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Multicomponent non-pharmacological intervention to prevent delirium for hospitalised people with advanced cancer: study protocol for a phase II cluster randomised controlled trial

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Abstract

Introduction

Delirium is a significant medical complication for hospitalised patients. Up to one-third of delirium episodes are preventable in older inpatients through non-pharmacological strategies that support essential human needs, such as physical and cognitive activity, sleep, hydration, vision and hearing. We hypothesized that a multicomponent intervention similarly may decrease delirium incidence, and/or its duration and severity, in inpatients with advanced cancer. Prior to a phase III trial, we aimed to determine if a multicomponent non-pharmacological delirium prevention intervention is feasible and acceptable for this specific inpatient group.

Methods and analysis

The study is a phase II cluster randomised wait-listed controlled trial involving inpatients with advanced cancer at four Australian palliative care inpatient units. Intervention sites will introduce delirium screening, diagnostic assessment and a multicomponent delirium prevention intervention with six domains of care: preserving natural sleep; maintaining optimal vision and hearing; optimising hydration; promoting communication, orientation and cognition; optimising mobility; and promoting family partnership. Interdisciplinary teams will tailor intervention delivery to each site, and to patient need. Control sites will first introduce only delirium screening and diagnosis, later implementing the intervention, modified according to initial results. The primary outcome is adherence to the intervention during the first seven days of admission, as measured for 60 consecutively admitted eligible patients. Secondary outcomes relate to fidelity and feasibility, acceptability and sustainability of the study intervention, processes and measures in this patient population, using quantitative and qualitative measures. Delirium incidence and severity will be measured to inform power calculations for a future phase III trial.

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Ethics and dissemination

Ethical approval was obtained for all four sites. Trial results, qualitative sub-study findings, and implementation of the intervention will be submitted for publication in peer-reviewed journals, and reported at conferences, to study sites and key peak bodies.

Trial registration

ACTRN12617001070325p

Key words

Delirium, cancer, neoplasms, inpatients, palliative care, clinical trial, feasibility studies

Strengths and limitations of this study

- Strengths are the cluster RCT design; inclusion of patient and family perspectives; and sponsorship by the Palliative Care Clinical Trials Collaborative (PaCCSC), a national, multi-site clinical trials group which provides rigorous research governance.
- A limitation is that site and research staff will not be blinded to the intervention.
- The study is being conducted in Australian palliative care inpatient settings and will include only patients with advanced cancer, which will limit the generalisability of results for other settings and people with other advanced illnesses.

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Introduction

Delirium is a serious acute neurocognitive disorder and medical complication for people with advanced cancer receiving palliative care in hospital, where it occurs for up to one in two patients and is reversible in only up to half of cases, at best.[1-3] It causes sudden disruption to attention and cognition, such as memory and language deficit, disorientation, and perception.[1] During delirium, feelings of fear, humiliation, confusion and isolation are common,[4] at a time when connection with family, friends and health professionals is important and highly valued. [5] Family experience high levels of distress as a result.[5] Delirium is further associated with increased falls, pressure areas, longer-term cognitive and functional decline, duration of hospital stay, mortality, and health care costs.[6-8]

Despite the incidence of delirium and its profound impacts on people with advanced illness, there are limited treatment options and, to date, no effective pharmacological intervention.[9-11] Nor have evidence-based processes for delirium prevention, recognition or assessment been translated in palliative care units.[12,13] The most effective strategy for delirium in older patients across a range of hospital settings is prevention through non-pharmacological strategies to meet essential needs, such as physical and cognitive activity, sleep, hydration, vision and hearing. When implemented as a 'multicomponent intervention', these strategies have reduced delirium incidence by one-third.[9,14] A meta-analysis (n=4,267) of randomised or matched trials of non-pharmacological prevention strategies reported significant reduction in delirium incidence, with the odds of delirium 53% lower in the intervention group compared with controls (odds ratio (OR) 0.47, 95% confidence interval (CI) 0.38-0.58, p<0.001).[14] A Cochrane Review of 39 randomised controlled trials (n=16,082) of non-pharmacological, medication or anaesthetic interventions reported that seven non-pharmacological intervention studies (n=1,950) reduced delirium incidence (relative risk (RR) 0.69, 95% CI 0.59 to 0.81), while evidence for most medication and anaesthetic

interventions was uncertain.[9] There was moderate quality evidence that the non-pharmacological interventions reduced length of hospital admission and improved the likelihood of return to independent living, with low quality evidence of decreased delirium duration and severity.[9] Studies of non-pharmacological interventions for delirium have mainly focused on older patients, yet often excluded patients with advanced cancer and other life-threatening illnesses.[15] Also, strategies within the interventions were diverse, some were better operationalised than others, and not all used a randomised design.[14]

The one study testing a non-pharmacological delirium prevention intervention in people with advanced cancer (n=1,516) in seven Canadian specialist palliative care inpatient units reported no statistically significant difference in delirium incidence, total days in delirium, duration of first episode, severity or delirium-free survival.[16] Strategies were fewer and less targeted to essential needs of patients than those reported in the more recent meta-analysis and Cochrane review;[9,14] and included: i) orientating patients to time, person and place each shift; ii) informing family about delirium, its symptoms and prevention of confusion; and iii) assessing pharmacological risk factors for delirium before querying physicians about consequent planned medication change. There also was inadequate rate and timeliness of completion of the primary measure, the Confusion Assessment Method. While adherence to the intervention was greater than 80%, there was no difference in overall use of psychoactive medication between the two arms. Given that such medication is associated with delirium,[17,18] this factor may partly explain the study's negative results.[16]

There are possible barriers to implementation of non-pharmacological delirium prevention strategies for people with advanced cancer. These include their common frailty and fatigue which reduces capacity to participate in activities such as exercise. Patients and family may not realise the serious risks associated with an episode of delirium, or prioritise prevention strategies without this knowledge. Some clinicians may perceive that delirium is inevitable

and innocuous in advanced cancer and palliative care contexts;[19,20] and presume that preventing delirium is not possible, necessary or likely to be effective. Clinicians historically have relied on pharmacological intervention for delirium, rather than intentionally striving to prevent delirium through non-pharmacological means. With competing demands and without evidence of effectiveness, hospital managers may not value the importance of preventing delirium or allocate the required resources or personnel for non-pharmacological strategies, particularly for people approaching the end of their life.

Based on the body of research conducted with older people in hospital described above,[9,14] we hypothesised that a similar multicomponent intervention would reduce delirium incidence and/or decrease its duration and severity for inpatients with advanced cancer. Given the noted possible barriers to implementation in this specific patient group, piloting the intervention and study design was required prior to testing the hypothesis in a phase III (efficacy) trial.

Aim

To determine if a multicomponent non-pharmacological delirium prevention intervention is feasible and acceptable for inpatients with advanced cancer.

Methods and analysis

Design

A phase II, cluster randomised controlled trial (RCT) with a waitlist control.[21] Participating sites will be randomised to the intervention (screening and immediate implementation of intervention) or control (screening and waitlist to the modified-intervention) (Figure 1).

The use of this design in the phase II trial was to inform the feasibility and design, delivery methods and power calculations of a future multi-site phase III cluster RCT. A cluster approach was chosen because the proposed intervention is more suited to implementation at a site level, and a traditional RCT design would risk contamination in the control arm. The use

of a cluster RCT design is an advance on prior studies of non-pharmacological prevention interventions that used non-randomised designs. A waitlist control arm was chosen as key stakeholders at interested sites considered that the delirium prevention strategies were important, that participation in a trial that enabled access to the intervention was more appealing and ethically sound, and that the intervention strategies were well established as effective in other hospital settings and the potential benefit s were clear, in principle. The waitlist control adds to the resource and time requirements of the trial, but will allow the intervention and study processes to be modified and/or refined at the two waitlist control sites, should initial results indicate that this is required.[21]

Sites (clusters) and patient population

The participating sites are four Australian palliative care units, where approximately 75% of patients have a primary diagnosis of advanced cancer.[22]

In line with the cluster RCT design, consent to participate was obtained at the site level from the person with the delegation to approve participation. Data will be collected for all admitted patients aged ≥18 years with a diagnosis of advanced cancer, for which no individual patient consent will be required.

Intervention

Intervention sites will implement i) delirium screening; ii) delirium diagnosis assessments; and iii) the multicomponent delirium prevention intervention.

Bedside nurses will undertake the Nursing Delirium Screening Scale (Nu-DESC)[23] for all eligible patients at the end of every shift. Within 24 hours of the patient assessed as having a Nu-DESC score ≥2, a trained physician will apply Diagnostic and Statistical Manual of Mental Disorders, Fifth edition (DSM-5) diagnostic criteria for delirium,[1] operationalised

using the Delirium Rating Scale-Revised-1998 (DRS-R-98).[24] These processes currently are not routine at the participating sites and therefore will be additional to usual care.

The multicomponent delirium prevention intervention involves five domains of care that, when delivered in combination, significantly reduced delirium incidence in older hospitalised patients in previous clinical trials.[9,14] We added family partnership as an additional domain, as it was recommended by our consumer investigators and an expert working group, is highly valued by patients and family members,[5,25] and identified as essential by the Australian Commission for Safety and Quality in Healthcare (ACSQHC) in a new Delirium Standard, if preferred by the patient.[26]

The delirium prevention intervention will be delivered to all eligible patients from admission until discharge or death by members of the interdisciplinary team and volunteers. The domains and strategies of the multicomponent intervention are presented in Table 1.

Control sites will initially implement only delirium screening and diagnosis. Once the intervention sites achieve their sample, control sites will implement the intervention.

All sites will continue usual care with respect to treatment of patients with delirium.

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Table 1: Multicomponent delirium prevention intervention

Domain	Strategies	Implementation
Preserve natural sleep	• Offer ear plugs to patients who have low risk of falls • Offer eye shades to patients who have low risk of falls • Reduce noise outside patient rooms during 21:00-06:00 • Normal day-night light variation in room and unit • Exposure to natural light during daylight hours • Schedule care activities to allow uninterrupted sleep during the night • Avoid caffeine after 4pm	• The patient wears ear plugs at night • The patient wear eye shades at night • Room curtains/blinds are open during the day • Room lights are off or minimised at night • The patient spends time outside during the day • The patient drinks no caffeinated drinks after 4pm • The patient reports uninterrupted night-time sleep
Maintain optimal sensory perception	• Assess hearing • Assist with and re-inforce use of hearing aids and special communication techniques • Ear wax clearing as needed • Assess need for visual aids (glasses, magnifying lenses) • If needed, ask family to provide for the patient; • Assist with and reinforce use of visual aids	• The patient has their hearing assessed • The patient has ear wax cleaning • The patient wears functioning hearing aids • The patient has their vision assessed • The patient wears their glasses appropriately • The patient uses visual aids
Optimise hydration	• Encourage oral fluids • Physical assistance with drinks and meals, as required • Drinking aids, as required • Be alert and respond to reversible causes of poor oral intake within 24 hours e.g. nausea, vomiting, drowsiness, sore mouth	• The patient is encouraged to drink • The patient is assisted with meals • Drinking aids are provided e.g. straws • Intervention for reversible causes of poor oral intake are in place
Promote communication, orientation and cognition	• Interpreter and translation for people with NESB • Greet the patient by name • Introduce self by name and role • Refer to person, time and place when talking with the patient • Time aids in room e.g. watch, personal or wall clock; wall, desk or electronic calendar • Update in-room whiteboards daily with date, day, place, reason for admission, team member names, schedule • Minimise number of transfers to other beds or rooms within the unit • Discuss current events with the patient	• Interpreter is available and used • Orientating information is translated into the patient's native language • The patient can see the time, day, date and month in their room • The patient remains in the same bed location within the unit • The patient discusses current events • The patient reminisces and/or talks about their life and family • The patient spends time in cognitively stimulating

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	• Encourage the patient to reminisce and talk • Encourage the patient to engage in cognitively stimulating activities	activities e.g. reading, puzzles, games, knitting, music • Cognitive stimulating activities are in the patient's care plan
Optimise mobility	• Minimise use of tethers e.g. intravenous line, indwelling catheter, drain, oxygen • Minimise use of physical restraints e.g. bed rails, lock-in chair tables, vest restraints, limb restraints • Encourage and/or assist the patient to undertake physical activity throughout the day according to their capacity o Level 0: No activity planned (state reason), o Level 1: Active range of movement exercises in bed and/or sitting position in bed e.g. regular bed adjustment, assistance with re-positioning o Level 2: Assistance to sit on the side of the bed o Level 3: Sitting out of bed in a chair, standing o Level 4: Walking (marching in place, independent or assisted walking around room and unit) o Level 5: Attend inpatient gym, walking outside of unit	• The patient is free of tethers • The patient is free of physical restraint • The patient moves and/or exercises to their optimal capacity
Family partnership	• Ask family about the patient's baseline cognition • Inform the patient and family about delirium risk • Inform the patient and family about delirium prevention strategies and invite participation	• Family are asked about the patient's baseline cognition on admission • Delirium information brochure is provided to the patient and family • Verbally inform of delirium risk and prevention • Patients and family are invited to participate in delirium prevention strategies

Site engagement, education and training

The phase II trial will not pre-determine delivery methods for the intervention, instead observing the methods of each site. Engagement of site staff and volunteers will be guided by Michie's Behaviour Change Wheel (BCW), an evidenced-based framework for changing health-related behaviours. [27] Each site will form an interdisciplinary working group of medical, nursing, allied health, pastoral care, volunteer coordinator and managerial staff. The function of the working groups will be to determine how to deliver the intervention with the available resources, composition and capabilities of their site team. [27] Working group members will communicate the study to the whole team, promote the delirium screening, diagnosis and prevention strategies, and inform patients and family about delirium and the prevention strategies. Site teams will be encouraged to tailor the intervention strategies to each patient's assessed needs and preferences to ensure person-centred care, as well as to adopt simple and feasible methods of delivery and documentation of the intervention.

Education and training of site staff and volunteers in the delirium screening and prevention strategies will be standardised, interdisciplinary and based on Biggs' educational model. [28,29] This model will align educational objectives and methods with the delirium learning needs of staff, and promote critical reflection on attitudes, practice and functional knowledge of the complexities of caring for a person with advanced cancer in hospital. [28,29] Education and training will take place for two-months prior to data collection. A brief, simple study overview manual also will be developed.

Study investigators and/or project staff will attend sites to: i) promote fidelity to the study processes and aims; ii) assist with education and training activities; iii) resolve issues that delay implementation of the intervention or threaten its integrity; iv) act as a 'delirium resource person'; and v) support and encourage site staff and volunteer participation in the intervention.

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The frequency, duration and mode of administration of education and training will be determined prior to implementing delirium screening, diagnosis and prevention strategies in collaboration with participating sites, then standardised for each. Based on the learnings obtained in this phase II trial, we will develop a replicable standardised education resource for the phase III trial.

Randomization

Randomization of sites will take place after Human Research Ethics Committee (HREC) and local governance approvals are obtained. In keeping with the method of the anticipated phase III trial, we will use a permuted block randomisation method with various block sizes to allocate sites to the intervention or waitlist control. Randomisation will be performed by the study statistician (LL) from the coordinating centre, the University of Technology Sydney (UTS).

Blinding and avoidance of contamination

The study design and nature of the intervention means that blinding of site staff will not be possible. Written information for patients and family caregivers will provide only general information about the study aims, rather than specifics of the design or site allocation. Attention will be focused on research nurse training and standardization of data collection to limit the potential for bias.

To avoid contamination between sites, personnel collecting data at an intervention site will not collect data in a control site, and vice versa. Site investigators, research nurses and project staff will be asked not to discuss the intervention in joint tele-meetings with control sites. Clinicians at control sites initially will receive information and training on delirium screening and diagnosis only, and only general information about the prevention intervention in discussions and promotion, until they move into the intervention phase.

Data collection

Research nurses will collect baseline data from sites' most recent Palliative Care Outcomes Collaborative (PCOC) report (a national program which measures and benchmarks patient outcomes in palliative care using standardised clinical assessment tools) [23] (Figure 2) and from key personnel. Research nurses will screen consecutively admitted patients for eligibility, collect delirium screening and diagnostic assessment measures for enrolled patients and record these in a Case Report Form (CRF). At intervention sites, specially designed checklists will capture family caregivers, staff and volunteers' delivery (or otherwise) of delirium prevention strategies within each domain of the multicomponent intervention (Table 1), as well as who delivered it. Whenever the patient does not receive the strategy, the reason will be recorded according to the following categories:

- Not required
- Patient choice
- Not clinically appropriate
- Not possible with current resources
- Other

At study completion, the project team will collect PCOC data for the study time-frame (Age, Gender, Country of birth, Preferred language, Aboriginal or Torres Strait Islander status, Primary diagnosis, Length of stay, Performance status [Australian-modified Karnofsky Performance Status (AKPS)[30] and Resource Utilisation Groups - Activities of Daily Living (RUG-ADL)],[31] Palliative care phase).[32]

Assessments

Figure 2 gives the schedule of study measures and time points; Text Box 1 provides information on the palliative care and delirium measures.

Text Box 1: Description of study measures

The **Australian-modified Karnofsky Performance Status (AKPS)** was adapted from the Karnofsky Performance Status with good face validity and longitudinal test-retest reliability. [30] The AKPS measures patients' overall performance status, using 10-point increments along a scale of 100-10. A score of 100 denotes normal function with no evidence of disease, decreasing to a minimum score of 10, assigned when patients are comatose or barely rousable. Routinely applied on an at least daily basis in most Australian inpatient unit palliative care services. The AKPS will be used to report the patient cohort's performance status at participating sites.
The **Resource Utilisation Groups - Activities of Daily Living (RUG-ADL)** [31] is a validated functional assessment tool which assigns a score of 4-18, based on what a patient does in relation to bed mobility, transfers, eating and toileting, rather than they can do. Higher scores indicate the need for more assistance to undertake activities and that more resources are required to provide this assistance. Applied on an at least daily basis in most Australian inpatient unit palliative care services. The measure will be used to report the patient cohort's functional status at participating sites.
The **Palliative Care Phase** [32] classification is not a validated tool, but is applied on an at least daily basis in most Australian palliative care services to describe the needs of the patient and family and prompt a timely and appropriate clinical response. Phases are: 1. Stable (problems and symptoms are adequately managed and there is a plan of care); 2. Unstable (urgent intervention required because a new symptom or problem develops, or an existing problem rapidly escalates); 3. Deteriorating (a gradual decline in function AND worsening of an existing problem or development of a new but anticipated problem); 4. Terminal (death is likely within days); and 5. Bereavement (post death support). The measure will be used to report the patient cohort's palliative care needs at participating sites.
The **Nursing Delirium Screening Scale (Nu-DESC)** [24] was validated in an oncology inpatient population with a sensitivity of 85.7% and specificity of 86.8%. [24] It is a brief (less than one minute) five-item and low burden tool, incorporating nurses' observation of disorientation, inappropriate behavior, inappropriate communication, illusions/hallucinations and psychomotor retardation. Nurses assign a score of 0–2 for each item, giving a maximum score of 10. The psychomotor retardation item improves recognition of hypoactive delirium, [33] the most prevalent subtype in palliative care inpatient populations.[3] The Nu-DESC has been used in previous research in inpatient palliative care populations[11] and considered feasible and acceptable by palliative care nurses.[19] The Nu-DESC will be used by bedside nurses to screen patients for delirium every eight-hour shift.
The **DSM-5 diagnostic criteria for delirium** are within the most current version of the American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders.[1] Criteria are: A.

Disturbed attention and awareness; B. Disturbance developed over a short period of time (usually hours to a few days), is a change from baseline attention and awareness, and fluctuates in severity; C. An additional disturbance in cognition; D. Disturbances in A and C are not caused by another neurocognitive disorder nor occur in the context of severely reduced level of arousal; and E. The disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal, exposure to a toxin, or has multiple aetiologies. Treating physicians will use the DSM-5 to determine a delirium diagnosis.
The **Delirium Rating Scale-Revised-98 (DRS-R-98)** [25] is a 16-item delirium severity and diagnostic scale with scores of up to 46. It had high inter-rater reliability, sensitivity and specificity in the original validation study, [25] high sensitivity and adequate internal consistency and factor validity in cancer patients,[34] and has been used in research with palliative care inpatients.[35,36] The DRS-R-98 was designed to measure a wider range of delirium symptoms than are contained within diagnostic criteria and in different settings had good discriminative capacity for all, including in a patient population with a high prevalence of dementia [37,38]. Severity items are: sleep-wake cycle disturbance; perceptual disturbances and hallucinations; delusions; lability of affect; language; thought process abnormalities; motor agitation; motor retardation; orientation; attention; short-term memory; long-term memory; visuospatial ability. Diagnostic items are temporal onset of symptoms; fluctuation of symptom severity; physical disorder. Information is obtained from all sources, including physical examination, history gathering and formal cognitive testing. Requires clinician training, with guidance for use contained within the tool. Trained treating physicians and nurses will use the DRS-R-98 to operationalize delirium diagnosis and measure delirium severity. We will use a diagnostic cut-off score of $\geq$15.[38]

Outcomes

The primary outcome is adherence to the intervention. A rate of at least 60% of patients having at least four completed domains for at least five of the first seven days of admission will be considered minimum evidence that the intervention is feasible without need for major modification of the intervention or its delivery methods. Endpoints will be at completion of the intervention and modified-intervention arms (Figure 1).

We chose this moderate endpoint because of the potential patient, clinician and system level challenges to the non-pharmacological strategies in the context of advanced cancer. Consensus by investigators was this endpoint would be the minimum to still have impact, realistic to achieve in practice, and ensure that further evaluation of this complex intervention was not prematurely stopped. The waitlist control design will allow two endpoints and thereby maximize the potential to reach this level of adherence to the intervention.

Secondary outcomes will further inform of the feasibility, acceptability and potential efficacy of a phase III trial of the intervention in this patient population and setting, as follows:

1. Coverage: delivery rate of the multicomponent intervention to consecutive eligible patients admitted to the unit, reasons why the intervention was not delivered, weekend coverage;
2. Fidelity to delirium screening, diagnosis and the intervention: degree of alignment with the protocol, rationales for adaptation, rate of protocol deviations without reasons;
3. Methods, areas and levels of interdisciplinary involvement in delivery of the intervention;
4. Feasibility and acceptability of the study intervention and measures for patients, caregivers, staff and volunteers, measured via brief interviews during and shortly after the intervention phase;

5. Sustainability of the intervention: Adherence will be measured for all inpatients over one week, six months after commencement of data collection at the intervention sites;
6. Feasibility of the sample: percentage of participants included in data collection, reasons for non-inclusion, time to achieve sample size;
7. Number of people with advanced breast cancer admitted to the units, number of these who are in underserved populations (patients over 70, indigenous patients, and culturally and linguistically diverse backgrounds), and the number who experience an episode of delirium (total, and in under-served populations);
8. Percentage completion of all study measures;
9. Rate of patients with a positive delirium screen, measured according to a score of 2 or more on the Nu-DESC at least once during each 24-hour period;
10. Delirium incidence, measured at first onset according to the DSM-5 diagnostic criteria for delirium applied within 24-hours of a positive delirium screen;
11. Delirium severity measured at first onset, using the DRS-R-98;
12. Number of falls related to the intervention; and
13. Complaints related to the intervention.

Sub-study

A qualitative sub-study will be conducted to obtain patient, family caregiver, staff and volunteer perceptions of the feasibility and acceptability of the intervention strategies, via brief interviews. (Figure 2)

Inclusion and exclusion criteria for the sub-study

1. **Patients** will be included if they are aged 18 years or older; have a diagnosis of advanced cancer; admitted to an intervention site and received the intervention; speak English or have access to a health care interpreter; and able to give fully informed written consent. Patients with advanced breast cancer will be purposively recruited to

participate in the interviews. Patients will be excluded if they have an AKPS [30] score less than 30 and are in the 'terminal' Palliative Care Phase; [32]

2. **Family caregivers** will be included if they are aged 18 years or older; identified as a caregiver of a patient who received the intervention; English speaking or have availability of a health care interpreter; and are able to give fully informed written consent;

3. **Site staff** will be included if they are employed at an intervention site and involved in implementing the delirium measures and/or the intervention; and

4. **Site volunteers** will be included if they are aged 18 years or older, enrolled in a formal volunteer program at an intervention site and involved in implementing the intervention.

Sub-study consent process

A researcher who is not a study investigator will obtain written informed consent from patients, family caregivers, staff and volunteers to participate in the brief interviews. For patients and family caregivers, the researcher will check with the clinical team to make sure the person meets the broad criteria for consideration of eligibility, is well enough, and has given permission to be approached by a researcher, before introducing him or herself to the person and explaining the study. For staff and volunteers, the researcher will consult with the site investigator before approaching potential participants.

Participant consent will be a process of information exchange between the researcher, the potential participant and any other person the potential participant believes should be included in the discussion. Participant information sheets will be the basis for discussion and cover all procedures and possible benefits and burdens of participating. The potential participant will be given sufficient opportunity to consider the study and ask questions. Any questions will be addressed and answered fully. The completed consent form will be copied

and one copy will be given to the participant, one copy inserted in the medical file (for patients), and one copy filed in study file.

Analysis

Statistical analysis of primary outcome (adherence)

Adherence will be calculated as the rate to which patients have completed domains on a daily basis for the first seven days of admission. Degree of adherence to individual strategies will also be calculated as proportions.

Statistical analysis of secondary outcomes

Data on all outcomes will be summarised with descriptive statistics including their distribution. Frequency and percentage will be used for summarising categorical variables and mean, standard deviation, median, and interquartile range for continuous variables. Delirium incidence and severity will be determined at both the intervention and control sites.

Qualitative analysis

Participant interviews will be analysed using thematic content analysis to identify emergent themes and trends related to participants' perceptions of the feasibility and acceptability of the intervention elements and delirium measures.[39]

Sample size

A sample size of four sites and 40 patient participants was considered sufficient for reasonable estimation of feasibility and percentage completion of study processes and measures during the first phase. [40] We will collect de-identified data on all eligible patients admitted to all sites until data is collected for 40 patients overall, with at least 20 in the intervention arm. If the intervention is found to need modification, data will be collected for a further 20 patient participants at the two waitlist control sites.

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This sample size was based on that projected for the future phase III cluster RCT of the intervention with: two parallel arms, 50% delirium incidence in the control, 30% delirium incidence in the intervention group, cluster size of 30 and intra-class correlation of 0.05, type I error rate of 5%, 80% power to reject the null hypothesis, and 30% attrition. This calculation results in a projected phase III trial sample size of nine clusters and 280 patient participants.

For the sub-study, sample size will be determined when data saturation is achieved.

Trial monitoring

In addition to falls and complaints, all adverse events will be recorded. Site investigators will assess the adverse event, assign the degree of relationship to the intervention, and provide information to the coordinating centre (UTS), and the approving HREC if required. Adverse events will be followed until the event is resolved, can be explained, or if the participant is lost to follow-up. Reports will contain details of follow-up investigations, results or other consultation. The investigator team will stop the study if reporting of adverse events indicates that major review of the study protocol is required. The UTS project team will report adverse event related to the intervention to the PaCCSC Trial Management Committee (TMC) within two weeks of knowledge of the event. The TMC discussions will be minuted, with actions detailed and reviewed at the subsequent meeting. The TMC chairperson's report to the PaCCSC Scientific Committee will contain a summary of the discussions of the adverse event report and agreed outcomes.

Data management

An Excel spreadsheet master index will contain confidential participant contact information and be the only link between individual site and patient participants and their allocated identification number (ID). Study data will be collected and stored on paper CRFs and electronic Excel spreadsheets and then entered onto and managed on a Research Electronic

Data Capture (REDCap) [41] database. Audio data from participant interviews will be identified only by ID, collected on a digital recording medium and stored temporarily at the study sites until uploaded to the REDCap database. Original files will then be destroyed. Data will be held, administered, checked and analysed at the coordinating site according to relevant PaCCSC Standard Operating Procedures (SOP). Errors detected during the data checking process will generate a site data report form recording details of the query and correction and resolution instructions. The database will be updated according to site instructions via email to provide an audit trail of data changes. The coordinating site will maintain a register of data checks for monitoring purposes. Data collected at each site, such as CRFs, any corrected and amended data, copies of adverse incident reports and file notes, will be securely stored and identified by ID number only. All identifiable data (e.g. signed consent forms) will be separately stored during the recruitment period. Site research staff will send copies of study documents (with the exception of signed consent forms) to the coordinating site by registered mail for collation and archiving. All study documents will be stored in accordance with relevant State government regulations regarding the retention and disposal of participant records.

Ethics and dissemination

The study was approved by the South Western Sydney Local Health District HREC on July 19, 2017, reference number HREC/17/LPOOL/224; and ratified by the UTS HREC on August 22, 2017, reference number ETH17-1697. Minor protocol amendments were approved on April 13, 2018 (V1.1).

Reporting of this protocol adheres to the Standard Protocol Items: Recommended for Interventional Trials. [42] Reporting of results will adhere to the Consolidated Standards of Reporting Trials (CONSORT) guidelines for cluster RCTs and non-pharmacological treatment trials. [43,44] Reporting of the qualitative sub-study and implementation findings will be guided by the Consolidated Criteria for Reporting Qualitative Research (COREQ).[45] A comprehensive dissemination strategy will ensure that the trial results (either positive or negative) inform future research and clinical practice. Dissemination will include publication in peer-reviewed journals, presentations at conferences, study sites and key peak bodies. The investigators have no publication restrictions.

Strengths and limitations

The primary strengths of this study are the cluster RCT design and that it is supported by the PaCCSC, a national, multi-site phase III clinical trials group which provides well-established rigorous research governance and access to sites with research experience and capacity. The intervention includes family partnership, which is highly valued by both patients and family.[5,26] We will obtain the perspectives of patients and family, which are largely absent in trials of previous multicomponent delirium interventions.[15]

Limitations include that site and research staff will not be blinded to the intervention. Active steps will be taken to minimize contamination between intervention and waitlist control sites. The study will be conducted in Australian palliative care inpatient settings and include only

patients with advanced cancer, limiting the generalizability of results for services in other geographical regions and health care systems, and for patients with other advanced illnesses.

Trial status

The study has been approved by local health district and university HRECs, local governance approvals obtained, sites randomised, the two-month period completed and data collection is underway.

List of abbreviations

AKPS: Australia-modified Karnofsky Performance Status; **ACSQHC**: Australian Commission for Safety and Quality in Health Care; **BCW**: Behaviour Change Wheel; **CI**: Confidence Interval; **CONSORT**: Consolidated Standards of Reporting Trials; **COREQ**: Consolidated Criteria for Reporting Qualitative Research; **DRS-R-98**: Delirium Rating Scale-Revised-1998; **DSM-5**: Diagnostic and Statistical Manual of Mental Disorders, Fifth edition; **HREC**: Human Research Ethics Committee; **ID**: identification number; **Nu-DESC**: Nursing Delirium Screening Scale; **OR**: Odds Ratio; **PaCCSC**: Palliative Care Clinical Studies Collaborative; **PCOC**: Palliative Care Outcomes Collaborative; **RCT**: Randomised Controlled Trial; **REDCap**: Research Electronic Data Capture; **RR**: Relative Risk; **RUG-ADL**: Resource Utilisation Groups - Activities of Daily Living; **SOP**: Standard Operating Procedures; **UTS**: University of Technology Sydney

Declarations

Clinical trials registration

ACTRN12617001070325p, Australian New Zealand Clinical Trials Registry (ANZTR), http://www.anzctr.org.au/, 24/07/2017. The ANZTR is a Primary Registry of the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP).

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Consent for publication

Participant information includes an explanation that results will be published in a form that maintains the confidentiality of sites and individual participants.

Availability of data and material

Participant information sheets and consent forms are available at https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=373168&isReview=true

Funding

This work was supported by an Australian National Breast Cancer Foundation (NBCF) 2017 Pilot Study Grant (Grant code PS-17-030), contact details Level 9, 10 Barrack Street, Sydney, NSW 2000, Australia; T: +61 2 8098 4800 E: info@nbcf.org.au, W: https://nbcf.org.au/.

Competing interests

The authors declare that they have no competing interests.

Sponsor

The trial sponsor is PaCCSC, contact details: Level 3, 235 Jones St Ultimo NSW 2007, Australia; T. +61 (2) 9514 4862 (Sydney) /+61 (8) 7421 9726 (Adelaide), E: paccsc@uts.edu.au, W: uts.edu.au/paccsc. PaCCSC supports optimal trial governance through SOPs for electronic data handling, completion of CRFs, monitoring, dissemination, archiving of research materials, and record destruction; and trial infrastructure through Trials Management and Scientific Committees.

Roles and responsibilities

Chief study investigators MA, AH and JP retain ultimate responsibility for the trial. Investigators and a project team coordinated the trial from IMPACCT - Improving Palliative, Aged and Chronic Care through Clinical Research and Translation, UTS. The investigator team meet at least twice yearly to support progress of the trial and inform related activities, such as dissemination.

Authors' contributions

AH, MA and JP are the co-lead authors and AH is the corresponding author for this manuscript. MA, JP and AH devised the adaptation of the multicomponent intervention for people with advanced cancer in hospital. MB and BN provided consumer insight into the adaptation of the intervention. AC provided guidance on the extent of alignment of the intervention and delirium screening diagnosis processes with the ACSQHC Delirium Clinical Care Standard. LL devised the statistical analysis and randomization process. JMD and ML provided insights into the waitlist design. SK contributed to the development of the site engagement and educational processes. SK, GC, RC, BL, EWE, PL and SB contributed clinical and research expertise into study design, process, measures and/or analysis. LB, BF, SLC and LE contributed to various aspects of the study protocol, including data collection, entry and storage, reporting of adverse effects, minimization of contamination, and/or site training. All authors have read and approved the final manuscript.

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Figure 1: Study Diagram
Standardised delirium screening at all sites + delirium prevention strategies at intervention sites; control sites wait listed for intervention

∗ Modified if required

Figure 2: Schedule of study measures and time points [43]

Note: Characteristics indicated with a ∗ will be collected at baseline from the sites most recent PCOC report, and then again at study completion directly from PCOC for the specific time-frame of data collection at each site.

Table 1: Multicomponent delirium prevention intervention

Study diagram

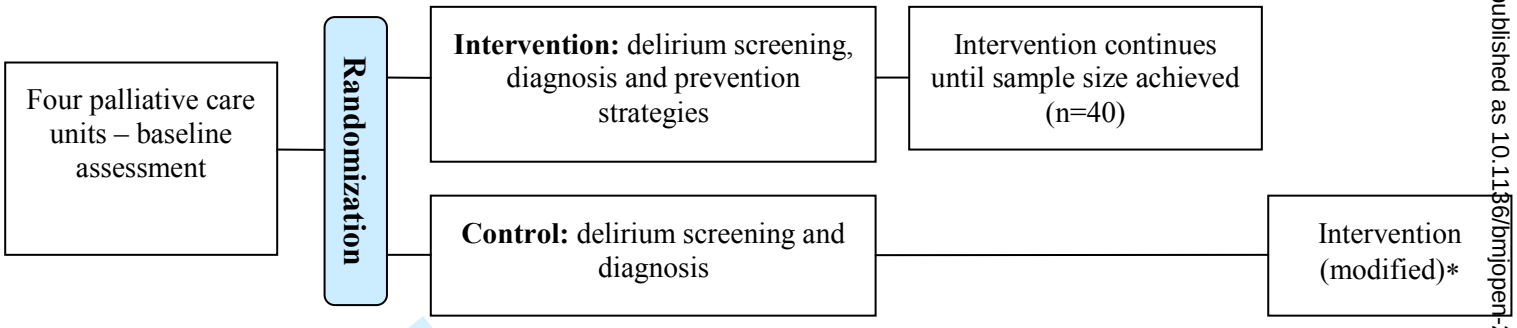

Figure 1: Study Diagram
Standardized delirium screening at all sites + delirium prevention strategies at intervention sites; control sites wait listed for intervention
* Modified if required.

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Figure 2: Schedule of study measures and time points [42]

Measures	Study period						
	Control and intervention sites					Intervention sites	
	Baseline	Eligibility screen on admission	Admission days 1-7	Nu-DESC +ve	Study completion	Admission days 1-7	Intervention completion
UNIT LEVEL							
Geographical location	X						
Type and level of service provision	X						
Number of beds	X						
Team composition	X						
Clinical documentation method	X						
Delirium process and measures	X						
Patient demographics*	X				X		
Patient function AKPS, RUG-ADL*	X				X		
Palliative care phases*	X				X		
PATIENT LEVEL							
Primary diagnosis		X					
Age		X					
Nu-DESC			X				
DSM-5 diagnostic criteria for delirium				X			
DRS-R-98				X			
Adherence to delirium prevention strategies						X	
SUB-STUDY							
Brief interviews with patients, family, staff and volunteers							X

Note: Characteristics indicated with a * will be collected at baseline from the sites most recent PCOC report, and then again at study completion directly from PCOC for the specific time-frame of data collection at each site.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Title page
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2 and 21
	2b	All items from the World Health Organization Trial Registration Data Set	21
Protocol version	3	Date and version identifier	19
Funding	4	Sources and types of financial, material, and other support	21
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Title page
	5b	Name and contact information for the trial sponsor	21
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	21
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	21-22

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-5
	6b	Explanation for choice of comparators	5-6
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5-6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6; 14-15
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6-7
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	7-8
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	7-8
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	13-14
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 2
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	16-17

Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	16-17
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8-9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8-9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8-9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9-12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	NA
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	17-18
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	NA

	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	NA
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	17
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	17
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	17
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	19
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	NA
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6, 14-16
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	17-18
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	21
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	21-22

Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	19
	31b	Authorship eligibility guidelines and any intended use of professional writers	22
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	21
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	21
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

BMJ Open

Multicomponent non-pharmacological intervention to prevent delirium for hospitalised people with advanced cancer: study protocol for a phase II cluster randomised controlled trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-026177.R1
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Title: Multicomponent non-pharmacological intervention to prevent delirium for hospitalised people with advanced cancer: study protocol for a phase II cluster randomised controlled trial

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Abstract

Introduction

Delirium is a significant medical complication for hospitalised patients. Up to one-third of delirium episodes are preventable in older inpatients through non-pharmacological strategies that support essential human needs, such as physical and cognitive activity, sleep, hydration, vision and hearing. We hypothesized that a multicomponent intervention similarly may decrease delirium incidence, and/or its duration and severity, in inpatients with advanced cancer. Prior to a phase III trial, we aimed to determine if a multicomponent non-pharmacological delirium prevention intervention is feasible and acceptable for this specific inpatient group.

Methods and analysis

The study is a phase II cluster randomised wait-listed controlled trial involving inpatients with advanced cancer at four Australian palliative care inpatient units. Intervention sites will introduce delirium screening, diagnostic assessment and a multicomponent delirium prevention intervention with six domains of care: preserving natural sleep; maintaining optimal vision and hearing; optimising hydration; promoting communication, orientation and cognition; optimising mobility; and promoting family partnership. Interdisciplinary teams will tailor intervention delivery to each site, and to patient need. Control sites will first introduce only delirium screening and diagnosis, later implementing the intervention, modified according to initial results. The primary outcome is adherence to the intervention during the first seven days of admission, as measured for 40 consecutively admitted eligible patients. Secondary outcomes relate to fidelity and feasibility, acceptability and sustainability of the study intervention, processes and measures in this patient population, using quantitative and qualitative measures. Delirium incidence and severity will be measured to inform power calculations for a future phase III trial.

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Ethics and dissemination

Ethical approval was obtained for all four sites. Trial results, qualitative sub-study findings, and implementation of the intervention will be submitted for publication in peer-reviewed journals, and reported at conferences, to study sites and key peak bodies.

Trial registration

ACTRN12617001070325p

Key words

Delirium, cancer, neoplasms, inpatients, palliative care, clinical trial, feasibility studies

Strengths and limitations of this study

- Strengths are the cluster RCT design; inclusion of patient and family perspectives; and sponsorship by the Palliative Care Clinical Trials Collaborative (PaCCSC), a national, multi-site clinical trials group which provides rigorous research governance.
- A limitation is that site and research staff will not be blinded to the intervention.
- The study is being conducted in Australian palliative care inpatient settings and will include only patients with advanced cancer, which will limit the generalisability of results for other settings and people with other advanced illnesses.

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Introduction

Delirium is a serious acute neurocognitive disorder and medical complication for people with advanced cancer receiving palliative care in hospital, where it occurs for up to one in two patients and is reversible in only up to half of cases, at best.[1-3] It causes sudden disruption to attention and cognition, such as memory and language deficit, disorientation, and perception.[1] During delirium, feelings of fear, humiliation, confusion and isolation are common,[4] at a time when connection with family, friends and health professionals is important and highly valued. [5] Family experience high levels of distress as a result.[5] Delirium is further associated with increased falls, pressure areas, longer-term cognitive and functional decline, duration of hospital stay, mortality, and health care costs.[6-8]

Despite the incidence of delirium and its profound impacts on people with advanced illness, there are limited treatment options and, to date, no effective pharmacological intervention.[9-11] Nor have evidence-based processes for delirium prevention, recognition or assessment been translated in palliative care units.[12,13] The most effective strategy for delirium in older patients across a range of hospital settings is prevention through non-pharmacological strategies to meet essential needs, such as physical and cognitive activity, sleep, hydration, vision and hearing. When implemented as a 'multicomponent intervention', these strategies have reduced delirium incidence by one-third.[9,14] A meta-analysis (n=4,267) of randomised or matched trials of non-pharmacological prevention strategies reported significant reduction in delirium incidence, with the odds of delirium 53% lower in the intervention group compared with controls (odds ratio (OR) 0.47, 95% confidence interval (CI) 0.38-0.58, p<0.001).[14] A Cochrane Review of 39 randomised controlled trials (n=16,082) of non-pharmacological, medication or anaesthetic interventions reported that seven non-pharmacological intervention studies (n=1,950) reduced delirium incidence (relative risk (RR) 0.69, 95% CI 0.59 to 0.81), while evidence for most medication and anaesthetic

interventions was uncertain.[9] There was moderate quality evidence that the non-pharmacological interventions reduced length of hospital admission and improved the likelihood of return to independent living, with low quality evidence of decreased delirium duration and severity.[9] Studies of non-pharmacological interventions for delirium have mainly focused on older patients, yet often excluded patients with advanced cancer and other life-threatening illnesses.[15] Also, strategies within the interventions were diverse, some were better operationalised than others, and not all used a randomised design.[14]

The one study testing a non-pharmacological delirium prevention intervention in people with advanced cancer (n=1,516) in seven Canadian specialist palliative care inpatient units reported no statistically significant difference in delirium incidence, total days in delirium, duration of first episode, severity or delirium-free survival.[16] Strategies were fewer and less targeted to essential needs of patients than those reported in the more recent meta-analysis and Cochrane review;[9,14] and included: i) orientating patients to time, person and place each shift; ii) informing family about delirium, its symptoms and prevention of confusion; and iii) assessing pharmacological risk factors for delirium before querying physicians about consequent planned medication change. There also was inadequate rate and timeliness of completion of the primary measure, the Confusion Assessment Method. While adherence to the intervention was greater than 80%, there was no difference in overall use of psychoactive medication between the two arms. Given that such medication is associated with delirium,[17,18] this factor may partly explain the study's negative results.[16]

There are possible barriers to implementation of non-pharmacological delirium prevention strategies for people with advanced cancer. These include their common frailty and fatigue which reduces capacity to participate in activities such as exercise. Patients and family may not realise the serious risks associated with an episode of delirium, or prioritise prevention strategies without this knowledge. Some clinicians may perceive that delirium is inevitable

and innocuous in advanced cancer and palliative care contexts;[19,20] and presume that preventing delirium is not possible, necessary or likely to be effective. Clinicians historically have relied on pharmacological intervention for delirium, rather than intentionally striving to prevent delirium through non-pharmacological means. With competing demands and without evidence of effectiveness, hospital managers may not value the importance of preventing delirium or allocate the required resources or personnel for non-pharmacological strategies, particularly for people approaching the end of their life.

Yet, to fulfil the remit of palliative care to help patients live as actively as possible, the adversity of delirium impels further empirical testing to definitively determine whether it can be prevented during advanced cancer. Based on the body of research conducted with older people in hospital described above,[9,14] we hypothesised that a similar multicomponent intervention would reduce delirium incidence and/or decrease its duration and severity for this inpatient population. Given the above-noted possible barriers to implementation, piloting the intervention and study design was required prior to testing the hypothesis in a phase III (efficacy) trial.

Aim and objectives

To determine if a multicomponent non-pharmacological delirium prevention intervention is feasible and acceptable for inpatients with advanced cancer.

The objectives are to:

1. To develop a multi-component non-pharmacological delirium prevention intervention ('non-pharmacological delirium prevention intervention'), derived from highly efficacious interventions for older adults in hospital, for people with advanced cancer and palliative care inpatient unit settings;

2. To describe the strategies used by participating sites to implement the delirium measurement tools and non-pharmacological delirium prevention intervention;

3. To determine if a non-pharmacological delirium prevention intervention is feasible, acceptable and deliverable with high adherence and fidelity in oncology and palliative care units;

4. To determine the feasibility and design of a phase III trial to test the efficacy of the non-pharmacological delirium prevention intervention in people with advanced cancer in hospital.

Methods and analysis

Design

A phase II, cluster randomised controlled trial (RCT) with a waitlist control.[21] Participating sites will be randomised to the intervention (screening and immediate implementation of intervention) or control (screening and waitlist to the modified-intervention) (Figure 1).

The use of this design in the phase II trial was to inform the feasibility and design, delivery methods and power calculations of a future multi-site phase III cluster RCT. A cluster approach was chosen because the proposed intervention is more suited to implementation at a site level, and a traditional RCT design would risk contamination in the control arm. The use of a cluster RCT design is an advance on prior studies of non-pharmacological prevention interventions that used non-randomised designs. A waitlist control arm was chosen as key stakeholders at interested sites considered that the delirium prevention strategies were important, that participation in a trial that enabled access to the intervention was more appealing and ethically sound, and that the intervention strategies were well established as effective in other hospital settings and the potential benefits were clear, in principle. The waitlist control adds to the resource and time requirements of the trial, but will allow the

intervention and study processes to be modified and/or refined at the two waitlist control sites, should initial results indicate that this is required.[21]

Sites (clusters) and patient population

The participating sites are four Australian palliative care units, where approximately 75% of patients have a primary diagnosis of advanced cancer.[22]

In line with the cluster RCT design, consent to participate was obtained at the site level from the person with the delegation to approve participation. Data will be collected for all admitted patients aged ≥18 years with a diagnosis of advanced cancer, for which no individual patient consent will be required.

Intervention

Intervention sites will implement i) delirium screening; ii) delirium diagnosis assessments; and iii) the multicomponent delirium prevention intervention.

Bedside nurses will undertake the Nursing Delirium Screening Scale (Nu-DESC)[23] for all eligible patients at the end of every shift. Within 24 hours of the patient assessed as having a Nu-DESC score ≥2, a trained physician will apply Diagnostic and Statistical Manual of Mental Disorders, Fifth edition (DSM-5) diagnostic criteria for delirium,[1] operationalised using the Delirium Rating Scale-Revised-1998 (DRS-R-98).[24] These processes currently are not routine at the participating sites and therefore will be additional to usual care.

The multicomponent delirium prevention intervention involves five domains of care that, when delivered in combination, significantly reduced delirium incidence in older hospitalised patients in previous clinical trials.[9,14] We added family partnership as an additional domain, as it was recommended by our consumer investigators and an expert working group, is highly valued by patients and family members,[5,25] and identified as essential by the Australian Commission for Safety and Quality in Healthcare (ACSQHC) in a new Delirium Standard, if

preferred by the patient.[26] We did not include a pharmacological component (such as minimising polypharmacy) because there was less evidence that this component of care effectively prevents delirium, compared to that which addresses fundamental human needs for physical and cognitive activity, sleep, hydration, vision and hearing. 9, 14

The delirium prevention intervention will be delivered to all eligible patients for the first seven days of admission by members of the interdisciplinary team, family caregivers and volunteers. The domains and strategies of the multicomponent intervention are presented in Table 1.

Control sites will initially implement only delirium screening and diagnosis. Once the intervention sites achieve their sample, control sites will implement the intervention.

All sites will continue usual care with respect to treatment of patients with delirium.

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Table 1: Multicomponent delirium prevention intervention

Domain	Strategies	Implementation
Preserve natural sleep	• Offer ear plugs to patients who have low risk of falls • Offer eye shades to patients who have low risk of falls • Reduce noise outside patient rooms during 21:00-06:00 • Normal day-night light variation in room and unit • Exposure to natural light during daylight hours • Schedule care activities to allow uninterrupted sleep during the night • Avoid caffeine after 4pm	• The patient wears ear plugs at night • The patient wear eye shades at night • Room curtains/blinds are open during the day • Room lights are off or minimised at night • The patient spends time outside during the day • The patient drinks no caffeinated drinks after 4pm • The patient reports uninterrupted night-time sleep
Maintain optimal sensory perception	• Assess hearing • Assist with and re-inforce use of hearing aids and special communication techniques • Ear wax clearing as needed • Assess need for visual aids (glasses, magnifying lenses) • If needed, ask family to provide for the patient; • Assist with and reinforce use of visual aids	• The patient has their hearing assessed • The patient has ear wax cleaning • The patient wears functioning hearing aids • The patient has their vision assessed • The patient wears their glasses appropriately • The patient uses visual aids
Optimise hydration	• Encourage oral fluids • Physical assistance with drinks and meals, as required • Drinking aids, as required • Be alert and respond to reversible causes of poor oral intake within 24 hours e.g. nausea, vomiting, drowsiness, sore mouth	• The patient is encouraged to drink • The patient is assisted with meals • Drinking aids are provided e.g. straws • Intervention for reversible causes of poor oral intake are in place
Promote communication, orientation and cognition	• Interpreter and translation for people with NESB • Greet the patient by name • Introduce self by name and role • Refer to person, time and place when talking with the patient • Time aids in room e.g. watch, personal or wall clock; wall, desk or electronic calendar • Update in-room whiteboards daily with date, day, place, reason for admission, team member names, schedule • Minimise number of transfers to other beds or rooms within the unit • Discuss current events with the patient	• Interpreter is available and used • Orientating information is translated into the patient's native language • The patient can see the time, day, date and month in their room • The patient remains in the same bed location within the unit • The patient discusses current events • The patient reminisces and/or talks about their life and family • The patient spends time in cognitively stimulating

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	• Encourage the patient to reminisce and talk • Encourage the patient to engage in cognitively stimulating activities	activities e.g. reading, puzzles, games, knitting, music • Cognitive stimulating activities are in the patient's care plan
Optimise mobility	• Minimise use of tethers e.g. intravenous line, indwelling catheter, drain, oxygen • Minimise use of physical restraints e.g. bed rails, lock-in chair tables, vest restraints, limb restraints • Encourage and/or assist the patient to undertake physical activity throughout the day according to their capacity o Level 0: No activity planned (state reason), o Level 1: Active range of movement exercises in bed and/or sitting position in bed e.g. regular bed adjustment, assistance with re-positioning o Level 2: Assistance to sit on the side of the bed o Level 3: Sitting out of bed in a chair, standing o Level 4: Walking (marching in place, independent or assisted walking around room and unit) o Level 5: Attend inpatient gym, walking outside of unit	• The patient is free of tethers • The patient is free of physical restraint • The patient moves and/or exercises to their optimal capacity
Family partnership	• Ask family about the patient's baseline cognition • Inform the patient and family about delirium risk • Inform the patient and family about delirium prevention strategies and invite participation	• Family are asked about the patient's baseline cognition on admission • Delirium information brochure is provided to the patient and family • Verbally inform of delirium risk and prevention • Patients and family are invited to participate in delirium prevention strategies

Site engagement, education and training

The phase II trial will not pre-determine delivery methods for the intervention, instead observing the methods of each site in order to learn from the site teams about their established practice, as well as what practices they needed to establish. Engagement of site staff and volunteers will be guided by Michie's Behaviour Change Wheel (BCW), an evidenced-based framework for changing health-related behaviours. [27] Each site will form an interdisciplinary working group of medical, nursing, allied health, pastoral care, volunteer coordinator and managerial staff. The function of the working groups will be to determine how to deliver the intervention with the available resources, composition and capabilities of their site team. [27] Working group members will communicate the study to the whole team, promote the delirium screening, diagnosis and prevention strategies, and inform patients and family about delirium and the prevention strategies. Site teams will be encouraged to tailor the intervention strategies to each patient's assessed needs and preferences to ensure person-centred care, as well as to adopt simple and feasible methods of delivery and documentation of the intervention.

Education and training of site staff and volunteers in the delirium screening and prevention strategies will be standardised, interdisciplinary and based on Biggs' educational model. [28,29] This model will align educational objectives and methods with the delirium learning needs of staff, and promote critical reflection on attitudes, practice and functional knowledge of the complexities of caring for a person with advanced cancer in hospital. [28,29] Education and training will take place for two-months prior to data collection. A brief, simple study overview manual also will be developed.

Study investigators and/or project staff will attend sites to: i) promote fidelity to the study processes and aims; ii) assist with education and training activities; iii) resolve issues that delay implementation of the intervention or threaten its integrity; iv) act as a 'delirium

resource person'; and v) support and encourage site staff and volunteer participation in the intervention.

The frequency, duration and mode of administration of education and training will be determined prior to implementing delirium screening, diagnosis and prevention strategies in collaboration with participating sites, then standardised for each. Based on the learnings obtained in this phase II trial, we will develop a replicable standardised education resource for the phase III trial.

Randomisation

Randomisation of sites will take place after Human Research Ethics Committee (HREC) and local governance approvals are obtained. In keeping with the method of the anticipated phase III trial, we will use a permuted block randomisation method with various block sizes to allocate sites to the intervention or waitlist control. Randomisation will be performed by the study statistician (LL) from the coordinating centre, the University of Technology Sydney (UTS).

Blinding and avoidance of contamination

The study design and nature of the intervention means that blinding of site staff will not be possible. Written information for patients and family caregivers will provide only general information about the study aims, rather than specifics of the design or site allocation. Attention will be focused on research nurse training and standardisation of data collection to limit the potential for bias.

To avoid contamination between sites, personnel collecting data at an intervention site will not collect data in a control site, and vice versa. Site investigators, research nurses and project staff will be asked not to discuss the intervention in joint tele-meetings with control sites. Clinicians at control sites initially will receive information and training on delirium

screening and diagnosis only, and only general information about the prevention intervention in discussions and promotion, until they move into the intervention phase.

Data collection

Research nurses will collect baseline data from sites' most recent Palliative Care Outcomes Collaborative (PCOC) report (a national program which measures and benchmarks patient outcomes in palliative care using standardised clinical assessment tools) [23] (Figure 2) and from key personnel. Research nurses will screen consecutively admitted patients for eligibility, collect delirium screening and diagnostic assessment measures for enrolled patients and record these in a Case Report Form (CRF). At intervention sites, specially designed checklists will capture family caregivers, staff and volunteers' delivery (or otherwise) of delirium prevention strategies within each domain of the multicomponent intervention (Table 1), as well as who delivered it. From this, we will determine the level of involvement of family caregivers, interdisciplinary staff, and volunteers for each strategy. Whenever the patient does not receive the strategy, the reason will be recorded according to the following categories:

- Not required
- Patient choice
- Not clinically appropriate
- Not possible with current resources
- Other

At study completion, the project team will collect PCOC data for the study time-frame (Age, Gender, Country of birth, Preferred language, Aboriginal or Torres Strait Islander status, Primary diagnosis, Length of stay, Performance status [Australian-modified Karnofsky Performance Status (AKPS)[30] and Resource Utilisation Groups - Activities of Daily Living

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(RUG-ADL)],[31] Palliative care phase).[32] For the sustainability outcome, site research nurses will collect intervention adherence data at six months for all inpatients for one week.

Assessments

Figure 2 gives the schedule of study measures and time points; Text Box 1 provides information on the palliative care and delirium measures.

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Text Box 1: Description of study measures

The **Australian-modified Karnofsky Performance Status (AKPS)** was adapted from the Karnofsky Performance Status with good face validity and longitudinal test-retest reliability. [30] The AKPS measures patients' overall performance status, using 10-point increments along a scale of 100-10. A score of 100 denotes normal function with no evidence of disease, decreasing to a minimum score of 10, assigned when patients are comatose or barely rousable. Routinely applied on an at least daily basis in most Australian inpatient unit palliative care services. The AKPS will be used to report the patient cohort's performance status at participating sites.
The **Resource Utilisation Groups - Activities of Daily Living (RUG-ADL)** [31] is a validated functional assessment tool which assigns a score of 4-18, based on what a patient does in relation to bed mobility, transfers, eating and toileting, rather than they can do. Higher scores indicate the need for more assistance to undertake activities and that more resources are required to provide this assistance. Applied on an at least daily basis in most Australian inpatient unit palliative care services. The measure will be used to report the patient cohort's functional status at participating sites.
The **Palliative Care Phase** [32] classification is not a validated tool, but is applied on an at least daily basis in most Australian palliative care services to describe the needs of the patient and family and prompt a timely and appropriate clinical response. Phases are: 1. Stable (problems and symptoms are adequately managed and there is a plan of care); 2. Unstable (urgent intervention required because a new symptom or problem develops, or an existing problem rapidly escalates); 3. Deteriorating (a gradual decline in function AND worsening of an existing problem or development of a new but anticipated problem); 4. Terminal (death is likely within days); and 5. Bereavement (post death support). The measure will be used to report the patient cohort's palliative care needs at participating sites.
The **Nursing Delirium Screening Scale (Nu-DESC)** [24] was validated in an oncology inpatient population with a sensitivity of 85.7% and specificity of 86.8%. [24] It is a brief (less than one minute) five-item and low burden tool, incorporating nurses' observation of disorientation, inappropriate behavior, inappropriate communication, illusions/hallucinations and psychomotor retardation. Nurses assign a score of 0–2 for each item, giving a maximum score of 10. The psychomotor retardation item improves recognition of hypoactive delirium, [33] the most prevalent subtype in palliative care inpatient populations.[3] The Nu-DESC has been used in previous research in inpatient palliative care populations[11] and considered feasible and acceptable by palliative care nurses.[19] The Nu-DESC will be used by bedside nurses to screen patients for delirium every eight-hour shift.
The **DSM-5 diagnostic criteria for delirium** are within the most current version of the American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders.[1] Criteria are: A.

Disturbed attention and awareness; B. Disturbance developed over a short period of time (usually hours to a few days), is a change from baseline attention and awareness, and fluctuates in severity; C. An additional disturbance in cognition; D. Disturbances in A and C are not caused by another neurocognitive disorder nor occur in the context of severely reduced level of arousal; and E. The disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal, exposure to a toxin, or has multiple aetiologies. Treating physicians will use the DSM-5 to determine a delirium diagnosis.
The **Delirium Rating Scale-Revised-98 (DRS-R-98)** [25] is a 16-item delirium severity and diagnostic scale with scores of up to 46. It had high inter-rater reliability, sensitivity and specificity in the original validation study, [25] high sensitivity and adequate internal consistency and factor validity in cancer patients,[34] and has been used in research with palliative care inpatients.[35,36] The DRS-R-98 was designed to measure a wider range of delirium symptoms than are contained within diagnostic criteria and in different settings had good discriminative capacity for all, including in a patient population with a high prevalence of dementia [37,38]. Severity items are: sleep-wake cycle disturbance; perceptual disturbances and hallucinations; delusions; lability of affect; language; thought process abnormalities; motor agitation; motor retardation; orientation; attention; short-term memory; long-term memory; visuospatial ability. Diagnostic items are temporal onset of symptoms; fluctuation of symptom severity; physical disorder. Information is obtained from all sources, including physical examination, history gathering and formal cognitive testing. Requires clinician training, with guidance for use contained within the tool. Trained treating physicians and nurses will use the DRS-R-98 to operationalize delirium diagnosis and measure delirium severity. We will use a diagnostic cut-off score of $\geq$15.[38]

Outcomes

The primary outcome is adherence to the intervention. A rate of at least 60% of patients having at least four completed domains for at least five of the first seven days of admission will be considered minimum evidence that the intervention is feasible without need for major modification of the intervention or its delivery methods. Endpoints will be at completion of the intervention and modified-intervention arms (Figure 1).

We chose this moderate endpoint because of the potential patient, clinician and system level challenges to the non-pharmacological strategies in the context of advanced cancer. Consensus by investigators was this endpoint would be the minimum to still have impact, realistic to achieve in practice, and ensure that further evaluation of this complex intervention was not prematurely stopped. The waitlist control design will allow two endpoints and thereby maximize the potential to reach this level of adherence to the intervention.

Secondary outcomes will further inform of the feasibility, acceptability and potential efficacy of a phase III trial of the intervention in this patient population and setting, as follows:

1. Coverage: delivery rate of the multicomponent intervention to consecutive eligible patients admitted to the unit, reasons why the intervention was not delivered, weekend coverage, measured via screening logs and case report forms;
2. Fidelity to delirium screening, diagnosis and the intervention: degree of alignment with the protocol, rationales for adaptation, rate of protocol deviations without reasons, measured via case report forms;
3. Methods, areas and levels of interdisciplinary involvement in delivery of the intervention, measured via intervention checklist;
4. Feasibility and acceptability of the study intervention and measures for patients, caregivers, staff and volunteers, measured via brief interviews during and shortly after the intervention phase;

5. Sustainability of the intervention: Adherence will be measured for all inpatients over one week, six months after commencement of data collection at the intervention sites;
6. Feasibility of the sample: percentage of participants included in data collection, reasons for non-inclusion, time to achieve sample size, measured via screening logs and case report forms;
7. Number of people with advanced breast cancer admitted to the units, number of these who are in underserved populations (patients over 70, indigenous patients, and culturally and linguistically diverse backgrounds), and the number who experience an episode of delirium (total, and in under-served populations) (for the purposes of reporting to the trial funder, the National Breast Cancer Foundation);
8. Percentage completion of all study measures, measured via case report form;
9. Rate of patients with a positive delirium screen, measured according to a score of 2 or more on the Nu-DESC at least once during each 24-hour period;
10. Delirium incidence, measured at first onset according to the DSM-5 diagnostic criteria for delirium applied within 24-hours of a positive delirium screen;
11. Delirium severity measured at first onset, using the DRS-R-98; and
12. Number of falls, complaints and other adverse events related to the intervention.

Sub-study

A qualitative sub-study will be conducted to obtain patient, family caregiver, staff and volunteer perceptions of the feasibility and acceptability of the intervention strategies (e.g. receiving information from staff about delirium) and study measures via brief, semi-structured interviews (Figure 2).

Inclusion and exclusion criteria for the sub-study

1. **Patients** will be included if they are aged 18 years or older; have a diagnosis of advanced cancer; admitted to an intervention site and received the intervention; speak English or have access to a health care interpreter; and able to give fully informed

written consent. Patients with advanced breast cancer will be purposively recruited to participate in the interviews. Patients will be excluded if they have an AKPS [30] score less than 30 and are in the 'terminal' Palliative Care Phase; [32]

2. **Family caregivers** will be included if they are aged 18 years or older; identified as a caregiver of a patient who received the intervention; English speaking or have availability of a health care interpreter; and are able to give fully informed written consent;

3. **Site staff** will be included if they are employed at an intervention site and involved in implementing the delirium measures and/or the intervention; and

4. **Site volunteers** will be included if they are aged 18 years or older, enrolled in a formal volunteer program at an intervention site and involved in implementing the intervention.

Sub-study consent process

A researcher who is not a study investigator will obtain written informed consent from patients, family caregivers, staff and volunteers to participate in the brief interviews. For patients and family caregivers, the researcher will check with the clinical team to make sure the person meets the broad criteria for consideration of eligibility, is well enough, and has given permission to be approached by a researcher, before introducing him or herself to the person and explaining the study. For staff and volunteers, the researcher will consult with the site investigator before approaching potential participants.

Participant consent will be a process of information exchange between the researcher, the potential participant and any other person the potential participant believes should be included in the discussion. Participant information sheets will be the basis for discussion and cover all procedures and possible benefits and burdens of participating. The potential participant will be given sufficient opportunity to consider the study and ask questions. Any

questions will be addressed and answered fully. The completed consent form will be copied and one copy will be given to the participant, one copy inserted in the medical file (for patients), and one copy filed in study file.

Analysis

Statistical analysis of primary outcome (adherence)

Adherence will be calculated as the rate to which patients have completed domains on a daily basis for the first seven days of admission. Degree of adherence to individual strategies will also be calculated as proportions.

Statistical analysis of secondary outcomes

Data on all outcomes will be summarised with descriptive statistics including their distribution. Frequency and percentage will be used for summarising categorical variables and mean, standard deviation, median, and interquartile range for continuous variables. Delirium incidence and severity will be determined at both the intervention and control sites.

Qualitative analysis

Participant interviews will be analysed using thematic content analysis to identify emergent themes and trends related to participants' perceptions of the feasibility and acceptability of the intervention elements and delirium measures.[39]

Sample size

A sample size of four sites and 40 patient participants (10 from each site) was considered sufficient for reasonable estimation of feasibility and percentage completion of study processes and measures during the first phase. [40] We will collect de-identified data on all eligible patients admitted to all sites until data is collected for 40 patients overall, with at

least 20 in the intervention arm. If the intervention is found to need modification, data will be collected for a further 20 patient participants at the two waitlist control sites.

This sample size was based on that projected for the future phase III cluster RCT of the intervention with: two parallel arms, 50% delirium incidence in the control, 30% delirium incidence in the intervention group, cluster size of 30 and intra-class correlation of 0.05, type I error rate of 5%, 80% power to reject the null hypothesis, and 30% attrition. This calculation results in a projected phase III trial sample size of nine clusters and 280 patient participants.

For the sub-study, sample size will be determined when data saturation is achieved.

Trial monitoring

In addition to falls and complaints, all adverse events will be recorded. Site investigators will assess the adverse event, assign the degree of relationship to the intervention, and provide information to the coordinating centre (UTS), and the approving HREC if required. Adverse events will be followed until the event is resolved, can be explained, or if the participant is lost to follow-up. Reports will contain details of follow-up investigations, results or other consultation. The investigator team will stop the study if reporting of adverse events indicates that major review of the study protocol is required. The UTS project team will report adverse event related to the intervention to the PaCCSC Trial Management Committee (TMC) within two weeks of knowledge of the event. The TMC discussions will be minuted, with actions detailed and reviewed at the subsequent meeting. The TMC chairperson's report to the PaCCSC Scientific Committee will contain a summary of the discussions of the adverse event report and agreed outcomes.

Data management

An Excel spreadsheet master index will contain confidential participant contact information and be the only link between individual site and patient participants and their allocated

identification number (ID). Study data will be collected and stored on paper CRFs and electronic Excel spreadsheets and then entered onto and managed on a Research Electronic Data Capture (REDCap) [41] database. Audio data from participant interviews will be identified only by ID, collected on a digital recording medium and stored temporarily at the study sites until uploaded to the REDCap database. Original files will then be destroyed. Data will be held, administered, checked and analysed at the coordinating site according to relevant PaCCSC Standard Operating Procedures (SOP). Errors detected during the data checking process will generate a site data report form recording details of the query and correction and resolution instructions. The database will be updated according to site instructions via email to provide an audit trail of data changes. The coordinating site will maintain a register of data checks for monitoring purposes. Data collected at each site, such as CRFs, any corrected and amended data, copies of adverse incident reports and file notes, will be securely stored and identified by ID number only. All identifiable data (e.g. signed consent forms) will be separately stored during the recruitment period. Site research staff will send copies of study documents (with the exception of signed consent forms) to the coordinating site by registered mail for collation and archiving. All study documents will be stored in accordance with relevant State government regulations regarding the retention and disposal of participant records.

Patient and Public Involvement

The study rationale and processes were informed by the literature pertaining to patients' experiences of delirium, as outlined in the introduction.[4,5] Low-burden outcome measures, such as the Nursing Delirium Screening Scale, were deliberately chosen in order to minimise the impact of the study on patients with advanced illness. No patients were directly involved in the design, recruitment to or conduct of the study. Two family caregiver consumers are associate investigators of the study (MB and BN). We will include the perspectives of patients about the feasibility and acceptability of the intervention through brief semi-

structured interviews. Investigators will not have access to the names or contact information of patient or family caregiver participants in order to directly provide feedback about the study to them. At study completion, a written and verbal report of the results and findings will be provided to the participating sites.

Ethics and dissemination

The study was approved by the South Western Sydney Local Health District HREC on July 19, 2017, reference number HREC/17/LPOOL/224; and ratified by the UTS HREC on August 22, 2017, reference number ETH17-1697. Minor protocol amendments were approved on April 13, 2018 (V1.1).

Reporting of this protocol adheres to the Standard Protocol Items: Recommended for Interventional Trials. [42] Reporting of results will adhere to the Consolidated Standards of Reporting Trials (CONSORT) guidelines for cluster RCTs and non-pharmacological treatment trials. [43,44] Reporting of the qualitative sub-study and implementation findings will be guided by the Consolidated Criteria for Reporting Qualitative Research (COREQ).[45] A comprehensive dissemination strategy will ensure that the trial results (either positive or negative) inform future research and clinical practice. Dissemination will include publication in peer-reviewed journals, presentations at conferences, study sites and key peak bodies. The investigators have no publication restrictions.

Strengths and limitations

The primary strengths of this study are the cluster RCT design and that it is supported by the PaCCSC, a national, multi-site phase III clinical trials group which provides well-established rigorous research governance and access to sites with research experience and capacity. The intervention includes family partnership, which is highly valued by both patients and family.[5,26] We will obtain the perspectives of patients and family, which are largely absent in trials of previous multicomponent delirium interventions.[15]

Limitations include that site and research staff will not be blinded to the intervention. Active steps will be taken to minimize contamination between intervention and waitlist control sites. The study will be conducted in Australian palliative care inpatient settings and include only patients with advanced cancer, limiting the generalizability of results for services in other geographical regions and health care systems, and for patients with other advanced illnesses.

Trial status

The study has been approved by local health district and university HRECs, local governance approvals obtained, sites randomised, the two-month period completed and data collection is underway.

List of abbreviations

AKPS: Australia-modified Karnofsky Performance Status; **ACSQHC**: Australian Commission for Safety and Quality in Health Care; **BCW**: Behaviour Change Wheel; **CI**: Confidence Interval; **CONSORT**: Consolidated Standards of Reporting Trials; **COREQ**: Consolidated Criteria for Reporting Qualitative Research; **DRS-R-98**: Delirium Rating Scale-Revised-1998; **DSM-5**: Diagnostic and Statistical Manual of Mental Disorders, Fifth edition; **HREC**: Human Research Ethics Committee; **ID**: identification number; **Nu-DESC**: Nursing Delirium Screening Scale; **OR**: Odds Ratio; **PaCCSC**: Palliative Care Clinical Studies Collaborative; **PCOC**: Palliative Care Outcomes Collaborative; **RCT**: Randomised Controlled Trial; **REDCap**: Research Electronic Data Capture; **RR**: Relative Risk; **RUG-ADL**: Resource Utilisation Groups - Activities of Daily Living; **SOP**: Standard Operating Procedures; **UTS**: University of Technology Sydney

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Declarations

Clinical trials registration

ACTRN12617001070325p, Australian New Zealand Clinical Trials Registry (ANZTR), http://www.anzctr.org.au/, 24/07/2017. The ANZTR is a Primary Registry of the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP).

Consent for publication

Participant information includes an explanation that results will be published in a form that maintains the confidentiality of sites and individual participants.

Availability of data and material

Participant information sheets and consent forms are available at https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=373168&isReview=true

Funding

This work was supported by an Australian National Breast Cancer Foundation (NBCF) 2017 Pilot Study Grant (Grant code PS-17-030), contact details Level 9, 10 Barrack Street, Sydney, NSW 2000, Australia; T: +61 2 8098 4800 E: info@nbcf.org.au, W: https://nbcf.org.au/.

Competing interests

The authors declare that they have no competing interests.

Sponsor

The trial sponsor is PaCCSC, contact details: Level 3, 235 Jones St Ultimo NSW 2007, Australia; T. +61 (2) 9514 4862 (Sydney) /+61 (8) 7421 9726 (Adelaide), E: paccsc@uts.edu.au, W: uts.edu.au/paccsc. PaCCSC supports optimal trial governance through SOPs for electronic data handling, completion of CRFs, monitoring, dissemination, archiving of research materials, and record destruction; and trial infrastructure through Trials Management and Scientific Committees.

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Roles and responsibilities

Chief study investigators MA, AH and JP retain ultimate responsibility for the trial. Investigators and a project team coordinated the trial from IMPACCT - Improving Palliative, Aged and Chronic Care through Clinical Research and Translation, UTS. The investigator team meet at least twice yearly to support progress of the trial and inform related activities, such as dissemination.

Authors' contributions

AH, MA and JP are the co-lead authors and AH is the corresponding author for this manuscript. MA, JP and AH devised the adaptation of the multicomponent intervention for people with advanced cancer in hospital. MB and BN provided consumer insight into the adaptation of the intervention. AC provided guidance on the extent of alignment of the intervention and delirium screening diagnosis processes with the ACSQHC Delirium Clinical Care Standard. LL devised the statistical analysis and randomization process. JMD and ML provided insights into the waitlist design. SK contributed to the development of the site engagement and educational processes. SK, GC, RC, BL, EWE, PL and SB contributed clinical and research expertise into study design, process, measures and/or analysis. LB, BF, SLC and LE contributed to various aspects of the study protocol, including data collection, entry and storage, reporting of adverse effects, minimization of contamination, and/or site training. All authors have read and approved the final manuscript.

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Figure 1: Study Diagram
Standardised delirium screening at all sites + delirium prevention strategies at intervention sites; control sites wait listed for intervention

∗ Modified if required

Figure 2: Schedule of study measures and time points [43]

Note: Characteristics indicated with a ∗ will be collected at baseline from the sites most recent PCOC report, and then again at study completion directly from PCOC for the specific time-frame of data collection at each site.

Table 1: Multicomponent delirium prevention intervention

Study diagram

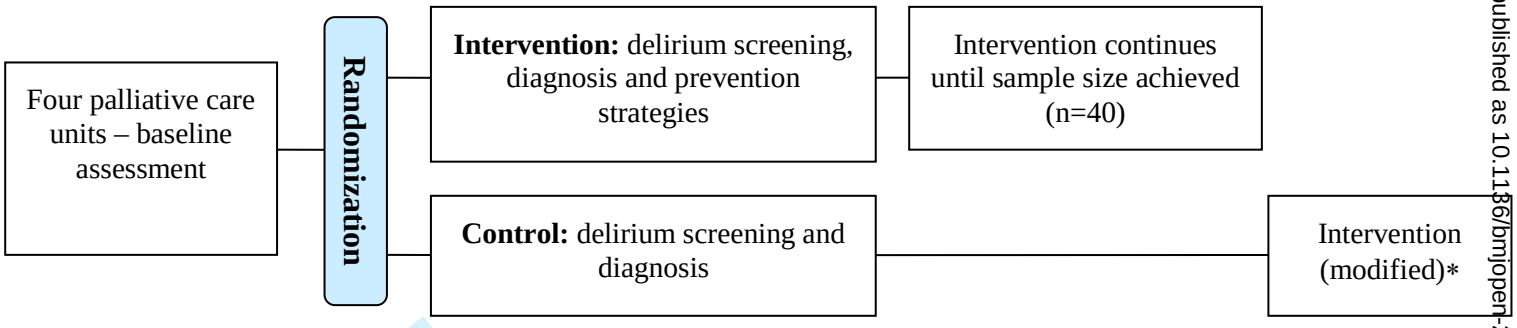

Figure 1: Study Diagram
Standardized delirium screening at all sites + delirium prevention strategies at intervention sites; control sites wait listed for intervention
* Modified if required.

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Figure 2: Schedule of study measures and time points [42]

Measures	Study period						
	Control and intervention sites					Intervention sites	
	Baseline	Eligibility screen on admission	Admission days 1-7	Nu-DESC +ve	Study completion	Admission days 1-7	Intervention completion
UNIT LEVEL							
Geographical location	X						
Type and level of service provision	X						
Number of beds	X						
Team composition	X						
Clinical documentation method	X						
Delirium process and measures	X						
Patient demographics*	X				X		
Patient function AKPS, RUG-ADL*	X				X		
Palliative care phases*	X				X		
PATIENT LEVEL							
Primary diagnosis		X					
Age		X					
Nu-DESC			X				
DSM-5 diagnostic criteria for delirium				X			
DRS-R-98				X			
Adherence to delirium prevention strategies						X	X (six months post)
SUB-STUDY							
Brief interviews with patients, family, staff and volunteers							X

Note: Characteristics indicated with a ∗ will be collected at baseline from the sites most recent PCOC report, and then again at study completion directly from PCOC for the specific time-frame of data collection at each site.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Title page
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3 and 25
	2b	All items from the World Health Organization Trial Registration Data Set	25
Protocol version	3	Date and version identifier	24
Funding	4	Sources and types of financial, material, and other support	26
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Title page
	5b	Name and contact information for the trial sponsor	26
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	26
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	26

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
	6b	Explanation for choice of comparators	7-8
Objectives	7	Specific objectives or hypotheses	6-7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7-8
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8; 19-20
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	8-9, 12
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12-13
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	18-19
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 2
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	21-22

Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	21-22
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	13
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	13
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	13
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13-14
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	14-15
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	NA
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	22-23
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	21
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	NA

	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	NA
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	22
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	22
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	22
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	24
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	NA
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8, 20-21
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	22-23, 26
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	26
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	22-24

Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	24
	31b	Authorship eligibility guidelines and any intended use of professional writers	27
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	26
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	26
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

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Multicomponent non-pharmacological intervention to prevent delirium for hospitalised people with advanced cancer: study protocol for a phase II cluster randomised controlled trial

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Title: Multicomponent non-pharmacological intervention to prevent delirium for hospitalised people with advanced cancer: study protocol for a phase II cluster randomised controlled trial

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Abstract

Introduction

Delirium is a significant medical complication for hospitalised patients. Up to one-third of delirium episodes are preventable in older inpatients through non-pharmacological strategies that support essential human needs, such as physical and cognitive activity, sleep, hydration, vision and hearing. We hypothesized that a multicomponent intervention similarly may decrease delirium incidence, and/or its duration and severity, in inpatients with advanced cancer. Prior to a phase III trial, we aimed to determine if a multicomponent non-pharmacological delirium prevention intervention is feasible and acceptable for this specific inpatient group.

Methods and analysis

The study is a phase II cluster randomised wait-listed controlled trial involving inpatients with advanced cancer at four Australian palliative care inpatient units. Intervention sites will introduce delirium screening, diagnostic assessment and a multicomponent delirium prevention intervention with six domains of care: preserving natural sleep; maintaining optimal vision and hearing; optimising hydration; promoting communication, orientation and cognition; optimising mobility; and promoting family partnership. Interdisciplinary teams will tailor intervention delivery to each site, and to patient need. Control sites will first introduce only delirium screening and diagnosis, later implementing the intervention, modified according to initial results. The primary outcome is adherence to the intervention during the first seven days of admission, as measured for 40 consecutively admitted eligible patients. Secondary outcomes relate to fidelity and feasibility, acceptability and sustainability of the study intervention, processes and measures in this patient population, using quantitative and qualitative measures. Delirium incidence and severity will be measured to inform power calculations for a future phase III trial.

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Ethics and dissemination

Ethical approval was obtained for all four sites. Trial results, qualitative sub-study findings, and implementation of the intervention will be submitted for publication in peer-reviewed journals, and reported at conferences, to study sites and key peak bodies.

Trial registration

ACTRN12617001070325p

Key words

Delirium, cancer, neoplasms, inpatients, palliative care, clinical trial, feasibility studies

Strengths and limitations of this study

- Strengths are the cluster RCT design; inclusion of patient and family perspectives; and sponsorship by the Palliative Care Clinical Trials Collaborative (PaCCSC), a national, multi-site clinical trials group which provides rigorous research governance.
- A limitation is that site and research staff will not be blinded to the intervention.
- The study is being conducted in Australian palliative care inpatient settings and will include only patients with advanced cancer, limiting the generalisability of results for other settings and people with other advanced illnesses.

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Introduction

Delirium is a serious acute neurocognitive disorder and medical complication for people with advanced cancer receiving palliative care in hospital, where it occurs for up to one in two patients and is reversible in only up to half of cases, at best.[1-3] It causes sudden disruption to attention and cognition, such as memory and language deficit, disorientation, and perception.[1] During delirium, feelings of fear, humiliation, confusion and isolation are common,[4] at a time when connection with family, friends and health professionals is important and highly valued. [5] Family experience high levels of distress as a result.[5] Delirium is further associated with increased falls, pressure areas, longer-term cognitive and functional decline, duration of hospital stay, mortality, and health care costs.[6-8]

Despite the incidence of delirium and its profound impacts on people with advanced illness, there are limited treatment options and, to date, no effective pharmacological intervention.[9-11] Nor have evidence-based processes for delirium prevention, recognition or assessment been translated in palliative care units.[12,13] The most effective strategy for delirium in older patients across a range of hospital settings is prevention through non-pharmacological strategies to meet essential needs, such as physical and cognitive activity, sleep, hydration, vision and hearing. When implemented as a 'multicomponent intervention', these strategies have reduced delirium incidence by one-third.[9,14] A meta-analysis (n=4,267) of randomised or matched trials of non-pharmacological prevention strategies reported significant reduction in delirium incidence, with the odds of delirium 53% lower in the intervention group compared with controls (odds ratio (OR) 0.47, 95% confidence interval (CI) 0.38-0.58, p<0.001).[14] A Cochrane Review of 39 randomised controlled trials (n=16,082) of non-pharmacological, medication or anaesthetic interventions reported that seven non-pharmacological intervention studies (n=1,950) reduced delirium incidence (relative risk (RR) 0.69, 95% CI 0.59 to 0.81), while evidence for most medication and anaesthetic

interventions was uncertain.[9] There was moderate quality evidence that the non-pharmacological interventions reduced length of hospital admission and improved the likelihood of return to independent living, with low quality evidence of decreased delirium duration and severity.[9] Studies of non-pharmacological interventions for delirium have mainly focused on older patients, yet often excluded patients with advanced cancer and other life-threatening illnesses.[15] Also, strategies within the interventions were diverse, some were better operationalised than others, and not all used a randomised design.[14]

The one study testing a non-pharmacological delirium prevention intervention in people with advanced cancer (n=1,516) in seven Canadian specialist palliative care inpatient units reported no statistically significant difference in delirium incidence, total days in delirium, duration of first episode, severity or delirium-free survival.[16] Strategies were fewer and less targeted to essential needs of patients than those reported in the more recent meta-analysis and Cochrane review;[9,14] and included: i) orientating patients to time, person and place each shift; ii) informing family about delirium, its symptoms and prevention of confusion; and iii) assessing pharmacological risk factors for delirium before querying physicians about consequent planned medication change. There also was inadequate rate and timeliness of completion of the primary measure, the Confusion Assessment Method. While adherence to the intervention was greater than 80%, there was no difference in overall use of psychoactive medication between the two arms. Given that such medication is associated with delirium,[17,18] this factor may partly explain the study's negative results.[16]

There are possible barriers to implementation of non-pharmacological delirium prevention strategies for people with advanced cancer. These include their common frailty and fatigue which reduces capacity to participate in activities such as exercise. Patients and family may not realise the serious risks associated with an episode of delirium, or prioritise prevention strategies without this knowledge. Some clinicians may perceive that delirium is inevitable

and innocuous in advanced cancer and palliative care contexts;[19,20] and presume that preventing delirium is not possible, necessary or likely to be effective. Clinicians historically have relied on pharmacological intervention for delirium, rather than intentionally striving to prevent delirium through non-pharmacological means. With competing demands and without evidence of effectiveness, hospital managers may not value the importance of preventing delirium or allocate the required resources or personnel for non-pharmacological strategies, particularly for people approaching the end of their life.

Despite these barriers, the remit of palliative care to help patients live as actively as possible makes it important to study whether delirium can be prevented during advanced cancer. Based on the body of research conducted with older people in hospital described above, [9,14] we hypothesised that a similar multicomponent intervention would reduce delirium incidence and/or decrease its duration and severity for this inpatient population. Given the above-noted possible barriers to implementation, piloting the intervention and study design was required prior to testing the hypothesis in a phase III (efficacy) trial.

Aim and objectives

To determine if a multicomponent non-pharmacological delirium prevention intervention is feasible and acceptable for inpatients with advanced cancer.

The objectives are to:

1. To develop a multi-component non-pharmacological delirium prevention intervention ('non-pharmacological delirium prevention intervention'), derived from highly efficacious interventions for older adults in hospital, for people with advanced cancer and palliative care inpatient unit settings;

2. To describe the strategies used by participating sites to implement the delirium measurement tools and non-pharmacological delirium prevention intervention;

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3. To determine if a non-pharmacological delirium prevention intervention is feasible, acceptable and deliverable with high adherence and fidelity in oncology and palliative care units;

4. To determine the feasibility and design of a phase III trial to test the efficacy of the non-pharmacological delirium prevention intervention in people with advanced cancer in hospital.

Methods and analysis

Design

A phase II, cluster randomised controlled trial (RCT) with a waitlist control.[21] Participating sites will be randomised to the intervention (screening and immediate implementation of intervention) or control (screening and waitlist to the modified-intervention) (Figure 1).

The use of this design in the phase II trial was to inform the feasibility and design, delivery methods and power calculations of a future multi-site phase III cluster RCT. A cluster approach was chosen because the proposed intervention is more suited to implementation at a site level, and a traditional RCT design would risk contamination in the control arm. The use of a cluster RCT design is an advance on prior studies of non-pharmacological prevention interventions that used non-randomised designs. A waitlist control arm was chosen as key stakeholders at interested sites considered that the delirium prevention strategies were important, that participation in a trial that enabled access to the intervention was more appealing and ethically sound, and that the intervention strategies were well established as effective in other hospital settings and the potential benefits were clear, in principle. The waitlist control adds to the resource and time requirements of the trial, but will allow the intervention and study processes to be modified and/or refined at the two waitlist control sites, should initial results indicate that this is required.[21]

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Sites (clusters) and patient population

The participating sites are four Australian palliative care units, where approximately 75% of patients have a primary diagnosis of advanced cancer.[22]

In line with the cluster RCT design, consent to participate was obtained at the site level from the person with the delegation to approve participation. Data will be collected for all admitted patients aged ≥18 years with a diagnosis of advanced cancer, for which no individual patient consent will be required.

Intervention

Intervention sites will implement i) delirium screening; ii) delirium diagnosis assessments; and iii) the multicomponent delirium prevention intervention.

Bedside nurses will undertake the Nursing Delirium Screening Scale (Nu-DESC)[23] for all eligible patients at the end of every shift. Within 24 hours of the patient assessed as having a Nu-DESC score ≥2, a trained physician will apply Diagnostic and Statistical Manual of Mental Disorders, Fifth edition (DSM-5) diagnostic criteria for delirium,[1] operationalised using the Delirium Rating Scale-Revised-1998 (DRS-R-98).[24] These processes currently are not routine at the participating sites and therefore will be additional to usual care.

The multicomponent delirium prevention intervention involves five domains of care that, when delivered in combination, significantly reduced delirium incidence in older hospitalised patients in previous clinical trials.[9,14] We added family partnership as the sixth domain, as it was recommended by our consumer investigators and an expert working group, is highly valued by patients and family members,[5,25] and identified as essential by the Australian Commission for Safety and Quality in Healthcare (ACSQHC) in a new Delirium Standard, if preferred by the patient.[26] We did not include a pharmacological component (such as minimising polypharmacy) because there was less evidence that this effectively prevents

delirium, compared to that which addresses fundamental human needs for physical and cognitive activity, sleep, hydration, vision and hearing. 9, 14

The delirium prevention intervention will be delivered to all eligible patients for the first seven days of admission by members of the interdisciplinary team, family caregivers and volunteers. The domains and strategies of the multicomponent intervention are presented in Table 1.

Control sites will initially implement only delirium screening and diagnosis. Once the intervention sites achieve their sample, control sites will implement the intervention.

All sites will continue usual care with respect to treatment of patients with delirium.

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Table 1: Multicomponent delirium prevention intervention

Domain	Strategies	Implementation
Preserve natural sleep	• Offer ear plugs to patients with low risk of falls • Offer eye shades to patients with low risk of falls • Reduce noise outside patient rooms during 21:00-06:00 • Normal day-night light variation in room and unit • Exposure to natural light during daylight hours • Schedule care activities to allow uninterrupted sleep during the night • Avoid caffeine after 4pm	• The patient wears ear plugs at night • The patient wears eye shades at night • Room curtains/blinds are open during the day • Room lights are off or minimised at night • The patient spends time outside during the day • The patient drinks no caffeinated drinks after 4pm • The patient reports uninterrupted night-time sleep
Maintain optimal sensory perception	• Assess hearing • Assist with and re-inforce use of hearing aids and special communication techniques • Ear wax clearing as needed • Assess need for visual aids (glasses, magnifying lenses) • If needed, ask family to provide for the patient; • Assist with and reinforce use of visual aids	• The patient has their hearing assessed • The patient has ear wax cleaning • The patient wears functioning hearing aids • The patient has their vision assessed • The patient wears their glasses appropriately • The patient uses visual aids
Optimise hydration	• Encourage oral fluids • Physical assistance with drinks and meals, as required • Drinking aids, as required • Be alert and respond to reversible causes of poor oral intake within 24 hours e.g. nausea, vomiting, drowsiness, sore mouth	• The patient is encouraged to drink • The patient is assisted with meals • Drinking aids are provided e.g. straws • Intervention for reversible causes of poor oral intake are in place
Promote communication, orientation and cognition	• Interpreter and translation for people of non-English speaking background (NESB) • Greet the patient by name • Introduce self by name and role • Refer to person, time and place when talking with the patient • Time aids in room e.g. watch, personal or wall clock; wall, desk or electronic calendar • Update in-room whiteboards daily with date, day, place, reason for admission, team member names, schedule • Minimise number of transfers to other beds or rooms within the unit	• Interpreter is available and used • Orientating information is translated into the patient's native language • The patient can see the time, day, date and month in their room • The patient remains in the same bed location within the unit • The patient discusses current events • The patient reminisces and/or talks about their life and family

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	• Discuss current events with the patient • Encourage the patient to reminisce and talk • Encourage the patient to engage in cognitively stimulating activities	• The patient spends time in cognitively stimulating activities e.g. reading, puzzles, games, knitting, music • Cognitive stimulating activities are in the patient's care plan
Optimise mobility	• Minimise use of tethers e.g. intravenous line, indwelling catheter, drain, oxygen • Minimise use of physical restraints e.g. bed rails, lock-in chair tables, vest restraints, limb restraints • Encourage and/or assist the patient to undertake physical activity throughout the day according to their capacity o Level 0: No activity planned (state reason), o Level 1: Active range of movement exercises in bed and/or sitting position in bed e.g. regular bed adjustment, assistance with re-positioning o Level 2: Assistance to sit on the side of the bed o Level 3: Sitting out of bed in a chair, standing o Level 4: Walking (marching in place, independent or assisted walking around room and unit) o Level 5: Attend inpatient gym, walking outside of unit	• The patient is free of tethers • The patient is free of physical restraint • The patient moves and/or exercises to their optimal capacity
Family partnership	• Ask family about the patient's baseline cognition • Inform the patient and family about delirium risk • Inform the patient and family about delirium prevention strategies and invite participation	• Family are asked about the patient's baseline cognition on admission • Delirium information brochure is provided to the patient and family • Verbally inform of delirium risk and prevention • Patients and family are invited to participate in delirium prevention strategies

Site engagement, education and training

The phase II trial will not pre-determine delivery methods for the intervention, instead observing the methods of each site in order to learn from each team about their established practice, as well as what practices they needed to establish. Engagement of site staff and volunteers will be guided by Michie's Behaviour Change Wheel (BCW), an evidenced-based framework for changing health-related behaviours. [27] Each site will form an interdisciplinary working group of medical, nursing, allied health, pastoral care, volunteer coordinator and managerial staff. The function of the working groups will be to determine how to deliver the intervention with the available resources, composition and capabilities of their site team. [27] Working group members will communicate the study to the whole team, promote the delirium screening, diagnosis and prevention strategies, and inform patients and family about delirium and the prevention strategies. Site teams will be encouraged to tailor the intervention strategies to each patient's assessed needs and preferences to ensure person-centred care, as well as to adopt simple and feasible methods of delivery and documentation of the intervention.

Education and training of site staff and volunteers in the delirium screening and prevention strategies will be standardised, interdisciplinary and based on Biggs' educational model. [28,29] This model will align educational objectives and methods with the delirium learning needs of staff, and promote critical reflection on attitudes, practice and functional knowledge of the complexities of caring for a person with advanced cancer in hospital. [28,29] Education and training will take place for two-months prior to data collection. A brief, simple study overview manual also will be developed.

Study investigators and/or project staff will attend sites to: i) promote fidelity to the study processes and aims; ii) assist with education and training activities; iii) resolve issues that delay implementation of the intervention or threaten its integrity; iv) act as a 'delirium

resource person'; and v) support and encourage site staff and volunteer participation in the intervention.

The frequency, duration and mode of administration of education and training will be determined prior to implementing delirium screening, diagnosis and prevention strategies in collaboration with participating sites, then standardised for each. Based on the learnings obtained in this phase II trial, we will develop a replicable standardised education resource for the phase III trial.

Randomisation

Randomisation of sites will take place after Human Research Ethics Committee (HREC) and local governance approvals are obtained. In keeping with the method of the anticipated phase III trial, we will use a permuted block randomisation method with various block sizes to allocate sites to the intervention or waitlist control. Randomisation will be performed by the study statistician (LL) from the coordinating centre, the University of Technology Sydney (UTS).

Blinding and avoidance of contamination

The study design and nature of the intervention means that blinding of site staff will not be possible. Written information for patients and family caregivers will provide only general information about the study aims, rather than specifics of the design or site allocation. Attention will be focused on research nurse training and standardisation of data collection to limit the potential for bias.

To avoid contamination between sites, personnel collecting data at an intervention site will not collect data in a control site, and vice versa. Site investigators, research nurses and project staff will be asked not to discuss the intervention in joint tele-meetings with control sites. Clinicians at control sites initially will receive information and training on delirium

screening and diagnosis only, and only general information about the prevention intervention in discussions and promotion, until they move into the intervention phase.

Data collection

Research nurses will collect baseline data from sites' most recent Palliative Care Outcomes Collaborative (PCOC) report (a national program which measures and benchmarks patient outcomes in palliative care using standardised clinical assessment tools) [23] (Figure 2) and from key personnel. Research nurses will screen consecutively admitted patients for eligibility, collect delirium screening and diagnostic assessment measures for enrolled patients and record these in a Case Report Form (CRF). At intervention sites, specially designed checklists will capture family caregivers, staff and volunteers' delivery (or otherwise) of delirium prevention strategies within each domain of the multicomponent intervention (Table 1), as well as who delivered it. From this, we will determine the level of involvement of family caregivers, interdisciplinary staff, and volunteers for each strategy and domain. Whenever the patient does not receive the strategy, the reason will be recorded according to the following categories:

- Not required
- Patient choice
- Not clinically appropriate
- Not possible with current resources
- Other

At study completion, the project team will collect PCOC data for the study time-frame (Age, Gender, Country of birth, Preferred language, Aboriginal or Torres Strait Islander status, Primary diagnosis, Length of stay, Performance status [Australian-modified Karnofsky Performance Status (AKPS)[30] and Resource Utilisation Groups - Activities of Daily Living

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(RUG-ADL)],[31] Palliative care phase).[32] For the sustainability outcome, site research nurses will collect intervention adherence data at six months for all inpatients for one week.

Assessments

Figure 2 gives the schedule of study measures and time points; Text Box 1 provides information on the palliative care and delirium measures.

Text Box 1: Description of study measures

The **Australian-modified Karnofsky Performance Status (AKPS)** was adapted from the Karnofsky Performance Status with good face validity and longitudinal test-retest reliability. [30] The AKPS measures patients' overall performance status, using 10-point increments along a scale of 100-10. A score of 100 denotes normal function with no evidence of disease, decreasing to a minimum score of 10, assigned when patients are comatose or barely rousable. Routinely applied on an at least daily basis in most Australian inpatient unit palliative care services. The AKPS will be used to report the patient cohort's performance status at participating sites.
The **Resource Utilisation Groups - Activities of Daily Living (RUG-ADL)** [31] is a validated functional assessment tool which assigns a score of 4-18, based on what a patient does in relation to bed mobility, transfers, eating and toileting, rather than they can do. Higher scores indicate the need for more assistance to undertake activities and that more resources are required to provide this assistance. Applied on an at least daily basis in most Australian inpatient unit palliative care services. The measure will be used to report the patient cohort's functional status at participating sites.
The **Palliative Care Phase** [32] classification is not a validated tool, but is applied on an at least daily basis in most Australian palliative care services to describe the needs of the patient and family and prompt a timely and appropriate clinical response. Phases are: 1. Stable (problems and symptoms are adequately managed and there is a plan of care); 2. Unstable (urgent intervention required because a new symptom or problem develops, or an existing problem rapidly escalates); 3. Deteriorating (a gradual decline in function AND worsening of an existing problem or development of a new but anticipated problem); 4. Terminal (death is likely within days); and 5. Bereavement (post death support). The measure will be used to report the patient cohort's palliative care needs at participating sites.
The **Nursing Delirium Screening Scale (Nu-DESC)** [24] was validated in an oncology inpatient population with a sensitivity of 85.7% and specificity of 86.8%. [24] It is a brief (less than one minute) five-item and low burden tool, incorporating nurses' observation of disorientation, inappropriate behavior, inappropriate communication, illusions/hallucinations and psychomotor retardation. Nurses assign a score of 0–2 for each item, giving a maximum score of 10. The psychomotor retardation item improves recognition of hypoactive delirium, [33] the most prevalent subtype in palliative care inpatient populations.[3] The Nu-DESC has been used in previous research in inpatient palliative care populations[11] and was considered feasible and acceptable by palliative care nurses.[19] The Nu-DESC will be used by bedside nurses to screen patients for delirium every eight-hour shift.

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The **DSM-5 diagnostic criteria for delirium** are within the most current version of the American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders.[1] Criteria are: A. Disturbed attention and awareness; B. Disturbance developed over a short period of time (usually hours to a few days), is a change from baseline attention and awareness, and fluctuates in severity; C. An additional disturbance in cognition; D. Disturbances in A and C are not caused by another neurocognitive disorder nor occur in the context of severely reduced level of arousal; and E. The disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal, exposure to a toxin, or has multiple aetiologies. Treating physicians will use the DSM-5 to determine a delirium diagnosis.
The **Delirium Rating Scale-Revised-98 (DRS-R-98)** [25] is a 16-item delirium severity and diagnostic scale with scores of up to 46. It had high inter-rater reliability, sensitivity and specificity in the original validation study, [25] high sensitivity and adequate internal consistency and factor validity in cancer patients,[34] and has been used in research with palliative care inpatients.[35,36] The DRS-R-98 was designed to measure a wider range of delirium symptoms than are contained within diagnostic criteria and in different settings had good discriminative capacity for all, including in a patient population with a high prevalence of dementia [37,38]. Severity items are: sleep-wake cycle disturbance; perceptual disturbances and hallucinations; delusions; lability of affect; language; thought process abnormalities; motor agitation; motor retardation; orientation; attention; short-term memory; long-term memory; visuospatial ability. Diagnostic items are temporal onset of symptoms; fluctuation of symptom severity; physical disorder. Information is obtained from all sources, including physical examination, history gathering and formal cognitive testing. Requires clinician training, with guidance for use contained within the tool. Trained treating physicians and nurses will use the DRS-R-98 to operationalize delirium diagnosis and measure delirium severity. We will use a diagnostic cut-off score of $\geq$15.[38]

Outcomes

The primary outcome is adherence to the intervention. A rate of at least 60% of patients having at least four completed domains for at least five of the first seven days of admission will be considered minimum evidence that the intervention is feasible without need for major modification of the intervention or its delivery methods. Endpoints will be at completion of the intervention and modified-intervention arms (Figure 1).

We chose this moderate endpoint because of the potential patient, clinician and system level challenges to the non-pharmacological strategies in the context of advanced cancer. Consensus by investigators was this endpoint would be the minimum to still have impact, realistic to achieve in practice, and ensure that further evaluation of this complex intervention was not prematurely stopped. The waitlist control design will allow two endpoints and thereby maximize the potential to reach this level of adherence to the intervention.

Secondary outcomes will further inform of the feasibility, acceptability and potential efficacy of a phase III trial of the intervention in this patient population and setting, as follows:

1. Coverage: delivery rate of the multicomponent intervention to consecutive eligible patients admitted to the unit, reasons why the intervention was not delivered, weekend coverage, measured via screening logs and case report forms;
2. Fidelity to delirium screening, diagnosis and the intervention: degree of alignment with the protocol, rationales for adaptation, rate of protocol deviations without reasons, measured via case report forms;
3. Methods, areas and levels of interdisciplinary involvement in delivery of the intervention, measured via intervention checklist;
4. Feasibility and acceptability of the study intervention and measures for patients, caregivers, staff and volunteers, measured via brief interviews during and shortly after the intervention phase;

5. Sustainability of the intervention: Adherence will be measured for all inpatients over one week, six months after commencement of data collection at the intervention sites;
6. Feasibility of the sample: percentage of participants included in data collection, reasons for non-inclusion, time to achieve sample size, measured via screening logs and case report forms;
7. Number of people with advanced breast cancer admitted to the units, number of these who are in underserved populations (patients over 70, indigenous patients, and culturally and linguistically diverse backgrounds), and the number who experience an episode of delirium (total, and in under-served populations) (for the purposes of reporting to the trial funder, the National Breast Cancer Foundation);
8. Percentage completion of all study measures, measured via case report form;
9. Rate of patients with a positive delirium screen, measured according to a score of 2 or more on the Nu-DESC at least once during each 24-hour period;
10. Delirium incidence, measured at first onset according to the DSM-5 diagnostic criteria for delirium applied within 24-hours of a positive delirium screen;
11. Delirium severity measured at first onset, using the DRS-R-98; and
12. Number of falls, complaints and other adverse events related to the intervention.

Sub-study

A qualitative sub-study will be conducted to obtain patient, family caregiver, staff and volunteer perceptions of the feasibility and acceptability of the intervention strategies (e.g. receiving information from staff about delirium) and study measures via brief, semi-structured interviews (Figure 2).

Inclusion and exclusion criteria for the sub-study

1. **Patients** will be included if they are aged 18 years or older; have a diagnosis of advanced cancer; admitted to an intervention site and received the intervention; speak English or have access to a health care interpreter; and able to give fully informed

written consent. Patients with advanced breast cancer will be purposively recruited to participate in the interviews. Patients will be excluded if they have an AKPS [30] score less than 30 and are in the 'terminal' Palliative Care Phase; [32]

2. **Family caregivers** will be included if they are aged 18 years or older; identified as a caregiver of a patient who received the intervention; English speaking or have availability of a health care interpreter; and able to give fully informed written consent;
3. **Site staff** will be included if they are employed at an intervention site and involved in implementing the delirium measures and/or the intervention; and
4. **Site volunteers** will be included if they are aged 18 years or older, enrolled in a formal volunteer program at an intervention site and involved in implementing the intervention.

Sub-study consent process

A researcher who is not a study investigator will obtain written informed consent from patients, family caregivers, staff and volunteers to participate in the brief interviews. For patients and family caregivers, the researcher will check with the clinical team to make sure the person meets the broad criteria for consideration of eligibility, is well enough and has given permission to be approached by a researcher, before introducing him or herself to the person and explaining the study. For staff and volunteers, the researcher will consult with the site investigator before approaching potential participants.

Participant consent will be a process of information exchange between the researcher, the potential participant and any other person the potential participant believes should be included in the discussion. Participant information sheets will be the basis for discussion and cover all procedures and possible benefits and burdens of participating. The potential participant will be given sufficient opportunity to consider the study and ask questions. Any

questions will be addressed and answered fully. The completed consent form will be copied and one copy will be given to the participant, one copy inserted in the medical file (for patients), and one copy filed in study file.

Analysis

Statistical analysis of primary outcome (adherence)

Adherence will be calculated as the rate to which patients have completed domains on a daily basis for the first seven days of admission. Degree of adherence to individual strategies will also be calculated as proportions.

Statistical analysis of secondary outcomes

Data on all outcomes will be summarised with descriptive statistics including their distribution. Frequency and percentage will be used for summarising categorical variables and mean, standard deviation, median, and interquartile range for continuous variables. Delirium incidence and severity will be determined at both the intervention and control sites.

Qualitative analysis

Participant interviews will be analysed using thematic content analysis to identify emergent themes and trends related to participants' perceptions of the feasibility and acceptability of the intervention elements and delirium measures.[39]

Sample size

A sample size of four sites and 40 patient participants (10 from each site) was considered sufficient for reasonable estimation of feasibility and percentage completion of study processes and measures during the first phase. [40] We will collect de-identified data on all eligible patients admitted to all sites until data is collected for 40 patients overall, with at

least 20 in the intervention arm. If the intervention is found to need modification, data will be collected for a further 20 patient participants at the two waitlist control sites.

This sample size was based on that projected for the future phase III cluster RCT of the intervention with: two parallel arms, 50% delirium incidence in the control, 30% delirium incidence in the intervention group, cluster size of 30 and intra-class correlation of 0.05, type I error rate of 5%, 80% power to reject the null hypothesis, and 30% attrition. This calculation results in a projected phase III trial sample size of nine clusters and 280 patient participants.

For the sub-study, sample size will be determined when data saturation is achieved.

Trial monitoring

In addition to falls and complaints, all adverse events will be recorded. Site investigators will assess the adverse event, assign the degree of relationship to the intervention, and provide information to the coordinating centre (UTS), and the approving HREC if required. Adverse events will be followed until the event is resolved, can be explained, or if the participant is lost to follow-up. Reports will contain details of follow-up investigations, results or other consultation. The investigator team will stop the study if reporting of adverse events indicates that major review of the study protocol is required. The UTS project team will report adverse event related to the intervention to the PaCCSC Trial Management Committee (TMC) within two weeks of knowledge of the event. The TMC discussions will be minuted, with actions detailed and reviewed at the subsequent meeting. The TMC chairperson's report to the PaCCSC Scientific Committee will contain a summary of the discussions of the adverse event report and agreed outcomes.

Data management

An Excel spreadsheet master index will contain confidential participant contact information and be the only link between individual site and patient participants and their allocated

identification number (ID). Study data will be collected and stored on paper CRFs and electronic Excel spreadsheets and then entered onto and managed on a Research Electronic Data Capture (REDCap) [41] database. Audio data from participant interviews will be identified only by ID, collected on a digital recording medium and stored temporarily at the study sites until uploaded to the REDCap database. Original files will then be destroyed. Data will be held, administered, checked and analysed at the coordinating site according to relevant PaCCSC Standard Operating Procedures (SOP). Errors detected during the data checking process will generate a site data report form recording details of the query and correction and resolution instructions. The database will be updated according to site instructions via email to provide an audit trail of data changes. The coordinating site will maintain a register of data checks for monitoring purposes. Data collected at each site, such as CRFs, any corrected and amended data, copies of adverse incident reports and file notes, will be securely stored and identified by ID number only. All identifiable data (e.g. signed consent forms) will be separately stored during the recruitment period. Site research staff will send copies of study documents (with the exception of signed consent forms) to the coordinating site by registered mail for collation and archiving. All study documents will be stored in accordance with relevant State government regulations regarding the retention and disposal of participant records.

Patient and Public Involvement

The study rationale and processes were informed by the literature pertaining to patients' experiences of delirium, as outlined in the introduction.[4,5] Low-burden outcome measures, such as the Nursing Delirium Screening Scale, were deliberately chosen in order to minimise the impact of the study on patients with advanced illness. No patients were directly involved in the design, recruitment to or conduct of the study. Two family caregiver consumers are associate investigators of the study (MB and BN). We will include the perspectives of patients about the feasibility and acceptability of the intervention through brief semi-

structured interviews. Investigators will not have access to the names or contact information of patient or family caregiver participants in order to directly provide feedback about the study to them. At study completion, a written and verbal report of the results and findings will be provided to the participating sites.

Ethics and dissemination

The study was approved by the South Western Sydney Local Health District HREC on July 19, 2017, reference number HREC/17/LPOOL/224; and ratified by the UTS HREC on August 22, 2017, reference number ETH17-1697. Minor protocol amendments were approved on April 13, 2018 (V1.1).

Reporting of this protocol adheres to the Standard Protocol Items: Recommended for Interventional Trials. [42] Reporting of results will adhere to the Consolidated Standards of Reporting Trials (CONSORT) guidelines for cluster RCTs and non-pharmacological treatment trials. [43,44] Reporting of the qualitative sub-study and implementation findings will be guided by the Consolidated Criteria for Reporting Qualitative Research (COREQ).[45] A comprehensive dissemination strategy will ensure that the trial results (either positive or negative) inform future research and clinical practice. Dissemination will include publication in peer-reviewed journals, presentations at conferences, study sites and key peak bodies. The investigators have no publication restrictions.

Strengths and limitations

The primary strengths of this study are the cluster RCT design and that it is supported by the PaCCSC, a national, multi-site phase III clinical trials group which provides well-established rigorous research governance and access to sites with research experience and capacity. The intervention includes family partnership, which is highly valued by both patients and family.[5,26] We will obtain the perspectives of patients and family, which are largely absent in trials of previous multicomponent delirium interventions.[15]

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Limitations include that site and research staff will not be blinded to the intervention. Active steps will be taken to minimize contamination between intervention and waitlist control sites. The study will be conducted in Australian palliative care inpatient settings and include only patients with advanced cancer, limiting the generalizability of results for services in other geographical regions and health care systems, and for patients with other advanced illnesses.

Trial status

The study has been approved by local health district and university HRECs, local governance approvals obtained, sites randomised, the two-month period completed and data collection is underway.

List of abbreviations

AKPS: Australia-modified Karnofsky Performance Status; **ACSQHC**: Australian Commission for Safety and Quality in Health Care; **BCW**: Behaviour Change Wheel; **CI**: Confidence Interval; **CONSORT**: Consolidated Standards of Reporting Trials; **COREQ**: Consolidated Criteria for Reporting Qualitative Research; **DRS-R-98**: Delirium Rating Scale-Revised-1998; **DSM-5**: Diagnostic and Statistical Manual of Mental Disorders, Fifth edition; **HREC**: Human Research Ethics Committee; **ID**: identification number; **Nu-DESC**: Nursing Delirium Screening Scale; **OR**: Odds Ratio; **PaCCSC**: Palliative Care Clinical Studies Collaborative; **PCOC**: Palliative Care Outcomes Collaborative; **RCT**: Randomised Controlled Trial; **REDCap**: Research Electronic Data Capture; **RR**: Relative Risk; **RUG-ADL**: Resource Utilisation Groups - Activities of Daily Living; **SOP**: Standard Operating Procedures; **UTS**: University of Technology Sydney

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Declarations

Clinical trials registration

ACTRN12617001070325p, Australian New Zealand Clinical Trials Registry (ANZTR), http://www.anzctr.org.au/, 24/07/2017. The ANZTR is a Primary Registry of the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP).

Consent for publication

Participant information includes an explanation that results will be published in a form that maintains the confidentiality of sites and individual participants.

Availability of data and material

Participant information sheets and consent forms are available at https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=373168&isReview=true

Funding

This work was supported by an Australian National Breast Cancer Foundation (NBCF) 2017 Pilot Study Grant (Grant code PS-17-030), contact details Level 9, 10 Barrack Street, Sydney, NSW 2000, Australia; T: +61 2 8098 4800 E: info@nbcf.org.au, W: https://nbcf.org.au/.

Competing interests

The authors declare that they have no competing interests.

Sponsor

The trial sponsor is PaCCSC, contact details: Level 3, 235 Jones St Ultimo NSW 2007, Australia; T. +61 (2) 9514 4862 (Sydney) /+61 (8) 7421 9726 (Adelaide), E: paccsc@uts.edu.au, W: uts.edu.au/paccsc. PaCCSC supports optimal trial governance through SOPs for electronic data handling, completion of CRFs, monitoring, dissemination, archiving of research materials, and record destruction; and trial infrastructure through Trials Management and Scientific Committees.

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Roles and responsibilities

Chief study investigators MA, AH and JP retain ultimate responsibility for the trial. Investigators and a project team coordinated the trial from IMPACCT - Improving Palliative, Aged and Chronic Care through Clinical Research and Translation, UTS. The investigator team meet at least twice yearly to support progress of the trial and inform related activities, such as dissemination.

Authors' contributions

AH, MA and JP are the co-lead authors and AH is the corresponding author for this manuscript. MA, JP and AH devised the adaptation of the multicomponent intervention for people with advanced cancer in hospital. MB and BN provided consumer insight into the adaptation of the intervention. AC provided guidance on the extent of alignment of the intervention and delirium screening diagnosis processes with the ACSQHC Delirium Clinical Care Standard. LL devised the statistical analysis and randomization process. JMD and ML provided insights into the waitlist design. SK contributed to the development of the site engagement and educational processes. SK, GC, RC, BL, EWE, PL and SB contributed clinical and research expertise into study design, process, measures and/or analysis. LB, BF, SLC and LE contributed to various aspects of the study protocol, including data collection, entry and storage, reporting of adverse effects, minimization of contamination, and/or site training. All authors have read and approved the final manuscript.

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Figure 1: Study Diagram
Standardised delirium screening at all sites + delirium prevention strategies at intervention sites; control sites wait listed for intervention

* Modified if required

Figure 2: Schedule of study measures and time points [43]

Note: Characteristics indicated with a * will be collected at baseline from the sites most recent PCOC report, and then again at study completion directly from PCOC for the specific time-frame of data collection at each site.

Table 1: Multicomponent delirium prevention intervention

Study diagram

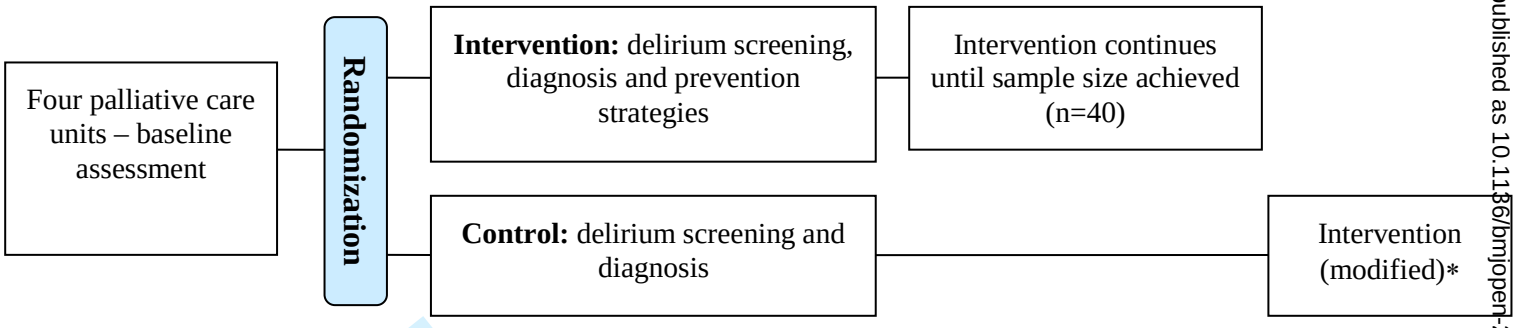

Figure 1: Study Diagram
Standardized delirium screening at all sites + delirium prevention strategies at intervention sites; control sites wait listed for intervention
* Modified if required.

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Figure 2: Schedule of study measures and time points [42]

Measures	Study period						
	Control and intervention sites					Intervention sites	
	Baseline	Eligibility screen on admission	Admission days 1-7	Nu-DESC +ve	Study completion	Admission days 1-7	Intervention completion
UNIT LEVEL							
Geographical location	X						
Type and level of service provision	X						
Number of beds	X						
Team composition	X						
Clinical documentation method	X						
Delirium process and measures	X						
Patient demographics*	X				X		
Patient function AKPS, RUG-ADL*	X				X		
Palliative care phases*	X				X		
PATIENT LEVEL							
Primary diagnosis		X					
Age		X					
Nu-DESC			X				
DSM-5 diagnostic criteria for delirium				X			
DRS-R-98				X			
Adherence to delirium prevention strategies						X	X (six months post)
SUB-STUDY							
Brief interviews with patients, family, staff and volunteers							X

Note: Characteristics indicated with a ∗ will be collected at baseline from the sites most recent PCOC report, and then again at study completion directly from PCOC for the specific time-frame of data collection at each site.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Title page
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3 and 25
	2b	All items from the World Health Organization Trial Registration Data Set	25
Protocol version	3	Date and version identifier	24
Funding	4	Sources and types of financial, material, and other support	26
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Title page
	5b	Name and contact information for the trial sponsor	26
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	26
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	26

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
	6b	Explanation for choice of comparators	7-8
Objectives	7	Specific objectives or hypotheses	6-7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7-8
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8; 19-20
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	8-9, 12
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12-13
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	18-19
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 2
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	21-22

Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	21-22
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	13
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	13
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	13
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13-14
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	14-15
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	NA
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	22-23
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	21
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	NA

	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	NA
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	22
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	22
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	22
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	24
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	NA
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8, 20-21
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	22-23, 26
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	26
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	22-24

Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	24
	31b	Authorship eligibility guidelines and any intended use of professional writers	27
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	26
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	26
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.