the subsequent larger trial
STUDY DESIGN

Study Design
This will be a prospective, observational, single centre feasibility study of a complex intervention for delirium management in critically ill patients.

Study Flow Diagram

Baseline Measurements (12 weeks)
- Demographics
- Assessments

Intervention training for staff (4 weeks)
- Didactic lectures
- One to one training on orientation/ cognitive stimulation and train the trainer

Post intervention Data Collection (12 weeks)
- Demographics
- Assessments
- Adherence to components of the interventions

Follow up
- to ICU discharge or 28 days
Patient flow diagram in pre and post implementation phases

Pre-implementation phase (12 weeks):
- Patients admitted to critical care
- Patients screened for eligibility
- Informed consent obtained for participation
- Data collection
- Follow up to ICU discharge or 28 days whatever happens first

Post-implementation phase (12 weeks):
- Patients admitted to critical care unit
- Patients screened for eligibility
- Informed consent obtained for participation
- Delivery of interventions (see TIDieR diagram) and data collection
- Follow up until ICU discharge or 28 days whatever happens first

Intended study duration:
Recruitment will take place over a total of 24 weeks, 12 weeks before and 12 weeks after implementation, with the implementation period lasting 4 weeks in between these phases.

End of study
The study is intended to end when data collection is complete after the 28-day follow-up of the patients recruited during the 12 week post-implementation period. However, the trial will be stopped prematurely if:
- Mandated by the Research Ethics Committee (REC)
- Mandated by the sponsor

The REC that originally gave a favourable opinion of the trial will be notified in writing when the trial has concluded or if it is terminated early.
OUTCOME MEASURES

As this is a feasibility study, we will measure feasibility outcomes and efficacy outcomes.

Primary Outcome Measure

The primary outcome is adherence with a multicomponent non-pharmacological intervention for delirium management in critically ill patients.

The proportion of adherence to each component of the intervention will be measured to explore the links between adherence and outcomes, and between stopping the intervention and outcomes.

During the study period, any changes to standard care will be documented to detect any bias that might arise between the before and after groups.

Bedside nursing checklists will be used to document data on adherence with the multicomponent intervention and reasons for non-adherence.

Secondary Outcome Measures

Efficacy outcomes will be collected on:

1) Delirium incidence, as measured by the ICDSC \(^{(29)}\)

Feasibility outcomes will be collected on the following by measuring adherence to completing;

1) The Intensive Care Delirium Screening Checklist (ICDSC) \(^{(29)}\)
2) The Richards Campbell Sleep Questionnaire (RCSQ) \(^{(30)}\)
3) The Richmond Agitation Sedation Score (RASS) \(^{(31)}\)
4) The Manchester Mobility Scale (MMS) \(^{(32)}\)

In addition, qualitative interviews with clinical staff after the post implementation phase will identify barriers and facilitators to the delivery of the interventions.

Patient outcomes will be measured at baseline (Day one) and up to day 28 or ICU discharge, whatever happens first.

Discharge from critical care is defined as discharge to a medical ward in the hospital or another hospital. A transfer between ICUs is not considered a discharge for critical care. Hospital discharge is the first date that the patient is discharged to home or community. A transfer between hospitals is not considered as a hospital discharge.

Further details on how outcomes will be assessed can be found below in Tables 3 and 4.

Study Assessments

Table 3: Study assessments (Efficacy outcomes)
Table 4: Standard care assessments (Feasibility outcomes)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Tool used for data collection</th>
<th>Score documented</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delirium</td>
<td>Intensive Care Delirium Screening Checklist (ICDSC) 23</td>
<td>Highest ICDSC score in 24 hour period*</td>
</tr>
</tbody>
</table>

*24 hour period from 00:00 to 23:59 hrs

Table 4: Standard care assessments (Feasibility outcomes)

<table>
<thead>
<tr>
<th>Sedation</th>
<th>Richmond Agitation Sedation Score (RASS 20)</th>
<th>Was RASS score completed once a shift?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep quality</td>
<td>Richards Campbell Sleep Questionnaire (RCSQ 21)</td>
<td>Was RCSQ completed daily?</td>
</tr>
<tr>
<td>Activity level</td>
<td>Manchester Mobility Score (MMS 22)</td>
<td>Was MMS score completed daily?</td>
</tr>
</tbody>
</table>

The ICDSC is an eight-item checklist based on DSM criteria and features of delirium. Each item that is present is valued at 1 point and a score of > 4 indicates that delirium is present, a score of 1-3 indicates subsyndromal delirium (22).

The Richmond Agitation Sedation Scale (RASS) will be used to measure sedation and agitation levels in critically ill patients. A patient is scored from 4 to -5 on a 10-point scale with four scores for agitation (1, 2, 3, 4), one score for alert and oriented (0) and 5 scores for sedation (-1, -2, -3, -4, -5) (20).

RCSQ is a subjective 6-item questionnaire, which evaluates sleep depth, sleep latency, awakenings, returning to sleep, sleep quality and noise. A scale from 0-100 will be used for each of the six items, with higher scores preferable. Question 6 was not part of the original 5-item Richards Campbell Sleep Questionnaire but has been included in many studies as an important element of sleep assessment (21).

Exercise level will be assessed by the Manchester Mobility Scale (MMS). The MMS has been shown to be feasible for recording rehabilitation in ICU. It is quick and easy to complete and has a good inter-rater reliability across staff grades and professions (22).
STUDY SETTING AND ELIGIBILITY

Study setting
The study will be conducted in a 25-bed ICU in Belfast, Northern Ireland.

Population
Critically ill adult patients.

Eligibility criteria

Inclusion criteria
- All patients ≥ 16 years old and admitted to Intensive Care, receiving mechanical ventilation or vasopressors or oxygen therapy and expected to remain in critical care to the day after tomorrow (i.e. no plan for discharge the next day).

Exclusion criteria
- Inability to understand or speak English (unless there is an interpreter available to translate the study materials).
- Treatment withdrawal imminent within 24 hours.
- Consent declined.

Eligibility criteria are designed so that we will include patients who reflect the general population of critically ill patients who may benefit from the intervention.

Co-enrolment Guidelines
Patients in this study are potentially eligible for co-enrolment in other studies. This will be decided on a case-by-case basis in keeping with UK guidelines for critical care research. Co-enrolment with other studies will be recorded in the case report form (CRF).
RECRUITMENT

Screening procedure
Adult patients ≥ 16 years old admitted to ICU will be prospectively screened daily, based on the eligibility criteria. Screening may be performed by any qualified individual who is a member of the clinical care team designated by the Principal Investigator (PI) and listed on the delegation log as having responsibility for this aspect of the study. In most instances, it is expected that this will be a research nurse or clinical fellow.

The PI will be responsible for maintaining a screening log. Entries may be made by any qualified individuals designated by the PI.

Informed Consent/Assent Procedure
Consent will be taken either from the patient, personal consultee or registered medical practitioner (RMP) as determined by common law. No interventions will be tested or data collected without consent having first been obtained.

The PI is responsible for ensuring that informed consent for study participation is obtained for each patient or considered by an appropriate consultee. Any qualified individual designated by the PI and listed on the delegation log as having responsibility for this aspect of the study may take consent. Patient information sheets and consent forms approved by the Research Ethics Committee (REC) will be provided. Wherever possible, consent will be taken directly from the patient; however, the incapacitated nature of many patients in ICU will usually preclude obtaining prospective informed consent from them. For instance, patients may be unable to give informed consent due to the effects of sedation, infection, delirium and mechanical ventilation. Consent will therefore be obtained in line with the legal requirement for obtaining consent in patients without capacity. These processes have worked successfully in several ongoing and previous studies (e.g. OSCAR (34), REST (35), BREATHE (36) and ABLE (37)).

Where a participant loses capacity after enrolment into the study, the study will continue providing the protocol as REC approved. The possibility of this often temporary circumstance is explicit in the patient information sheet and consent form. Participants will be asked to consider this eventuality at the time of initial consent.

In Northern Ireland, consent procedures where a potential participant lacks capacity on formal assessment are governed by common law. For the purposes of this study, the consent processes used in England and Wales (38) will be used. Practice will adhere to local regulations as outlined below, compliant with published Health Research Authority (HRA) advice, where the patient’s next of kin will fulfill the role of personal consultee.

For patients without the capacity to provide their own consent, the researcher should seek advice from a Personal Consultee (who may be a relative, partner or friend of the potential participant). This should normally take place during a face-to-face meeting. An authorised staff member/researcher will describe the study to the individual, and provide them with a covering statement, patient information sheet and consent form for Personal Consultee. The researcher will seek their views about whether the patient should take part in the study. They will be asked for their opinion of the wishes and feelings of the patient if they had capacity.

After the researcher has checked that the information sheet is understood, the researcher will invite the Personal Consultee to sign the form and the researcher will then countersign it.
A copy of the form will be placed in the patient's medical notes, a copy will be given to the personal consultee and the original will be filed in the investigator site file (ISF).

If the Personal Consultee is not available at site, the researcher may contact the Personal Consultee by telephone and seek verbal agreement. This verbal agreement will be recorded in the Consultee Telephone Agreement Form. The Consultee Telephone Agreement Form will be signed by a second member of staff who has witnessed the telephone consent. This witness may be a member of the site study team or site medical staff. A copy of the Consultee Telephone Agreement Form will be placed in the patient's medical notes and a copy filed in the ISF. Written agreement will be obtained as soon as possible after this telephone agreement.

Professional legal representative consent
If the patient is unable to give informed consent and no Personal Consultee is available, a doctor who is not connected with the conduct of the study may act as a professional legal representative. The doctor will be informed about the trial by the responsible clinician or a member of the research team and given a copy of the PIS. If the doctor decides that the patient is suitable for entry into the study, they will be asked to sign two copies of the professional legal representative consent form. The doctor will retain one copy of the signed consent form. The second copy will be photocopied and the photocopy placed in the patient's medical records; the original will be retained in the trial site file.

Retrospective patient consent
Patients will be informed of their participation in the study by the responsible clinician or a member of the research team once they regain capacity to understand the details of the study. The responsible clinician or a member of the research team will discuss the study with the patient and the patient will be given a copy of the PIS to keep. The patient will be asked for consent to continue to participate in the trial and to sign two copies of the consent to continue form, which will then be countersigned by the person taking consent. The patient will retain one copy of the signed consent form. The second copy will be photocopied and the photocopy placed in the patient's medical records. The original will be retained in the trial site file.

Where consent to continue is not obtained, consent from the legal representative will remain valid. If the patient refuses consent, permission to use data collected to that point and to access medical records for trial data will be requested from the patient.

Withdrawal of consent
Patients with capacity, or patients who recover capacity, may withdraw consent at any time without prejudice. Participants lacking capacity will be withdrawn immediately if a legal representative or a personal or nominated consultee advises that they should be withdrawn. Any data already acquired either with the agreement of an independent doctor, or with previous consent will be included in the study analysis, unless consent to use data is also withdrawn. Copies of all information sheets and declaration forms for all patients screened must be kept in the patient notes and in the site file.
DATA COLLECTION & DATA MANAGEMENT

Study visits and Procedures

All data for an individual patient will be collected by the PI or their delegated nominees and recorded in the CRF up to ICU discharge. For routinely collected clinical data, the NHS record will be the source document and for study specific clinical measurements, the CRF will be the source document.

Patient identification in the CRF will be through their unique Participant Study Number allocated at the time of enrolment and initials. Submitted data will be reviewed for completeness. Due care will be taken to ensure data safety and integrity, and compliance with the Data Protection Act 1998 (23) and subsequent legislation as necessary.

Baseline data (day 0) is the 24 hours preceding the recruitment to the study. Day 1 is from the time of recruitment to the end of that calendar day.

Day 0 (baseline) data

Baseline patient demographics including routinely collected data will be collected retrospectively once informed consent has been obtained from participants.

Routinely collected data such as age, sex, birth date, Acute Physiologic and Chronic Health Evaluation score II (APACHE II), Glasgow Coma Scale (GCS), Alcohol use, Richmond Agitation Sedation Score (RASS), Richards Campbell Sleep Questionnaire (RCSQ), Manchester Mobility Scale (MMS) and Intensive Care Delirium Screening Checklist (ICDSC) will be collected.

In addition, we will collect;
- Pre-DELIrIC score (Wasenaar) (22).
- IQCODE score completed by family or friend who has known the patient for> 10 years (Jorm, 1995) (22).
- Clinical frailty scale (Rockwood et al, 2005) (41).
- Charlson co-morbidity index (Frenkel et al, 2014) (42).

Days 1-28 (daily data)

- GCS
- RASS
- ICDSC
- RCSQ
- MMS
- Adherence with components of the intervention

The CRF may be completed by any qualified individual designated by the local PI and listed on the delegation log as having responsibility for this aspect of the study. Completed CRFs will be stored in a locked cabinet in a locked room at the Belfast Health and Social Care Trust (BHSCT).

Data Quality
The PI will provide training to site staff on trial processes and procedures including CRF completion and data collection. Within the BHSCT, the clinical data management process is
governed by Standard Operating Procedures (SOPs), which help ensure standardisation and adherence to International Conference on Harmonisation Good Clinical Practice (ICH-GCP) guidelines and regulatory requirements.

On-site monitoring visits during the study will check the accuracy of the data entered into the CRF against source documents alongside adherence to the protocol, study specific procedures and Good Clinical Practice (GCP). This monitoring will be carried out as directed by the sponsor.

Changes to data will be recorded and fully auditable. Data error will be documented and corrective actions implemented.

Data validation will be implemented and discrepancy reports will be generated following data entry to identify data that may be out of range or inconsistent, or protocol deviations, based on data validation checks programmed into the clinical trial database.

**Data management**

The PI (or designee) will collect all data and record this in the CRF. Each participant will be allocated a unique participant study number at study entry and this will be used to identify him or her on the CRF for the duration of the study. The CRFs will be kept at the BHSCT.

**Data storage**

All essential documentation and trial records will be stored by the PI in conformance with the applicable regulatory requirements and access to stored information will be restricted to authorised personnel.

**Archiving**

Trial documentation and data will be archived after completion of the trial in keeping with the applicable regulatory requirements.
STUDY COMMITTEES

Trial Management Group
A Trial Management Group (TMG) will be established and chaired by the CI. It will consist of the PI, co-investigators and other members of the study team as appropriate. The TMG will meet face to face or by teleconference on a bimonthly basis and will communicate between times via telephone and email as needed. All day-to-day activity will be managed by the co-investigator (LB).
REPORTING REQUIREMENTS

Table 2. Terms and definitions for adverse events

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Adverse Event (AE)</td>
<td>Any untoward medical occurrence in a participant to whom a study intervention has been administered including occurrences which are not necessarily caused by or related to the intervention.</td>
</tr>
<tr>
<td>Adverse Reaction (AR)</td>
<td>Any untoward and unintended response in a participant to a study, which is related to any intervention administered to that participant.</td>
</tr>
<tr>
<td>Unexpected Adverse Reaction (UAR)</td>
<td>An adverse reaction the nature and severity of which is not consistent with the intervention being delivered.</td>
</tr>
<tr>
<td>Serious Adverse Event (SAE)</td>
<td>Respectively, any adverse event, adverse reaction or unexpected adverse reaction that:</td>
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</tbody>
</table>
| Serious Adverse Reaction (SAR) | • results in death  
• is life-threatening  
• requires hospitalisation or prolongation of existing hospitalisation*  
• results in persistent or significant disability or incapacity  
• consists of a congenital anomaly or birth defect or is any other important medical event(s) that carries a real, not hypothetical, risk of one of the outcomes above. |

Adverse event reporting

AEs that occur between study entry and completion of the study will be reported.

The PI or their delegated investigator is responsible for recording AEs observed during the study period.

As this study is recruiting in a population that is already in a life-threatening situation, it is expected that many of the patients will experience AEs. Events that are suspected in this population (i.e. events in keeping with the underlying condition) should not be reported as AEs.

The investigator should attempt, if possible, to establish a diagnosis based on the patient’s signs and symptoms. When a diagnosis for the reported signs or symptoms is known, the investigator should report the diagnosis as the AE, rather than reporting the individual symptoms.

The investigator should follow all AEs observed during the study until they are resolved or stabilized, or the events are otherwise explained. All AEs should be treated appropriately. Treatment may include one or more of the following: no action taken (i.e., further observation only); drug therapy given; discontinuation of study intervention; patients hospitalized. The action taken to treat the AE will be recorded in the CRF. When an AE is detected, it should be followed until its resolution or stabilisation, or the events are otherwise explained and the outcome recorded in the CRF.

For both AEs and SAEs, the appropriate event report section in the CRF will be completed.
The PI must send all SAE/SAR reports to the Sponsor (QUB Research Office) within 24 hours.

**Urgent safety measures**

The sponsor and investigator may take appropriate urgent safety measures to protect clinical trial participants from any immediate hazard to their health and safety. The investigator may implement urgent safety measures without prior approval from the REC.

The PI should report the urgent safety measure to the Sponsor (QUB Research Office) immediately, using the dedicated email address: researchgovernance@qub.ac.uk.

The Research Office will notify the main REC providing full details of the information they have received and the decision making process leading to the implementation of the urgent safety measure within 3 days.

The notification should include a covering letter detailing the measures taken, the reason for them and the medical assessor contacted and any supporting documentation.
STATISTICAL CONSIDERATIONS

Sample Size
As this is a feasibility study, a sample of convenience has been chosen to explore the feasibility of a large-scale trial, rather than to provide power to detect a definitive effect estimate. We will seek to recruit all patients admitted to ICU who fulfill the eligibility criteria within the two 12-week recruitment periods. This will give us adequate data to assess feasibility. This plan has been developed in collaboration with Professor Mike Clarke, the Director of the Northern Ireland Methodology Hub and an expert in research methodology.

Planned Analyses
The potential for the intervention to have a beneficial effect will be assessed in relation to difference in delirium between the before and after groups, adjusted as far as possible for potential confounders. We will measure proportion of adherence to components of the intervention and use descriptive statistics to assess the characteristics of the study sample and adherence to the intervention. Descriptive statistics will be presented as mean +/- SD or median and interquartile ranges, depending on distribution.

Missing data
Where data are incomplete despite the efforts to ensure continuous high quality data collection and reporting (as detailed in the data collection section of this protocol), information relating to the corresponding participant will be excluded from relevant analyses.
RESEARCH GOVERNANCE AND REGULATORY APPROVALS

The study will comply with the principles, requirements and standards set out in the Research Governance Framework.

Sponsorship
Queen’s University Belfast (QUB) will act as sponsor for the study and the CI will take overall responsibility for the conduct of the study. All study related activity will be undertaken according to the principles set out in the EU directive on Good Clinical Practice including subsequent relevant amendments and the Department of Health Research Governance Framework [43, 44].

Regulatory approvals
The study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki [45]. Approval from a REC and a Clinical Trial Authorisation is needed before the start of the trial.

The trial will be registered on the clinical trials.org website (http://www.clinicaltrials.org) [46].

The trial may be adopted to the Northern Ireland Clinical Research Network (NICRN) for Critical Care Clinical Research Portfolio. Accrual data on patient recruitment will be forwarded to the NICRN Co-ordinating Centre on a monthly basis.

Funding
The Health and Social Care (HSC) Research and Development (R&D) division of the Public Health Agency (PHA) will provide research costs for the study (EAT/5092/14).

User Involvement or any other relevant committees
The study will be registered with the INVOLVE open-access database which registers research healthcare projects involving members of the public as partners in the research process (http://www.involve.org.uk) [47]. ICUsteps members will continue to be involved and will be consulted on study issues. The study will comply with the principles, requirements and standards set out in the Research Governance Framework.

Ethical considerations
The vulnerability of this study group is fully appreciated and every effort will be undertaken to protect their safety and well-being. In line with the Research Governance Framework [44], consenting processes are standardised and a robust SOP for consenting participants will be adhered to.

Patient Confidentiality
Patient confidentiality will be maintained at every stage and the study procedures will be in compliance with the Data Protection Act (1998) [50].

Good clinical practice
The study will be carried out in accordance with the principles of the International Conference on Harmonisation Good Clinical Practice (ICH-GCP) guidelines (www.ich.org) [43].

Study monitoring
Site monitoring will be directed by the sponsor according to the study risk assessment. Site visits will be performed on a regular basis to ensure that all regulatory requirements are met and to monitor the quality of the data collected. Site monitoring visits will involve source data verification where applicable.
[V1.1 FINAL 14/05/18]

Indemnity
QUB will provide indemnity for any negligent harm caused to patients.

Safety and wellbeing of study participants
Participant safety and well-being are protected by implementation of the sponsor’s SOPs as set out in the Research Governance Framework (40). As sponsor, QUB requires all research to be managed through a dedicated Research Management System. Systems are in place to ensure that all investigators are able to demonstrate that they are qualified by education, training or experience to fulfill their roles and those systems and procedures are in place, which can assure the quality of every aspect of the trial.

Safety of investigators
QUB and BHSCT have Health and Safety Policies applicable to all employees. All personnel should also ensure that they adhere to any other Health and Safety regulations relating to their area of work. The PI will ensure that all personnel have been trained appropriately to undertake their specific tasks.

As the study fits closely to standard practice, there are few risks identified which are hazardous to the investigators. The study team will complete GCP and consent training prior to start up.

Study management
The PI will take responsibility for the need to change the protocol for any reason, reviewing relevant information from other sources and considering recommendations from the TMG. Day to day management will be undertaken via the TMG, composed of the PI and supporting staff. They will meet on a bimonthly basis to discuss study issues.

Study schedule
Investigative site preparation: March 2018
Planned recruitment period: April 2018 – September 2018
Planned completion of last patient: September 2018
Analysis and writing up of results: October 2018
Gantt chart of study milestones

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<thead>
<tr>
<th>Year</th>
<th>Period end month</th>
<th>Mar</th>
<th>Apr</th>
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Management

| Trial management group | X | x |
| Monitoring Visits | x | x |
| Trial Close Down | x |
| Data Analysis | x |
| Study Report | x |
| Dissemination | x | x |

Dissemination

The study is not a randomised trial but it will be reported in accordance with relevant sections of the Consolidated Standards of Reporting Trials (CONSORT) guidelines (www.consort-statement.org) (48).

Dissemination will be achieved in several ways: (1) the findings will be presented at national and international meetings, and (2) publication of the findings in high quality peer-reviewed journals.
open access (via PubMed) journals, in accordance with the open access policies proposed by the leading research funding bodies. This will secure a searchable compendium of these publications and make the results readily accessible to the public, healthcare professionals and scientists.

Due to limited resources, it will not be possible to provide each surviving patient with a personalised copy of the results of the trial. However, a layperson’s summary of the principal findings of the results will be sent to all patients involved in the study at their request. In addition, a lay person’s summary will be sent to local and national patient support and liaison groups (e.g. ICUsteps). Where appropriate, research details will also be posted on institutional websites available to the general public and the most significant results will be communicated to the public through media releases.
REFERENCES


7.3 Discussion

Although this protocol has been approved, the trial is currently on hold pending further funding. Ethics and governance have been informed and protocol registration has been suspended until the trial resumes. As a result, the protocol will need to be updated prior to the trial restarting particularly when taking into account the recent changes regarding ethical requirements for patients’ who lack capacity. The Mental Health Capacity Act Northern Ireland (2016) was enacted in December 2019\(^{257}\). Part 8 of the Act legislates for intrusive research projects involving people who lack capacity to consent and details requirements and safeguards that need to be put in place. As this study is focusing on critically ill patients that often lack capacity to consent, I will need to ensure safeguards are in place to identify a person close to the individual who is prepared to be consulted about the patient’s involvement and able to advocate for the patients’ wishes regarding inclusion in a research study.

To facilitate collection of this information, a preliminary CRF has been designed (Appendix X) with Patient Information Sheet (PIS) and assent forms for registered medical practitioner (Appendices S and T), personal consultee PIS and assent forms (Appendix U), recovered capacity PIS and consent forms (Appendix V) and telephone assent for relatives/close friend (Appendix W). The qualitative information from focus group interviews after the feasibility study will also inform whether the intervention needs further modification prior to the definitive trial. Any modifications will be detailed thoroughly using the TIDieR framework to facilitate translating evidence into practice.

This trial has a number of strengths including a clearly described intervention using the TIDIEIR framework as a guide, standardisation of how the intervention should be delivered through development of a training manual and a full description of the explicit methods used to develop the intervention. The use of qualitative interviews are essential to help identify contextual barriers and facilitators that are specific to the intervention as it is being tested in clinical practice. The limitations of this study include the non-randomised study design and the potential influence of factors that cannot be controlled by randomisation, readers will be urged to consider this when interpreting the results of the study. The challenges to delivery have been outlined in chapter 6. Using the CFIR and Pronovost model for quality improvement to plan implementation of the interventions will help to ensure this can be repeated for the subsequent RCT. Depending on the outcome of this study, I plan to test the intervention for efficacy in a definitive multicentre randomised controlled trial. A protocol for multicentre stepped wedged cluster RCT of non-pharmacological
interventions similar to my proposed intervention has been recently published and this will be discussed further in chapter 8.

7.4 Conclusion
The proposed intervention embodies a novel approach to delirium management in the ICU, but there is limited evidence to support efficacy and impact on outcomes. This protocol has been approved by ethics and governance in Northern Ireland and the results will inform the planning and design of a definitive RCT, providing information on feasibility, rates of recruitment, retention and ease of data collection.
Chapter 8. Discussion of the findings

8.1 Introduction

Chapter 7 brought together the findings and conclusions of the earlier elements in my programme of research to provide an overview of the feasibility study that would be used to measure adherence with components of the non-pharmacological intervention for delirium management in critically ill patients.

In this final chapter, I summarise the findings from each of the research studies, highlighting how they follow the guidance from the MRC framework on the development of complex interventions, and summarise the implications for clinical practice and research. The evidence base on the effects of the various elements in the intervention have been thoroughly investigated and the intervention has been designed with feedback from international delirium experts, critical care staff, survivors and their families. To complete the MRC framework for the development of complex interventions, the next steps would be an evaluation of the new intervention (allowing an assessment of its clinical and cost effectiveness and an understanding of the change process) and, if effective, its implementation (dissemination, surveillance and monitoring and long-term follow up).

Therefore, although the steps in this programme of research would depend on the results of the feasibility study, I present a proposed design of a definitive randomised trial to test the intervention towards the end of this chapter. As the systematic reviews and meta-analysis were completed to determine the level of evidence at a point in time to inform a prototype intervention to present to delirium experts, ICU staff and survivors, I did not update the systematic review to the current date. However, I have continually kept myself up to date with the literature on delirium and I have included in this chapter a review of the studies published since 2018 that might be pertinent to this research project. Finally, this chapter and my thesis as a whole concludes with my reflections on the learnings from my PhD studies.

8.2 Summary of Systematic Review findings (identifying the evidence)

Significant heterogeneity in settings, interventions and outcomes made it difficult to summarise results and present data in a meaningful way in the systematic review and meta-analysis of non-pharmacological interventions for delirium management in critically ill patients. However, the findings indicated that there was limited evidence from randomised trials to support the use of these interventions. There was moderate quality evidence from non-randomised trials judged as low risk of bias to indicate that the awakening, breathing
combination, delirium management and early mobility (ABCDE) protocol, education, family participation, cognitive stimulation, orientation, modifying sedation, sleep protocol, targeting risk factors and extended visiting may be effective in reducing incidence and/or duration of delirium. Evidence from randomised trials did not demonstrate any positive effects on delirium outcomes associated with targeting risk factors, combined awakening and breathing trials, earplugs and modifying sedation. This lack of evidence supporting the effectiveness of targeting risk factors for delirium in ICU was surprising, because studies in other patient populations have achieved significant reductions in delirium by targeting known risk factors (11, 13).

In an attempt to investigate this more deeply, the qualitative investigations in the systematic review explored the perceptions of ICU staff, ICU survivors and their families towards non-pharmacological interventions for delirium and content analysis identified key barriers and facilitators to consider when assessing the potential effectiveness of these interventions. A qualitative review by Collinsworth and colleagues identified similar barriers and facilitators to the introduction of a non-pharmacological protocol for delirium, which included enhancing family presence, education and training for staff and strong leadership to promote the use of interventions (207). The qualitative review showed education to be an important facilitator but failed to identify a superior format for staff education on delirium and further research is required in this area.

8.3 Expert panel and focus group meetings (modelling)

The evidence from randomised trials, non-randomised studies and qualitative research from the systematic review and meta-analysis was presented to an international panel of delirium experts.

The evidence highlighted conflicting scientific evidence and the approach I took was similar to that by Hodgson and colleagues who used an expert consensus approach to determine safety parameters to use when mobilising mechanically ventilated patients in the ICU (213).

In my project, findings were reviewed by a multidisciplinary, international group of experts and despite the lack of evidence from randomised trials to support the inclusion of sedation minimisation, the participants felt the inclusion of a sedation minimization protocol was essential to reduce the impact of confounding in any trial of the new intervention bundle. Although participants agreed that that earplugs and eye masks, mobilisation of mechanically ventilated patients and involvement of the pharmacist on ward rounds may not be feasible, they felt it was important to take them forward to the
next phase in which the perceptions of ICU staff, survivors and families on feasibility would be determined. Finally, participants agreed that the bundle should be simple, straightforward to follow and memorable.

The bundle that was presented in focus group interviews with ICU staff, ICU survivors and their families was refined based on expert opinions. A presentation was shown to ICU staff and ICU survivors and their families as outlined in chapter 5, with a focus on gathering opinions on whether it would be feasible to introduce the new bundle in clinical practice. The overwhelming view of participants in staff groups was that it was feasible and they commented that although large components were already part of standard care practice, these were not delivered consistently by every staff member. Although staff felt the intervention was acceptable, they had concerns about the delivery of early mobilisation for mechanically ventilated patients and noted that extra staff resources would be required to meet the complex needs of this component of the intervention. The feedback from clinical pharmacists in particular indicated that they were very interested and keen to be involved in delirium care in the ICU, but funding restrictions mean that it was not feasible to have a pharmacist deliver this role during a multidisciplinary ward round. ICU staff agreed with expert opinion that the mobilisation of MV patients was not feasible without additional resources and that patients should be given the option of earplugs and eye masks but felt it would not necessarily be suitable for everyone. Participants identified several barriers that should be addressed. These were mainly lack of resources and lack of education. Family presence was a facilitator for both staff and survivors, although staff felt that rules were necessary to ensure a symbiotic relationship between staff and relatives. Survivors felt that a return to a normal routine facilitated their ability to participate in interventions and welcomed tools to help them relax and communicate. Staff felt protocols and explicit guidelines could help facilitate pain and sedation management and early mobilisation.

With feedback from the focus groups and publication of a pilot randomised trial on occupational therapy showing benefit in delirium reduction (246) (which was highlighted by the research team and included in the review), the multicomponent intervention was restructured into four components; Education and family participation, sedation minimisation and PAD protocol, physical therapy and environmental interventions which included sleep, orientation, communication and cognitive stimulation activities. At this point, the step in the MRC framework relating to modelling for the intervention was complete. I then reviewed theoretical frameworks for the implementation of research into clinical practice to help plan the implementation strategy and to address barriers and
facilitators identified in focus group interviews. Finally, I developed a protocol for a feasibility study, using the TIDieR framework to describe the intervention to staff (Chapter 6). Due to time constraints, the feasibility study could not be undertaken within the timeline of the PhD however, the protocol has been approved by ethics and governance. In addition, an intervention booklet and implementation plan has been devised and the bundle is ready to be taken forward.

Strengths and limitations

Following the recommendations of the MRC framework for the development of complex interventions was a major strength of this thesis. This ensured the development of a robust intervention that was designed using the best available evidence and deemed feasible and acceptable by ICU clinical staff, ICU survivors and their families.

Another strength of this programme of research was the strong patient and public involvement (PPI) in this project. From its inception, ICU survivors were involved in reviewing and providing feedback on the funding application, patient information documents and study materials. The key stakeholders, namely ICU staff, ICU survivors and their families were interviewed in focus group interviews about their perceptions of this complex intervention, supporting the development of a pragmatic intervention.

The research also has some limitations, arising in part from general challenges with ICU-based research. For example, there is a lack of standardised outcome reporting for delirium and although a core outcome set has recently been completed, results have not yet been published (208,209) and I was not able to draw on this for my research. The delay in achieving ethical and governance approvals to start the feasibility study also meant that this could not be included within this thesis, but allowed more time to take the huge step of defining the intervention and planning for a smooth implementation process.

8.4 Study implications

This study is an integral component of a larger body of planned research that will have implications for education and future research.

Implications and recommendations for further research

Recommendation 1: Further testing of a multicomponent non-pharmacological intervention for delirium management in critically ill patients should incorporate education and family participation, sedation minimisation, physical rehabilitation and environmental
interventions, as they may be effective in reducing delirium incidence, duration or both in critically ill patients

Further research is needed to determine

If this bundle is effective in reducing delirium and improving cognitive and functional outcomes after discharge from ICU before specific recommendations can be made for its use in clinical practice. The evidence to support the bundle is mainly from non-randomised studies, which suggest that a delirium management bundle incorporating education and family participation, sedation minimisation, physical rehabilitation and environmental interventions may be effective in reducing delirium incidence and/or duration in critically ill patients; but whether this translates to better long-term outcomes is unknown. Studies that included sedation minimisation often reported increased delirium but this may be because sedation is no longer masking their delirium. As these interventions are generally low risk, clinicians may find them helpful to use as part of a clinical delirium care bundle in their clinical area. The intervention has been fully described using the TIDieR framework and is easy for staff to follow. The materials, such as the cognitive stimulation booklet are available in English and images have been modified to suit a Northern Ireland context (Appendix O). These images could be modified further to suit other parts of the UK or a more global audience.

To determine feasibility of this bundle, adherence with its components will need to be measured accurately. Previously, Collinsworth and colleagues have shown how the electronic health record could be used to measure adherence to an ICU delirium care bundle and future work should draw on their example. They achieved this by creating structured data fields in the EHR to document process measures and then extracted this data to measure compliance. They observed that achieving buy in from nursing staff, streamlining the process to reduce double documentation and frequently retraining and communicating with staff on the importance of this documentation and how to record data to allow for extraction helped facilitate the process. In addition, they noted that documentation enthusiasm waned at approximately the 4-month mark and required further training. Most ICU nurses in the UK already use the electronic record to document medication administration, counselling and patient care activities, so it would be reasonable to expect that charting administration of components of the delirium management bundle would not lead to a significant increase in their workload.
Recommendation 2: Ensure facilitators (education, active feedback, explicit protocols, validated tools for assessing delirium and pain and a robust leadership plan) and barriers (resource limitations, flexibility of visiting times and educational needs of the patient, relatives and staff) are addressed when introducing a multicomponent non-pharmacological delirium bundle in critical care.

The focus group interviews showed that addressing barriers and facilitators to the implementation of the interventions was an important step in ensuring the successful development of a multicomponent delirium bundle. Although it is unclear which education format is the best for teaching delirium bundles, focus group participants advised that education programmes should include active feedback from ICU survivors telling their story about their ICU journey to help engage staff. Providing explicit protocols (in particular for sedation minimisation and physical rehabilitation) provided staff with clear, failsafe guidelines to follow. Using validated tools to identify pain and sedation levels also helped staff to target interventions. Getting medical staff to champion the study and management of delirium and help identify patients that may be suitable for sedation breaks was another element that could be implemented before intervention rollout.

As this body of research progresses and if non-pharmacological interventions are shown to improve outcomes, then there would be an argument for ICU management to provide funding for extra resources (mainly staff and equipment) to deliver the interventions. Resource limitations were cited as the main barrier to the delivery of interventions in focus group interviews with both staff and survivors. With major advances in technology and the widespread availability of communication applications for patients, some funding in this area might also be helpful for patients and staff. Staff should also educate relatives about the important of creating a calm, safe environment for patients. More flexible visiting hours with clear guidelines for relatives on how they can support a patient’s recovery during visiting would help address the barriers of anxious relatives and help improve the patient’s sense of security. Investigating a patient’s normal routine and trying to replicate that during their recovery and improving their ability to communicate (perhaps with help from technology) would help overcome barriers identified by both staff and ICU survivors. Education of relatives could also help address their fear of lines and tubes, which was identified as a barrier to their participation in care.

Overall, incorporating qualitative interviews into the design of interventions in order to identify barriers and facilitators to implementation can only enhance my ability to
implement complex interventions successfully. In addition, future work should also incorporate a process evaluation alongside the main trial to determine if the intervention was delivered as directed, if the implementation plan was sufficient, outline the process through which the outcomes were achieved and identify if there were different contextual factors that influenced the intervention in a positive or negative way.

Recommendation 3: Test the intervention for efficacy in a large, robust well conducted randomised trial to provide the evidence required

If the feasibility study concludes that this new bundle is feasible and there is greater than 80% adherence with each component of the intervention, it should be tested for efficacy in a definitive randomised trial. Considerations for the design of such a trial are outlined below.

Formulating the research question

Future trials should include a structure for development of their research question; an example of this would be PICOT\(^{(259)}\):

P (population) - the sample of participants to be target for recruitment.

I (intervention) - the treatment that participants in the study will receive.

C (comparison) - the treatment that this new treatment/ intervention will be compared with (which might be usual care or another treatment/ intervention)

O (outcomes) – the clinical findings and tests that will be used to determine any difference in the effects of the intervention and the comparison.

T (time) - the temporal period for collecting information for the study.

For this randomised trial, the PICOT would be:

Population: Adults >16 years being nursed in a critical care unit and identified as high risk of developing delirium using the PRE-DELIIRC risk assessment scale\(^{(260)}\). Patients who are unable to speak English and for whom an interpreter is not available will be not be eligible for practical reasons, and patients receiving end of life care will also be excluded.

Intervention: A multicomponent non-pharmacological intervention for delirium management in critically ill patients incorporating (1) education and family participation, (2) sedation minimization and pain, agitation and delirium protocol, (3) early physical
rehabilitation and (4) environmental interventions for (a) sleep, (b) orientation, (c) communication and (d) cognitive stimulation.

Comparison: Usual care would include non-protocolised orientation, sleep management, sedation interruption and physical rehabilitation.

Outcomes: The primary outcome would be delirium-free days. Pending the availability of a core outcome set, the secondary outcomes would probably be incidence of delirium, duration of delirium, severity of delirium, sleep quality measured by the Richards Campbell Sleep Questionnaire \(^{(261)}\), functional status at 3 months, 6 months and 12 months, cognitive function at 3 months, 6 months and 12 months using the MMSE \(^{(262)}\).

Time: Data collection would continue until one year after a patient’s enrolment in the study to follow up their functional and cognitive status.

Study design

The results of the feasibility study will drive the decision about the design of the definitive trial. For instance, if I found that contamination occurred between intervention and control participants, I would consider a cluster or step wedged cluster design; and the intervention might be modified depending on the results of the feasibility study.

Cluster randomised trials are trials in which groups of individuals (called clusters) are randomised to one of different forms of treatment being tested \(^{(263)}\). Many cluster-randomised trials are pragmatic trials but they can be challenging and consent may be required from clusters, individuals or both. Eldridge and Kerry felt a cluster-randomised trial design should be chosen if;

1. the intervention necessarily acts at the cluster level
2. there are practical or ethical difficulties in randomising participants at an individual level
3. there will be contamination between the groups at health professional level
4. there will be contamination between members of a cluster
5. there is a cost of administrative convenience
6. that special efforts are needed to ensure that the intervention is fully implemented
7. there is access to routine data at the cluster level.
A stepped wedged design is an alternative to a parallel cluster trial design. In the initial period, no clusters are exposed to the intervention and then at specified time points, one cluster is randomised to cross from control to intervention so that all clusters are exposed to the intervention by the end of the study. There is a risk of selection bias associated with this trial design as it prevents concealment of allocation and blinding and it can be confounded by temporal changes (264). It would be preferable to a parallel cluster trial if only a small number of ICUs are available to participate, because it has increased statistical power due to the ability to carry out comparisons between groups and within groups (265).

Hemming and colleagues have provided formulas to help determine sample sizes for stepped wedge and cluster randomised designs and these can be used to inform decisions about which approach to use (266) and the designs have been used recently in critical care trials of interventions: the Psychological Outcomes following a nurse-led Preventative Psychological Intervention for critically ill patients (POPPI) (267) and Sedation and weaning in Children (SANDWICH) (268).

A quality improvement (QI) research approach is an alternative design for this type of research. However, these are typically designed as before and after studies and can be impacted by temporal effects over time. They also lack the robustness of the randomised design and thus the confidence in findings is reduced.

The trial design most suited to conduction of a definitive randomised trial will be chosen when the feasibility trial has been completed.

**Recommendation 4: Use a framework to plan the implementation for the intervention.**

Implementation planning has become an extremely important element for implementation of interventions, with some journals now requesting details of the steps taken to ensure effective implementation on studies evaluating interventions (248). Chapter 6 reviewed some of the theoretical frameworks for implementation of interventions and concluded that use of the consolidated framework for advancing implementation science in combination with Pronovost’s quality improvement model would ensure proper consideration of elements that might influence the success or failure of a complex non-pharmacological bundle for delirium management in critically ill patients. Some elements may not be applicable to a particular intervention or context but research teams can consider this in a structured way using the CFIR framework. The Pronovost model would then be used to guide the actual process of implementation in particular step 4, the ‘4 E’s’: engage, educate, execute and evaluate (252).
There have been calls for further experimental work to determine factors relevant to intervention implementation and in particular, for studies that use manipulation of elements (248). In addition, Durlak and DuPre argues that direct comparison may also uncover how programs work in different contexts.

It would be useful to have a framework for measuring the dose of intervention that is delivered and Legrand and colleagues have made some progress in this area with the Pralimap framework (269). However further work is required to ensure transferability to contexts other than health promotion.

8.5 Literature update
Chapter three describes the systematic review of RCTs, non-randomised studies and qualitative studies and this was completed in 2018. As discussed in chapter three, the rationale for this chapter was to obtain a current overview of the evidence on the effectiveness of non-pharmacological interventions for delirium management in critically ill patients. The purpose was to inform the interventions presented at an international interdisciplinary expert panel consensus meeting and focus groups with ICU staff, survivors and families at that point in time in the research process. Therefore, I have not provided an update on the systematic review to the present date. However, I have kept up to date with the literature published on delirium carrying out regular searches of the PUBMED database using the key terms ‘delirium’ and critically ill’ or ‘intensive care unit’ and ‘non-pharmacological interventions’.

This identified six papers of significant importance to the subject of this thesis, published since 2018 (3 x systematic review papers, 2 x protocols for stepped wedge RCTs examining non-pharmacological protocols for delirium and 1 x review of delirium in the context of COVID 19). Of particular interest was a systematic review estimating the effect size of non-pharmacological interventions for prevention of delirium in ICU patients (searches 2013-2016, published 2018) (270). Studies were divided into 9 different intervention types. 15 of the 35 studies were included in meta-analysis and the combined effect size for delirium incidence (OR) and duration (SMD) was statistically significant for preventive nonpharmacological interventions; odds ratio (OR) of 0.66 (95% confidence interval [CI], 0.50-0.86) for delirium occurrence, and an OR of 0.31 (95% CI, 0.10-0.94) for duration of delirium. In this review, results were pooled for all interventions regardless of the intervention category. Similar to my review, there was significant heterogeneity ($I^2 = 60\%$) for the outcome’s delirium occurrence and duration. This makes it difficult to attach
meaning to these results. Even when interventions are similar, they are often delivered in
different ways using different assessment measures and this further exacerbates the
heterogeneity. Measuring different interventions using different assessment tools may not
provide an accurate effect size due to clinical heterogeneity. For this reason, I only
performed meta-analysis if outcomes were measured in the same way for two or more
studies and interventions were similar (i.e. the same intervention type for example physical
rehabilitation).

A more recent systematic review and network meta-analysis published in December 2020
included 26 studies (over 7000 participants) on the effectiveness of non-pharmacological
interventions for delirium in critically ill patients (searches to end of June 2019). Studies
were grouped into seven intervention types. Using SUCRA analysis, the authors determined
that family participation and multicomponent interventions had a statistically significant
impact on reducing incidence of delirium compared to usual care. Interestingly, family
participation was deemed superior to other interventions, including multicomponent
interventions, in reducing the incidence of delirium. However, it should be noted that only
two studies on family participation were included, one with a relatively small sample size so
this would need to be tested further. Similar to my systematic review, the authors
concluded that their analysis was limited by heterogeneity in types of interventions
studied, implementation and outcomes and inclusion of non-randomised studies. They
acknowledged promising results for multicomponent interventions, family participation
and exercise programs for targeting many outcomes but advised further research\(^\text{[271]}\). The
authors welcomed the publication of a core outcome set for delirium\(^\text{[208, 209]}\) (awaiting
publication). In relation to my research, this review was published in December 2020 and
no further interventions were identified that were not presented in my expert panel
consensus meeting and focus group interviews\(^\text{[267]}\).

Another new paper of significant important to my project was a protocol for a stepped
wedged cluster RCT for a nurse led intervention, which was published this year\(^\text{[272]}\). The
study commenced in May 2019 and was expected to be completed by May 2020; study
details are not accessible on ClinicalTrials.org and despite contacting the author, I have not
received an update. This study design is a stepped wedge cluster design to test the
hypothesis that non-pharmacological interventions are effective in reducing the incidence
and duration of delirium in critically ill patients. The current incidence of delirium in the
four ICUs in this study is unknown and the interventions are informed by two systematic
reviews in hospitalised patients and one systematic review of critically ill patients and
modelled on the interventions tested in the UNDERPIN study \(^{(273)}\) (results not yet available). In contrast to my body of research, there have been no investigations into local or national contextual issues or testing of feasibility of the interventions in practice. I feel that qualitative investigation into barriers and facilitators to implementation of the intervention and testing of feasibility are integral to the success of a study. In addition, omission of a feasibility study means that it is not possible to decipher compliance with screening tools such as CAM-ICU, case report file, and prior publication of an implementation plan.

I feel that the exclusion of this feasibility testing will be a major barrier to the success of the trial as they have not been given an opportunity to address any potential barriers to implementation. These interventions and their introduction to clinical practice are incredibly complex and these complexities need to be addressed \(^{(272)}\). In addition, I await the result of the UNDERPIN ICU study which was completed in May 2020 (ClinicalTrials.gov identifier NCT03002701) This study is a stepped wedge design using protocols aimed at addressing different risk factors for delirium such as visual and hearing impairment, sleep deprivation, cognitive impairment and immobility \(^{(273)}\). In addition to the interventions being tested in the above-named studies, my proposed intervention includes structured protocols to aim for lower sedation levels and higher levels of mobility, an evidenced based eLearning communication training module and a cognitive stimulation booklet that can be adapted to suit different countries and can also be used by family members. Prior to the proposed RCT, my intervention will have been tested for feasibility and will provide data on incidence that can be used to calculate a sample size and the case report file will also be tested. An education plan and implementation plan have also been developed a priori for staff.

A systematic review of 19 studies involving 1379 ICU and non-ICU participants looked at the use of earplugs and eyemasks for quality sleep and delirium (searches up to 2015). They reported potential positive effects on sleep quality and delirium (only three studies measured delirium incidence as an outcome). Results were not pooled for this outcome. Meta-analysis was not performed and results are not confirmative \(^{(274)}\).

Furthermore, the emergence of the coronavirus 19 has placed overwhelming pressure on our critical care services in 2020. A study by Cipriani and colleagues \(^{(275)}\) reviewed the evidence on delirium and SARS-CoV 2 in the critically ill and highlighted that delirium and altered level of consciousness may actually be one of the first signs of COVID-19. Symptoms of COVID-19 including fever and hypoxaemia may also precipitate delirium meaning that
incidence of delirium may be higher in acutely ill patients with COVID-19. Adjusting to the needs of a changing healthcare system in the face of this pandemic means it is more important than ever to ensure there are effective therapies to tackle delirium.

This update is not exhaustive but I have included the literature identified in my searches, published since 2018, that might have an impact on the proposed studies emerging from this thesis. Reassuringly, no additional non-pharmacological interventions were identified in these studies that were not included in my intervention prototype.

8.6 Reflections

According to Ng and colleagues, reflection ‘refers to cognitive and affective processes of consideration’ (276). I conclude this chapter with my thoughts on what I have learned throughout the process of undertaking this PhD study; looking back and considering how I might do things differently now.

There are some lessons that I have learned during this process that I would like to share, in the hope that these will help others like me to bridge from practice into research. Firstly, having a passion for the area that you choose to study is essential and keeps you motivated through the difficult times in your studies. As an intensive care nurse with 11 years’ experience when I embarked on my PhD studies, I had a thorough clinical knowledge of ICU delirium but felt frustrated at the lack of nursing attention being focused on this substantial problem. The unit where I worked did not use a screening tool to identify patients with delirium and this meant that staff only identified the hyperactive subtype. Even on the rare occasions that delirium was documented in a patient’s medical notes or chart, there was no obvious protocol or guidelines to follow for treatment of this syndrome. This meant that it was constantly being reinforced to staff that delirium was not an important medical problem, contributing to a culture where delirium management is not a priority in ICU.

Being passionate about a project ensures you remain motivated through some of the more difficult periods of your PhD studies and, to maintain motivation, I would highly recommend that students plan for publication of key pieces of their research from the beginning of their PhD studies. I published three papers during my doctoral fellowship: the systematic review protocol, the qualitative findings from the focus group interviews and the findings of the systematic review and meta-analysis in the Intensive Care Medicine Journal. In addition to enhancing my writing and critical thinking skills, being published allowed me to present my findings at national and international meetings and I have been invited to give presentations at the European Delirium Association meeting in Oslo and
national meetings in Ireland, which has been an excellent confidence booster. This also provided excellent networking opportunities and I have recently been approached to collaborate on a grant for development of a peri-operative delirium bundle.

One learning from this process would have been to apply for ethics at the beginning and then apply for amendments as the intervention was modified and adapted throughout the research process. Two separate ethics applications over a three-year doctoral fellowship period slowed down the progress of the project and delayed the start of the feasibility study. I have recently been asked to mentor future PhD students about to embark on projects that involve developing complex interventions and I have advised these students to liaise with the relevant ethics committees early in the process to minimise any delays.

Whilst it is difficult to plan for the many setbacks that can occur juggling the write up with return to work and personal responsibilities, I feel that having a robust plan for the structure of my thesis prior to commencing the write up is essential. I had several medical issues during my write up period including a stay in critical care in which I ironically developed delirium. Add that to a global pandemic and redeployment back to frontline ICU services with no childcare meant I needed to be more resourceful with my writing. Delays resulting from temporary withdrawal due to medical issues meant returning to the writing process often felt like starting all over again, which can be very disheartening. My learning through the writing process was that having a supportive research team and ‘tribe’ was fundamental to my success at this point. In addition, I learned to keep precise records of feedback given from supervisors and how I had addressed that feedback. This allowed my supervisor and I to keep updated on the writing progress as each draft was submitted.

8.7 Conclusions

Using the MRC framework for developing complex intervention allowed me to ensure internal and external validity of the intervention and provided a structure for reporting this programme of research. The intervention has been developed using explicit methodology and could be easily reproduced. My series of research studies ensures that I have an evidenced-based, pragmatic intervention that is approved by key stakeholders, has had due consideration of potential positive and negative influences for its success and is now ready for testing. The plans for future testing have been clearly delineated in this thesis and this research process will continue beyond this thesis.
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11 Appendices
Appendix A  Search strategies for systematic review

01: Search strategy for MEDLINE (via OVID 1950 to March 2018)

1. Delirium
2. ICU syndrome
3. Cognitive failure
4. Acute brain syndrome
5. Acute confusional state
6. Reversible dementia
7. ICU psychosis
8. Altered mental state
9. Pseudosenility
10. Toxic encephalopathy
11. Septic encephalopathy
12. Transient organic brain syndrome
13. Acute brain failure
14. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. Critically ill patients
16. Critical* and ill*
17. Intensive care
18. Critical care
19. Intensive or critical and unit*
20. 15 or 16 or 17 or 18 or 19
21. Earplugs or ear protective devices
22. Eyemasks
23. Relaxation
24. Cogni*
25. Sound masking
26. Orientat*
27. Education or Educat*
28. Bright light therapy
29. Sleep and (promot* or help* or support* or initiat*)
30. Noise and (reduct* or control)
31. Lighting and (reduct* or control)
32. Therapeutic touch
33. Famil*
34. Sedat*
35. Exercise*
36. Music or complementary or alternative or cognitive or behavioural or physical (and therap*)
37. Pharmac* and (services or protocol or guidelines or interventions)
38. 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37
39. 14 and 20 and 38
02. Search strategy for Cinahl via EBSCO host < 1982 to March 2018>

S52  S15 AND S21 AND S45
S45  S22 OR S23 OR S24 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S34 OR S37
OR S38 OR S39 OR S40 OR S41 OR S44
S44  "pharmac* and (services or protocol or guidelines or interventions)"
S43  "music or complementary or alternative or cognitive or behavioural or physical and therap**"
S42  "exercise**"
S41  (MH "Sedation") OR "sedat**"
S40  "fami**"
S39  (MH "Therapeutic Touch")
S38  "lighting control"
S37  "lighting reduc**"
S36  "noise control"
S35  "noise reduction"
S34  "noise and (reduct* or control)"
S33  "sleep and (promot* or help* or support* or initat*)"
S32  (MH "Phototherapy") OR "bright light therapy"
S31  "education or educat**"
S30  "orientat**" OR (MH "Orientation")
S29  "sound masking"
S28  "cogni**"
S27  (MH "Relaxation")
S26  "eye masks"
S25  "eyemask or eye mask"
S24  (MH "Ear Protective Devices")
S23  "ear plugs or earplugs or ear-plugs"
S22  S16 OR S17 OR S18 OR S19 OR S20
S21  "intensive or critical and unit**"
S20  (MH "Critical Care")
S19  "intensive care"
S18  "critical* and ill**"
S17  (MH "Critically Ill Patients")
S16  S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S11 OR S12 OR S13 OR S14
S14  "acute brain failure"
S13  "transient organic brain syndrome"
S12  "transient organic brain syndrome"
S11  "septic encephalopathy"
S10  "toxic encephalopathy"
S9  "pseudosenility"
S8  "altered mental state"
S7  (MH "ICU Psychosis")
S6  "reversible dementia"
S5  "acute confusional state"
S4  "acute brain syndrome"
S3  "cognitive failure"
S2  "icu syndrome"
S1  (MH "Delirium")
03: Search strategy for EMBASE < 1980 to March 2018 <
1. Delirium
2. ICU syndrome
3. Cognitive failure
4. Acute brain syndrome
5. Acute confusional state
6. Reversible dementia
7. ICU psychosis
8. Altered mental state
9. Pseudosenility
10. Toxic encephalopathy
11. Septic encephalopathy
12. Transient organic brain syndrome
13. Acute brain failure
14. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. Critically ill patients
16. Critical* and ill*
17. Intensive care
18. Critical care
19. Intensive or critical and unit*
20. 15 or 16 or 17 or 18 or 19
21. Earplugs or ear protective devices
22. Eyemasks
23. Relaxation
24. Cogni*
25. Sound masking
26. Orientat*
27. Education or Educat*
28. Bright light therapy
29. Sleep and (promot* or help* or support* or initiat*)
30. Noise and (reduct* or control)
31. Lighting and (reduct* or control)
32. Therapeutic touch
33. Famil*
34. Sedat*
35. Exercise*
36. Music or complementary or alternative or cognitive or behavioural or physical (and therap*)
37. Pharmac* and (services or protocol or guidelines or interventions)
38. 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37
39. 14 and 20 and 38
04: Search strategy for ISI Web of Science <1970 to March 2018 >
#39  #38 AND #20 AND #14
#38  #37 OR #36 OR #35 OR #34 OR #32 OR #31 OR #30 OR #29 OR #28 OR #27 OR #26 OR #25 OR #24 OR #23 OR #22 OR #21
#37 TOPIC: (pharmac* and (services or protocol or guidelines or interventions or review))
#36 TOPIC: (music or complementary or alternative or cognitive or behavioural or physical and therap*)
#35 TOPIC: (exercis*)
#34 TOPIC: (sedat*)
#33 TOPIC: (famil*)
#32 TOPIC: (therapeutic touch)
#31 TOPIC: (lighting and (reduct* or control))
#30 TOPIC: (noise and (reduct* or control))
#29 TOPIC: (sleep and (promot* or help* or suppo* or initiat*))
#28 TOPIC: (bright light therapy or phototherapy)
#27 TOPIC: (education or educat*)
#26 TOPIC: (orientat*)
#25 TOPIC: (sound masking)
#24 TOPIC: (cogni*)
#23 TOPIC: (relaxation)
#22 TOPIC: (eye masks)
#21 TOPIC: (earplugs or ear protective devices)

#20 #19 OR #18 OR #17 OR #16 OR #15
#19 TOPIC: (intensive or critical and unit*)
#18 TOPIC: (critical care)
#17 TOPIC: (intensive care)
#16 TOPIC: (critical* and ill*)
#15 TOPIC: (critically ill patients)
#14 #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR
#1
#13 TOPIC: (acute brain failure)
#12 TOPIC: (transient organic brain syndrome)
#11 TOPIC: (septic encephalopathy)
#10 TOPIC: (toxic encephalopathy)
#9 TOPIC: (pseudosenility)
#8 TOPIC: (altered mental state)
#7 TOPIC: (ICU psychosis)
#6 TOPIC: (reversible dementia)
#5 TOPIC: (acute confusional state)
#4 TOPIC: (acute brain syndrome)
#3 TOPIC: (cognitive failure)
#2 TOPIC: (ICU syndrome)
#1 TOPIC: (DELIRIUM)

05: Search strategy for PSYCINFO < 2000 to March 2018>
1. Delirium/
2. ICU syndrome.mp.
3. cognitive failure.mp.
4. acute brain syndrome.mp.
5. acute confusional state.mp.
6. reversible dementia.mp.
7. ICU psychosis.mp.
8. altered mental state.mp.
9. toxic encephalopathy.mp.
10. septic encephalopathy.mp.
12. acute brain failure.mp.
13. 1 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. critically ill patients.mp.
15. (critical* and ill*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
16. Intensive Care/
17. critical care.mp.
18. ((intensive or critical) and unit*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
19. 14 or 15 or 16 or 17 or 18
20. (earplugs or ear protective devices).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
21. eye masks.mp.
22. Relaxation/
23. cogni*.mp.
24. sound masking.mp.
25. orientation.mp.
26. (education or educat*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
27. bright light therapy.mp. or Phototherapy/
28. (sleep and (promot* or help* or support* or initiat*)).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
29. (noise and (reduct* or control)).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
30. (lighting and (reduct* or control)).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
31. therapeutic touch.mp.
32. exp Family Therapy/ or famil*.mp.
33. sedat*.mp.
34. Exercise/ or exercise*.mp.
35. ((music or complementary or alternative or cognitive or behavioural or physical) and therap*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
36. (pharmac* and (services or protocol or guidelines or interventions or review)).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
37. 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36
38. 13 and 19 and 37

06: Search strategy for the Cochrane library
Delirium AND Intensive care AND Non-pharmacological interventions
07: Search strategy for AMED <1980 to Jan 2016>
1. Delirium
2. ICU syndrome
3. Cognitive failure
4. Acute brain syndrome
5. Acute confusional state
6. Reversible dementia
7. ICU psychosis
8. Altered mental state
9. Pseudosenility
10. Toxic encephalopathy
11. Septic encephalopathy
12. Transient organic brain syndrome
13. Acute brain failure
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29. Sleep and (promot* or help* or support* or initiat*)
30. Noise and (reduct* or control)
31. Lighting and (reduct* or control)
32. Therapeutic touch
33. Famil*
34. Sedat*
35. Exercise*
36. Music or complementary or alternative or cognitive or behavioural or physical (and therap*)
37. Pharmac* and (services or protocol or guidelines or interventions)
38. 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or
37
39. 14 and 20 and 38
Expert panel consensus: defining a non-pharmacological intervention for delirium management in critically ill patients
Leona Bannon
London, December 8th, 2015

Aims of the meeting
- Discussion on individual and multifactorial non-pharmacological interventions that are:
  - targeted for delirium management in ICU
  - that can be combined into a bundle
  - evidence based and feasible for clinical staff in ICU
  - robust enough to be tested in a future trial

It’s not...
- Discussion of:
  - drug treatments that are best for delirium management in ICU
  - instruments that are the best for measuring delirium in ICU

Methodology
- Systematic review - non-pharmacological interventions
  - Search: OMAHL, MEDLINE, EMBASE, Web of Science, PsychINFO
  - Inclusion criteria: pragmatic; feasible in UK; RCTs, controlled trials and qualitative studies
  - Meta-analysis or narrative presentation of results

- Expert panel consensus
  - Review findings/validating bundle
  - Agree feasibility and acceptability of findings for bundle
  - Participants: multidisciplinary

Methodology
- Focus group interviews nurses
  - Practicality of intervention
  - Feasibility of implementation re: workload

- Focus group interviews ICU survivors & families
  - Acceptability & their views

- Feasibility study
  - 1 ICU in Belfast
  - Feasibility and acceptability in practice
  - Barriers and facilitators to implementation

Systematic review results
- 367 records identified through database searching
- 237 records identified through other sources
- 472 records after duplicates removed
- 38 studies included in the review
### Environmental interventions (8)

<table>
<thead>
<tr>
<th>Study details</th>
<th>Summary evidence for primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RCT</strong></td>
<td>Incidence of delirium</td>
</tr>
<tr>
<td>Right light therapy post intra-abdominal surgery vs standard care</td>
<td>122</td>
</tr>
<tr>
<td>Incidence of delirium</td>
<td>Control vs intervention: 5/12 vs 1/30, (n.s. not statistically significant, n.s. p value listed)</td>
</tr>
<tr>
<td>Right light therapy post operative patient</td>
<td>11</td>
</tr>
<tr>
<td>Incidence of delirium</td>
<td>Control vs intervention: 16/61 vs 40%, p = 0.42;</td>
</tr>
<tr>
<td>Eclampsia versus standard care</td>
<td>334</td>
</tr>
<tr>
<td>Incidence of delirium &amp; mild confusion</td>
<td>Control vs intervention: mild confusion, 24% vs 15%; p = 0.006;</td>
</tr>
<tr>
<td><strong>Observational</strong></td>
<td>Delirium incidence and duration of delirium (study vs control)</td>
</tr>
<tr>
<td>Nutritional and sleep intervention protocol vs standard care</td>
<td>453</td>
</tr>
<tr>
<td>Incidence of delirium and time spent from ICU admission to delirium development</td>
<td>ICU: 0.025; Pre vs post incidence, ICU: 0.0; Pre vs post duration, ICU: 0.0; Pre vs post incidence, ICU: 0.0; Pre vs post duration, ICU: 0.0</td>
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</tbody>
</table>

### Environmental interventions

<table>
<thead>
<tr>
<th>Study details</th>
<th>Summary evidence for primary outcome</th>
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</thead>
<tbody>
<tr>
<td><strong>RCT</strong></td>
<td>Incidence of delirium</td>
</tr>
<tr>
<td>Delirium prevention protocol vs standard care</td>
<td>123</td>
</tr>
<tr>
<td>Incidence of delirium</td>
<td>Control vs intervention: 31% vs 20%; p = 0.30;</td>
</tr>
<tr>
<td><strong>Observational</strong></td>
<td>Delirium incidence and duration of delirium (study vs control)</td>
</tr>
<tr>
<td>Nutritional and sleep intervention protocol vs standard care</td>
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<td>ICU: 0.025; Pre vs post incidence, ICU: 0.0; Pre vs post duration, ICU: 0.0; Pre vs post incidence, ICU: 0.0; Pre vs post duration, ICU: 0.0</td>
</tr>
</tbody>
</table>

### Discussion

- Early mobilisation
- Earplugs
- Drug management protocol
- Orientation protocol
- Sleep promotion protocol

### Multifactorial (4)

<table>
<thead>
<tr>
<th>Study details</th>
<th>Summary evidence for primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Observational</strong></td>
<td>Delirium incidence and duration</td>
</tr>
<tr>
<td>Delirium prevention program vs standard care</td>
<td>123</td>
</tr>
<tr>
<td>Incidence of delirium and duration of delirium (study vs control)</td>
<td>ICU: 0.025; Pre vs post incidence, ICU: 0.0; Pre vs post duration, ICU: 0.0; Pre vs post incidence, ICU: 0.0; Pre vs post duration, ICU: 0.0</td>
</tr>
<tr>
<td><strong>Observational</strong></td>
<td>Delirium incidence and duration of delirium (study vs control)</td>
</tr>
<tr>
<td>Nutritional and sleep intervention protocol vs standard care</td>
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</tr>
<tr>
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<td>ICU: 0.025; Pre vs post incidence, ICU: 0.0; Pre vs post duration, ICU: 0.0; Pre vs post incidence, ICU: 0.0; Pre vs post duration, ICU: 0.0</td>
</tr>
</tbody>
</table>

- Odds ratio
  - Overall odds ratio was 0.67 (p = 0.031) comparing updated vs baseline cohort.
### Multifactorial

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Summary evidence for primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observations</td>
<td>Daily physical activity and postural alignment in the ICU. BCTN (NCT02777547).</td>
</tr>
<tr>
<td></td>
<td>Incidence and prevalence of delirium</td>
</tr>
<tr>
<td></td>
<td>Pre vs post incidence: 25% vs 14%, p = 0.03</td>
</tr>
<tr>
<td></td>
<td>Pre vs post prevalence: 47% vs 53%, p = 0.06</td>
</tr>
</tbody>
</table>

### Published abstracts (5)


**Figure, 2006**. "The impact of an intervention on the incidence of delirium in the ICU." *Intensive Care Medicine* 32(1), 2006. In press of being published. Contact: Mario Figure

### Ongoing trials (9)

- **Tricoli, E.** "An innovative virtual environment for rehabilitation of patients with virtual reality technology in the ICU." (NCT02547777).
- **Nogueira, E.** "A virtual reality system for the prevention of delirium in the ICU." (NCT02547777).
- **Nuno, S.** "Quality improvement program in surgical intensive care units." (NCT02547777). Contacted author for further information.
- **Maffei, A.** "The impact of a virtual reality system on the incidence of delirium in the ICU." (NCT02547777). Contacted author for further information.

### Ongoing trials (cont’d)

- **Detweiler, B.** "The impact of a virtual reality system on the incidence of delirium in the ICU." (NCT02547777).
- **Simons, 2014**. "The impact of a virtual reality system on the incidence of delirium in the ICU." (NCT02547777).
- **Witombo, C.** "The impact of a virtual reality system on the incidence of delirium in the ICU." (NCT02547777).
- **Visintainer, B.** "The impact of a virtual reality system on the incidence of delirium in the ICU." (NCT02547777). Contacted author for further information.
- **Stillman, B.** "The impact of a virtual reality system on the incidence of delirium in the ICU." (NCT02547777). Contacted author for further information.
- **Dubois, B.** "The impact of a virtual reality system on the incidence of delirium in the ICU." (NCT02547777). Contacted author for further information.
<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Year</th>
<th>Title</th>
<th>Journal/Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kieferthaler et al.</td>
<td>2013</td>
<td>&quot;Physical therapy in the critically ill&quot;</td>
<td>Deutsche medizinische Wochenschrift, 138 (14), pp. 713-714</td>
</tr>
</tbody>
</table>
Appendix C  Sponsor letter: Focus group interviews

Ref: B16/35
18 April 2016

Study:  Feasibility and acceptability of non-pharmacological interventions for the management of delirium in critically ill patients: protocol for focus group interviews

Chief Investigator:  Dr B Blackwood

QUB Investigators:  Prof. Danny McAuley, Miss Leona Bannon, Prof. Mike Clarke

I confirm that, subject to the appropriate ethical approval, Queen’s University Belfast will act as Sponsor for the above named research study, in accordance with the Research Governance Framework for Health and Social Care. However, the University will not give approval for any research to proceed until a favourable ethical opinion has been obtained. All necessary management permissions must be in place before commencing work at a research site.

The study must be recorded on the University’s Human Subject Projects Database prior to commencing. The database will be checked to ensure it has been completed, but remains the responsibility of the Chief Investigator (named above) to populate and maintain.

All human tissue and organs held by staff for research purposes must be recorded on the University’s Human Tissue Database and there must be adherence to the current approved University policy to ensure compliance with Human Tissue Act 2004.

Yours sincerely

[Signature]

Stephen Leggett
Research Governance Manager
Appendix D  Ethics approval: FG interviews

11 May 2016

Dr B Blackwood
OG:020, Wellcome-Wolfson Institute for Experimental medicine,
School of Medicine, Dentistry and Biomedical Science
Queen’s University Belfast
BT9 7BL

Dear Dr Blackwood

<table>
<thead>
<tr>
<th>Study title:</th>
<th>Feasibility and acceptability of non-pharmacological interventions for the management of delirium in critically ill patients: protocol for focus group interviews</th>
</tr>
</thead>
<tbody>
<tr>
<td>REC reference:</td>
<td>16/EM/0208</td>
</tr>
<tr>
<td>Protocol number:</td>
<td>001</td>
</tr>
<tr>
<td>IRAS project ID:</td>
<td>205123</td>
</tr>
</tbody>
</table>

The Proportionate Review Sub-Committee of the East Midlands - Nottingham 1 Research Ethics Committee reviewed the above application on 10 May 2016.

Provisional opinion

The Sub-Committee would be content to give a favourable ethical opinion of the research, subject to clarification of the following issues and/or the following changes being made to the documentation for study participants:

1. Explicitly explain what the non-pharmacological interventions would be and why the second peer reviewer felt they may be distressing.
2. Correct the typographical and grammatical errors in both the Staff and Patient Participant Information Sheets.
3. Put Contact details for the researchers at the top of both of the Participant Information Sheets.

When submitting a response to the Sub-Committee, the requested information should be electronically submitted from IRAS. A step-by-step guide on submitting your response to the REC provisional opinion is available on the HRA website using the following link: http://www.hra.nhs.uk/nhs-research-ethics-committee-rec-submitting-response-provisional-opinion

Please submit revised documentation where appropriate underlining or otherwise highlighting the changes which have been made and giving revised version numbers and dates. You do not have to make any changes to the REC application form unless you have been specifically requested to do so by the REC.

Authority to consider your response and to confirm the final opinion on behalf of the Committee has been delegated to Ms Ellen Milazzo.
Please contact George Martin nrescommittee.eastmidlands-nottingham1@nhs.net if you need any further clarification or would find it helpful to discuss the changes required with the lead reviewer.

The Committee will confirm the final ethical opinion within 7 days of receiving a full response. A response should be submitted by no later than 10 June 2016.

Summary of discussion at the meeting

**Social or scientific value; scientific design and conduct of the study**

The PR Sub-Committee noted that the study will utilise a total of four focus groups and that thorough peer review has been conducted. The members also noted that the second peer review raised an issue with the study as it suggested that some of the participants will have gone through an extremely distressing experience and may be vulnerable as a result. The members discussed the issues raised and concluded that as the participants are only talking about non-pharmacological interventions and not being put through them; the experience would not be that distressing and would therefore not constitute an ethical issue. Yet the PR Sub-Committee agreed that the application was not explicit in explaining what the suggested non-pharmacological interventions would be; and agreed that further explanation of what exactly the interventions would be and why the second peer reviewer thought they may be distressing for participants.

**Recruitment arrangements and access to health information, and fair participant selection**

The PR Sub-Committee noted that recruitment will take place in hospital wards from patients who are recovering from a critical illness.

**Informed consent process and the adequacy and completeness of participant information**

The PR Sub-Committee noted a number of typographical errors in both of the Participant Information Sheets (PIS). The members agreed that the PIS for patients needs to be corrected as it refers to them as experts, and that the PIS for Staff is patronising as it does not explain who the ‘multi-professional panel of delirium experts’ are, just that a panel of experts was assembled. The members also noted a number of grammatical errors in both of the PIS documents and agreed that contact details of the researchers need to be included at the top of both of the PIS documents.

**Documents reviewed**

The documents reviewed were:

<table>
<thead>
<tr>
<th>Document</th>
<th>Version</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Copies of advertisement materials for research participants [Advertisement ICUsteps]</td>
<td>1</td>
<td>08 January 2016</td>
</tr>
<tr>
<td>Covering letter on headed paper [Cover letter]</td>
<td>1</td>
<td>19 April 2016</td>
</tr>
<tr>
<td>Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Indemnity certificate]</td>
<td>1</td>
<td>20 July 2015</td>
</tr>
<tr>
<td>Interview schedules or topic guides for participants [Topic guide]</td>
<td>1</td>
<td>08 January 2016</td>
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<tr>
<td>IRAS Checklist XML [Checklist_28042016]</td>
<td></td>
<td>26 April 2016</td>
</tr>
<tr>
<td>Letter from sponsor [Sponsor letter]</td>
<td>1</td>
<td>18 April 2016</td>
</tr>
<tr>
<td>Other [Advertisement BACCN]</td>
<td>1</td>
<td>08 January 2016</td>
</tr>
</tbody>
</table>
Other [Referee report no.2] 1 13 April 2015
Other [Clinical staff consent form] 1 08 January 2016
Other [Clinical staff Patient Information Sheet] 1 08 January 2016
Other [No Material issues tool] 3.4 26 July 2016
Other [Support letter BACCN] 1 10 April 2016
Other [Support letter ICU steps] 1 18 March 2016
Other [Insurance- clinical trials coverage] 1 20 July 2015
Other [Supervisor CV] 1 04 April 2016
Participant consent form [Support group member consent form] 1 08 January 2016
Participant information sheet (PIS) [Support group member PIS] 1 08 January 2016
REC Application Form [REC_Form_27042016] 27 April 2016
Referee’s report or other scientific critique report [Gov 1 review JM] 1 09 February 2016
Research protocol or project proposal [Protocol] 1 08 January 2016
Summary CV for Chief Investigator (CI) [BB CV] 1 04 April 2016
Summary CV for student [LB CV] 1 29 February 2016
Summary CV for supervisor (student research) [Supervisor CV] 1 01 January 2016

Membership of the Committee

The members of the Committee who were present at the meeting are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

16/EM/0208 Please quote this number on all correspondence

Yours sincerely

Dr Carl Edwards
Chair

Email: NRESCommittee.EastMidlands-Nottingham1@nhs.net

Enclosures: List of names and professions of members who took part in the review

Copy to: Sponsor Contact - Mr Stephen Liggett
R&D - Ms Alison Murphy, Belfast Health and Social Care Trust
East Midlands - Nottingham 1 Research Ethics Committee

Attendance at PRS Sub-Committee of the REC meeting on 10 May 2016

Committee Members:

<table>
<thead>
<tr>
<th>Name</th>
<th>Profession</th>
<th>Present</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Carl Edwards - Chair</td>
<td>Investment Advisor</td>
<td>Yes</td>
</tr>
<tr>
<td>Mrs Sarah Lennon</td>
<td>Ex-Surgical Registrar (GMC registration maintained)</td>
<td>Yes</td>
</tr>
<tr>
<td>Ms Ellen Milazzo</td>
<td>Development and Change Management Consultant</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Also in attendance:

<table>
<thead>
<tr>
<th>Name</th>
<th>Position (or reason for attending)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mr George R. Martin</td>
<td>REC Assistant (Minutes)</td>
</tr>
</tbody>
</table>
Appendix E  Protocol: Focus group interviews

Version 1, 08/01/2016. Appendix 2

Feasibility and acceptability of non-pharmacological interventions
for the management of delirium in critically ill patients: protocol for
focus group interviews

1*Bannon, L., 2Clarke, M, 3McAuley, D, 8Blackwood, B

*corresponding author

1 Centre for Infection and Immunity, School of Medicine, Dentistry and Biomedical Sciences,
Queen’s University Belfast, 97 Lisburn Road, Belfast BT9 7BL, Northern Ireland

2 Centre for Public Health, School of Medicine, Dentistry and Biomedical Sciences, Queen’s
University Belfast, Belfast BT12 6BJ, Northern Ireland

Contact Address: Leona Bannon, School of Medicine, Dentistry and Biomedical Sciences,
Centre for infection and immunity, Queen’s University Belfast, 97 Lisburn road, Belfast BT9
7BL  Ibannon01@qub.ac.uk

Email addresses: Ibannon01@qub.ac.uk; m.clarke@qub.ac.uk; d.f.mcauley@qub.ac.uk;
b.blackwood@qub.ac.uk

1
Abstract

Background

Critically ill patients have an increased risk of developing delirium during their intensive care stay. To date, pharmacological interventions have not been effective for delirium management however non-pharmacological interventions have shown some promise. The aim of these focus group interviews is to gather data on the feasibility and acceptability of a list of interventions that have been developed based on best available evidence from a systematic review and expert opinion.

Methods

This is a two-part qualitative study. We will purposively sample 24-48 clinical Intensive care unit (ICU) staff participants consisting of nursing staff, pharmacists and physiotherapists and 6 -12 ICU survivors and their families in the United Kingdom (UK). We will recruit interested clinical staff participants by advertising in the British Association of Critical Care Nurses (BACCN) newsletter and on their website and contacting critical care education providers across the UK to pass on the information to their students. ICU survivors and their families will be contacted via the ICU steps charity which is a support group for survivors and their families. To be eligible, staff participants must have at least 6 months experience working in critical care. ICU survivors and their families must have had experience of delirium during their or their relatives stay whether this was experienced personally or observed in a family member. The interviews will be semi-structured but flexible. All discussion will be tape recorded and transcribed verbatim.

Discussion
Non-pharmacological interventions have been studied in non-intensive care unit populations and multi-component interventions have successfully reduced incidence and/or duration of delirium however no systematic review of non-pharmacological interventions specifically targeted delirium in critically ill patients has been undertaken. Results of these planned focus group interviews would allow us to ensure our interventions are acceptable to staff and patients before moving onto our subsequent feasibility study in which the interventions will be implemented in the clinical setting.

Conclusion

Interventions must be approved by stakeholders before we can attempt to implement them in a subsequent feasibility study.

Rationale and background information

Background

Description of the condition

Survivors of critical illness frequently experience ‘malfunction of the cognitive processes in the brain’, known as delirium (1). The American Psychiatric Association (2) define delirium as ‘a global disturbance of consciousness characterised by fluctuating mental status, inattention, and disorganised thinking’ which develops over a short period of time and tends to fluctuate throughout the course of the day. Delirium is not a disease but a syndrome with a wide spectrum of possible aetiologies (3). Critically ill patients have an increased risk of developing delirium during their hospital stay. This can be as a result of sepsis and disturbances in Inflammation and coagulation pathways leading to microvascular thrombosis (3). In addition, critical illness disrupts circadian rhythm and sleep patterns, and
along with sedatives such as benzodiazepines that are commonly used to treat delirium in septic patients, can impair immunity and contribute to delirium (1, 4).

The incidence of delirium is difficult to determine with studies in the United Kingdom (UK) finding 65% incidence in mechanically ventilated Intensive Care Unit (ICU) patients (5). In addition, international studies have demonstrated even higher incidence from up to 87% in critically ill patients (6, 7, 8, 9). Delirium screening practices in the UK remain inconsistent, which may account for the low incidence rates found (10). Other reasons for a broad range in incidence figures could be differences in incidence in subspecialty ICUs, populations with variable severity of illness and under-recognition of the syndrome (11, 12).

Delirium is potentially modifiable depending on the individual patients’ circumstances. In recent years, the need to introduce validated screening programmes in the ICU has been recognised (13). In the absence of a valid screening tool, delirium can go unnoticed in up to 70% of patients (12, 14). The gold standard for diagnosis of delirium is the DSM-IV criteria applied by a trained psychiatrist but this method is often not feasible in the hospital setting as psychiatric services are not available around the clock. As a result, multiple delirium detection tools have been developed and validated against DSM-IV criteria for use in the ICU. The Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC) are the most commonly used tools (6, 15). The cardinal feature of delirium, inattention (2) is included in both CAM-ICU and ICDSC tools.

Delirium screening and awareness of the associated risk factors are mutually dependent for the successful management of delirium. A study by Van den Boogaard (16) identified ten risk factors including age, Apache II score, admission group, coma, infection, metabolic acidosis,
use of sedatives and morphine, urea concentration and urgent admission. Many of these risk factors are irreversible but others, such as use of sedatives and morphine could potentially be modified.

Risk factors for delirium can be divided into three categories:

(1) Acute illness,

(2) Host factors including age or chronic health problems,

(3) Iatrogenic or environmental factors (17).

The iatrogenic or environmental factors include immobilisation, sensory deprivation, sleep deprivation and social isolation (17, 18, 19, 20, 21, 22, 23, 24, 25). Sleep deprivation can be caused by high levels of background noise, absence of natural light, patient care activities, mechanical ventilation, medication, pain, anxiety and stress (26, 27). These factors have been found to disrupt normal sleep-wake cycles causing sleep deprivation and increasing the risk of delirium (26). Disrupted sleep in the ICU has been identified as a modifiable precipitating risk factor for delirium (13, 19).

Patients who experience delirium during critical illness can experience short and long term sequelae. Short terms outcomes include prolonged duration of mechanical ventilation, ICU admission and hospital stay (7, 16, 28, 29). Evidence suggests that for every extra day patients test positive for delirium, it increases the risk of a prolonged hospital stay by 20% (8). Similarly, Salluh et al (30) in their systematic review and meta-analysis of outcomes of delirium in critically ill patients found that patients with delirium had an increased mean length of stay (approximately 1 day longer) and increased the mean duration of mechanical ventilation (almost 2 days longer) than patients without delirium, even after adjusting for
variables such as age, sex and Apache II scores. Prolonged duration of delirium increases the risk of these negative consequences (31,32). Several studies have also identified a link between delirium and in-hospital mortality (5, 12, 16, 26, 28, 33, 34). These findings suggest that an increased duration of mechanical ventilation, ICU admission and hospital stay often contribute to long term negative outcomes such as increased mortality and morbidity.

Pisani et al (23) found that the number of positive delirium days in ICU was significantly associated with time to death in the year following critical illness. Delirium in critical illness can also predict a ten-fold higher likelihood of cognitive impairment at one year (31). Studies show that up to 6 out of every 10 patients that survive critical illness struggle with significant cognitive impairment for months to years after their critical illness has resolved. This has significant implications on their quality of life, health care costs and lead to institutionalisation (31). In addition, delirium is a significant predictor of functional decline and inability to carry out activities of daily living, at both hospital discharge and three month follow up (35). These negative outcomes incur increased costs and more importantly result in long term persistent cognitive deficits such as dementia (32, 36) which can significantly impact on a patient’s ability to return to their normal lives.

A longer duration of delirium in ICU is associated with worse outcomes so removal or reversal of the underlying cause of delirium remains a top priority for successful management of the condition (2). There has been limited success with pharmacological therapies, results are inconsistent and therapies can be expensive (36). This lack of evidence on pharmacological therapies for prevention and treatment of delirium is highlighted in the 2013 pain, agitation and delirium guidelines of the American College of Critical Care Medicine (13). Prophylactic antipsychotics and dexmedetomidine have been shown to
reduce the prevalence of delirium in critically ill patients. However, no single pharmacologic intervention to prevent or treat delirium has been routinely able to improve mortality rates or hospital length of stay (4, 37, 38, 39, 40, 41, 42, 43, 44).

The American College of Critical Care Medicine’s pain, agitation and delirium guidelines recommend non-pharmacological interventions such as early mobilisation (13). Recently published NICE guidelines (45) recommend a number of non-pharmacological interventions to prevent delirium such as ensuring adequate fluid intake, encouraging exercise or range of motion exercise, introducing cognitively stimulating activities and providing appropriate lighting and clear signage. However it is worth noting these recommendations are based largely on studies in non-ICU patients (older adults, acute medical) (46, 47, 48). Although this strategy has not been tested on critically ill patients, these non-pharmacological interventions might also benefit ICU patients, but these patients are exposed to many more risk factors for delirium and therefore the proven effectiveness of these interventions in other patients may not be generalizable to them. Therefore, further research into use of these interventions in an ICU population is needed and a systematic review of the evidence would enable the development of a non-pharmacological intervention that is evidence based and ICU specific.

Description of the intervention

A non-pharmacological intervention is any non-drug intervention. Research in other patient populations is informative for ICU clinicians despite the lack of direct evidence from the ICU setting (48). Interventions are aimed at targeting risk factors associated with delirium in ICU such as immobilisation, sensory deprivation, sleep deprivation and social isolation and aim to reduce incidence and/or severity of delirium in critically ill patients.
Version 1, 08/01/2016. Appendix 2

How the intervention might work

It is hypothesised that a multi-component non-pharmacological intervention may reduce incidence and severity of delirium by targeting known risk factors such as sensory deprivation, sleep deprivation and immobilisation in critically ill patients. In other patient populations, multi-component interventions have been successful by targeting modifiable risk factors (46, 47, 48).

Some single intervention studies of non-pharmacological interventions have also shown promise in the ICU setting, including early mobilisation, earplugs and orientation programmes for patients (1, 22, 25).

To enable the development of a non-pharmacological intervention, the findings from the systematic review was discussed at an expert panel on delirium at the Intensive Care Society State of the Art (ICS SoA) meeting in London. The following interventions were identified as most clinically important;

1. Assess prevent & manage pain,
2. Both spontaneous awakening trials and spontaneous breathing trials,
3. Choice of analgesia and sedation,
4. Delirium: assess, prevent and manage,
5. Early mobility and exercise,
6. Family engagement and empowerment incorporating an orientation protocol,
7. Sleep promotion protocol
8. Drug management protocol. (8 items)

The next stage of this research is to ask clinical staff and ICUsteps members if they consider the interventions acceptable and practical for clinical practice prior to developing the intervention.
Version 1, 08/01/2016. Appendix 2

Aim of the study
To gather data to support implementation and development of a multi-component non-pharmacological intervention based on best available evidence and expert opinion in the field
To identify barriers and facilitators to implementation of interventions

Research questions
1. Can the interventions listed above be carried out as part of your daily duties in ICU?
2. Are they feasible and acceptable?

Study design
Qualitative study using semi structured focus group interviews.

Setting:
Focus group interviews with clinical staff will be held in a suitable non-clinical venue of the participants choosing. The researcher will travel to this venue to facilitate focus group interviews.

Focus group interviews with ICUsteps members will be held in a suitable venue where participants are happy to meet. The researcher will travel to this venue to facilitate the interviews.

Sample: How will participants be recruited?
The British Association of Critical Care Nurses (BACCN) have agreed to advertise for recruitment in their bi-monthly newsletter pending ethical approval. A copy of the post is included in the appendix (appendix 3). The BACCN has access to 200 + ICUs in the UK. Members will be contacted and asked to help recruit focus groups of ICU clinical staff to include nurses and Allied Health Professionals (AHP) in ICUs in Northern Ireland and England to give their opinions on a list of interventions for delirium management.

ICUsteps (a support group for ex patients of intensive care and their families) have agreed to advertise the project in their newsletter so that members can become involved if they are interested.
If more groups respond than the number we require then we will use purposive sampling taking geographical location and feasibility into consideration, to make a decision on inclusion.

**Inclusion/Exclusion criteria**

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<tr>
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<th>Inclusion criteria</th>
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<tr>
<td>Clinical staff</td>
<td>&gt;6 months experience working in critical care</td>
<td>&lt; 6 months critical care experience</td>
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<tr>
<td></td>
<td>Ideally sample with mix of ICU clinical experience, age, gender and geographical location.</td>
<td>Consent refusal</td>
</tr>
<tr>
<td>ICUsteps members</td>
<td>ICU survivor or carer</td>
<td>Consent refusal</td>
</tr>
<tr>
<td></td>
<td>Ideally sample with mix of gender, age and geographical location</td>
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**Data extraction:**

Focus group interviews will be recorded and data will be transcribed directly from the recordings by a professional transcriber who will be paid from the R & D fellowship fund.

**Data synthesis:**

Content analysis will be carried out based on qualitative questions [49]. The content will be analysed to answer specifically if each intervention is feasible and acceptable for clinical practice. The information (transcriptions and summary information on content analysis) will be checked by my supervisor BB.

**Ethical considerations:**

*Data management.*
The data collected during the focus group interviews will only be shared as themes. Information will be anonymised so it cannot be attributed to any specific person. The recordings and transcripts will be stored in a locked cabinet in the PhD room at the Wellcome Wolfson Building at Queen’s University Belfast (QUB) in adherence with QUB policy. Audiotapes will be destroyed after use and transcribed data will be backed up on the University server. Records will be kept for five years in accordance with guidelines and the Chief Investigator will have the ultimate responsibility regarding archiving.

Confidentiality.

I will ensure confidentiality of information is upheld at all times. Measures will be taken to ensure that participants cannot be identified from their comments and I will encourage participants not to share the issues discussed outside of the focus groups.

Emotional distress

There may be possibility that some of the ICU survivors and their families may become distressed as they recall traumatic events associated with their ICU stay however in my experience of working as an ICU nurse and a committee member at the ICUsteps NI meetings, this is not likely. However, in the event that a participant gets distressed, I will use my interpersonal skills to counsel these participants and provide support taking them into a private room if necessary away from the group meeting and I will also strongly encourage them to visit their General Practitioner (GP) for further help and advice.

Dissemination:

I plan to disseminate this information through national and international conferences.

Acknowledgements

I would like to thank Richard Fallis and Patricia Watt at the Medical library at Queen’s University Belfast and Belfast Health and Social Care Trust and Brenda Allen at the Biomedical library at Queen’s University Belfast.

Conflicts of interest

None.

Author’s contributions
LB developed this protocol under direct supervision of BB, DM & MC.
References


Clinical Staff Participant Information Sheet

Study title: Feasibility and acceptability of a multi-component non-pharmacological bundle for delirium management in critically ill patients: focus group interviews

You are being invited to take part in a focus group discussion. Before you decide whether to take part it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. If anything is not clear or you would like more information, please ask your researcher. This discussion will be audio recorded. Thank you for reading this information sheet.

What is the purpose of the study?

The purpose of this focus group is to understand the opinion of ICU staff on a list of non-drug interventions for delirium that we would like to put together in a package to reduce the number of patients who get delirium in ICU and reduce the amount of time they spend delirious. Delirium can cause hallucinations and loss of awareness and can even have effects after discharge home. There are currently no available drugs that prevent delirium however non-drug treatments have been shown to reduce delirium outside of ICU so we would like to test if they have a similar effect in ICU patients. From review of the evidence on non-drug treatments for delirium in critically ill patients, the most effective non-drug interventions for preventing delirium were identified. I facilitated a multi-professional discussion of this evidence with a group of delirium experts including Professor Wes Ely, Professor Dale Needham and Professor Michelle Balas and they provided recommendations on a bundle of treatments that they felt would work in practice. I have a list of treatments that there is strong evidence to suggest can help to reduce delirium and the purpose of the focus group interviews is to get your opinion on how the treatments will work in practice. Your input is extremely important because it is going to help determine what we can then test in clinical practice.
**Do I have to take part?**

Participation is voluntary and it is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and will be asked to sign a study consent form. You are still free to withdraw at any time and without giving a reason. If you decide not to take part the standard of care you receive will not be affected.

**What will I do if I take part?**

Participation involves attending a one hour informal focus group meeting with 6-12 participants, talking about your knowledge of delirium and experiences with non-drug treatments and giving your opinion on a list of non-drug interventions for delirium management in ICU. These discussions will be audio-recorded with your consent.

**What are the possible disadvantages and risks of taking part?**

There are no risks or disadvantages to taking part. You may be asked to talk about your clinical practice however this information will be kept confidential.

**What are the possible benefits of taking part?**

The benefits of taking part in this research are you have an opportunity for your voice to be heard and carefully considered in the development of a group of treatments that may be tested in your unit at a later date. Whilst there are no personal benefits to taking part in this study, the information you provide will be used to develop a group of non-drug treatments that could potentially reduce the number of people who get delirium in ICU and the length of time that they get delirium for.

**Will my taking part in this study be kept confidential?**

Whilst you may be asked to provide information about your clinical practice and opinions on interventions for delirium, all information provided by you will be kept confidential at all times. The audio recordings will be transcribed and tapes will be deleted. Transcribed information will be anonymised (i.e. it will be given a code so that you cannot be identified) and stored confidentially. The information provided will be summarised and help to develop a group of treatments. This information with relevant anonymised quotes may be used in future publications or presentations. All information provided by you will be stored anonymously on a computer with analysis of the information undertaken by the researcher at Queen’s University Belfast. Only members of the research team will have access to your information.
What will happen to the results of the research study?

The results from the analysis will be available in the following sources: scientific papers in peer reviewed academic journals, presentations at national and international conferences and local seminars.

Who is organising the research?

This project is funded by the Research and Development division of the Public Health Agency, Northern Ireland and is being undertaken as part of a PhD project at the School of Medicine, Dentistry and Biomedical Sciences at Queen’s University Belfast.

What happens if I have any questions, concerns or complaints about the study?

If you have any questions about participation in this focus group. Please contact Leona Bannon. (Contact details below)

Contact details: Researcher:
Name: Leona Bannon
Address: Room OG 015
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School of Medicine, Dentistry and Biomedical Sciences
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Direct line: +44 (0) 28 9097 6401

Contact details: Principal investigator
Name: Dr Bronagh Blackwood
Address: Room OG-020
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School of Medicine, Dentistry and Biomedical Sciences
Queen’s University Belfast
BT9 7BL
Direct line: +44 (0) 28 9097 6379
Appendix G  Focus group PIS ICU survivors

ICU Support Group Member Participant Information Sheet

Study title: Feasibility and acceptability of a multi-component non-pharmacological bundle for delirium management in critically ill patients: focus group interviews

You are being invited to take part in a focus group discussion. Before you decide whether to take part it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. If anything is not clear or you would like more information, please contact a member of the research team. Take time to decide whether or not you wish to take part. This discussion will be audio-taped with your consent. Thank you for taking the time to read this leaflet.

What is the purpose of the study?

The purpose of this focus group is to understand Intensive Care Unit (ICU) survivors and their families’ opinions on a list of non-drug interventions for delirium. We would like to put the interventions together in a package to reduce the number of patients who get delirium in ICU and reduce the amount of time they spend delirious. Delirium can cause hallucinations and loss of awareness and can even have effects after discharge home. From looking at the evidence on non-drug treatments for delirium in patients in ICU, I found out which non-drug treatments are the best at reducing delirium. I facilitated a multi-professional discussion on the evidence with a panel of delirium experts who provided recommendations on a bundle of treatments that would most likely work together. I have a list of treatments that there is strong evidence to suggest can help to reduce delirium and the purpose of the focus group interviews is to get your opinion on how these treatments will work in practice. There are currently no drugs proven to prevent delirium however non-drug treatments have been shown to reduce delirium outside of ICU so we would like to test if they have a similar effect in ICU patients. Your input is extremely important because it is going to help determine what is acceptable and practical in clinical practice.

Principal investigator:
Dr Bronagh Blackwood
OG020 Wellcome Wolfson Centre for Experimental Medicine, Queen’s University Belfast, Lisburn road, Belfast BT9 7LY.
Northern Ireland.
Phone no: 028 90 97 6379
**Do I have to take part?**

Participation is voluntary and it is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and will be asked to sign a study consent form. You are still free to withdraw at any time and you are not required to give any reason.

**What does taking part involve?**

Participation involves attending a one-hour informal focus group meeting in a group of approximately 6-12 people, talking about your knowledge of delirium and experiences with non-drug treatments and giving your opinion on a list of non-drug interventions for delirium management in ICU. These discussions will be audio-recorded with your consent.

**What are the possible disadvantages and risks of taking part?**

There are no risks or disadvantages to taking part however, talking about your experiences may bring back upsetting memories. This is only natural and to minimise this risk the interviews will be conducted by a trained nurse and there will be an opportunity to debrief at the end of the interview.

**What are the possible benefits of taking part?**

Whilst there are no personal benefits to taking part in this study, the information you provide will be used to develop a group of non-drug treatments that could potentially reduce the number of people who get delirium in ICU and the length of time that they get delirium for.

**Will my taking part in this study be kept confidential?**

Whilst you may be asked to provide your opinions on interventions for delirium, all information provided by you will be kept confidential at all times. The audio recordings will be transcribed and tapes will be deleted. The information provided will be summarised and help to develop a group of treatments. All responses and information provided by you will be anonymised i.e. it will be given a code so that you cannot be identified. Relevant anonymised quotes may be used in future publications or presentations. All information provided by you will be stored anonymously on a computer with analysis of the information undertaken by the researcher at Queen’s University Belfast. Only members of the research team will have access to the information. All information you provide to us will be kept confidential.
What will happen to the results of the research study?

The results from the analysis will be available in the following sources: scientific papers in peer reviewed academic journals, presentations at national and international conferences and local seminars.

Who is organising the research?

This project is funded by the Research and Development division of the Public Health Agency, Northern Ireland and is being undertaken at the School of Medicine, Dentistry and Biomedical Sciences at Queen’s University Belfast.

What happens if I have any questions, concerns or complaints about the study?

If you have any questions about participation in this focus group, please contact Leona Bannon or Dr Bronagh Blackwood (PI) (Contact details below)

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Contact details: Principal investigator
Name: Dr Bronagh Blackwood
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Direct line: +44 (0) 28 9097 6379
Appendix H  Focus group consent form staff

Clinical Staff Participant Consent Form

Title: Feasibility and acceptability of interventions for delirium management in critically ill patient: focus group interviews.

(Please initial box)

I confirm that I have read and understand the participant information sheet titled version 2, dated 14/05/2016.

I understand that participation is voluntary and I am free to withdraw at any time without giving a reason and without my legal right being affected.

I agree to the interview being audiotaped

I understand that all information that I provide will be dealt with in a confidential manner

I agree that my anonymised quotes may be used in publications resulting from the above titled study

I agree to take part in the study

Name of participant (please print): _____________________________________________

Signature: ________________________________________________________________

Date: _________________________________________________________________

Name of person taking consent: ______________________________________________
Appendix I Focus group consent form ICU survivors

ICU Support Group Member Participant Consent Form

Title: Feasibility and acceptability of interventions for delirium management in critically ill patient: focus group interviews.

(Please initial box)

I confirm that I have read and understand the participant information sheet titled version 2, dated 14/05/2016.

I understand that participation is voluntary and I am free to withdraw at any time.

I agree to the interview being audiotaped

I understand that all the information that I provide will be dealt with in a strictly confidential manner.

I agree that my anonymised quotes may be used in publications resulting from the above titled study.

I agree to take part in the study

Name of participant (please print): _____________________________________________

Signature: ________________________________________________________________

Date: _____________________________________________________________________

Name of person taking consent: ______________________________________________
Delirium intervention booklet

DELIRIUM MANAGEMENT INTERVENTION

This delirium intervention is a complex care bundle with 4 separate components. Each component is equally important.

The components of the care bundle are:
1. Education and family participation
2. Sedation minimization and pain, agitation and delirium (PAD) protocol
3. Early mobilisation
4. Environmental interventions

1. EDUCATION AND FAMILY PARTICIPATION

WHO DELIVERS THE INTERVENTION?

Staff education: ICU nurses

Family education: A nurse will provide education about delirium and how to orientate a patient (from the booklet) to any family member of close friend that visits the patient in ICU on a regular basis.

WHAT DOES THE INTERVENTION ENTAIL?

Staff education:

- Patient experience
- Information on family participation, sedation minimization, PAD, early mobilisation, sleep, communication, orientation and cognitive stimulation.
- Train the trainer- teaching staff how to teach families to orientate their loved ones.

Family education
• Distribution of education booklet with information for ICU relatives on how to orientate their relative (ICU patient)
• Staff provide training to families on how to communicate with and orientate the patient and encourage this daily.

WHEN WILL THE INTERVENTION BE DELIVERED?

Staff education:

• Prior to implementation of the bundle.

Family education:

• Booklet should be distributed as soon as the patients’ condition has been stabilised after their ICU/HDU admission

WHERE WILL THE INTERVENTION BE DELIVERED?

Staff education:

• In the conference room or on the unit.

Family education:

• At the bedspace or in the family room.

HOW WILL THE INTERVENTION BE DELIVERED?

Staff education:

• The researcher will provide written and verbal information to staff about how to educate families to communicate and orientate their relatives in the ICU.

Family education:

• Day 1 (patient admitted to ICU)
Researcher or nurse to provide next of kin with a verbal and printed introduction to the booklet. Verbal and written information about the intervention and how and when to use the strategies outlined in the booklet was provided.

• Day 2 to transfer to ward
Nurses actively to seek opportunities to promote family access to patient by effective planning of routine care, maximising the time available for families to be with the patient. When families were with the patient, nurses were to verbally encourage them to interact by talking and holding the patient’s hand. This verbal encouragement was to be given only once during each visit.
2. SEDATION MINIMIZATION AND PAD PROTOCOL

WHO WILL DELIVER THE INTERVENTION?
ICU medical or nursing staff.

WHAT IS THE INTERVENTION?

- Sedation interruption protocol

HOW SHOULD I DELIVER THIS INTERVENTION?

Apply the following safety criteria

1. Is the patient receiving a sedative infusion for active seizures or alcohol withdrawal?
2. Is the patient receiving escalating sedative doses due to on-going agitation?
3. Is the patient receiving neuromuscular blockade?
4. Does the patient have evidence of active myocardial ischaemia in the previous 24h?
5. Does the patient have evidence of increased intracranial pressure?

If the answer is no to all of the above questions then the patient has passed the safety screen.

Patients who fail the screen (Answer yes to any of the above questions) are reassessed the following morning.

What happens if they pass?

Patients who pass the screen undergo an SAT; all sedatives and analgesics used for sedation are interrupted. Analgesics needed for active pain are continued. Patients are monitored by staff for up to 4 hours or more for presence of failure criteria. Patients passed the SAT if they tolerated sedative interruption for 4h or more. When patients fail restart the sedatives at half the previous dose and then titrate to achieve patient comfort.

What are the failure criteria? Conditions denoting failure

1. Active seizures
2. Alcohol withdrawal
3. Neuromuscular blockade
4. Evidence of increased ICP
5. Evidence of active myocardial ischemia in the previous 24h
6. Sustained anxiety
7. Pain
8. RR > 35 bpm for 5 min or longer
9. Acute cardiac dysthyrias
10. 2 or more of the following, bradycardia, tachycardia, use of accessory muscles, abdominal paradox, diaphoresis or marked dyspnoea).

When will it be delivered?
Daily in the morning approximately 8am (Times can be modified to suit unit routine)

Where will it be delivered?
At the patient beds pace

3. EARLY MOBILISATION – Exercise, positioning, activities of daily living

EARLY MOBILITY

WHAT IS THE INTERVENTION?

- Protocol that mandates early mobility based on safety criteria

WHEN SHOULD IT BE DELIVERED?

- Daily for approximately 30 minutes during episodes of sedation interruption provided that the patient passes safety criteria.

HOW?

Every morning a nurse will assess the following safety criteria;

1. Does the patient have a raised ICP?
2. Does the patient have an active GI blood loss?
3. Does the patient have an acute myocardial ischaemia?
4. Does the patient have continuing procedures for example intermittent dialysis?
5. Is the patient agitated and did they need increased sedative administration in the previous 30 min?
6. Does the patient have an unsecure airway?
7. Is the patient distressed? (evidenced by non-verbal cues or gestures)
8. Is the patient being physically combative?
9. Is there a new arrhythmia?
10. Is there a concern for myocardial ischemia?
11. Is there a concern for airway integrity?

What happens if they fail?

If they answer ‘yes’ to any questions then they have failed the safety screen and no early mobilisation should be performed. The patient should be reassessed on the following day.

What happens if they pass?

Unresponsive patients in the intervention group undertake passive range of motion exercises. Therapy will be delivered by a physical therapist or a nurse in consultation with a physiotherapist and coordinated with daily interruption of sedation. Once patient interaction is achieved, sessions progress to active range of motion exercises, bed mobility, sitting/ balance, transfer training and finally pre-gait exercises and walking as tolerated. Progression of activities will be dependent on patient tolerance and stability. Therapy intervention continues on a daily basis throughout the patient’s hospital stay until he or she returns to a previous level of function or is discharged.

What criteria will indicate early mobilisation should be discontinued?

Early mobilisation will be discontinued if the patient has;

1. MAP < 65 mmHg or more than 110 mmHg
2. SBP > 200 mmHg
3. HR < 40 bpm or > 130bpm
4. RR < 5 BPM OR > 40 BPM
5. Pulse oximetry < 88%

POSITIONING:
Daily discussion between physiotherapist and nurse regarding devices for a comfortable position, as well as support elements used for the prevention of pressure ulcers, decreased range of motion and foot drop.

ACTIVITIES OF DAILY LIVING:

Staff and relatives should encourage the patient to carry out grooming, dressing and personal care activities.

4. ENVIRONMENTAL INTERVENTIONS (Sleep, orientation, communication and cognitive stimulation).

SLEEP CHECKLIST

WHO DELIVERS THE INTERVENTION?

• Nurse

WHAT IS THE INTERVENTION?

• Patient daytime interventions:
  - Blinds raised
  - Less than 50% of day shift spent napping

• Patient night-time interventions:
  - Room lights dimmed & curtains closed & warm bath before 11pm
  - Unnecessary alarms prevented
  - Room temperature optimized
  - Pain appropriately controlled
  - Television off
  - Soft music, eye mask and earplugs offered and accepted
  - Medication given per sleep guideline
  - Hallway lights dimmed by 11pm

HOW WILL IT BE DELIVERED?

Daytime interventions:
In the morning from 7am, the nurse will raise the blinds. Staff will also discourage long period of napping throughout the day.

Night-time interventions:

- After 11pm, the nurse will dim lights, turn off TVs, reduce alarm volumes where applicable, offer soft music, earplugs and eye masks to patients and ensure patients are warm and pain free.

WHEN WILL IT BE DELIVERED?

Daytime interventions:

- Daily from 7am.

Night-time interventions:

- Every night from 11pm to 6am.

WHERE WILL IT BE DELIVERED?

In the ICU and at the patient bedside.

ORIENTATION

WHO DELIVERS THE INTERVENTION?

- Nurses and patients’ relatives

What do we need to deliver the intervention?

WHAT IS THE INTERVENTION?

- ‘all about me’ board- a whiteboard with information on a patients preferred names and likes and dislikes completed by patients relatives
- A reorientation strategy informing patients with each interaction about;
  - Who you are?
  - What happened to them?
  - When it happened?
  - Where they are?
  - Why it happened?
  - How it happened?

A clock and calendar with date and time

HOW IS THE INTERVENTIONS DELIVERED?
- Verbal and written Information on ‘all about me’ boards should be given to family as soon as patient is admitted to ICU and stabilised so they can complete the board.
- Staff reorientation strategy by using the five Ws and one H scale, commenced timely as soon as a \(-3 \leq \text{RASS} \leq +3\) is reached and before the onset of the delirium.

- Who are you? Who is the nurse/physician?
- What happened?
- When did it happen?
- Where are you/we?
- Why did it happen?
- How? How did it happen?

- Staff will be encouraged to frequently call the patient by their first name and give information on the ward, hospital, illness progression, length of stay and recent clinical findings, date and time and family details.
- A wall clock & calendar will be placed in front of every ICU bed and the patients will be asked to read newspapers/books, listen music or radio.

WHEN WILL THE INTERVENTION BE DELIVERED?

- With every patient interaction

WHERE WILL THE INTERVENTION BE DELIVERED?

- In the hospital setting

COMMUNICATION

WHO DELIVERS THE INTERVENTION?

- All staff & relatives under supervision of staff

WHAT IS THE INTERVENTION?

- Improving communication for the patient during their ICU stay.

HOW IS THE INTERVENTION DELIVERED?

- Staff will be encouraged to undertake an e-learning communication module (SPEACS 2) and will also be provided with communication tools e.g. picture boards etc.

WHEN WILL THE INTERVENTION BE DELIVERED?

- With each patient interaction
WHERE WILL THE INTERVENTION BE DELIVERED?

- In the ICU environment usually at the patient’s bedspace.

COGNITIVE STIMULATION

WHO DELIVERS THE INTERVENTION?

- Nurses and relatives under supervision of nurses

WHAT IS THE INTERVENTION?

- Staff and/or relatives are encouraged to perform cognitive stimulation (exercises will be provided in a booklet) with patients.

HOW IS THE INTERVENTION DELIVERED?

- If patient has a RASS score of -1 to +1, nurses or family members will do exercises to activate mental functions, grouped into the following areas: alertness, visual perception, memory, calculus, problem solving, praxis, and language for 15 minutes twice a day. Each patient will be given a notebook for cognitive exercises.
- Eye glasses and hearing aids applied as required to patients with sensory deficits.

WHEN IS THE INTERVENTION DELIVERED?

- Twice daily once the patient has a RASS score of -1 to +1.

WHERE IS THE INTERVENTION DELIVERED?

- At the patients’ bedspace.

Table 1: Summary of interventions: who, what, when, where and how

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Education and family participation</td>
<td>- Staff education</td>
<td>Delirium champion</td>
<td>PowerPoint presentation</td>
<td>Prior to implementation of the intervention</td>
<td>Staff room</td>
</tr>
<tr>
<td>Sedation minimization and PAD</td>
<td>- Sedation interruption</td>
<td>Nurse/researcher</td>
<td>Information booklet</td>
<td>Daily as applicable</td>
<td>Relatives room or bedside Bedside</td>
</tr>
<tr>
<td></td>
<td>Assess pain, agitation and delirium (CPOT)</td>
<td>Nurse</td>
<td>Following a protocol. (outlined above) BRS or CPOT pain assessment tool. RASS sedation</td>
<td>Daily</td>
<td>Bedside</td>
</tr>
<tr>
<td><strong>Early mobilisation</strong></td>
<td><strong>Nurse/Physio</strong></td>
<td><strong>Daily</strong></td>
<td><strong>Bedside and around the unit as applicable</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------------</td>
<td>------------------</td>
<td>-----------</td>
<td>---------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Exercise&lt;br&gt; - Positioning&lt;br&gt; - Activities of Daily Living</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positioning</td>
<td>Nurse</td>
<td>With assistance from other nursing staff, nurse will roll patient into a new position</td>
<td>2-4hrly as required</td>
<td>Bed</td>
<td></td>
</tr>
<tr>
<td>ADLs</td>
<td>Nurse/ nurse assistant</td>
<td>Will assist with hygiene needs</td>
<td>Daily</td>
<td>Bedside or bathroom</td>
<td></td>
</tr>
<tr>
<td><strong>Environmental interventions</strong></td>
<td><strong>Nurse</strong></td>
<td>Will follow a protocol to ensure sleep interventions applied.</td>
<td>Daily</td>
<td>Bedside</td>
<td></td>
</tr>
<tr>
<td>Sleep checklist</td>
<td>Nurse</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orientation</td>
<td>Nurse/ family member</td>
<td>Will follow a guideline for orientation and display information about patients likes and dislikes on a ‘this is me’ board</td>
<td>4 hourly</td>
<td>Bedside</td>
<td></td>
</tr>
<tr>
<td>Communication</td>
<td>Nurse/ family member</td>
<td>(1) Nurses will complete one hour online e-learning module. (2) There will be a dedicated box/ trolley with communicatio n materials.</td>
<td>(1) prior to implementatio n of MCT intervention (2) Daily</td>
<td>Bedside</td>
<td></td>
</tr>
<tr>
<td>Cognitive stimulation</td>
<td>Nurse/ family</td>
<td></td>
<td>Twice daily</td>
<td>Bedside</td>
<td></td>
</tr>
</tbody>
</table>
members will use exercises from a cognitive stimulation booklet to help engage the patient.
THE INTENSIVE CARE UNIT ENVIRONMENT

Advice and guidance now that your loved one is a patient in ICU

ADJUSTMENTS

Admission to an intensive care unit (ICU) is often a difficult and stressful event for both the patient and their family. When you first visit the ICU, the surroundings can seem confusing, noisy and overpowering. However, as you spend time visiting you will gradually adjust to the number of nurses and doctors and the amount of equipment that is necessary at the patient's bedside. Explanations and reassurance provided by the staff will help you to understand the care that is being given.

Even though the patient may be given medication to make them sleep, they are still able to hear and to pick up information about their surroundings. Once the level of sedation being received by the patient is reduced, they can slowly wake up to what is happening around them. If you can remember your feelings when you first came into the unit, you will have some understanding of what the patient is now experiencing.

EXPERIENCES

The combination of illness, medication, treatment and being unable to identify the things they see around them may result in the patient experiencing an altered awareness of their surroundings. This problem can be made worse by their inability to experience the usual day and night rhythm of time, which we normally take for granted. Their efforts to understand and come to terms with being in intensive care can often result in a variety of behavioural changes that can be assessed by nurses. Confusion and disorientation are common reactions, often accompanied by having strange dreams. This is called ICU Delirium or ICU Psychosis. This can, understandably, lead to restlessness and fear at times.

SOLUTIONS

Nursing research has suggested various ways in which the effects of these behavioural changes may be reduced. To build new ICUs with plenty of windows and interesting views would be an ideal but impractical solution. Other methods of providing re-orientation for the patient can include clocks and calendars positioned where they can be seen by patients, the use of a television or radio, or listening to their choice of music.

These actions can only be really effective when the patient is awake and can let their family or the nurse know what they would prefer. While the patient is sedated, they can only recognise sound from their environment. If you bear in mind that the voices of nurses are initially those of a stranger, it would make sense to believe that the sound of voices of family members can often be the only recognisable link that patients have with life prior to the uncertainty of their admission to ICU. If those familiar voices are able to give orientation and reassurance to the patient, his or her experience of confusion, fear and vulnerability may be reduced.
GUIDELINES FOR PROVIDING ORIENTATION

WHEN

- Any time which you spend visiting in ICU is an ideal opportunity to use to provide orientation – remember visiting is welcome any time between 2pm and 8pm.

WHAT CAN I DO?

- Greet the patient in your usual manner.
- Begin by letting the patient know what day it is, what time it is and where they are and why. Include any events or occasions that are taking place which you feel the patient would be interested in hearing about.
- Describe the weather and if it has affected your plans of things to do. Remember that the patient will still be familiar with, and interested in the home routine.
- Tell them details of friends and other family members who have called or telephoned home and sent their get well messages. Let the patient know if other members of the family are planning to visit. This means that the patient can think about and anticipate the visit.
- Read out the messages in any cards or letters you or the patient have received. Don’t be afraid to bring these into the ICU – when fully awake the patient will appreciate looking at these. The same goes for any favourite photographs which you feel they would like to see.
- Let them know of family plans for the next few days. Feeling involved in what is happening at home is an important link with reality.

- If the patient has a particular hobby, favourite pet or interest in current news events, make sure that they are kept up to date with the latest!
- Avoid distressing news.
- Tell the patient when you are leaving even for a short break and when you plan to return.

HOW

- There will be times when you may feel awkward talking, particularly if the patient is unable to respond due to sedation or being ventilated. Try not to worry about this, the patient will appreciate hearing the sound of your voice.
- There will also be times when you may feel sad or distressed by the experience you are all going through. Again, just feeling your presence by your holding of their hand can be comforting for both the patient and yourself.
- Remember to sit close enough to the bedside for the patient to hear you. The nurse will be able to advise and assist you if there is lots of equipment around.
- When the patient is able to respond to you, by eye contact or by nodding or shaking their head, try to phrase your questions so that a simple nod or shake will allow them to answer you. Eventually the patient may feel strong enough to use pen and paper to write down their answers (and their questions!). This way they will feel involved in the conversation and will avoid the frustration of being unable to express themselves adequately in spoken words.

Remember that there will always be a nurse nearby to help and reassure you should you feel it necessary. Please ask us.

Additional information

Visiting times
14.00 -20.00

TELEPHONE No’s.
02890 633286 ICU reception 1
02890 633336 ICU reception 2

Where can I park?
Parking cards are available from the ICU receptionist to park in designated parking areas for relatives of critically ill patients.

Accommodation
Accommodation is provided on a nightly basis (check in 10pm check out 10am). Rooms are allocated on a needs basis. Please speak to the bedside nurse.

Useful online resources
ICUSTEPS is a charity that supports ICU survivors and their families. They hold drop in meetings every six weeks on a Wednesday at the Bradbury Clinic, Lisburn Road, Belfast from 18:30 to 20:30. Refreshments provided.

Further information can be found on the ICUsteps website https://belfast.icusteps.org or on our facebook page ICU steps Belfast

Post Intensive Care Unit (ICU) information
Videos and patient testimonials

https://www.icudelirium.org

Breathing techniques for insomnia and anxiety
Some people may find these breathing techniques useful.
1. Buteyko breathing method

http://buteykobreathingireland.ie/controlling-anxiety/

2. 4-7-8 breathing technique


Legal
For information on legal issues and power of attorney please visit:

We are involved in the **DIGNIFY Study**

**Delirium** non-pharmacological interventions in critically ill patients: a **Feasibility Study**

**ICU Delirium**

**INTENSIVE CARE UNIT**

**DIGNIFY** is testing a bundle of non-drug interventions to see if these are feasible and acceptable in ICU.

For more information see the **DIGNIFY** leaflet.

Delirium is a change in awareness and understanding which develops over a short period of time.

In ICU, having delirium is associated with poorer outcomes.

This study is funded by the
PHA Research and Development fund
IRAS no. 223395
## Sleep Checklist

<table>
<thead>
<tr>
<th>Intervention</th>
<th>( N = 735 ) patient-days, n (%)&lt;sup&gt;a,b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blinds raised</td>
<td></td>
</tr>
<tr>
<td>Caffeine avoided after 3pm&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Less than 50% of day shift spent napping&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intervention</th>
<th>( N = 826 ) patient-nights, n (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Room lights dimmed before 10pm</td>
<td></td>
</tr>
<tr>
<td>Room curtain closed before 10pm</td>
<td></td>
</tr>
<tr>
<td>Warm bath before 10pm</td>
<td></td>
</tr>
<tr>
<td>Unnecessary alarms prevented</td>
<td></td>
</tr>
<tr>
<td>Room temperature optimized</td>
<td></td>
</tr>
<tr>
<td>Pain appropriately controlled</td>
<td></td>
</tr>
<tr>
<td>Television off</td>
<td></td>
</tr>
<tr>
<td>Estimated number of nurse interruptions between 10pm-7am</td>
<td></td>
</tr>
<tr>
<td>0-5 interruptions</td>
<td></td>
</tr>
<tr>
<td>6-10 interruptions</td>
<td></td>
</tr>
<tr>
<td>&gt;10 interruptions</td>
<td></td>
</tr>
<tr>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>Soft music offered and accepted&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Eye mask offered and accepted&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Earplugs offered and accepted&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Medication given per sleep guideline&lt;sup&gt;f&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ICU-wide nighttime interventions (( N = 88 ) days), n (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hallway lights dimmed by 10pm</td>
<td>None</td>
</tr>
<tr>
<td>Overhead pages after 10pm</td>
<td>1-3</td>
</tr>
<tr>
<td></td>
<td>&gt;3</td>
</tr>
<tr>
<td></td>
<td>Unknown&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
Appendix N    This is me orientation document

THIS IS ME

Please use this space to attach a photo of your relative/friend, plus anyone who is important to them (including yourself), with details of who they are and what relation they are.

<table>
<thead>
<tr>
<th>Name:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>I like to be called:</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Communication:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>(newspaper, books, large markers, alphabet board)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hearing and vision:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>(glasses, hearing aid)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Daily routine:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>(times, activities)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sleep:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>(routine-what helps)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hobbies/interests:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>(sport, politics, music)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Completed by &amp; date:</th>
<th></th>
</tr>
</thead>
</table>
Appendix O Sample pages Cognitive stimulation booklet
MANUAL OF THERAPEUTIC ACTIVITIES


Please note that this document is not a test of knowledge and understanding and it is perfectly normal to get several answers wrong. Do not worry if you/your relative cannot answer some of these exercises, the process of trying to answer the questions is the important part.
ACTIVITIES FOR COGNITIVE STIMULATION

ORIENTATION TO TIME

Mark the following events in the calender:
- Beginning of new seasons: Spring, summer, autumn, winter
- Bank holidays
ACTIVITIES FOR COGNITIVE STIMULATION

TIME ORIENTATION
MARK IN EACH CLOCK THE TIME STATED BELOW

12:00  11:30  2:20
3:10  15:50  21:15

TIME ORIENTATION
MARK IN EACH CLOCK THE USUAL TIME FOR:

AT HOME
Tomar
Breakfast
Almuerzo
Lunch
Visitting
Time
Lunch
Visita del
Doctors
Round
Watching the
News
ACTIVITIES FOR COGNITIVE STIMULATION

SPATIAL ORIENTATION

IN WHICH AREA CAN YOU FIND THE FOLLOWING PLACES?
### SUSTAINED ATTENTION

Point out the black squares

|   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
SELECTIVE ATTENTION
NAME THE FOLLOWING OVERLAPPING OBJECTS
ACTIVITIES FOR COGNITIVE STIMULATION

+MEMORY

I AM GOING TO TELL YOU A STORY AND WHEN I FINISH, YOU WILL HAVE TO REPEAL WHAT YOU HAVE LISTENED TO WITH AS MUCH DETAIL AS POSSIBLE

"ANA WENT GROCERY SHOPPING AT THE FRUIT SHOP WITH HER TWO YEAR OLD DAUGHTER MARTA. ON THEIR WAY THERE, THEY OBSERVED AN INCIDENT IN WHICH A MIDDLE-AGED MAN STOLE A PURPLE BAG FROM A YOUNG GIRL. THEY DECIDED TO GO TO REPORT IT AT THE POLICE OFFICE AT UNIVERSITY STREET. THE POLICE OFFICER TOOK NOTES OF THE INFORMATION AND ANA AND HER DAUGHTER WERE ABLE TO GO AND DO THEIR PLANNED SHOPPING.

REGISTER THE INFORMATION THAT THE PERSON IS ABLE TO REMEMBER IN AN IMMEDIATE MANNER AND AFTER A 20 MINUTE PERIOD ASK THEM TO REPEAL THE STORY WITH AS MUCH DETAIL AS POSSIBLE

SHORT TERM

MEDIUM TERM
ACTIVITIES FOR COGNITIVE STIMULATION

IMMEDIATE MEMORY

CUT OUT IMAGES AND ASK PATIENT TO MATCH
Answer the information requested.
1. Two wrongs don't...  
2. The early bird ...  
3. The pen is mightier...  
4. When in Rome,...  
5. Fortune favors...  
6. No man is ...  
7. Better late,...  
8. People who live in glass houses...  
9. There's no place...  
10. You can’t judge a book...  
11. Don’t put all your eggs...  
12. Keep your friends close...  
13. Don’t bite the hand...  
14. All that glitters...  
15. Birds of a feather...  
16. Actions speak louder...  
17. A watched kettle...
ACTIVITIES FOR COGNITIVE STIMULATION

EXECUTIVE FUNCTION

Categorisation

Instructions: Ask “What do these words have in common?”

1. Car, bike, motorbike.
2. Ship, boat, submarine.
3. Guitar, drums, saxophone.
4. Trousers, sweater, shirt.
5. Falcon, sparrow, seagull.
6. Pencil, pen, fountain pen.
7. Armchair, shelf, table.
8. Avocado tree, lemon tree, apple tree.
9. Horse, cow, cat.
10. Fork, knife, spoon.
11. Lettuce, cabbage, carrot.
12. Sea, river, lake.
13. Green, blue, yellow.
15. Candle, lamp, streetlight.
16. Plate, cup, pot.
17. Shoe, sandal, slipper.
ACTIVITIES FOR COGNITIVE STIMULATION

LANGUAGE

Understanding

Instructions: Complete the following words with the missing letter:

<table>
<thead>
<tr>
<th>APPL</th>
<th>FLOO</th>
<th>BE</th>
<th>POSSIBL</th>
</tr>
</thead>
<tbody>
<tr>
<td>BACO</td>
<td>MISTE</td>
<td>BANAN</td>
<td>STRAWBERR</td>
</tr>
<tr>
<td>MARKET</td>
<td>SAN</td>
<td>BELFAS</td>
<td>LON</td>
</tr>
<tr>
<td>TRACTO</td>
<td>COLONE</td>
<td>CAMA</td>
<td>XRA</td>
</tr>
<tr>
<td>HOSPITA</td>
<td>BICYCL</td>
<td>LI</td>
<td>SOF</td>
</tr>
</tbody>
</table>
### ACTIVITIES FOR COGNITIVE STIMULATION

#### CALCULATIONS

**IDENTIFICATION OF NUMBERS**

Instructions: Pair the numbers with the text:

<table>
<thead>
<tr>
<th>Numbers</th>
<th>Text</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>Two hundred and twelve</td>
</tr>
<tr>
<td>120</td>
<td>Twenty one</td>
</tr>
<tr>
<td>1200</td>
<td>Two hundred twenty one</td>
</tr>
<tr>
<td>21</td>
<td>Twelve</td>
</tr>
<tr>
<td>212</td>
<td>One hundred and twenty</td>
</tr>
<tr>
<td>2012</td>
<td>Twenty</td>
</tr>
<tr>
<td>221</td>
<td>Two hundred and twelve</td>
</tr>
<tr>
<td>20</td>
<td>One thousand two hundred</td>
</tr>
</tbody>
</table>

Instructions: Put the numbers in order on the line below:

56  45  68  23  52  69  87  78
ACTIVITIES FOR COGNITIVE STIMULATION

Calculation
IDENTIFY THE NUMBERS
Instructions: Complete the sudokus

```
2 3 4 1
1 3
4 2
1 3
```

```
2 4
1 3
4 2
```
ACTIVITIES FOR MOTOR STIMULATION

MOVEMENTS TO FACILITATE ROM

- The exercises marked with a * can be performed with weights to aid muscle strength. Each move is repeated 2 to 5 times, depending on the patient’s tolerance.

Exercise 1*

Areas of work: shoulders, arms, elbows.
Impact: they allow ROM maintenance for reaching, household activities and self care.
Level 1

1. Raise straight arms to shoulder level with palms facing in.
2. Breathe in bringing the elbows backwards, which will lead to scapula adduction.
3. Keep the belly tight.
MOVEMENTS TO IMPROVE STRENGTH

It is recommended to consider the specific characteristics of the patient to determine the intensity of the exercise and the degree of resistance of the elastic band. We do series of 3, starting with repeats of 2 up to a limit of 10. All the movements must be performed slowly, fitting a proper breathing pace.

Exercise 1:
Impact: Maintains ROM for reaching activities of the lower body, getting dressed (lower body).

Level 1 Level 2

1. The subject seats on a wide surface, hands on the sides at hip level.

   Elbows lightly flexed.

   1. Hands on the sides at hip level; elbows lightly flexed.

   2. Take air, extending the elbows, which leads to pushing the body up.

   3. Maintain for 10 to 20 seconds

Exercise 2:
Impact: Maintains ROM for activities that involve reaching of the mid body. Resistance degree: progressively modifiable according to the colour of the elastic band.

Materials: elastic band, 1 lb dumbbells

1. Patient in supine position

2. Adjust elastic band to the stretchers rails. Raise to the ceiling.
<table>
<thead>
<tr>
<th>Activity</th>
<th>Description</th>
<th>Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Domino</td>
<td>Arrange the domino pieces using the last and second last fingers</td>
<td>Change fingers in use (thumb/index, thumb/middle finger, thumb/ting finger and thumb/pinky)</td>
</tr>
<tr>
<td>Threading balls between fingers.</td>
<td>Take the ball with one hand and thread through fingers.</td>
<td>Not applicable.</td>
</tr>
<tr>
<td>Write.</td>
<td>Copy a paragraph from a book, magazine or newspaper.</td>
<td>Increase the length of the paragraph.</td>
</tr>
</tbody>
</table>
HOW CAN THE FAMILY PARTICIPATE?

Favouring the independence of their relative in the basic every day activities (e.g. allowing them, whenever possible, to eat and to do their minor self care activities such as teeth brushing, face and hand washing and hair combing on their own).

Bringing objects that are familiar to the patient such as photographs, watches, music and personal belongings.

Stimulating the patient during visit hours with activities that include cognitive demand (e.g. boardgames - domino, cards... wordsearch and crossword puzzles).

Collaborating in the patient's orientation, reminding them which day or time it is.

Accompaining the patient during the hospitalisation time.

The company and participation of the family is fundamental during hospitalization. We hope we can count on you!
Appendix P  Compliance Checklist

Adherence checklist
Please circle as appropriate (to be completed by day shift nurse by 7pm)

| Education | 1. Did you encourage the family to orientate the patient and participate in care as outlined in the booklet? | Yes/ no/ NA |
| Sedation minimization | 2. Did the patient pass safety criteria for SAT? | Yes/ No |
| | 3. Was sedation stopped? | Yes/ No/ NA |
| Early mobilisation | 4. Did the patient pass safety criteria for early mobilisation? | Yes/ No |
| | 5. Was mobilisation achieved as per protocol? | Yes/ No/ NA |
| Environmental | 6. Did you apply daytime interventions? (Open blinds, discourage napping) | Yes/ No/ NA |
| | 7. Did you use communication tools with your patient? | Yes/ no/ NA |
| | 8. Which tools? ................. | (Dropdown options) |
| | | Picture boards |
| | | Pen & paper |
| | | Electronic device |
| | | other |
| | 9. Did you orientate your patient regularly? | Yes/ no/ NA |
| | 10. Did you carry out cognitive stimulation with this patient? | Yes/ no/ NA |
| | 11. Did the relative carry out cognitive stimulation with this patient? | Yes/ no/ NA |
| | 12. How long was the cognitive stimulation time in total? | _______ minutes |
| | 13. What pages did you cover in the booklet? | Pages _............________ |

Checklist no. 2: Nighttime activities checklist for intervention compliance (Complete at 11pm)
Adherence checklist
Please circle as appropriate (to be completed by night shift nurse by 7am)

<p>| Did the nurse apply night-time interventions? (TV, Lights off by 11pm, personalise alarm limits, offer soft music/earplugs/ eye mask, warm bed bath by 11pm) | Yes/ no/ NA |
| If no, why? (insert intervention that has not been delivered and reason) | Freeform row |</p>
<table>
<thead>
<tr>
<th>Construct</th>
<th>Short Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>I. INTERVENTION CHARACTERISTICS</strong></td>
<td></td>
</tr>
<tr>
<td><strong>A</strong> Intervention Source</td>
<td>• Educate staff about how the intervention was developed using current evidence (Systematic review) and feedback from experts and service providers and users</td>
</tr>
<tr>
<td><strong>B</strong> Evidence Strength &amp; Quality</td>
<td>• Discuss the findings from the systematic review and focus group interviews with staff</td>
</tr>
<tr>
<td><strong>C</strong> Relative Advantage</td>
<td>• Discuss any alternative solutions with staff and get their input</td>
</tr>
<tr>
<td><strong>D</strong> Adaptability</td>
<td>• Discuss with local stakeholders how the intervention can be tailored and adapted to meet the needs of their unit</td>
</tr>
<tr>
<td><strong>E</strong> Trialability</td>
<td>• Discuss with stakeholders the plan to roll out the intervention in a feasibility study over a three month period and provide a channel for them to communicate any issues</td>
</tr>
<tr>
<td><strong>F</strong> Complexity</td>
<td>• Share with stakeholders the barriers identified in focus group interviews (Poor education/awareness of delirium, safety concerns, ICU culture, relatives anxiety, poor communication skills, staff workload) and plans to overcome these (education/awareness sessions with all staff over a one month period about delirium outcomes, patients perspective of delirium and interventions prior to implementation of the intervention, communication training and provision of tools, education booklet for relatives with guidelines for educating them to assist with orientation, communication and cognitive stimulation, protocols to ensure safety during early mobilization and sedation minimization and open communication with management to ensure unit adequately staff to ensure staff workload is not excessive).</td>
</tr>
<tr>
<td><strong>G</strong> Design Quality &amp; Packaging</td>
<td>• The bundle will be presented in an intervention booklet with information on how each component should be delivered and detailed protocols on sedation minimization, orientation, early mobilization and sleep. Laminated safety criteria will be available for the bedspace to ensure they adhere to infection control guidelines.</td>
</tr>
</tbody>
</table>
### Cost

- Materials for the intervention have been provided from an R & D Doctoral Fellowship Award;
  - Tablets x 20 £3169.80
  - Day and month digital clock x 20 £779.80
  - Resistance bands x 20 £179.80
  - white boards x 20  £199.80
  - Storage trolley for communication tools £59.59
  - Communication picture boards x 10 £598.80

Access to SPEACS 2 communication e learning for 100-150 staff £800 ($1000)

- Additional costs will be required to purchase laminate paper, paper, ink, materials for communication trolley such as wide grip markers, communication applications on the tablet and printing costs for posters.

### II. OUTER SETTING

<table>
<thead>
<tr>
<th>A</th>
<th>Patient Needs &amp; Resources</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Include management and senior staff in discussions about prioritizing education for the bundle and ensuring adequate staffing to deliver the bundle</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B</th>
<th>Cosmopolitanism</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Discuss networking opportunities i.e. patient visits to provide feedback to staff on their experiences,</td>
</tr>
<tr>
<td></td>
<td>Discuss opportunities with nursing management for staff to go and visit other organisations that have initiated similar programmes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>C</th>
<th>Peer Pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Discuss opportunities with nursing management to benchmark against other organisations</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>D</th>
<th>External Policy &amp; Incentives</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Discuss with management recommendations and guidelines from the Society of Critical Care Medicine (SCCM) and NICE that recommend non-pharmacological interventions for critically ill patients to address delirium.</td>
</tr>
</tbody>
</table>

### III. INNER SETTING

<table>
<thead>
<tr>
<th>A</th>
<th>Structural Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Discuss structural characteristics of the unit for example; areas available for mobilisation, space for storage of communication trolley, mobilisation aids etc.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B</th>
<th>Networks &amp; Communications</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Discuss the best forms of communication to deliver information directly related to the bundle for example posters in the staff room, toilets, emails to staff email, face to face at bedside and team study days</td>
</tr>
<tr>
<td>C</td>
<td>Culture</td>
</tr>
<tr>
<td>D</td>
<td>Implementation Climate</td>
</tr>
<tr>
<td>1</td>
<td>Tension for Change</td>
</tr>
<tr>
<td>2</td>
<td>Compatibility</td>
</tr>
<tr>
<td>3</td>
<td>Relative Priority</td>
</tr>
<tr>
<td>4</td>
<td>Organizational Incentives &amp; Rewards</td>
</tr>
<tr>
<td>5</td>
<td>Goals and Feedback</td>
</tr>
<tr>
<td>6</td>
<td>Learning Climate</td>
</tr>
<tr>
<td>E</td>
<td>Readiness for Implementation</td>
</tr>
<tr>
<td>1</td>
<td>Leadership Engagement</td>
</tr>
<tr>
<td>2</td>
<td>Available Resources</td>
</tr>
<tr>
<td>3</td>
<td>Access to Knowledge &amp; Information</td>
</tr>
<tr>
<td>IV. CHARACTERISTICS OF INDIVIDUALS</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>Knowledge &amp; Beliefs about the Intervention</td>
</tr>
</tbody>
</table>
### B  Self-efficacy
- Assess individuals personal needs and assist with additional training if necessary

### C  Individual Stage of Change
- Assess what stage of change an individual is at; skilled, enthusiastic and sustained use of the intervention

### D  Individual Identification with Organization
- Assess loyalty of individuals to the organization and discuss how they can use implementation of the bundle to improve person centred care in the organisation

### E  Other Personal Attributes
- Assess individuals learning style and motivations and try to align these with educational approach

### V. PROCESS
#### A  Planning
- Use a framework to develop the interventions (for example MRC framework for the development of complex interventions)
- Use a framework to plan out your implementation
  - Pronovost translating evidence into practice model
  - Summarise the evidence (SR)
  - Identify local barriers (focus groups or questionnaires or informal discussions with staff)
  - Do a ‘walk through’ of the bundle to identify problems
  - Measure performance (Choose outcome and process measures, measure baseline period, adherence to the intervention, get feedback from staff)
  - Ensure all patients receive the interventions
  1. engage staff- explain why bundle is important
  2. educate staff – share evidence from SR
  3. execute – Design an intervention booklet with standardized protocols for sedation minimization, early mobilization, orientation, communication and sleep to address barriers identified
  4. evaluate- Assess performance measures for example adherence of the intervention and qualitative interviews or questionnaires

#### B  Engaging
- Explain the importance of the intervention

#### 1  Opinion Leaders
- Recruit champions from the senior staff and management
<table>
<thead>
<tr>
<th></th>
<th>Role</th>
<th>Tasks</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Formally Appointed</td>
<td>Identify somebody to lead the project</td>
</tr>
<tr>
<td></td>
<td>Internal Implementation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Leaders</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Champions</td>
<td>Recruit delirium champions from the nursing staff</td>
</tr>
<tr>
<td>4</td>
<td>External Change Agents</td>
<td>Invite prominent delirium experts to speak to staff</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Invite ICU survivors to discuss their delirium journey</td>
</tr>
<tr>
<td>C</td>
<td>Executing</td>
<td>Design an intervention booklet which explicitly describes how each</td>
</tr>
<tr>
<td></td>
<td></td>
<td>component of the bundle should be delivered, set reminders on</td>
</tr>
<tr>
<td></td>
<td></td>
<td>computer system to deliver intervention components</td>
</tr>
<tr>
<td>D</td>
<td>Reflecting &amp; Evaluating</td>
<td>Request informal feedback from staff during implementation period</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carry out qualitative interviews or questionnaires post implementation phase</td>
</tr>
</tbody>
</table>
PART B Implementation plan using Pronovost model for translating evidence into practice

1. Summarise the evidence

Identify interventions associated with improved outcomes (Systematic review)
Select interventions with the largest benefit and lowest barriers to use (Systematic review, expert panel and focus group interviews)
Convert interventions to behaviours i.e. what behaviours are required for intervention to be implemented

2. Identify local barriers to implementation

Observe staff performing the interventions (trial introduction of interventions)
'Walk the process' to identify each step of implementation (Trial introduction of interventions)
Enlist all stakeholders to share concerns and identify potential gains and losses associated with implementation (delirium champions MDT)

3. Measure performance

Select measures (process or outcome) (Delirium outcomes and intervention adherence and fidelity)
Develop and pilot test measures (adherence checklist)
Measure baseline performance (before and after)

4. Ensure all patients receive the intervention

Engage (explain why interventions are important)
Educate (group and one to one teaching)
Execute (intervention manual with standardised protocols, checklists and tools)

Evaluate (Measure adherence and do qualitative work to assess barriers)
Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study:

1. In the Registered Medical Practitioner (RMP) Information Sheet under the section entitled “Does the patient have to take part?” the 3rd sentence beginning “If you advise us that…” should be replaced with wording as follows: “If you advise us that in your opinion, inclusion of the patient in this research study is in his/her best medical interests and therefore you would have no objection to the patient taking part in the study, you will be given this information sheet to keep and will be asked to sign a registered medical practitioner assent form.”

2. In the RMP Assent Form at number 3, the wording must be strengthened as follows: “In my opinion, inclusion of the above named patient in this research study is in his/her best medical interests. I have no objection and am not aware of any objections to the patient named above being enrolled in the above named study.”

3. The term ‘personal consultant’ or ‘personal representative’ is not relevant in Northern Ireland and should be replaced with ‘close relative/husband’. The following documentation should therefore be amended accordingly:
   - RMP Assent Form
   - RMP Information Sheet
   - Personal Consultant Covering Statement and Information Sheet
   - Personal Consultant Assent Form
   - Personal Consultant Assent Form after RMP Assent
   - Personal Consultant Telephone Assent Form
   - Telephone Assent Script
   - Any other participant facing documentation which contains the term ‘personal consultant’ that has not been mentioned above.

4. A statement must be added to the Telephone Consultant Agreement Form as follows: “I confirm that the close relative/husband (indicate status) of the patient has given verbal assent for the patient to take part in the study.”

5. The term ‘legal representative’ in the Risk Assessment document is not a valid term for non-CITMP study and must therefore be removed.

The Sub-committee recommended, for information and noting, that future applications to the Committee should include all relevant documentation/information for review at the REC Meeting. For example the Committee had raised a concern with regard to re-commencement ofедакцию as it was not clear that if cessation was re-started at the normal dose, it would then be titrated in line with the patient's condition.

You should notify the REC once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. Revised documents should be submitted to the REC electronically from IRAS. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which you can make available to host organisations to facilitate their permission for the study. Failure to provide the final version to the REC may cause delay in obtaining permissions.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all HSC organisations involved in the study in accordance with HSC research governance arrangements. Each HSC organisation must confirm, through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centres"), guidance should be sought from the R&D office on the information it requires to give permission for the activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS Star page) must be registered on a publicly accessible database within 5 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the RRC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact info.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non-registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the IRAS website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS R&D office prior to the start of the study (see "Conditions of the favourable opinion" above).

Non-NHS sites

The Committee has not yet completed any site-specific assessment (SSA) for any non-NHS research sites taking part in this study. The favourable opinions do not therefore apply to any non-NHS site at present. We will write to you again as soon as an SSA application(s) has been reviewed. In the meantime no study procedures should be initiated at non-NHS sites.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

<table>
<thead>
<tr>
<th>Document</th>
<th>Version</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Copies of advertisement materials for research participants</td>
<td>1.0</td>
<td>30 January 2018</td>
</tr>
<tr>
<td>Covering letter on headed paper (Consultant)</td>
<td></td>
<td>03 March 2018</td>
</tr>
<tr>
<td>Covering letter on headed paper (Response letter to RRC)</td>
<td></td>
<td>03 March 2018</td>
</tr>
<tr>
<td>Evidence of Sponsor insurance or indemnity (non NHS Sponsors only)</td>
<td></td>
<td>28 March 2018</td>
</tr>
<tr>
<td>Interview schedules or topic guides for participants Interview guide</td>
<td>1.0</td>
<td>01 March 2018</td>
</tr>
<tr>
<td>RAS Application Form (RAS Form)</td>
<td>1.0</td>
<td>28 March 2018</td>
</tr>
<tr>
<td>RAS Checklist, IN (Chesham)</td>
<td>1.0</td>
<td>28 March 2018</td>
</tr>
<tr>
<td>RAS Checklist, IN (Chesham)</td>
<td>1.0</td>
<td>28 March 2018</td>
</tr>
<tr>
<td>Letter from sponsor</td>
<td>1.0</td>
<td>28 March 2018</td>
</tr>
<tr>
<td>Other Study materials</td>
<td>1.0</td>
<td>03 March 2018</td>
</tr>
<tr>
<td>Other (Governor of AS)</td>
<td>1.0</td>
<td>28 April 2018</td>
</tr>
<tr>
<td>Other (IRAS A Response Memo From Sponsor)</td>
<td>1.0</td>
<td>28 April 2018</td>
</tr>
<tr>
<td>Other (Registered Medical Practitioner Consent Form)</td>
<td>1.0</td>
<td>28 April 2018</td>
</tr>
<tr>
<td>Other (Registered Medical Practitioner Information sheet)</td>
<td>1.0</td>
<td>28 April 2018</td>
</tr>
<tr>
<td>Other (Personal care homes covering statement and information leaflet)</td>
<td>1.0</td>
<td>28 April 2018</td>
</tr>
<tr>
<td>Other (Personal Consultancy Consent form)</td>
<td>1.0</td>
<td>28 April 2018</td>
</tr>
<tr>
<td>Other (Personal Care Homes Care Consent form)</td>
<td>1.0</td>
<td>28 April 2018</td>
</tr>
<tr>
<td>Other (Personal Consultancy Telephone consent form)</td>
<td>1.0</td>
<td>28 April 2018</td>
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<tr>
<td>Other (Street View Stereo)</td>
<td>1.0</td>
<td>28 April 2018</td>
</tr>
<tr>
<td>Other (Letter from ICU Consultant Risk Assessment of Dublin study Dr Jim Stenhouse)</td>
<td>1.0</td>
<td>28 April 2018</td>
</tr>
<tr>
<td>Other (Letter from Co-Investigator DNA response to RRC risk assessment)</td>
<td>1.0</td>
<td>28 April 2018</td>
</tr>
<tr>
<td>Other (Clinical Staff Participant Information sheet for Focus group)</td>
<td>1.0</td>
<td>28 April 2018</td>
</tr>
<tr>
<td>Other (Clinical Staff participant consent form for focus group interview)</td>
<td>1.0</td>
<td>28 April 2018</td>
</tr>
<tr>
<td>Other (CINSYS Risk Assessment 1: 20 April 2019 signed by CI and AS)</td>
<td>1.0</td>
<td>28 April 2018</td>
</tr>
<tr>
<td>Patient consent form (Enrolled capacity Patient Information sheet)</td>
<td>1.0</td>
<td>28 April 2018</td>
</tr>
<tr>
<td>Patient consent form (Enrolled Capacity Consent Form)</td>
<td>1.0</td>
<td>28 April 2018</td>
</tr>
<tr>
<td>Referees' report or other scientific critique report (Peer review report)</td>
<td>1.0</td>
<td>28 April 2018</td>
</tr>
<tr>
<td>Research protocol or project proposal (Protocol Feasibility study)</td>
<td>1.0</td>
<td>28 April 2018</td>
</tr>
<tr>
<td>Summary CV for Chief Investigator (CI)</td>
<td>1.0</td>
<td>28 April 2018</td>
</tr>
<tr>
<td>Summary CV for student (Student CV)</td>
<td>1.0</td>
<td>28 April 2018</td>
</tr>
<tr>
<td>Summary CV for supervisor (student) (Supervisor CV)</td>
<td>1.0</td>
<td>28 April 2018</td>
</tr>
</tbody>
</table>

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees.
Committees in the UK.

After ethical review

Reporting requirements

The attached document “After ethical review – guidance for researchers” gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: [http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/](http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/).

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at [http://www.hra.nhs.uk/hra-training/](http://www.hra.nhs.uk/hra-training/).

| 18/NI/0053 | Please quote this number on all correspondence |

With the Committee’s best wishes for the success of this project.

Yours sincerely

pp
Dr Alastair Walker
Acting Chair, HSC REC A

Email: [RECA@hseni.net](mailto:RECA@hseni.net)

Enclosures: “After ethical review – guidance for researchers”

Copy to: Mr Stephen Liggett, Queens University Belfast
Dr Alison Murphy, Belfast Health and Social Care Trust
Appendix S  RMP information sheet
Use of Delirium non-pharmacological interventions in critically ill patients: a Feasibility study (DIGNIFY)

Registered Medical Practitioner (RMP) Information Sheet

What is the purpose of the study?
Many patients admitted to the Intensive Care Unit (ICU) have a high risk of developing delirium. This delirium has been associated with worse outcomes for patients; longer time spent in hospital, as well as difficulty concentrating and impaired memory. We carried out a systematic review and meta-analysis to determine which non-pharmacological interventions were effective in reducing the incidence and/or duration of delirium in ICU and asked international delirium experts, United Kingdom multidisciplinary ICU staff, ICU survivors and their families their opinions on the interventions tested. There is evidence that a group of non-drug interventions have been effective in reducing delirium in non-ICU patients but it is unclear if this strategy is effective in critically ill patients. This study wants to determine if there is adherence with the non-drug interventions (education of staff and relatives, reducing sedation, early physical and occupational therapy and environmental interventions such as sleep promotion, orientation, communication and cognitive and sensory stimulation) that were identified in the systematic review and deemed feasible by experts, staff and survivors in clinical practice in the ICU.

Why has the patient been chosen?
The intensive care staff have decided your this patient may be at high risk of developing delirium. We do not know if non-drug interventions will stop them getting delirious or reduce the time they spend delirious or if they are practical to deliver in the intensive care unit i.e. do staff have the time and resources required. Therefore, we would like them to take part in this study to help us find out whether non-drug interventions are practical to deliver to critically ill patients in the intensive care unit.

Does the patient have to take part?
It is up to you to decide whether or not you wish to provide us with this advice. As we are unable to contact a close relative/friend for the patient at present, we are asking for your advice.

If you advise us that in your opinion, inclusion of the patient in this research study is in his/her best medical interests and therefore you would have no objection to the patient taking part in the study, you will be given this information sheet to keep and will be asked to sign a registered medical practitioner assent form.‘

You are still free at any time to request the patient is withdrawn from the study without giving a reason. If a close relative/friend becomes available then they will be approached to ask their advice/ assent on whether the patient would like to be included in the study. This assent will override the registered medical practitioner assent.

What will happen to the patient if they take part?

Patients who join the study in phase one will receive the same care as other critically ill patients but data will be collected on their sedation and delirium scores, sleep, and exercise during their ICU stay. Patients who join the study in phase two will be managed on a protocol delivered by ICU staff that will include education and family participation, sedation minimization, early physical and occupational therapy and environmental interventions incorporating sleep promotion, orientation, communication and cognitive stimulation.

Education involves receiving a booklet that outlines what delirium is and how you can help your relative while they are in the intensive care unit. This will also be encouraged by nursing staff. Reducing sedation involves a protocol that nursing staff will follow to stop sedation daily once the patient meets safety criteria to assess their level of awareness. Early mobilisation will take place during this period of reducing sedation and will start with passive range of motion (ROM) (moving the patients limbs) and active ROM (asking patients to move their own limbs) and progress daily once patients meet safety criteria. The environmental protocol will include a sleep checklist, an orientation board that will be completed by families with details about patients likes and dislikes so staff can communicate with the patients more effectively and communication, orientation and cognitive and multisensory stimulation. During this phase, information will be collected on delirium status, sedation scores, sleep, exercise and compliance with the bundle of non-drug interventions.
Their medical notes will be reviewed by the doctors and nurses, to find out if the treatment that the patient has received has been delivered. The study team will review the patient's progress on a daily basis.

What are the possible benefits and disadvantages of taking part?
Taking part in this study may contribute to improved treatment of patients at risk of delirium in the future. A similar study was carried out in hospitalised older patients in a general medicine cohort and they found that there were no adverse effects associated with the interventions. This protocol targeted six risk factors for delirium cognitive impairment, sleep deprivation, immobility, visual impairment, hearing impairment and dehydration.
To minimise any potential risks, interventions such as reducing sedation and early mobilisation will not be performed unless certain safety criteria have been met. This will be discussed and agreed with the consultant body of the intensive care unit.

The doctors will monitor all people taking part in the study to ensure that any side effects are picked up early, and they will stop the study treatment if a serious adverse event occurs.

What if something goes wrong?
Every effort will be made to ensure that no patient taking part in this study is put at risk or harmed in any way. It is unlikely that anything will go wrong as a result of taking part in this study. If you have any concerns about any aspect of this study, you should contact the CI, Professor Bronagh Blackwood (contact details below), who will do her best to answer your questions. If you remain unhappy and wish to complain formally, you can do this through the normal NHS Complaints Procedure.
If something does go wrong and your relative/friend/partner is harmed due to someone's negligence, then they may have grounds for a legal action against their NHS Trust but you may have to pay for it.

Would the patient taking part in this study be kept confidential?
Any information collected about the patient during the course of the study will be kept strictly confidential and will only be seen by staff involved in the study from the NHS Trust, Queen’s University Belfast and people from regulatory authorities who ensure that studies such as this are carried out correctly. All of them will have a duty of confidentiality to the patient as a research participant.
Because we need to contact your patient after they leave hospital, the principle investigator will need to keep records of their name, address and other contact details. Confirmation of their health status may also be sought from their GP surgery. In addition, information held and maintained by central UK NHS bodies, and organisations contracted to provide services to the NHS, may be used to access data collected routinely during your relative/friend/partner’s stay in hospital and to ascertain their long term patient health status. In this instance only their NHS number/ hospital number, postcode and date of birth will be used. All other personal data will remain anonymised. This information will be used only for this study and will not be given to anyone else.

The patient has the right to see their personal health information related to the research study, but they will not be able to review some parts of the information until after the study has finished. When any information from the study is published it will not contain any personal information and it will not be possible to identify any individual.

The data from this study will be kept for at least 5 years after its conclusion (medical records will be kept for 15 years), and may be used in other research studies; data may be retained by the Belfast Health and Social Care Trust and Queen’s University Belfast. Any study data retained/used will have all personal identifiers removed and it will not be possible to identify any individual.

**What will happen to the results of the research study?**

The study is expected to take six months. It is envisaged that publication of the results will follow shortly after this, through medical publications, websites and press releases. At this point we will be happy to forward a summarised version of the principle findings of the results of the study at the patient’s request.

**Who is organising and funding the study?**

The above named study is being organised by a group of doctors and nurses led by Professor Bronagh Blackwood, who is a chair in critical care research at Queen’s University Belfast, Northern Ireland. It is funded by a Research and Development Fellowship from the Public Health Agency in Northern Ireland. The Sponsor of the study is Queen’s University Belfast.
Who has reviewed the study?
This research has been reviewed by an independent group of people, called a Research Ethics Committee (REC), to protect the patient’s safety, rights, wellbeing and dignity. This study has been given a favourable opinion by the REC.

What happens if I have any questions, concerns or complaints about the study?
If you have any questions about the patient’s participation in this study or concerns about the way it has been carried out, you should contact your hospital’s Principle Investigator or a member of the research team.

What happens if I don’t want the patient to carry on with the study?
You are free to request the patient is withdrawn from the study at any time and without giving a reason. This will not affect the standard of care they receive. Your study team can take them out of the study at any time if it is in their best medical interests to stop their participation.

If you have any questions that remain unanswered, the study doctor or research nurse will be happy to answer these for you. If you require any further information you may contact the Principle Investigator [details below].

Thank you for taking the time to read this Information Sheet.

CONTACT DETAILS:
Chief Investigator:
Name: Prof Bronagh Blackwood
Address: Wellcome Wolfson Institute for Experimental Medicine
Queen’s University Belfast,
Lisburn road,
Belfast,
Northern Ireland.

BT9 7BL
Telephone: 028 9097 6379

One original to ISF. Copy to RMP. Copy to patient’s medical notes
Registered Medical Practitioner Form
Principal Investigator
Name: Leona Bannon
Address: Regional Intensive Care Unit
         Royal Victoria Hospital
         Grosvenor road
         Belfast
         BT12 6BA
Telephone: 028 9063 3286

Complaints/concerns:
Name: Dr Aoibhin Hutchinson
Address: Regional Intensive Care Unit
         Royal Victoria Hospital
         Grosvenor road
         Belfast
         BT12 6BA
Telephone: 028 9063 3286
Appendix T  RMP assent form

Use of Delirium non-pharmacological interventions in critically ill patients: a Feasibility study (DIGNIFY)

Registered Medical Practitioner Assent Form
To be given with Information Sheet

This form should be completed by a doctor who is unconnected with this research study only in situations where there is no close relative/friend/partner available to provide assent.

Name of Participant: ...........................................................................................................

Participant Study No: .................................................................................................

Name of Investigator: ........................................................................................................

Please initial box

1. I confirm that I am the doctor responsible for the Intensive Care Unit treatment of the patient named above and I agree to act as a Registered Medical Practitioner (RMP) for the patient. I confirm that I am not connected with the conduct of this study.

2. I have read the Information Sheet and understand what the study involves, including inclusion and exclusion criteria.

3. In my opinion, inclusion of the above named patient in this research study is in his/her best medical interests. I have no objection and am not aware of any objections to the patient named above being enrolled in the above named study.

4. I understand that in the event that a close relative/friend is identified after RMP advice is obtained, the close relative/friend declaration will be sought. I agree that the close relative/friend’s declaration will override my advice.

5. I understand that should the patient regain capacity they will be informed of the decision to enter them into this study and consent will be sought from them for their continued participation. I agree that the patient’s consent will override my advice when the patient is able to give informed consent.

______________________________  ____________________  ____________________
Name of Registered Medical Practitioner  Date  Signature

______________________________  ____________________  ____________________
Name of Person taking consent  Date  Signature

One original to ISF. Copy to RMP. Copy to patient’s medical notes
Registered Medical Practitioner Form  v1.2_14.05.18
Use of *Delirium non-pharmacological interventions in critically ill patients: a Feasibility study (DIGNIFY)*

**Covering Statement and Information Sheet for close relative/ friend**

A study to determine whether a multicomponent non-pharmacological intervention for delirium is feasible in critically ill patients.

We would like your relative/friend/partner to take part in a research study while they are a patient in this Intensive Care Unit. Unfortunately, your relative/friend/partner is not well enough to be able to decide for themselves whether or not to participate. Therefore we ask if you would read the Information Sheet carefully and give your opinion as to whether or not you think your relative/friend/partner would be willing to participate in this medical research. You may discuss this with others if you wish.

When your relative/friend/partner has regained consciousness and has the ability to understand the purpose of this study, we will explain the study to them and seek their permission to continue to participate in the research. Your relative/friend/partner’s decision to continue in the study or withdraw will override the assent you have given.

If you have any further questions either now or at any time subsequently, please feel free to contact a member of the research team (details at the end of the Information Sheet).

**Thank you for your time in considering this request.**

One original to ISF.  Copy to close relative/friend.  Copy to Patient’s medical notes

Covering Statement, IS and Consent Form for close relative/friend  _v1.2_ 14.05.18
Use of Delirium non-pharmacological interventions in critically ill patients: a Feasibility study (DIGNIFY)

What is the purpose of the study?
Many patients admitted to the Intensive Care Unit (ICU) have a breathing machine, or ventilator, to help them breathe and ensure that enough oxygen gets into their blood. They need some sedative and painkilling drugs while they are on the ventilator to keep them comfortable. For reasons that are unclear often patients in this condition become temporarily confused, delirious, while on the ICU. This delirium has been associated with worse outcomes for patients; longer time spent in hospital, as well as difficulty concentrating and impaired memory. There is evidence that a group of non-drug interventions have been effective in reducing delirium in non-ICU patients but it is unclear if this strategy is effective in critically ill patients. This study is to see if these non-drug interventions (education of staff and relatives, reducing sedation, early physical and occupational therapy and environmental interventions such as sleep promotion, orientation, communication and cognitive and sensory stimulation) are actually feasible in ICU.

Why has your relative/friend/partner been chosen?
The intensive care doctors have decided your relative/friend/partner may be at risk of developing delirium. We do not know if non-drug interventions will stop them getting delirium or reduce the time they spend delirious or if they are practical to deliver in the intensive care unit i.e. do staff have the time and resources required. Therefore, we would like them to take part in this study to help us find out whether non-drug interventions are practical to deliver to critically ill patients in the intensive care unit.
Does my relative/friend/partner have to take part?

It is up to you to decide whether or not your relative/friend/partner takes part. If you do decide that they can take part, you will be given this information sheet to keep and will be asked to sign a study assent form. You are still free at any time to withdraw your assent for your relative/friend/partner to take part without giving a reason. If you decide that your relative/friend/partner should not take part the standard of care they will receive will not be affected.

What will happen to my relative/friend/partner if they take part?

Patients who join the study in phase one will receive the same care as other critically ill patients but data will be collected on their sedation and delirium scores, sleep, and exercise during their ICU stay. Patients who join the study in phase two will be managed on a protocol delivered by ICU staff that will include education of families, reducing sedation, early physical activity and exercise and an environmental checklist to ensure a good nights sleep, orientation, communication and stimulation of the brain and the senses.

Education involves receiving a booklet that outlines what delirium is and how you can help your relative while they are in the intensive care unit. This will also be encouraged by nursing staff. Reducing sedation involves a protocol that nursing staff will follow to stop sedation daily once the patient meets safety criteria to assess their level of awareness. Early mobilisation will take place during this period of reducing sedation and will start with passive range of motion (ROM) (moving the patients limbs) and active ROM (asking patients to move their own limbs) and progress daily once patients meet safety criteria. The environmental protocol will include a sleep checklist, an orientation board that will be completed by families with details about patients likes and dislikes so staff can communicate with the patients more effectively and communication, orientation and cognitive and multisensory stimulation. During this phase, information will be collected on delirium status, sedation scores, sleep, exercise and compliance with the bundle of non-drug interventions.

Their medical notes will be reviewed by the doctors and nurses, to find out if the treatment that your relative/friend/partner has received has been delivered. The study team will review your relative/friend/partner’s progress on a daily basis.
What are the possible benefits and disadvantages of taking part?
Taking part in this study may contribute to improved treatment of patients at risk of delirium in the future. A similar study was carried out in hospitalised older patients in general medicine and they found that there were no adverse effects associated with the interventions. This protocol targeted six risk factors for delirium cognitive impairment, sleep deprivation, immobility, visual impairment, hearing impairment and dehydration.
To minimise any potential risks, interventions such as reducing sedation and early mobilisation will not be performed unless certain safety criteria have been met. This will be discussed and agreed with the consultant body of the intensive care unit. The doctors will monitor all people taking part in the study to ensure that any side effects are picked up early, and they will stop the study treatment if a serious adverse event occurs.

What if something goes wrong?
Every effort will be made to ensure that no patient taking part in this study is put at risk or harmed in any way. It is unlikely that anything will go wrong as a result of taking part in this study. If you have any concerns about any aspect of this study, you should contact the CI, Professor Bronagh Blackwood (contact details below), who will do her best to answer your questions. If you remain unhappy and wish to complain formally, you can do this through the normal NHS Complaints Procedure. If something does go wrong and your relative/friend/partner is harmed due to someone’s negligence, then they may have grounds for a legal action against their NHS Trust but you may have to pay for it.

Would your relative/friend/partner taking part in this study be kept confidential?
Any information collected about your relative/friend/partner during the course of the study will be kept strictly confidential and will only be seen by staff involved in the study from the NHS Trust, Queen’s University Belfast and people from regulatory authorities who ensure that studies such as this are carried out correctly. All of them will have a duty of confidentiality to your relative/friend/partner as a research participant.
Because we may need to contact your relative/friend/partner after they leave hospital, the principle investigator will need to keep records of their name, address and other contact details. Confirmation of their health status may also be sought from their GP surgery. In
addition, information held and maintained by central UK NHS bodies, and organisations
contracted to provide services to the NHS, may be used to access data collected routinely
during your relative/friend/partner’s stay in hospital and to ascertain their long term patient
health status. In this instance only their NHS number/ hospital number, postcode and
date of birth will be used. All other personal data will remain anonymised. This information
will be used only for this study and will not be given to anyone else.

Your relative/friend/partner has the right to see their personal health information related
to the research study, but they will not be able to review some parts of the information
until after the study has finished. When any information from the study is published it will
not contain any personal information and it will not be possible to identify any individual.

The data from this study will be kept for at least 5 years after its conclusion (medical
records will be kept for 15 years), and may be used in other research studies; data may
be retained by the Belfast Health and Social Care Trust and Queen’s University Belfast.
Any study data retained/used will have all personal identifiers removed and it will not be
possible to identify any individual.

What will happen to the results of the research study?
The study is expected to take six months. It is envisaged that publication of the results
will follow shortly after this, through medical publications, websites (including INVOLVE
www.invo.org.uk) and press releases. At this point we will be happy to forward a
summarised version of the principle findings of the results of the study at your
relative/friend/partner’s request.

Who is organising and funding the study?
The above named study is being organised by a group of doctors and nurses led by
Professor Bronagh Blackwood, who is a chair in critical care research at Queen’s
University Belfast, Northern Ireland. It is funded by a Research and Development
Fellowship from the Public Health Agency in Northern Ireland. The Sponsor of the study
is Queen’s University Belfast.

Who has reviewed the study?
This research has been reviewed by an independent group of people, called a Research
Ethics Committee (REC), to protect your relative/friend/partner’s safety, rights, wellbeing

One original to ISF. Copy to close relative/friend. Copy to Patient’s medical notes
Covering Statement, IS and Consent Form for close relative/friend  _v1.2_14.05.18
and dignity. This study has been given a favourable opinion by the REC. The ongoing conduct of the study will be monitored by a separate group of doctors and independent members who will monitor all aspects of the research.

**What happens if I have any questions, concerns or complaints about the study?** If you have any questions about your relative/friend/partner’s participation in this study or concerns about the way it has been carried out, you should contact your hospital’s Principle Investigator or a member of the research team.

**What happens if I don’t want my relative/friend/partner to carry on with the study?**

You are free to withdraw your assent to your relative/friend/partner’s participation at any time and without giving a reason. This will not affect the standard of care they receive. Your study doctor can take them out of the study at any time if it is in their best medical interests to stop their participation.

If you have any questions that remain unanswered, the study doctor or research nurse will be happy to answer these for you. If you require any further information you may contact your hospital’s Principle Investigator.

**Thank you for taking the time to read this Patient Information Sheet.**

**CONTACT DETAILS:**

**Chief Investigator:**

Name: Prof Bronagh Blackwood  
Address: Centre for Experimental Medicine,  
Wellcome Wolfson Building  
Queen’s University Belfast,  
Lisburn road,  
Belfast,  
Northern Ireland.  
BT9 7BL  
Telephone: 028 9097 6379

**Principal Investigator**

Name: Leona Bannon  
Address: Regional Intensive Care Unit  
Royal Victoria Hospital  
Grosvenor road

One original to ISF. Copy to close relative/ friend. Copy to Patient’s medical notes

Covering Statement, IS and Consent Form for close relative/friend _v1.2_14.05.18
Belfast
BT12 6BA
Telephone: 028 9063 3286

Complaints/concerns:

Name: Dr Aoibhin Hutchinson
Address: Regional Intensive Care Unit
Royal Victoria Hospital
Grosvenor road
Belfast
BT12 6BA
Telephone: 028 9063 3286
Regarding patient *(insert patient's name)*:

1. I confirm that I have read and understood the Information Sheet for the above study and have had the opportunity to ask questions and discuss the study.

2. I understand that I am putting aside my own personal views to consider what my relative/friend/partner’s wishes would be. In my opinion, they would be willing to consent to take part in this study.

3. I understand that my relative/friend/partner’s participation is voluntary and that I am free to withdraw my consent at any time, without giving any reason and without their medical care or legal rights being affected.

4. I understand that sections of my relative/friend/partner’s medical notes may be inspected by responsible individuals from the NHS Trust, Queen’s University Belfast or regulatory authorities, where it is relevant to their taking part in this research. I give permission for these individuals to have access to my relative/friend/partner’s records. I agree to information related to this research being retained at the NHS Trust and Queen’s University Belfast and used in other research studies if required.
5. I understand that the research fellow will keep records of my relative/friend/partner’s name and contact details and may access information held by other central UK NHS bodies and organisations contracted to provide services to the NHS to access data collected routinely during their hospital stay, to ascertain their long term health status.

6. I agree to my relative/friend/partner receiving a multicomponent non-pharmacological intervention comprising education, sedation minimisation, early physical rehabilitation and environmental interventions for sleep, orientation, communication and cognitive stimulation that aims to reduce delirium in critically ill patients.

7. I agree that my relative/friend/partner’s consent will override my consent when they are able to give informed consent.

8. I agree to my relative/friend/partner’s GP being informed of their participation in the study and being contacted to ascertain their health status.

9. I agree to my relative/friend/partner taking part in this study.

Relationship to patient __________________________

I confirm that I am the personal consultee for ________________

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<tr>
<th>Name of personal consultee</th>
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<th>Name of person taking consent</th>
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One original to ISF. Copy to close relative/ friend. Copy to Patient’s medical notes

Covering Statement, IS and Consent Form for close relative/ friend

_v1.2_14.05.18
Appendix V  Recovered capacity PIS and consent form
Use of Delirium non-pharmacological interventions in critically ill patients: a Feasibility study (DIGNIFY)

Participant Information Sheet for Participant with Recovered Capacity

A study to determine whether a multicomponent non-pharmacological intervention for delirium is feasible in critically ill patients.

While you were unwell in the Intensive Care Unit (ICU), your relative/friend/partner/doctor gave assent/advice for you to take part in the above named research study. Your relative/friend/partner/doctor was asked to give this assent/advice on your behalf as you were not well enough to give consent yourself. Now that you have regained the capacity to consent we are seeking your permission to continue in this study. Please read the Patient Information Sheet carefully and if you have any questions or concerns in relation to the study, the study Research Nurse or Principal Investigator at your site will be happy to discuss these with you.

Thank you for your time in considering this request.

DIGNIFY PIS and Consent Form for Participant with Recovered Capacity. V1.1_24.04.18
One original to ISF. Copy to patient. Copy to patient medical notes.
Use of Delirium non-pharmacological interventions in critically ill patients: a Feasibility study (DIGNIFY)

What is the purpose of the study?
Many patients admitted to the Intensive Care Unit (ICU) have a breathing machine, or ventilator, to help them breathe and ensure that enough oxygen gets into their blood. They need some sedative and painkilling drugs while they are on the ventilator to keep them comfortable. For reasons that are unclear, often patients in this condition become temporarily confused, delirious, while on the ICU. This delirium has been associated with worse outcomes for patients; longer time spent in hospital, as well as difficulty concentrating and impaired memory. There is evidence that a group of non-drug interventions have been effective in reducing delirium in non-ICU patients but it is unclear if this strategy is effective in critically ill patients. This study is to see if these non-drug interventions (education of staff and relatives, reducing sedation, early physical and occupational therapy and environmental interventions such as sleep promotion, orientation, communication and cognitive and sensory stimulation) are actually feasible in the ICU.

Why have you been chosen?
The staff in the ICU found that you were at high risk for developing delirium. Neither the researchers nor the intensive care doctors know for sure whether these non-drug interventions are feasible. With the permission of a close relative or doctor caring for you in ICU we included you in this study to see if non-drug treatments such as education, reducing sedation, early physical therapy and environmental protocol with sleep checklist, orientation, communication and cognitive and sensory stimulation were feasible to deliver in critically ill patients. We are now inviting you to continue to take part in this study so that we can determine if these interventions are feasible in clinical practice.

Do I have to take part?

DIGNIFY PIS and Consent Form for Participant with Recovered Capacity. V1.1_24.04.18
One original to ISF. Copy to patient. Copy to patient medical notes.
It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and will be asked to sign a study consent form. You are still free at any time to withdraw your consent without giving a reason. If you decide not to take part the standard of care you will receive will not be affected.

**What happened to me after I was recruited to the study?**

If you joined the study in phase one you will have received the same care as other critically ill patients but data will have been collected on your sedation and delirium scores, sleep, and exercise during their ICU stay. If you joined the study in phase two you will have been managed on a protocol delivered by ICU staff that included education of families, reducing sedation, early physical activity and exercise and an environmental checklist to ensure a good night’s sleep, orientation, communication and stimulation of the brain and the senses.

Education involved your relative receiving a booklet that outlined what delirium is and how they could help you while you were in the intensive care unit. This was also encouraged by nursing staff. Reducing sedation involved a protocol that nursing staff followed to stop sedation daily once you met safety criteria to assess your level of awareness. Early mobilisation took place during this period of reduced sedation from passive range of motion (ROM) (moving the patients limbs) and active ROM (asking patients to move their own limbs) and progressed daily once patients met safety criteria. The environmental protocol included a sleep checklist, an orientation board that was completed by families with details about your likes and dislikes so staff could communicate with the you more effectively and communication, orientation and cognitive and multisensory stimulation. During this phase, information was collected on delirium status, sedation scores, sleep, exercise and adherence with the bundle of non-drug interventions.

Your medical notes would have been reviewed by the doctors and nurses, to find out if the treatments have been delivered. The study team reviewed your progress on a daily basis.

**What are the possible benefits and disadvantages of taking part?**
Taking part in this study may have contributed to improved treatment of patients at risk of developing delirium in the future. A similar study was carried out in hospitalised older patients in general medicine and they found that there were no adverse effects associated with the interventions. That protocol targeted six risk factors for delirium cognitive impairment, sleep deprivation, immobility, visual impairment, hearing impairment and dehydration.

To minimise any potential risks, interventions such as reducing sedation and early mobilisation were only performed when certain safety criteria had been met. This was discussed and agreed with the consultant body of the intensive care unit. The doctors monitored all people taking part in the study to ensure that any adverse were picked up early, and the study treatment was stopped if a serious adverse event occurred.

**What if something goes wrong?**

Every effort will be made to ensure that no patient taking part in this study is put at risk or harmed in any way. It is unlikely that anything will go wrong as a result of taking part in this study. If you have any concerns about any aspect of this study, you should contact your hospital’s Principal Investigator (contact details below), who will do their best to answer your questions. If you remain unhappy and wish to complain formally, you can do this through the normal NHS Complaints Procedure.

If something does go wrong and you are harmed due to someone’s negligence, then you may have grounds for a legal action against their NHS Trust.

**Would my taking part in this study be kept confidential?**

Any information collected about you during the course of the study will be kept strictly confidential and will only be seen by staff involved in the study from the NHS Trust, Queen’s University Belfast and people from regulatory authorities who ensure that studies such as this are carried out correctly. All of them will have a duty of confidentiality to you as a research participant.

In case we need to contact you after the study has finished, your NHS number/hospital number, postcode and date of birth will be kept on file for the duration of the study. All
other personal data will remain anonymised. This information will be used only for this study and will not be given to anyone else.

You have the right to see your personal health information related to the research study, but you will not be able to review some parts of the information until after the study has finished. When any information from the study is published it will not contain any personal information and it will not be possible to identify any individual.

The data from this study will be kept for at least five years after its conclusion (medical records will be kept for 15 years) and may be used in other research studies; data may be retained by the Belfast Health and Social Care Trust and Queen’s University of Belfast. Any study data retained/used will have all personal identifiers removed and it will not be possible to identify any individual.

What will happen to the results of the research study?
The study is expected to take six months. It is envisaged that publication of the results will follow shortly after this, through medical publications, websites and press releases. At this point we will be happy to forward a summarised version of the principle findings of the results of the study at your request.

Who is organising and funding the study?
The above named study is being organised by a group of ICU staff led by Professor Bronagh Blackwood, who is a chair in critical care research at Queen’s University Belfast, Northern Ireland. It is funded by a Research and Development Fellowship from the Public Health Agency in Northern Ireland. The Sponsor of the study is Queen’s University Belfast.

Who has reviewed the study?
This research has been reviewed by an independent group of people, called a Research Ethics Committee (REC), to protect your safety, rights, wellbeing and dignity. This study has been given a favourable opinion by the REC.

What happens if I have any questions, concerns or complaints about the study?

DIGNIFY PIS and Consent Form for Participant with Recovered Capacity. V1.1_24.04.18
One original to ISF. Copy to patient. Copy to patient medical notes.
If you have any questions about your participation in this study or concerns about the way it has been carried out, you should contact the Principal Investigator or a member of the research team.

**What happens if I don’t want to carry on with the study?**
You are free to withdraw your consent to participate at any time without giving a reason. This will not affect the standard of care you receive. Your study team can take you out of the study at any time if it is in your best medical interests to stop your participation.

If you have any questions that remain unanswered, the study team will be happy to answer these for you. If you require any further information you may contact your Principal Investigator as below.

Thank you for taking the time to read this Patient Information Sheet.

**CONTACT DETAILS:**

**Chief Investigator:**
Name: Prof Bronagh Blackwood  
Address: Wellcome Wolfson Institute for Experimental Medicine,  
Queen’s University Belfast,  
Lisburn road,  
Belfast,  
Northern Ireland.  
BT9 7BL  
Telephone: 028 9097 6379

**Principal Investigator**
Name: Leona Bannon  
Address: Regional Intensive Care Unit  
Royal Victoria Hospital  
Grosvenor road  
Belfast  
BT12 6BA  
Telephone: 028 9063 3286

**Complaints/concerns:**
Name: Dr Aoibhin Hutchinson  
Address: Regional Intensive Care Unit  
Royal Victoria Hospital

DIGNIFY PIS and Consent Form for Participant with Recovered Capacity.  
V1.1.24.04.18  
One original to ISF.  
Copy to patient.  
Copy to patient medical notes.
Use of Delirium non-pharmacological interventions in critically ill patients: a Feasibility study (DIGNIFY)

RECOVERED CAPACITY CONSENT TO CONTINUE FORM

Please initial each box

1. I confirm that I have read and understood the Patient Information Sheet for the above study and have had the opportunity to ask questions and discuss the study.

2. I confirm that I have been given sufficient time to consider whether or not I would like to continue to participate in the study.

3. I understand that my participation is voluntary and that I am free to withdraw my consent at any time, without giving any reason and without my medical care or legal rights being affected.

4. I understand that sections of my medical notes may be inspected by responsible individuals from the NHS Trust, Queen’s University of Belfast or regulatory authorities, where it is relevant to their taking part in this research. I give permission for these individuals to have access to my records. I agree to information related to this research being retained at the NHS Trust and the Queen’s University of Belfast and used in other research studies if required.

5. I agree to the Principal Investigator keeping a record of my name, date of birth, NHS/Hospital number and contact details and accessing information held by other central UK NHS bodies and organisations contracted to

DIGNIFY PIS and Consent Form for Participant with Recovered Capacity. V1.1_24.04.18
One original to ISF. Copy to patient. Copy to patient medical notes.
Use of *Delirium* non-pharmacological interventions in critically ill patients: a Feasibility study (*DIGNIFY*)

**TELEPHONE CONSULTEE AGREEMENT FORM FOR CLOSE RELATIVE/FRIEND**

This form is to be used in the event that a patient fulfills the criteria for inclusion in this study and has a close relative/friend who can give consent/advice on their behalf, but this person will not be available on site to meet the study deadlines.

To enable consent/advice to take place, the PI or designee (as delegated this duty on the Delegation Log), may make contact with the close friend/relative by telephone. This telephone contact must be witnessed by a second member of staff who may be a member of the site study team or site medical staff. This witness must sign as indicated below.

**Investigator to initial box**

1. I confirm that I have explained the study background to the relevant patient’s representative as detailed above and have read the Information Sheet to them.

2. I confirm that the close relative/friend of the patient has been allowed the opportunity to ask any questions or raise any concerns in relation to the study, and have received an answer to these where applicable.

3. I understand that written consent/advice must be obtained as soon as possible and the patient representative must be provided with a copy of the Information Sheet and written consent/advice process followed at this stage.

4. I confirm that the close relative/close friend (indicate status) of the patient has given verbal assent for the patient to take part in the study.

**Name of Participant: ……………………… Participant Study No ………………………………………**

**Name of Investigator: ………………………… Date: …………. Signature: ……………………………**

**Name of Witness: ……………………………. Date: …………. Signature: ……………………………**

**Witness Job Title: ………………………………………………………………………………………………………………………………..**

One original to ISF. Copy to person giving consent. Copy to patient’s medical notes

Telephone Consultee Agreement Form

v1.2_14.05.18
DIGNIFY CRF

Study Title: Delirium non-pharmacological bundle interventions for critically ill patients: A before and after Feasibility study.

PATIENT CASE REPORT FORM (CRF)

Patient Initials:  

Patient Number:  

For assistance, or if you are unsure how to proceed, please contact the Chief Investigator Professor Bronagh Blackwood on 07725839373, or the Clinical Research Fellow Leona Bannon on 07708043181.
**SECTION 1: PATIENT RANDOMISATION**

Please put a tick in the Yes/No/N/A box for each question

<table>
<thead>
<tr>
<th>INCLUSION CRITERIA</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 Is the patient receiving mechanical ventilation, vasopressors or oxygen therapy in the ICU/HDU?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.2 Does the clinician expect the patient to remain in their care until at least the day after tomorrow?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.3 Is the patient &gt; 16 years old?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*If the answer to any of Questions 1.1 to 1.3 is No, the patient is not eligible.*

<table>
<thead>
<tr>
<th>EXCLUSION CRITERIA</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.4 Does the patient have a pre-existing cognitive impairment?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.5 Is the patient unable to speak or understand the English language and there is no interpreter available?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.6 Is treatment withdrawal imminent?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.7 Has consent been declined?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*If the answer to any of Questions 1.3 to 1.7 is Yes, the patient is not eligible.*
**SECTION 1: PATIENT ALLOCATION**

Please put a tick in the yes or no box for each question (where applicable)

<table>
<thead>
<tr>
<th>1.11</th>
<th>Record date and time of patient allocation</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.12</td>
<td></td>
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</tr>
</tbody>
</table>

**SECTION 1: CONFIRMATION OF ELIGIBILITY AND WRITTEN CONSENT**

<table>
<thead>
<tr>
<th>1.11</th>
<th>Please confirm that the patient is eligible for this study?</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>INFORMED CONSENT</td>
<td></td>
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</tr>
<tr>
<td>1.12</td>
<td>Has consent been granted?</td>
<td></td>
<td></td>
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</tbody>
</table>

**Date of Consent:**

| D | D | M | M | Y | Y | Y | Y |

**Date of enrolment:**

| D | D | M | M | Y | Y | Y | Y |

**Time of enrolment:**

| H | H | M | M |

<table>
<thead>
<tr>
<th>1.13</th>
<th>Patient Number:</th>
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**Signature of person completing form**

**Please print name in block capitals:**

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<table>
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</table>

**Signature:**

<p>| |</p>
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**Date form completed:**

| D | D | M | M | Y | Y | Y | Y |
**SECTION 2: ICU ADMISSION FORM**

<table>
<thead>
<tr>
<th>Intensive Care Unit Admission details</th>
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<tr>
<td>Hospital admission</td>
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<td>Age</td>
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<table>
<thead>
<tr>
<th>Diagnosis</th>
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<tbody>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>Sepsis &amp; ARDS</td>
</tr>
<tr>
<td>Pneumonia</td>
</tr>
<tr>
<td>MI or CCF</td>
</tr>
<tr>
<td>Renal or hepatic failure</td>
</tr>
<tr>
<td>Other</td>
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</table>

<table>
<thead>
<tr>
<th>ICU admission type</th>
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</thead>
<tbody>
<tr>
<td>Emergency medical admission</td>
</tr>
<tr>
<td>Elective medical admission</td>
</tr>
<tr>
<td>Emergency surgical admission</td>
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<tr>
<td>Elective surgical admission</td>
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<table>
<thead>
<tr>
<th>Apache 2 score</th>
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<table>
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<tr>
<th>ICNARC Case Mix Programme (CMP) no.</th>
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<td>[ ] [ ] [ ] [ ] [ ]</td>
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<table>
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<th>Charlon co-morbidity</th>
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<table>
<thead>
<tr>
<th>Clinical Frailty score</th>
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<tr>
<td>Signature of person completing form</td>
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<td>Please print name in block capitals:</td>
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<td>[ ]</td>
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<p>| Signature: |
| [ ] |</p>
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<thead>
<tr>
<th>DAY NUMBER</th>
<th>TWO</th>
<th>THREE</th>
<th>FOUR</th>
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<tr>
<td>DATE DD/MM/YY</td>
<td>Lowest +/-</td>
<td>Lowest +/-</td>
<td>Lowest +/-</td>
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<tr>
<td></td>
<td>Highest +/-</td>
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<td>Highest +/-</td>
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<td>RASS SCORE</td>
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<td>Positive</td>
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<td>Positive</td>
<td>Positive</td>
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<tr>
<td>Negative</td>
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<td>Negative</td>
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<tr>
<td>Unable to</td>
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<td>Unable to</td>
<td>Unable to</td>
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<tr>
<td>assess</td>
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<td>assess</td>
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<tr>
<td>ICDSC SCORE</td>
<td>1. Depth 100 (0-100)</td>
<td>1. Depth 100 (0-100)</td>
<td>1. Depth 100 (0-100)</td>
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<tr>
<td></td>
<td>2. Latency (time to fall asleep) (0-100)</td>
<td>2. Latency (time to fall asleep) (0-100)</td>
<td>2. Latency (time to fall asleep) (0-100)</td>
</tr>
<tr>
<td></td>
<td>3. No of awakenings (0-100)</td>
<td>3. No of awakenings (0-100)</td>
<td>3. No of awakenings (0-100)</td>
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<tr>
<td></td>
<td>4. Efficiency (percent of time awake) (0-100)</td>
<td>4. Efficiency (percent of time awake) (0-100)</td>
<td>4. Efficiency (percent of time awake) (0-100)</td>
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<td>5. Quality (0-100)</td>
<td>5. Quality (0-100)</td>
<td>5. Quality (0-100)</td>
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<td>6. Noise (0-100)</td>
<td>6. Noise (0-100)</td>
<td>6. Noise (0-100)</td>
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<td>RCSO SCORE</td>
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<tr>
<td>MMS score (0-8)</td>
<td>Yes No</td>
<td>Yes No</td>
<td>Yes No</td>
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<tr>
<td>Advanced respiratory support</td>
<td>Yes No</td>
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<td>Advanced cardiovascular support</td>
<td>Yes No</td>
<td>Yes No</td>
<td>Yes No</td>
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<tr>
<td>SEDATION</td>
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<tr>
<td>Highest Propofol dose (mg/hr)</td>
<td>Yes No</td>
<td>Yes No</td>
<td>Yes No</td>
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<tr>
<td>Highest Midazolam dose (mg/hr)</td>
<td>Yes No</td>
<td>Yes No</td>
<td>Yes No</td>
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<tr>
<td>Highest Morphine dose (mg/hr)</td>
<td>Yes No</td>
<td>Yes No</td>
<td>Yes No</td>
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<tr>
<td>Highest alfentanil dose (mg/hr)</td>
<td>Yes No</td>
<td>Yes No</td>
<td>Yes No</td>
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<tr>
<td>Other unit</td>
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<tr>
<td>Level of Care</td>
<td>1 2 3</td>
<td>1 2 3</td>
<td>1 2 3</td>
</tr>
<tr>
<td>Intervention fidelity - SAT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Was criteria for SAT met?</td>
<td>Yes No</td>
<td>Yes No</td>
<td>Yes No</td>
</tr>
<tr>
<td>Active seizures</td>
<td>Yes No</td>
<td>Yes No</td>
<td>Yes No</td>
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<tr>
<td>Alcohol withdrawal</td>
<td>Yes No</td>
<td>Yes No</td>
<td>Yes No</td>
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<tr>
<td>Neuromuscular blockade</td>
<td>Yes No</td>
<td>Yes No</td>
<td>Yes No</td>
</tr>
<tr>
<td>Control of increased ICP</td>
<td>Yes No</td>
<td>Yes No</td>
<td>Yes No</td>
</tr>
<tr>
<td>ICP &gt; 20 mm Hg</td>
<td>Yes No</td>
<td>Yes No</td>
<td>Yes No</td>
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<tr>
<td>Receiving ECMO</td>
<td>Yes No</td>
<td>Yes No</td>
<td>Yes No</td>
</tr>
<tr>
<td>Documentation of MI in past 24 hours</td>
<td>Yes No</td>
<td>Yes No</td>
<td>Yes No</td>
</tr>
<tr>
<td>Current RASS &gt; 2</td>
<td>Yes No</td>
<td>Yes No</td>
<td>Yes No</td>
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</table>

372

366
<table>
<thead>
<tr>
<th>Description</th>
<th>Yes</th>
<th>No</th>
<th>Yes</th>
<th>No</th>
<th>Yes</th>
<th>No</th>
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<tbody>
<tr>
<td>Were all criteria for SAT met</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Were all criteria for early mobility met</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
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<td><strong>Intervention Fidelity Early mobility (1 - 28 days)</strong></td>
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<td>RASS &lt; -3</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td></td>
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<tr>
<td>Fio2 &gt; 0.6</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Set PEEP &gt; 10 cm H2O</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Increasing doses of vasopressor infusions in the last 2 hours</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Evidence of an active MI</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Administration of a new antiarrhythmic agent</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Receiving therapies that restricted mobility (e.g. ECMO, open abdomen etc)</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Injuries in which mobility is contraindicated (e.g. unstable fractures)</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td></td>
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<tr>
<td><strong>Early mobility readiness criteria</strong></td>
<td></td>
<td></td>
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<tr>
<td>Was an SAT performed</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>If No, why? (write reason in box)</td>
<td>Text</td>
<td></td>
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<td><strong>Early mobility</strong></td>
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<td>Start time of early mobility</td>
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<td>Finish time of early mobility</td>
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<tr>
<td><strong>EDUCATION</strong></td>
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<tr>
<td>Was there a meeting between family and primary nurse to discuss family participation?</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>If not, why? (Please write reasons in the space provided)</td>
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<td><strong>COMMUNICATION</strong></td>
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<tr>
<td>Were communication tools used when applicable?</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>If yes, please give details</td>
<td></td>
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<tr>
<td>Were efforts made to orientate the patient regularly?</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>If not, why?</td>
<td></td>
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<tr>
<td>Was a “this is me” board completed by relatives or staff?</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td></td>
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<tr>
<td>If not, why?</td>
<td></td>
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<tr>
<td>COGNITIVE STIMULATION</td>
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<tr>
<td>Was cognitive stimulation delivered by staff or patients relatives?</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td></td>
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<tr>
<td>If not, why?</td>
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<tr>
<td>Session 1: Start time: hh:mm. dd/ mm/ yy</td>
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<td>Session 1: End time: hh:mm. dd/ mm/ yy</td>
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<tr>
<td>Session 2: Start time: hh:mm. dd/ mm/ yy</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Session 2: End time: hh:mm. dd/ mm/ yy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pages achieved (mark pages from booklet)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### SECTION 5: CRITICAL CARE UNIT & HOSPITAL OUTCOME

Please complete Section 5 when the patient is discharged from critical care/hospital or dies prior to discharge.

<table>
<thead>
<tr>
<th>CRITICAL CARE UNIT DISCHARGE - Patient Discharged Alive</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.1 Date and time of first discharge to the ward</td>
</tr>
<tr>
<td><code>D D</code> / <code>M M</code> / <code>Y Y Y Y</code> / <code>H H M M</code></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient died prior to discharge from Critical Care Unit?</th>
</tr>
</thead>
<tbody>
<tr>
<td><code>Yes</code> ☐ <code>No</code> ☐</td>
</tr>
<tr>
<td><code>D D</code> / <code>M M</code> / <code>Y Y Y Y</code> / <code>H H M M</code></td>
</tr>
</tbody>
</table>
## SECTION 12: MORTALITY DETAILS

<table>
<thead>
<tr>
<th>12.1</th>
<th>Patient status at 28 days?</th>
<th>Alive ☐  Dead ☐</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Date of Assessment</td>
<td>D  D  M  M  Y  Y  Y  Y</td>
</tr>
</tbody>
</table>

| 12.2 | Patient died prior to discharge from hospital? | Yes ☐  No ☐ |

| 12.3 | If dead, record date and time of death | D  D  M  M  Y  Y  Y  Y  |
|      |                                          | H  H  M  M  |


SECTION 14: INVESTIGATOR STATEMENT

I certify that:

1. I have examined all entries and corrections of the eCase Report Form for this patient.
2. All the information entered onto the eCase Report Form for this patient at this time point is, to the best of my knowledge, correct.

Name of Investigator completing this form

Signature: ____________________________

PRINT Name: ____________________________

Date form completed: D D M M Y Y Y Y