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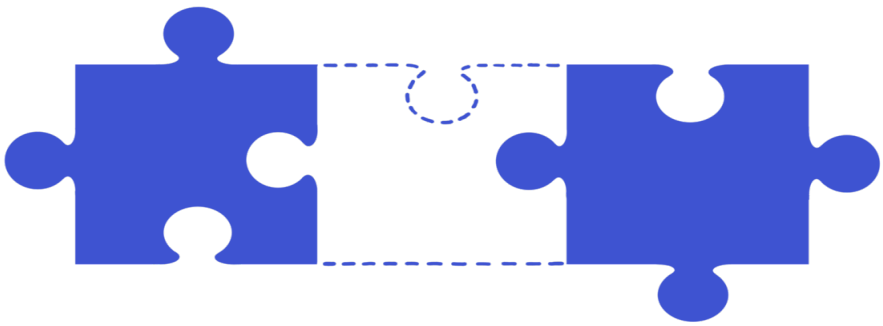
DAMPen-Delirium II



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Full Protocol Title	DAMPen-D II: Improving the Detection, Assessment, Management, and Prevention of Delirium in Palliative Care Units: a Cluster Randomised-Controlled Trial, Economic Analysis and Process Evaluation
Short Title (if appropriate)	DAMPen-Delirium II
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Co-Chief Investigator	Professor Mark Pearson
Co-Chief Investigator	Professor Fliss Murtagh
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This protocol has been written following the SPIRIT guidelines which are intended to facilitate the drafting of protocols and improve their completeness. High-quality protocols can promote proper trial implementation, reduce avoidable protocol amendments, and facilitate full appraisal of the study's scientific and ethical considerations

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Protocol amendments since Version V1.0

State “none” if no amendments			
List amendments made since the last REC approved version	Version number	Date	Provide reason for the amendment
			State which sections of the protocol were replaced, added or deleted

ABBREVIATIONS

HHTU, Hull Health Trials Unit
REC, Research Ethics Committee
HRA, Health Research Authority
CAG, Confidentiality Advisory Group

Table of Contents

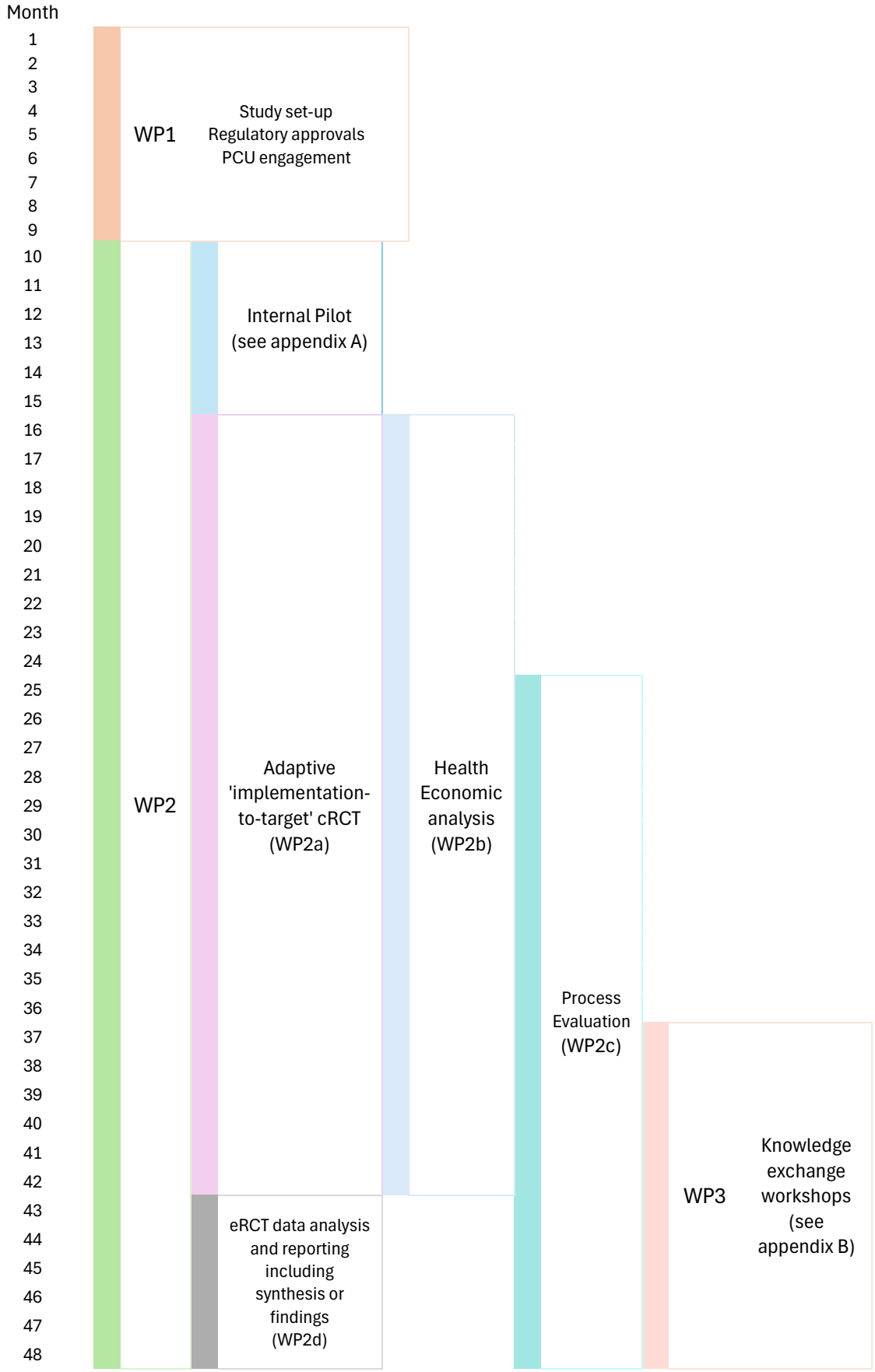
Trial Summary

Sponsor	University of Hull
Title of Study	DAMPen-Delirium II: Improving the Detection, Assessment, Management, and Prevention of Delirium in Palliative Care Units: a Cluster Randomised-Controlled Trial, Economic Evaluation and Process Evaluation
Trial Phase	Phase III Complex intervention
IRAS Study Number	351878
Intervention	The intervention to be tested (a clinical guideline implementation strategy we have called *CLECC-Pal Delirium*) comprises five components: training on delirium screening, assessment and management; mid-shift cluster discussions by the professionals delivering care; peer observations of practice; reflective discussions; and action learning sets (all designed to implement changes in delirium screening, assessment and management).
Aims and Objectives	**Aim** To evaluate the effectiveness and cost-effectiveness of a clinical guideline implementation strategy (CLECC-Pal Delirium) to improve the early detection, management and prevention of delirium among palliative care unit (PCU) in-patients. **Primary objective** To evaluate the effectiveness of the CLECC-Pal Delirium intervention compared to usual practice to reduce the proportion of inpatient days affected by delirium in PCUs in a fully powered cRCT. **Secondary objectives (process related outcomes and clinical outcomes):** 1. To identify adherence to delirium care guidelines (for the detection, assessment, management, and prevention of delirium) at baseline and follow up 2. To explore symptom burden and functional status during inpatient admissions, and their relationship with days affected and not affected by delirium. 3. To evaluate the cost-effectiveness of CLECC-Pal Delirium compared to usual practice on reducing the proportion of inpatient days affected by delirium in PCUs 4. To improve understanding of how CLECC-Pal-Delirium could be scaled-up across the UK
Study Design	Adaptive implementation-to-target cluster randomised controlled trial with concurrent economic evaluation and process evaluation. DAMPen-DII is broken down into 3 distinctive work packages (WP1, WP2 and WP3). WP1 involves the study set-up, obtaining regulatory approvals and engaging with Palliative Care Units who may want to participate in the study. WP2 involves the start of the cluster randomised controlled trial with an inbuilt

	pilot study. WP2 also includes a process evaluation section (WP2c) and health economic evaluation (WP2b) to evaluate the effectiveness and cost-effectiveness of CLECC-Pal Delirium compared to usual practise. WP3 aims to engage and inform stakeholders about study findings and explore how the CLECC-Pal Delirium implementation strategy could be adapted for use in other settings.
Number/Type of Participants	We will collate approximately 50 sequentially admitted inpatient records from each of the 20 PCU sites at 2 time points (approximately 1000 records at baseline and approximately 1000 records at follow up). Refer to Sample Size Rationale below.
Site PCU Eligibility	Inclusion criteria 1. Charitably-funded or NHS PCU providing specialist palliative care inpatient services 2. Willing to provide access to inpatient medical records 3. Capacity and capability to undertake intervention training. Exclusion criteria 1. Sites without capacity to support the intervention
Inpatient Eligibility	Inclusion criteria: 1. Sequentially admitted inpatients to a site PCU who have not opted out Exclusion criteria: 1. Any site PCU inpatient who has opted out of research (as documented either in the opt out register or medical records, or who has communicated to site staff that they do not want to take part) will be omitted from the consecutive inpatient list and data collection process.
Study Treatment(s)	Cluster RCT (cRCT) with site PCUs randomised (1:1) to the study intervention arm or the usual practice arm
End of Trial	Receipt and successful linkage of all HES data with the clinical record data, and completion of all patient/carer and staff interviews
Study Endpoints and Statistical Methods	**Primary outcome measures (clinical):** For inpatients who experience delirium during PCU admission, the proportion of inpatient days affected by delirium calculated as the number of days they experience delirium (as identified with Inouye tool by HHTU researchers) divided by their total number of inpatient days.

	Secondary outcomes (process related and clinical): **1. Guideline adherence** Number of inpatient records that contain evidence of adherence to delirium care guidelines (for the detection, assessment, management and prevention of delirium) at baseline and follow up. • Use of 4AT screening tool • Presence/absence of delirium risk assessment • Use of Richmond Agitation-Sedation Scale-Pal • Clinician-documented diagnosis of delirium • Clinician assessment of cause/reversibility • Presence/absence of delirium care plan • Use of antipsychotics in relation to documented harmful/distressing behaviour towards self or others **2. Cost-effectiveness** Incremental cost-effectiveness ratio quantifying the cost per PCU inpatient day affected by delirium which is avoided. **3. Inpatient Demographics** • Age • Sex • Diagnosis • Ethnicity • Postcode (converted to IMD score at data collection) • Primary Medical Condition • Date Of Death (if applicable) • Length of stay
Sample Size Rationale	This complex sample size rationale is based on a combination of i) numbers at risk of delirium, ii) numbers who incur delirium episodes, and iii) length of these delirium episodes. It is informed by patient and public partners perspective that – in the context of advanced illness - every day without delirium is a real gain and highly valued. So based on delirium episodes in the previous feasibility study, we expect a minimum of 50 consecutive inpatient records will be required (from each site and at two timepoints) to identify 30 delirium episodes at baseline and 30 episodes at follow up (total 1200 delirium data records). We will collate data records from PCU inpatients (stopping record identification at each site as soon as 30 delirium episodes have been identified) at both timepoints (baseline and follow up) to obtain a total of 1200 episodes of delirium (600 baseline and 600 follow-up,) to achieve a 92.3% power required to detect a 12% reduction of proportion of inpatient days affected by delirium, at 0.05 significance level, assuming an ICC of 0.03. We expect reduced duration of delirium episodes in the follow up group after the interventions, so will review adequate consecutive inpatient records during the follow-up period to ensure the data collection of 30 delirium episodes per site

Schedule Of Events (Dampen-DII Study)



Schedule Of Events (WP 2)

Activity	-12 weeks	- 4 weeks	Baseline	Intervention Period[C]	Follow Up[D]	Dissemination period
cRCT (WP2a)						
Site PCU set-up/contracting[A]	X					
Site PCU cluster randomisation		X				
Poster display[B]		X				
Screening			X			
Research 'Opt out' checks			X			
List of Baseline 50 consecutive inpatients sent to researcher			X			
Baseline data collection at site PCU[E]			X	X	X	
Study CLECC-Pal Delirium intervention (inc. training delivery)[F]				X		
List of Follow Up 50 consecutive inpatients sent to researcher				X	X	
Follow up data collection at site PCU[E]					X	
NHS England data collection[G]			X	X	X	X
Process Evaluation (WP2c)						
PIS and approach					X	
Consent					X	
Interviews					X	

[A] Including start-up facilitation with intervention sites (weekly phone/online call with clinical lead to discuss how common barriers for delirium guideline implementation can be addressed and core actions needed to achieve implementation-readiness)

[B] Display for 4 weeks before starting collation of records of consecutive patients who completed their inpatient stay during the time period from display of poster to start of intervention[C] study intervention to start in the intervention arm PCUs only after the baseline list of 50 sequential inpatients has been sent to the researcher[D] Follow up collation of consecutive patient records to start in order to capture patients who complete their inpatient stay from the beginning of the seventh calendar month after the PCU starts the intervention (in the intervention arm) or continues usual practice (in the control arm)[E] EMR e.g. SystmOne or EMIS, or paper records[F] Intervention to start only when implementation-readiness criteria are met (see section XX for more detail) [G] NHS England data collection can take place as soon as DARS application has been approved

1. Background & Rationale

People nearing the end of life have a high risk of delirium, [1, 2, 3, 4] a neurocognitive condition of impaired awareness, attention, and cognition. [5] Delirium is highly distressing for patients and families, increases health professionals' anxiety and stress, [6] and leads to poor clinical outcomes and higher care costs. [7, 8]

Delirium is a common occurrence, especially for those in-patient Palliative Care Units (PCUs), with the most advanced illness. One-third of people cared for by adult in-patient PCUs, such as hospices, have delirium on admission, with a further one-third developing delirium during their stay. [4] In practice, delirium is often underestimated due to hypoactive delirium (where patients are quiet and withdrawn) not being recognised. [9] About half of PCU in-patients are admitted for symptom management and discharged following optimised management, yet an episode of delirium carries a higher risk of subsequent cognitive decline, care home placement or repeat hospital admissions. [10] Effective delirium care needs prevention, timely detection and non-pharmacological management, with pharmacological interventions if appropriate. [11, 12] However, implementation of evidence-based guidelines[13, 14] and standards[15] to achieve this is poor. This leads to persistent poor practice such as routine use of antipsychotics to treat delirium[16] despite evidence to the contrary. [17, 18] In PCUs, the complex interactions between patients, family, and clinicians in diverse organisational and cultural contexts[19, 20, 21] means that not just education but practical and emotional support for staff is required to implement evidence-based change. [19]

An eight-study systematic review of PCUs showed delirium prevalence varied from 13.3% to 42.3% at admission and 26% to 62% during admission, [3] similar to our recent feasibility study findings (23% and 41%, respectively). [22] A review of 42 studies across all palliative settings gave delirium point prevalence estimates of 4% to 12% (community), 9% to 57% (hospital palliative care consultative services), and 6% to 74% (palliative care in-patient units). [4] A systematic review and meta-analysis (28 studies) of delirium risk factors in adults receiving specialist palliative care[1] found that although some were unmodifiable (type of cancer, older age and male sex), modifiable factors such as opioids, dehydration, hypoxaemia, and poor sleep were found, challenging views that 'nothing can be done' at this stage.

The impact of delirium and its psychological sequelae for patients, carers, and healthcare staff is under-acknowledged, despite the significance of the distress caused. [23, 24] Delirium is associated with poor outcomes, including increased post-discharge mortality, functional decline, longer hospital stays[25] and higher healthcare costs, [7, 26] new institutionalisation, and worsening dementia. [27, 28] Poor outcomes may appear less important for people with shorter prognoses, but gaining better quality time at home without mental deterioration is extremely important for many. Delirium also jeopardises care in the community, and our Public Advisory Group have confirmed

how preserving mental capacity and communicating with loved ones is crucial for decision-making and reducing distress.

Non-pharmacological interventions reduce delirium risk[29] and are recommended in National Institute for Health & Care Excellence (NICE) and Scottish Intercollegiate Guidelines Network (SIGN) guidelines. [13, 14] There is a limited role for medication. [30, 31] Despite this, and the person-centred culture and good staff levels in palliative care units, guideline-adherent delirium care is poorly implemented, [32] with action needed at patient, carer, clinician, team and system levels. [19, 21, 33, 34] Validated delirium risk-assessment tools such as the 4AT[35] support delirium management, but have low rates of use in PCUs. [32]

An information specialist search of databases (Medline, Embase, Psycinfo, CINAHL, CDSE, Epistemonikos, Caresearch) and registries (Europe PMC Grant finder, Clinical Trials.gov, UKCTG, Prospero, ISRCTN, WHO International Clinical Trials) conducted in August 2023 identified trials of multi-component delirium interventions (without implementation strategies) in hospital settings, with one pilot study in Australian PCUs. [36] Two quality improvement projects in PCUs[37, 38] and feasibility studies in PCUs[20] and care homes[39] give valuable insights, but little further guideline implementation research has been done in these settings other than our completed feasibility work. [22] In this completed study, we: i) tailored a staff educational and empowerment implementation strategy for use in PCUs (*CLECC-Pal Delirium*); ii) confirmed we can reliably collect data to assess both patient and implementation outcomes from patient records; iii) obtained data to calculate sample size for a national cluster randomised controlled trial; and iv) showed a signal of benefit (6% reduction in proportion of inpatient days affected by delirium, for those with a delirium episode). We have therefore demonstrated feasibility of the implementation strategy and trial, but now need to definitively test effectiveness in a powered trial.

About half a million people die in England each year, with a high proportion (42-88% across all settings) suffering delirium during last year of life, [4] often contributing to unplanned hospital admissions that account for 47% (£346m/year) of all health and social care costs in the last year of life. [40] Delirium causes increased length of hospital stay, staff time, and higher levels of hospital-associated adverse events, leading to higher costs of care (e.g. £349 average cost per palliative care bed day) [41] and additional suffering for patients. Although more evidence is needed, delirium interventions may be cost-effective by preventing and shortening delirium episodes, reducing falls, and improving functional ability. [42] Unplanned hospital admissions are also reduced. [43] However, implementing evidence-based delirium guidelines remains a challenge.

Evidence-based guidelines support the use of multi-component delirium care to prevent and manage delirium, [13, 14] but there is no evidence on how best to implement such care into routine practice and little rigorous evidence about the cost-effectiveness of

interventions to prevent and manage delirium. [42] A recent Cochrane review of non-pharmacological approaches to preventing delirium outside of intensive care concluded that future research should focus on implementation and how intervention components should be tailored for different settings. [29]

This study addresses James Lind Alliance research priority 17 in palliative care, [44] the NICE delirium research recommendations[13] (updated January 2023) regarding assessment and staff education for improving clinical outcomes, and our Public Involvement Group members' strong emphasis on the importance of implementing delirium assessment, management, and prevention in PCUs.

We will test the effectiveness and cost-effectiveness of a co-designed implementation strategy (*CLECC-Pal Delirium*) in the high prevalence setting of PCUs and explore its transferability to other high prevalence settings where implementing change in delirium care is challenging (care homes[39]) or has high impact (own home). [45]

2. The Study Intervention - CLECC-Pal Delirium

All site PCUs will continue to follow standard clinical care management during this study. Site PCUs randomised to the CLECC-Pal Delirium intervention arm will in addition follow the study intervention components (collectively termed the CLECC-Pal Delirium implementation strategy). The five components of CLECC-Pal Delirium include a study training day, mid-shift cluster discussions, peer observations of practice, reflective discussions, and action learning sets. The CLECC-Pal Delirium intervention aims to create a secure learning environment that delivers new ways of working, supporting implementation of delirium management guidelines and is described in Table 1.

A wide range of site PCU staff e.g. healthcare assistants, nurses, allied health professionals (e.g. physiotherapist, OTs), therapy professionals (e.g. music therapists), doctors, volunteers, care managers and executive board members will be expected to take part in the components of CLECC-Pal Delirium as part of their day-to-day practice.

Table 1: The Five Components of the CLECC-Pal Delirium Intervention

Component	Why	What	Who, how, where	When / How much
Study Day	Delirium management and prevention skills, CLECC-Pal Delirium components and how to put into practice	Presentations, interactive, discussions and planning	On-site with all hospice staff, day coordinated and led by researcher	One day
Mid-shift cluster discussions	Opportunities for feedback, group problem solving, and support to individual team members	Delirium focussed review	Ward staff at specified times during shifts	5 minutes a day
Peer Observation of practice	Opportunity to learn from constructive feedback	Feedback on observations of practice	PCU Delirium Lead during shifts	Depending on activities observed, 5-60 minutes per observation and feedback (6-10 occasions)
Reflective discussions	To prompt personal reflections and narratives about individual experiences	Scheduled meetings or drop-in sessions with planned activities	All team members including senior staff and temporary staff, facilitated by clinical lead	Number and frequency determined by hospice need (at least once)
Action learning needs	Share practice challenges and devise action plans	Group action plan development to address identified problems	All team members, including senor staff and temporary staff, facilitated by clinical lead	Number and frequency determined by hospice need (at least once)

2.1. Presence or Absence Delirium (Inouye Tool)

Clinical record data will be extracted using an expanded version of the prospectively validated (74% sensitivity, 83% specificity) chart-based instrument developed by Inouye et al. for detecting potential delirium diagnoses from clinical records. The instrument (CRF) will enable us to assess whether case-note recorded symptoms of delirium can be linked to time-points during the person's admission when actions around delirium assessment, management and prevention (consistent with guidelines) did or did not take place [48].

3. Aim And Objectives

3.1 Aim

To evaluate the effectiveness and cost-effectiveness of a clinical guideline implementation strategy (*CLECC-Pal Delirium*) to improve the early detection, management and prevention of delirium among palliative care unit (PCU) in-patients.

3.2 Primary Objective

To evaluate the effectiveness of the CLECC-Pal Delirium intervention compared to usual practice to reduce the proportion of inpatient days affected by delirium in PCUs in a fully powered cRCT.

3.3 Secondary Objectives (Process Related Outcomes And Clinical Outcomes):

1. To identify adherence to delirium care guidelines (for the detection, assessment, management, and prevention of delirium) at baseline and follow up
2. To explore symptom burden and functional status during inpatient admissions, and their relationship with days affected and not affected by delirium.
3. To evaluate the cost-effectiveness of CLECC-Pal Delirium compared to usual practice on reducing the proportion of inpatient days affected by delirium in PCUs
4. To improve understanding of how CLECC-Pal-Delirium could be scaled-up across the UK

3.4 Outcome measures

3.4.1 Primary Outcome Measure (Clinical)

For inpatients who experience delirium during PCU admission, the proportion of inpatient days affected by

delirium calculated as the number of days they experience delirium (as identified with Inouye tool by HHTU researchers) divided by their total number of inpatient days.

3.4.2 Secondary Outcomes (Process-Related And Clinical)

i. Guideline adherence

Number of inpatient records that contain evidence of adherence to delirium care guidelines (for the detection, assessment, management and prevention of delirium) at baseline and follow up.

- Use of 4AT screening tool
- Presence/absence of delirium risk assessment
- Use of Richmond Agitation-Sedation Scale-Pal
- Clinician-documented diagnosis of delirium
- Clinician assessment of cause/reversibility
- Presence/absence of delirium care plan
- Use of antipsychotics in relation to documented harmful/distressing behaviour towards self or others

ii. Costs

Incremental cost-effectiveness ratio quantifying the cost per PCU inpatient day affected by delirium which is avoided.

iii. Inpatient Demographics

- Age
- Sex
- Diagnosis
- Ethnicity
- Postcode (converted to IMD score at data collection)
- Primary medical condition
- Date of death (if applicable)
- Length of stay

4. Study Design

The study will be conducted in 3 related parts - Cluster RCT (cRCT) interventional study (Adaptive 'implementation-to-target' cRCT) with site PCUs randomised to the CLECC-Pal Delirium intervention or usual practice, health economic evaluation, and a parallel process evaluation (refer to 6 and 7 respectively). Information about the internal pilot (study set up feasibility and timelines) and Knowledge Exchange workshops (engagement with stakeholders about actions for future practice and policy) is included in Appendix A and B, respectively.

5. Cluster randomised-controlled trial

5.1 Site PCU inclusion criteria

1. Charitably-funded or NHS PCU providing specialist palliative care inpatient services
2. Willing to provide access to inpatient medical records
3. Capacity and capability to undertake intervention training.

5.2 Site PCU Exclusion criteria

1. Sites without capacity to support the intervention

5.3 Cluster Randomisation

There is no individual inpatient randomisation in this study. Randomisation will take place at site PCU level. Site PCUs will be randomised 1:1 via the web-based study database managed by the Hull Health Trials Team (HHTU) to receive the CLECC-Pal Delirium intervention or to continue following usual practice.

We will adopt the randomisation by minimisation approach, with three minimisation factors: number of referrals accepted annually size (as a binary), extent of specialist palliative care education/training provision (as a binary) and charity/NHS (binary).

5.4 Sample size

Based on delirium episodes in the previous feasibility study, we expect a minimum of 50 consecutive inpatient records will be required (from each site and at two timepoints) to identify 30 delirium episodes at baseline and 30 episodes at follow up (total 1200 delirium data records). We will collate data records from PCU inpatients (stopping record identification at each site as soon as 30 delirium episodes have been identified) at both timepoints (baseline and follow up) from 20 sites to obtain a total of 1200 episodes of delirium (600 baseline and 600 follow-up) to achieve a 92.3% power required to detect a 12% reduction of proportion of inpatient days affected by Delirium, at 0.05 significance level, assuming an ICC of 0.03.

5.5 Screening, Identification and Opt-Out Process

Inpatients admitted to all site PCUs will be cared for as per usual practice. There is no study specific Participant Information Sheet (PIS) for this study as eligible site PCU inpatients are not required to consent (see next section). All site PCUs will make available the study reading material (study poster, study intervention leaflet in inpatient admission packs) and, at an appropriate point in care, introduce the study to the patient (if considered clinically-appropriate) and family members/significant others. Delegated PCU staff will be responsible for checking that the consecutively admitted inpatient has not chosen to 'opt out' of research by checking the NHS National Data Opt Out register and the inpatient PCU records relating to admissions during the active study period. The Opt-out process is compliant with the National data opt-out operational policy guidance document, version 4.0, 25 Feb 2022 (compliance deadline 31-Jul-2022)[46]. Screening of the opt out register and medical records will only be performed by trained and delegated site PCU staff. If the inpatient has not opted out using the NHS National Data Opt Out or expressed this preference in their medical records, a delegated site PCU team member will confirm study eligibility and document that the process was followed correctly in the records and study data collection forms.

To maximise awareness of the study and understanding of the right to opt-out, we shall collect information about languages other than English typically spoken by inpatients as part of site information process with potential site PCUs so that translated posters can be prepared in advance for other languages. As highlighted by our Public Involvement Group, this will also enable us to identify staff who speak languages other than English so that they can communicate with inpatients and family members about the study in their first language. Where a PCU inpatient is known to have poor understanding of written English or whose awareness of study posters may be impacted (e.g. due to immobility or poor eyesight that affects reading), they (and/or their consultee) will be approached by the site principal investigator (or delegate) to ensure they are fully informed of their right to opt-out.

Inpatients will not be approached to consent to take part in this study. Inpatients who have opted out of research or state they do not want to be part of the study will be excluded from data collection. The study design is that data will be collected from consecutive inpatients admitted to the site PCU. However, in the event that an inpatient opts out, data collection will skip to the next consecutive patient admitted. Ethics and CAG approvals (or equivalent in the devolved nations, if relevant) will be obtained to support this approach. If a PCU inpatient chooses to opt-out, the site principal investigator (or delegate) should note in the medical records whether the patient is opting-out of this study only or declining use of their data in all research. An opt-out log for this study will be held and maintained by trained PCU staff for the purposes of ensuring opt-out is upheld (only PCU staff will have access to this log).

To ensure inpatients are aware that the study is taking place, a study intervention leaflet will be placed in the inpatient admission pack and a poster will be provided to each site PCU. At an appropriate point in care, PCU staff will introduce the study to the patient (if considered clinically-appropriate) and family members/significant others. The poster will be clearly displayed at the PCU for 4 weeks prior to screening and sequential enrolment of inpatients to highlight to all inpatients and their visitors that the DAMPen-D Delirium II study is being conducted at the site PCU. The poster will describe what the study is doing, what data is being collected and how that data is managed. The poster will include contact details and a link to the University website for anyone wanting to find out more information about the study.

Anyone that does not wish to be involved in the study and/or have their data collected can choose to 'opt out' by informing the Site PCU team. If the patient or their carer or their consultee, does not want confidential clinical records used in the study, the site PCU staff can provide information about the study to patients/consultee and discuss opt-out consent for study data collection. No reason needs to be provided and it will not affect their ongoing medical care.

5.6 Withdrawal

As site PCUs are randomised to study intervention or usual practice, withdrawal from the study will be at site PCU level. If a site PCU inpatient or their legal guardian/conservator decides to opt out from data collection, this will be recorded on the study data log and their data will not be included in the data analysis.
Site PCU inpatients may withdraw their data from NHS England HES data collection up to the time that the study database has been closed for analysis. After this point it cannot be removed as data will have been anonymised and the NHS number will no longer be available to trace medical records.

5.7 Implementation-readiness criteria

Intervention sites must meet three 'implementation-readiness' criteria before commencing the CLECC-Pal Delirium intervention:

1. Governance approval for use of rapid delirium assessment tool (e.g. 4AT) in clinical notes
2. Lead identified for a minimum of three CLECC-Pal Delirium components (including at least one nurse)
3. PCU management support expressed for using CLECC-Pal Delirium

If these criteria are not met, intervention sites will receive strategic facilitation (structured discussion and prioritisation of how to address implementation barriers; identification of individual motivations and support for exploring how to meet individual goals; identification of organisational drivers and support to explore alignment of these with delirium guideline implementation and use of CLECC-Pal Delirium).

5.8 Data collection

Site PCU inpatient data (see Table 2) will be collected by a study researcher based at the University of Hull, not by site PCU staff. If any case notes cannot be obtained or accessed for any reason, this will be recorded by the researcher on the study data collection forms. All outcome measures are considered to be part of usual practice and no additional questionnaires or tools will included as part of the study intervention.

Demographic data will be recorded in a way that decreases identifiability of the PCU inpatients (e.g. recording length of stay rather than date of admission and discharge). Postcode will be converted to an IMD score at the point of extraction.

We shall report the percentage of clinical records where information about each of these actions is recorded. Where a person experiences multiple episodes of delirium within one admission these

will be recorded on separate CRF and treated as separate episodes. Where judgements about what to record on the CRF need to be made, justification for these will be recorded on the form.

Any uncertainty about how the information in the case-notes should be recorded on the pro-forma will be discussed with a clinician and justification for the final decision recorded on the pro-forma.

Our 'expanded' version of the instrument will include questions about other actions to support delirium assessment, management and prevention that may be recorded in the notes. We shall report the percentage of clinical records where information about each of these actions is recorded. Where a person experiences multiple episodes of delirium within one admission these will be recorded on separate pro-forma and treated as separate episodes. Where judgements about what to record on the pro-forma need to be made, justification for these will be recorded on the form. Any uncertainty about how the information in the case-notes should be recorded on the pro-forma will be discussed with a clinician and justification for the final decision recorded on the pro-forma.

Table 2: Data Collection (Completed By HHTU Study Researchers)

Primary Endpoint	Measure	How	Timepoints
To evaluate the effectiveness of CLECC-Pal Delirium intervention compared to usual practice to reduce the total proportion of inpatient days affected by delirium in PCUs, in a fully powered cRCT.	For patients who experience delirium during PCU admission, the proportion of inpatient days affected by delirium, calculated as the number of days they experience delirium divided by their total number of inpatient days	Data extraction from • Paper • Medical records e.g. SystmOne/EMIS • NHS England HES data	Two timepoints: **Baseline** 50 consecutively admitted inpatients who completed their inpatient stay during the time period from display of poster to start of intervention *Note: As this is information entered into the inpatient records on the day of events, baseline data can be collected retrospectively at any point during the study* **Follow up** 50 consecutively admitted inpatients who completed their inpatient stay from the beginning of the seventh calendar month after starting the intervention (in the intervention arm) or continuing usual practice (in the control arm
Secondary Endpoints	**Measure**	**How**	**Timepoints**
To identify adherence to delirium care guidelines (for the detection, assessment, management, and prevention of delirium) at baseline and follow up • 4AT screening tool • Delirium risk assessment • Richmond Agitation-Sedation Scale • Clinician-documented diagnosis of delirium • Clinician assessment of cause/reversibility • Use of antipsychotics in relation to documented harmful/distressing behaviour towards self or others • Delirium care plan • Medication review	Present in the records? Yes / No	Data extraction from: • Paper records • Medical records e.g. SystmOne/EMIS • NHS England HES data	As above
To explore symptom burden and functional status during inpatient admissions • Integrated Palliative care Outcome Scale (IPOS) • Australian-modified Karnofsky Performance Scale (AKPS)	Tool score		
To evaluate the cost-effectiveness of CLECC-Pal Delirium compared to usual practice on reducing the proportion of in-patient days affected by delirium in PCUs	Cost		
Age, Sex, Primary medical condition, Ethnicity, Postcode (converted to IMD score at data collection), Primary medical condition, Date of death (if applicable), Length of stay.	Not applicable		

5.9 Statistical Analysis

5.9.1 Sample Size

Based on delirium episodes in the feasibility study, a minimum of 50 consecutive patient records are required (from each site, at each timepoint) to identify each sample of 30 delirium episodes. This figure will be revisited during the internal pilot.

The study requires 30 inpatients with a delirium episode from each of 20 PCUs
Size of cluster=30
Number of PCU clusters for randomisation=20
Total number of inpatient records required = 2000
Number of delirium episodes inpatient records required = 1200

Intraclass correlation coefficient (ICC) is generally smaller for clinical outcomes than for process outcomes, with a median value of 0.03. Our goal is to achieve 12% reduction (from 70% to 58%), leading to a moderate effect size of 0.4. No attrition rate is expected since each PCU will collect data from cross sectional cohorts (baseline and follow-up). The outlined sample size will provide 92.3% power to detect a 12% reduction of proportion of days affected by delirium, at 0.05 significance level, assuming an ICC of 0.03.

5.9.2 Planned recruitment rate

An internal pilot will be implemented for months 10-15 with provisional stop/go criteria (see appendix A) to be further developed and approved by the funder by May 2025.
Stop criteria equates to 0 site or records being recruited within this period. A warning criterion will be for if <10 site/records are recruited during this period. Go criteria will be for if $\geq$10 sites/records are recruited during this period. The stop/go will be reviewed by the TSC. There may be a funder requirement to close the study prematurely if recruitment does not achieve the Stop-Go targets.

5.9.3 Data Analysis

We will follow the CONSORT extension to cluster randomised trials[47] for analysis and reporting. Primary analyses will be conducted on intention-to-treat basis and follow a prespecified statistical analysis plan, overseen by Trial Steering Committee. Patient baseline demographics will be summarised for each group with descriptive statistics. Primary outcome (proportion of PCU inpatient delirium days) will be analysed by two level modelling with PCU as cluster, adjusting for intervention arms and stratification factors. We will also report the primary outcome by deceased/discharged patients and undertake a sub-group analysis via two-level modelling approach. A patient who dies shortly after admission has a shorter in-patient stay than a patient who is discharged. Additionally, the risk of delirium is greater in those closer to death. Drawing from our feasibility study data, we expect the deceased and

discharged patients in a 2:1 ratio. This assumption will be checked during the internal pilot and any natural variation in this ratio will be accounted for in a sub-group sensitivity analysis.

Additionally, we will collect the dates of hospital admission, first delirium and mortality (if applicable) for all participants. This data will be used to form the time to first delirium (in days) as a key secondary outcome, which competes with patient death. A competing risk analysis will be undertaken accordingly.

For other secondary outcomes, routinely assessed symptom burden and functional status (IPOS and AKPS) will be reported by intervention arms at each time-point. To evidence the guideline-adherence of delirium care processes, we will report on the process outcomes related to delirium early detection, delirium care and symptom distress, including the use of 4AT screening tool, presence/absence of delirium risk assessment, use of RASS-Pal, clinician-documented diagnosis of delirium, clinician assessment of cause/reversibility, presence/absence of delirium care plan, use of antipsychotics in relation to documented harmful/distressing behaviour towards self or others. For each PCU cluster, the proportion of patients with delirium will be summarised by intervention arms at each time-point. The linked Hospital Episode Statistics (HES) data will be summarised and used for health economic analysis.

6 Health Economic Evaluation (WP2b)

We will conduct a cost-effectiveness analysis (CEA) from the health system perspective using a lifetime horizon. The main source of data for the CEA will be the cRCT, supplemented with routine data and the published literature. To gain as much detail as possible to best inform the health economic evaluation, we will not stop the study early should one cRCT arm have clear emerging superiority.

6.1 Data collection

Following DARs approval, we will estimate costs (payer perspective) in two settings: PCU (via routine data) and acute hospital (via linked HES data), with all data housed and analysed exclusively in the University of Hull's Data Safe Haven. We will estimate the cost of a day in PCU, stratified by PCU type, using Personal Social Services Research Unit (PSSRU) data, differentiating between staffing costs for patients with and without delirium, based on staff logs and discussions with clinicians and managers.

We will identify acute hospital admissions via linked HES data and estimate associated costs using reference costs adjusted for HRG code, co-occurring conditions including delirium, and length of stay. We will adjust for the additional cost associated with an acute hospital admission ending in death. We will estimate the resources associated with *CLECC-Pal Delirium* through review of staff activity and discussions with clinicians and managers.

Missing outcome data will be addressed by using multiple imputation by chained equations.

6.2 Data Analysis

We will estimate incremental effectiveness of the intervention using the primary outcome (Site PCU inpatient days affected by delirium). We have chosen cost-effectiveness analysis over cost-utility analysis in the context of practical and ethical challenges in primary data collection of generic health related quality of life (HRQoL) data in our population and study design. In secondary analyses, we will explore relationships between IPOS and AKPS scores with delirium and non-delirium days at sites where these data are collected, and explore the scope for using these in cost-effectiveness analyses, thus investigating if incorporating a wider set of HRQoL domains affects our interpretation and conclusions.

Prior to conducting primary analysis, we will examine: (i) baseline differences on characteristics associated with outcome and where necessary control for baseline variables in analysis; and (ii) skew, kurtosis and heteroscedasticity in the cost data and fit an appropriate (most likely, nonlinear) model. We will address missing outcome data using multiple imputation. We will bootstrap each set of regressions with 1000 replications and combine these bootstrapped results in estimating cost-effectiveness acceptability curves. If data characteristics require it, we will account for correlated costs and effects using seemingly unrelated regressions. Recognising the uncertainty associated specifically with a cRCT, we will employ a stratified two-stage nonparametric bootstrap resampling procedure for clustered data. We will use discount rates in line with NICE guidance at the time of analysis. For the purposes of cost-effective analyses, each day affected by delirium will be treated as a 'whole (24 hour) day'.

Data analysis will include:

- Estimation of the cost of a day in PCU, stratified by PCU type, using personal social services research unit (PSSRU) data, differentiating between staffing costs for patients with and without delirium, based on staff logs and discussions with clinicians and managers.
- Estimation of associated hospital admission costs using reference costs adjusted for HRG code, co-occurring conditions including delirium, and length of stay. We will adjust for the additional cost associated with an acute hospital admission ending in death.
- Estimation of the resources associated with the CLECC-Pal Delirium study intervention through review of staff activity and discussions with clinicians and managers.
- Estimation of incremental effectiveness of the intervention using the primary outcome (PCU inpatient days affected by delirium).

- Estimation of cost-effectiveness using IPOS and AKPS scores at those site PCUs where these data were collected, thus investigating if incorporating a wider set of HRQOL domains affects our interpretation and conclusions.

7. Process Evaluation (WP2c)

7.1 Fidelity

We will measure the percentage of eligible staff overall, and by type of staff, participating in the training for each of the ten PCUs introducing *CLECC-Pal Delirium.*

7.2 Interviews

The CLECC-Pal Delirium intervention is based on Normalisation Process Theory (NPT), a social-psychological theory of the inter-relationships between what people do, the context they do it in, and the extent to which interventions are 'normalised' (implemented) into routine practice.

The interview part of the process evaluation will begin a 6 month timepoint after commencing the study CLECC-Pal Delirium intervention at each PCU site. The process evaluation NPT's four constructs will be used to structure data collection, analysis and interpretation for staff interviews. The constructs will enable understanding of key implementation challenges:

- coherence (do staff understand why *CLECC-Pal Delirium* it is being used?)
- cognitive participation (are staff engaged and committed to it?)
- collective action (are staff working together to use it?)
- reflexive monitoring (are staff appraising the consequences of using it?).

7.2.1 Sample size:

Four out of the ten intervention site PCUs will be selected for in-depth qualitative research. We will sample purposively based on: PCU type, PCU size, diversity of population served, and historical participation with interventional research. In each of the four site PCUs, we will interview 6-10 staff (total 24-40) and 6-10 inpatients and their informal carers (total 24-40).

7.2.2 Screening and approach

Each Site Principal Investigator (PI) will identify staff members who can be approached to participate in interviews with the research team, and inpatients and informal carers who can be approached to participate in interviews with the research team. The Site PI, in conjunction with relevant clinicians at their PCU, will assess whether patients have capacity to be approached about research, whether they need to be approached while their informal carer is present, and that they are no longer experiencing delirium. Inpatients and their family member/informal carer will be offered the option of telephone, virtual or in person interviews while the patient in staying in the PCU. Prior to interview, both the informal caregiver/and or the patient will be asked about their participation preferences. The informal carer and/or patient will be asked if they wish (i) the carer to join the patient interview to facilitate the patient's participation (ii) the carer join the patient interview to offer their own views about the care provided (iii) have separate interviews. They can select any or all of the three options. A Participant Information Sheet (PIS) will be provided to the staff member, inpatient and their informal carer prior to the interview by the site PI or suitably trained delegate. Translated Participant Information Sheets will be prepared if required, or staff members who can communicate in an inpatients' preferred language will approach patients and informal carers to facilitate inclusiveness of the recruitment process for inpatient/carers. For interviews, interpreters will be engaged where necessary.

7.2.3 Participant selection

The Site PI (or suitable delegated PCU staff member) will take informed consent from staff and inpatients/carers and contact details will be sent to the research team to secure HHTU study NHS email. After consenting inpatients/carers, PCU staff will promptly contact the HHTU team to schedule the HHTU researchers to come to the PCU to conduct the interviews of inpatients/carers. Interviews will be conducted with the inpatients/carers remotely, if preferred by participant.
When on site the HHTU researchers will review the completed consent forms for accuracy and completeness and will take the hard copies for secure storage at HHTU (ensuring copies remain at site).

The HHTU researchers will confirm with the PCU staff that no changes in capacity have occurred since consent was given prior to the interviews. When confirmed the PCU staff will help the HHTU researchers identify the correct PCU inpatients that have consented. For staff members that have consented to interview their details will be collected by the Site PI and emailed through to the HHTU research team. Consented staff members will be contacted remotely by the HHTU research team.

The research team will add the contact details and will upload the signed informed consent form to the secure web-based study database managed by HHTU.
Interviewees will be selected by the researcher to obtain maximum diversity of interviewees, that is, a range of type of staff roles and grades and a range of patients/families from different socio-economic backgrounds and ethnic groups.
Purposive sampling of inpatients will be undertaken to interview those who have experienced delirium and those who have not, as the intervention covers both prevention and management of delirium.

Not all those who have expressed an interest to be interviewed will be selected due to purposive sampling methodology.

Inpatients/Carers Inclusion Criteria:
-Inpatients with capacity to consent
-Carers of inpatients with capacity to consent

Inpatients/Carers Exclusion Criteria:
-Patients who do not have capacity at point of interview will be withdrawn
-Carers of inpatients without capacity to consent

Staff Inclusion Criteria
-PCU staff members with patient contact
-Member of PCU management or Executive

Staff Exclusion Criteria
-Staff without patient contact (not including managerial roles)

7.2.4 Informed Consent

Sufficient time will be given between the PIS and informed consent so that all questions can be answered by the Site PI in consultation with (where necessary) the process evaluation team.

7.2.5 Conduct of Interviews

Semi-structured interviews will be undertaken in the PCU. Every effort will be made to find a quiet and comfortable room to conduct the interview to maintain privacy as much as possible. All interviews will be recorded and transcribed.

Staff will be offered the option of telephone, virtual or in person interviews; interviews will be a maximum duration one hour. Interviews may be taken with frequent breaks to ensure that a patient is not fatigued by the process and will be stopped early if necessary or rearranged.

Palliative care patients who agree to participate in research can find the opportunity to discuss their situation helpful. However, there is potential that some patients and informal carers feel upset during the interview as a result of talking about their life circumstances, experiences of delirium, and the care they are receiving. The Qualitative Researcher undertaking the interviews will be an experienced palliative care researcher and will listen to patients and informal carers sensitively, and allow breaks or withdrawal from the interview if they wish. It will not be the Qualitative Researcher's role to offer any counselling but if the Qualitative Researcher is concerned about distress during or after the interview, with the interviewee's permission, the Qualitative Researcher will pass their concerns on to the PCU team. A study log will be kept of any instances where the Qualitative Researcher is made aware (by a participant, their family or the clinical team) of distress experienced around the time of conducting an interview. The anonymised log will be regularly monitored and action taken regarding the content, processes and/or conduct of interviews as appropriate. We shall also work with the PCUs to ensure that clear safeguarding policies and reporting mechanisms are in place.

The Qualitative Researcher may be distressed by the interviews. The Process Evaluation Lead will meet with the Qualitative Researcher regularly to debrief about their experiences and feelings. If there is anything that requires a clinical input, the Process Evaluation Lead will approach a senor clinical member of the research team for help (Prof Murtagh or Dr Taylor).

Interviews with staff will explore mechanisms of action, implementation of the intervention within each PCU, how contextual issues affected implementation and outcomes, and fidelity. Interviews with patients and informal carers will explore how delirium was managed (if they experienced delirium) and their experiences of actions expected by PCUs to prevent delirium (these will be offered as prompts).

If the Qualitative Researcher identities aspects of care that are concerning, these will be discussed with the Process Evaluation Lead and Chief Investigators before being raised with the Site PI, but will not be followed up.

7.2.6 Qualitative analysis

Interviews will be transcribed by an approved third party and stored anonymously.

We have successfully used the Framework approach for analysing the qualitative data in previous process evaluations. Normalisation Process Theory will form part of the thematic framework in the second step of the Framework approach for the staff interviews. Data from early interviews (about five patient/carer interviews, five staff interviews) will be co-analysed with public co-applicant Halliwell. We will analyse the data from different sources separately (fidelity, staff interviews and patient/carer interviews) before triangulating them using a joint display based on the Triangulation Protocol (see example in Wildman et al[74]) To explore variation in context and implementation between PCUs, we will consider quantitative data for all ten intervention PCUs, and both the qualitative and quantitative data for the four purposively-sampled PCUs.

8 Public Involvement

We have set up a Public Advisory Group made up of eight people with personal experience of delirium, either themselves, or caring for a loved one. Some members also have experience of caring for people with delirium through their work in home care or hospice care. The group includes those who were involved in the original feasibility study, with the addition of new members to add more diversity of experience and perspective. The group will meet four times per year throughout the trial, and we have already held a welcome meeting, and a meeting to discuss data collection and the opt out approach to accessing patient records. We are running the group in flexible way to take account of the differing needs of its members, and offering one to one conversations alongside group meetings as required.

The group is chaired by our public co-investigator Julie Halliwell, who acts as a link between the group and the Trial Management Group. She will join the monthly TMG meetings with other co-investigators. With support from Jackson and Roberts, she will plan agendas, organise meetings, and critically reflect on PAG activities and the working relationship with researchers on the study. Recognising how early engagement underpins impact, Halliwell will take a lead role in identifying opportunities with PAG members to engage with carers, palliative care unit staff, and opinion leaders (at both unit and policy levels) about the ongoing study and, subsequently, the implications of its findings.

In preparation for co-analysing a sub-set of interview data with researchers in the Work Package 2 process evaluation, Halliwell will take part in an online, two-day introductory workshop on qualitative data analysis and using NVIVO. We have revised our initial plan of cofacilitation of the Work Package 3 knowledge exchange workshops so that Halliwell's role can be co-development of workshops' content and structure.

The Study Steering Committee will have two public members, including one from a minoritised ethnic community, both of whom have personal experience of caring for a family member with delirium.

Gillian Jackson is coordinating public involvement in the study on a day to day basis, in collaboration with Halliwell. Public Involvement Coordinator Helen Roberts is acting in an advisory capacity, supporting both Jackson and Halliwell.

9 Quality Assurance

The study will be conducted in accordance with the principles of Good Clinical Practice (GCP) in clinical trials, as applicable under UK regulations, the NHS Research Governance Framework (RGF) and Scottish Executive Health Department Research Governance Framework for Health and Social Care 2006 (for studies conducted in Scotland), and through adherence to HHTU Standard Operating Procedures (SOPs).

9.1 Data Collection

Clinical record data will be collected and entered into a secure web-based electronic data capture system provided by the Hull Health Trials Unit (HHTU). See **Figure 1** for data flow summary.

The data collection forms will collate data to enable us to assess whether case-note recorded symptoms of delirium can be linked to time-points during the person's admission when actions around delirium assessment, management and prevention (consistent with guidelines) did or did not take place. Also included in the data collection form are questions about other actions undertaken to support delirium assessment, management and prevention that may be recorded in the notes.

Where an inpatient experiences multiple episodes of delirium within one admission, each episode will be treated as a separate episode. A period of five days without signs of delirium will be used to distinguish separate episodes.

Where judgements about what to record on the CRF need to be made, justification for these will be recorded. Any uncertainty about how the information in the medical records should be recorded will be discussed with a clinician and justification for the final decision recorded on the eCRF. We will also collect more detailed information on emergency and admitted inpatient care for the main trial and health economic analyses via NHS England to link records to Hospital Episode Statistics (HES) data.

To protect the identity of individuals, a separate linkage database (the patient information database) will be used. This database will securely store the identifiers, NHS numbers and dates of birth, and will generate a unique study ID for each individual. The study ID will then be used in the clinical record database to maintain data integrity while safeguarding personal identifiers. Additionally, the linkage database will be used to generate a list of identifiers to be shared with NHS England for linkage with Hospital Episode Statistics (HES) data. By separating direct identifiers from clinical records and relying on study IDs, this approach will ensure robust privacy protection while minimising the use of identifiable information.

To minimise the length of time that patient identifiable information is held on the patient information database, separate DARS requests for baseline and post-implementation data will be requested. At each timepoint, the linkage database will only be required until the

HES data has been obtained and successfully linked with the clinical record data. After this point, the linkage database will no longer be needed and can be securely destroyed, rendering the dataset anonymous in context. By separating direct identifiers from clinical records and relying on study IDs, this approach will ensure robust privacy protection while minimizing the use of identifiable information.

9.1.1 Electronic records

Firstly, personal identifiable information (name, date of birth, NHS number) will be collated locally by the PCU site. When 50 consecutive admissions have been collated, this list of PCU inpatient names, date of birth and NHS numbers will be sent by the PCU team to an HHTU NHS email address. These details will be used to access the electronic medical records of these in-patients at the Data Access Facilitator site. Pseudonymised data will be manually copied from the electronic medical records to the primary study database using a study ID generated in the personal identifiable information RCC database.

Only the date of birth and NHS number will be transferred from this NHS email to a secure, dedicated patient information RedCAP cloud database so that the HHTU research team can request linkage to HES data.

9.1.2 Paper records

PCUs that use paper records will collate consecutive patient admissions. When 50 consecutive admissions have been collated the PCU will segregate the selected records and make them available exclusively for on-site data extraction by the dedicated HHTU researchers.

9.2 Database

The HHTU researchers will manually extract from paper records NHS number and date of birth and input into secure, patient information RedCAP cloud database. When added to the database each dataset (NHS number and DOB) will be assigned a unique study identifier. When all of the study data is collected, and the database is completed this data (NHS number, DOB and study ID) will be sent to NHS England in a DARS submission to request their HES data. NHS England will then use the NHS number (with DOB used as validation to confirm the subject's record is correct) to retrieve the HES data. The study ID will allow the resulting dataset sent back from NHS England to be linked to the data collected by the HHTU researchers from the electronic health records.

Data from the primary RCC database and HES data will be transferred to, and analysed in, the UoH Data Safe Haven (see Figure 1). The patient information database will only be required until the HES data has been obtained and successfully linked with the clinical record data. After this point, the linkage database will no longer be needed and can be

securely destroyed, rendering the dataset anonymous in context. By separating direct identifiers from clinical records and relying on study IDs, this approach will ensure robust privacy protection while minimizing the use of identifiable information.

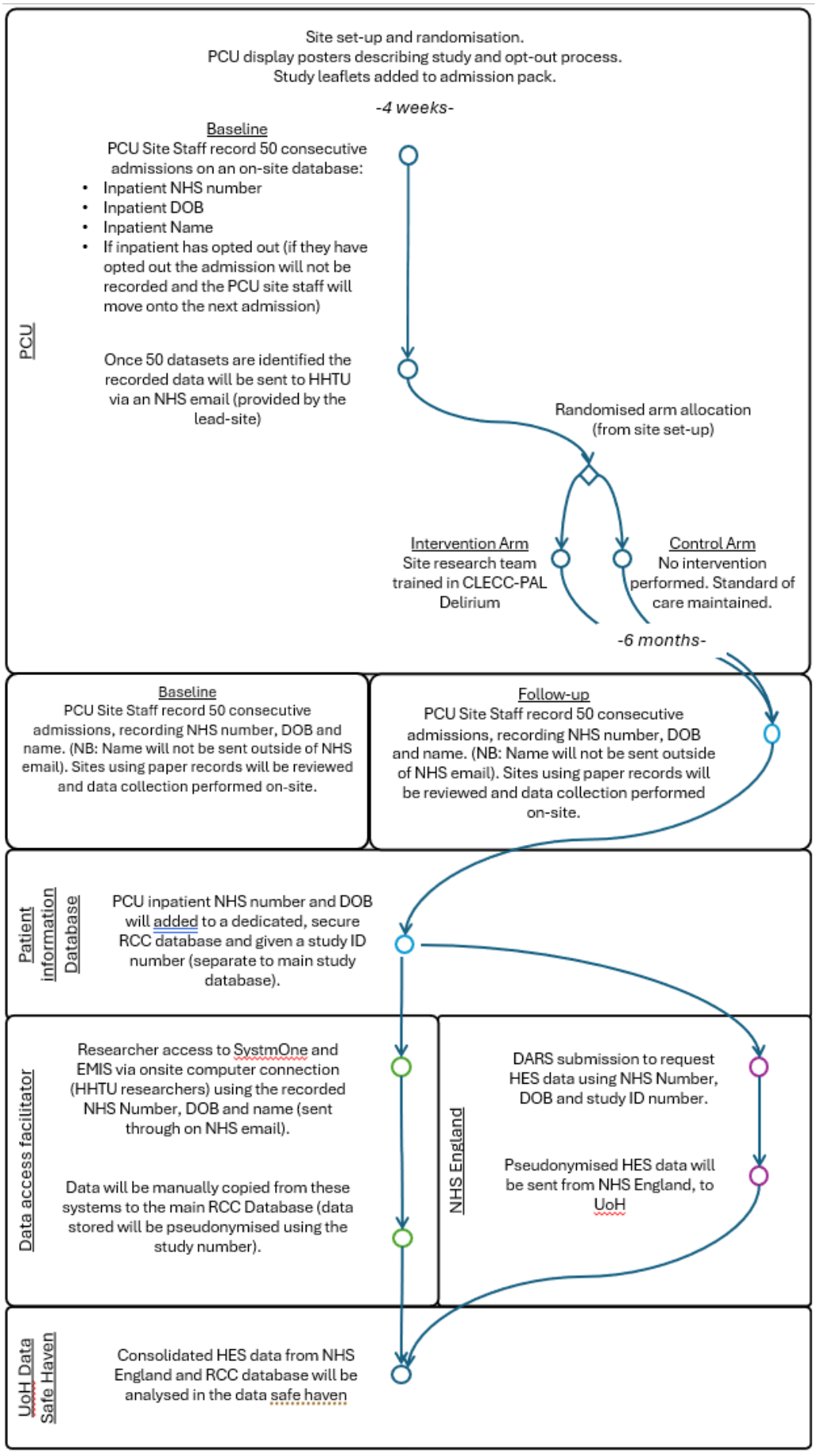
HHTU will develop the study database and data processes in accordance with HHTU SOPs. HHTU data systems are within scope of the HHTU NHS Data Security and Protection Toolkit (Organisation Code - EE133824-HHTU). An electronic case report form (eCRF) will be used for data capture. The eCRF will be developed by HHTU under their licence for a commercially available system (REDCap Cloud). Granular role-based permissions will ensure site staff can enter and view the information required for their own site only. Site staff will receive training from the central study team and enter data onto the eCRFs in accordance with the eCRF Completion Instructions.

RedCap Cloud (RCC) is a cloud-based EDC system provided by nPhase. Data is stored on dedicated RCC hardware in EU datacentres (including real-time backup) managed by Amazon Web Services to industry standards outlined in ISO 27001, PCI DSS, SOC 1 - 3, FISMA, CIS, CSA, NIST and UK Cloud Security Principles. Data is encrypted at rest and in transit. RCC themselves deliver compliance to HIPAA, CFR Part 11, and EMEA Annex 11. The University of Hull's contract with nPhase establishes them as a data processor and under GDPR they act solely on the instruction of the University of Hull.

Access to personal data for this specific project will be limited to named individuals at participating sites or the research team at The University of Hull. HHTU data systems have a full audit trail which cannot be edited by HHTU staff.

All hard copy data will be stored at study sites in a locked filing cabinet in accordance with data protection requirements for the retention of research data and local site data management policies.

Figure 1, Data Flow Summary



9.3 Trial Data Monitoring

Data (including data related to delirium days) will be monitored for quality and completeness by the HHTU. Missing data items will not be chased from inpatients or site PCUs. Independent Source Data Verification cannot be performed as there will be no access to medical records at the Site PCU for anyone other than the study researcher. A self-reported checklist will be completed by the researcher on a random selection of inpatients, to check for transcription errors. There will be ongoing central collection of consent forms (for process evaluation) and other relevant key documents.

The study specific monitoring plan will be generated and signed off by all stakeholders prior to study commencing. The monitoring plan will implement an adaptive approach; identifying and trending issues across sites to ensure inpatient safeguarding and data integrity is maintained throughout the study.

9.4 Oversight Committees

The Trial Management Group (TMG) is comprised of the CI and co-investigators, HHTU team, key external members of staff assigned responsibility for:

- trial management including protocol development, study set-up, data collection forms, data analysis
- obtaining regulatory approvals
- submitting contracts
- completing cost estimates
- facilitating TSC meetings
- reporting Serious Adverse Events
- monitoring compliance to screening, recruitment (interviews only), intervention and follow-up procedures
- auditing consent procedures, data collection, data validation, database development
- study promotion and publication of study results

Note: the TMG members will meet bi-monthly as a minimum

The Trial Steering Committee (TSC) is comprised of an Independent Chair, not less than two other independent members and a PPI representative following the NIHR Research Governance Guidelines. The TSC will provide overall supervision of the trial looking in particular:

- at study progress
- adherence to protocol
- participant safety
- consideration of new information.

Note: TMG members may attend the TSC meetings and present and report progress. The TSC will meet biannually as a minimum.

9.5 Safety Reporting

As the study intervention does not change the delivery of standard practice, no safety reporting is required. Any safety concerns from the site PCUs will be reported to HHTU and escalated to the CI, Sponsor and oversight committees where necessary.

9.6 Serious Breaches

PIs and researchers are required to promptly notify the HHTU of a serious breach (as defined in the latest version of the National Research Ethics Service (NRES).

A 'serious breach' is defined as a breach of the protocol or of the conditions or principles of GCP (or equivalent standards for conduct of non-CTIMPs) which is likely to affect to a significant degree the safety or physical or mental integrity of the trial subjects, or the scientific value of the research. In the event of doubt or for further information, the PI or researcher should contact the study Trial Manager at the HHTU.

Safety issues and queries can be raised at site to HHTU for assessment by the CI, Sponsor and oversight committees and for actions to be implemented where appropriate. Site teams are to be encouraged to raise concerns to ensure the intervention is being implemented accurately and ensure data integrity for the study endpoints is maintained. This is particularly important when the study sites are likely to be research naïve. Open dialogue between HHTU and the study site PCUs is encouraged throughout.

9.7 Ethical Considerations

The right to decline study participation without giving a reason will be respected. Participants will remain free to withdraw at any time without giving a reason and without prejudicing his/her further treatment. This study will be submitted for approval to the Hull York Medical School Ethics Committee, Health Research Authority (HRA) Research Ethics Committee, HRA Confidentiality Advisory Group (to ensure compliance with Section 251 of the NHS Act 2006), and the local Research and Development (R&D) departments at each participating site PCU prior to entering participants into the study. The HHTU will provide the local information pack and all relevant study documentation.

9.8 Confidentiality

All information collected during the course of the study will be kept strictly confidential. Information will be held securely either on paper and / or electronically at the HHTU. The HHTU will comply with all aspects of GDPR 2018. Operationally this will include:

- Appropriate storage arrangements for participants' personal and clinical details, including:
    - Not storing NHS number or date of birth in the study database (making data anonymous in context).
    - Separating consent for interviews from the clinical data in the study data

- Once all HES data has been collected and inpatient medical records have been reviewed for data collection, the patient information database will be deleted.
- Restricted access and disposal arrangements for participant personal and clinical details.
- Where anonymisation of documentation is required, the site PCU and researcher is responsible for ensuring only the instructed identifiers are present before sending to HHTU.

9.9 Archiving

Archiving of all study data will be completed and stored for 5 years from the end of study date.

9.10 Statement of Indemnity

A statement of indemnity should be given and will depend on and be provided by the sponsor.

9.11 Study Organisational Structure

- **Chief Investigator (CI) –** The CI will have overall responsibility for the study design, set-up, conduct, co-ordination and management,
- **Sponsor –** The University of Hull (interchangeably referred to as The Sponsor within this document) will be responsible for study management and financing of the study as defined by Directive 2001/20/EC. These responsibilities may delegated to the HHTU as detailed in the study contract.
- **Hull Health Trials Unit (HHTU) –** HHTU will have responsibility for study management as delegated by the Sponsor. HHTU will manage study set-up and monitoring in line with HHTU SOPs, partner SOPs (if applicable) and RGF as detailed in the UK Medicines for Human Use (Clinical Trials) Regulations, 2006. Responsibilities include: study administration, protocol development, data collection design, REC/HRA/CAG regulatory submissions, data management, randomisation design and service, database development and provision, database administrative functions, source data verification, monitoring, statistical analyses, HHTU and site training, study reports and results dissemination
- **Researchers –** Will work closely with HHTU and may be delegated some of the responsibilities outlined above as detailed on the central delegation log

9.12 Publication Policy

Prior to trial recruitment, the study will be registered with the ISRCTN according to the International Committee of Medical Journal Editors (ICMJE) Guidelines.

The success of the study depends upon the collaboration of all participants. For this reason, credit for the main results will be given to all those who have collaborated on the study, through authorship and contributions. Authorship guidelines will be provided for manuscripts submitted to medical journals. These state that authorship credit should be based only on substantial contribution to:

- conception and design, or acquisition of data, or analysis and interpretation of data
- drafting the article or revising it critically for important intellectual content
- and final approval of the version to be published
- and that all these conditions must be met (**www.icmje.org**)

The CI, Researcher and relevant senior HHTU staff will be named as authors in all publications. All collaborators will be listed as contributors for the main trial publication, alongside roles in study planning, conducting and reporting. To maintain trial scientific integrity, data will not be released before the first publication of primary endpoint analysis, either for publication or oral presentation, without TSC permission. Individual collaborators must not publish data concerning their participants before the first publication of primary endpoint analysis.

All publications will request approval from the funder (NIHR HSDR) before submission for publication or presentation.

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11 Appendices

Appendix A

INTERNAL PILOT STUDY

NB: Internal pilot to be further developed and approved by the funder by May 2025.

Site set up

Prospective sites (charitably-funded and NHS sites that provide specialist palliative care services in the UK) will have the opportunity to join online information events at which the study team will briefly present feasibility study findings and a study overview outlining what PCUs can expect if selected. This information will include details on randomisation, study timelines, and study requirements. Time will be provided for questions and discussions of potential challenges and local site governance. Incomplete site characteristic information will be collected to support to ensure maximal patient and PCU diversity and final site selection.

Site selection

PCUs will be approached to determine their interest in participating in the study and a feasibility assessment form will be completed. Selection of eligible PCU sites will be performed by the HHTU study team and the researcher. PCU site contracts will be generated and a HHTU PCU site greenlight process will be followed to ensure all necessary site eligibility criteria are fulfilled before permitting recruitment to take place. PCU selection will be confirmed if their PCU characteristics satisfy PCU randomisation stratification characteristics.

As the study is a cRCT, participating PCUs characteristics will be used to stratify the PCU randomisation allocation into either the intervention arm or the usual practice arm according to Firth's models of palliative care criteria.
PCU characteristics will be based on:

- Size: the number of referrals accepted annually
- Experience and training: the extent of educational and teaching provisions
- Geographical distribution: a diverse range of PCU patient catchment areas

Internal Pilot Stop-Go rules

Before the study can progress to WP2, the study sponsor and funder should be satisfied that the study internal pilot objectives have been reached.

The STOP-GO rules are as follows:

GO	≥10 sites / records*
WARNING	<10 sites / records*

STOP	0 sites / records*

**Remaining baseline data collected in phase 2 (n=50 baseline records per site)*

Should the Stop and Go rules not be achieved there may be funder requirements for the study to end prematurely. However, mitigations and barriers will be discussed at the TMG / TSC meetings in order to improve recruitment.

Appendix B

Knowledge exchange workshops

Knowledge exchange: Workshops with public and professional stakeholders to explore how the implementation strategy could be adapted and tailored for use in a range of other community settings.

1. Understand the variation in implementation of CLECC-Pal Delirium in participating PCUs

2. Identify lessons to improve use of CLECC-Pal Delirium in the future (if the cRCT shows positive results)

3. Engage and inform stakeholders (carers, service managers, health and care professionals, commissioners) about study findings

4. Facilitate stakeholders to plan how they will use study findings to inform their future practice or policy actions

5. Explore how the CLECC-Pal Delirium implementation strategy could be adapted for use in PCUs across the four nations and adapted for use in other settings (day care, people's homes, care homes)

In the knowledge exchange workshops, the four constructs of Normalisation Process Theory will provide a structure (but not the language) for presenting findings about implementation and for considering with stakeholders how *CLECC-Pal Delirium* can inform, or be adapted to, the implementation (and normalisation) of guideline-adherent delirium care in other settings such as care homes.