

# **A multicomponent non-pharmacological intervention to prevent delirium for hospitalized people with advanced cancer: a phase II cluster randomized waitlist controlled trial (the PRESERVE pilot study)**

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## **Document details**

Number of tables: 3 Number of figures: 3 Number of references: 38 Word count: 2936

## **Background**

Delirium is a common debilitating complication of advanced cancer.

## **Objective**

To determine if a multicomponent non-pharmacological delirium prevention intervention was feasible for adult patients with advanced cancer, prior to a phase III (efficacy) trial.

## **Design**

Phase II (feasibility) cluster randomized controlled trial. All sites implemented delirium screening and diagnostic assessment. Strategies within sleep, vision and hearing, hydration, orientation, mobility and family domains were delivered to enrolled patients at intervention sites admission days 1-7. Control sites then implemented the intervention ('waitlist sites').

## **Setting**

Four Australian palliative care units

## **Measurements**

The primary outcome was adherence, with an a priori endpoint of at least 60% patients achieving full adherence. Secondary outcomes were interdisciplinary care delivery, delirium measures and adverse events, analyzed descriptively and inferentially.

## **Results**

Sixty-five enrolled patients (25 control, 20 intervention, 20 waitlist) had 98% delirium screens and 75% diagnostic assessments completed. Nurses (67%), physicians (16%), allied health (8.4%), family (7%), patients (1%) and volunteers (0.5%) delivered the intervention. There was full adherence for 5% patients at intervention sites, partial for 25%. Both full and partial adherence was higher at waitlist sites: 25% and 45%, respectively. One-third of control site patients (32%) became delirious within seven days of admission compared to one-fifth (20%) at both intervention and waitlist sites ( $p=0.5$ ). Mean (SD) Delirium Rating Scale-Revised-1998 scores were 16.8 +12.0 control sites versus 18.4 +8.2 ( $p=0.6$ ) intervention and 18.7 +7.8 ( $p=0.5$ ) waitlist sites. The intervention caused no adverse events.

## **Conclusion**

The intervention requires modification for optimal adherence in a phase III trial.

## **Key words**

Cancer, clinical trial, delirium, inpatients, non-pharmacological, palliative care

## Introduction

Delirium is an acute, distressing and debilitating neurocognitive disorder of physiological etiology for more than one third of patients with advanced cancer in palliative care units.<sup>1-4</sup> Occurrence is higher again for those who die in this setting, with median (range) period prevalence of 75% (58%–88%).<sup>2</sup> The high prevalence contributes to widely-held assumptions that delirium is inevitable in people with advanced cancer, especially in the last weeks and days of life.<sup>5</sup> Yet potential to prevent this devastating complication exists, warranting systematic evaluation in oncology and palliative care contexts.<sup>6-8</sup>

Other clinical settings have decreased delirium incidence and risk in older and seriously ill patients, including intensive care units (ICU) where it was once thought unavoidable.<sup>9-14</sup> Overall, one-third reduction in delirium incidence has been reported for patients in non-ICU settings though multicomponent interventions targeting physical and cognitive activity, sleep, hydration, vision and hearing.<sup>9-11</sup> In a study of over 15,000 ICU patients, complete performance of a care bundle to improve pain, awareness, breathing, use of psychoactive medication, delirium detection, mobility and family engagement significantly reduced the likelihood of becoming delirious the following day (adjusted odds ratio 0.60 (0.49–0.72)  $p < 0.0001$ ).<sup>14</sup>

Achieving similar results for people with life-limiting illness in hospital would enable many to maintain mental and physical function and better attend to what and who is most important to them.<sup>15</sup> We therefore designed a program of research to evaluate whether targeting the fundamental care needs of people with advanced cancer in hospital would improve delirium-related outcomes, including for patients in the last weeks and days of life. In line with the Medical Research Council framework for complex interventions,<sup>16</sup> we first developed a multicomponent non-pharmacological delirium prevention intervention for patients with advanced cancer from existing evidence<sup>4, 7, 9-11</sup> then tested its methods and impact in a phase II (feasibility) trial, prior to embarking on a phase III (efficacy) trial of the intervention.

Results of the phase II trial are reported here according to Consolidated Standards of Reporting Trials guidelines.<sup>17</sup> The trial was registered with the Australian and New Zealand Clinical Trials Registry<sup>18</sup> and a protocol detailing its justification<sup>18</sup> and methods was published in January 2019.<sup>19</sup>

## Methods

### Design

A phase II cluster randomised controlled trial (RCT). We chose the cluster RCT design because the intervention suited site-level implementation and it reduced risk of contamination. As similar interventions have been effective in other patient populations and settings, site investigators

requested that control sites be given opportunity to later trial the intervention. We therefore integrated a 'waitlist' option for control sites into the study design, whereby sites randomized to control were given details of the intervention and option to deliver it after initial data collection at intervention sites.<sup>20</sup> Addition of the waitlist option furthermore provided opportunity to refine the intervention and/or study processes if initial data from intervention sites indicated need to do so. We also embedded a qualitative sub-study to obtain patient, family caregiver, staff and volunteer perspectives about feasibility and acceptability of the intervention and study measures, analysed according to the Theoretical Domains Framework for health-related behaviours.<sup>21</sup> Methods and findings of the sub-study will be reported in full elsewhere.

The overall study design is presented in figure 1.

### **Setting and participants**

Participating sites were four specialist palliative care inpatient units within hospitals in metropolitan Australia. Investigators MA and AH recruited sites in 2017. Patients eligible for enrolment were adults (i.e. aged 18 years or over) with advanced (stage 4) cancer.<sup>22</sup>

### **Randomisation**

The trial statistician LL allocated sites to intervention or control plus waitlist intervention conditions in October 2017 at UTS using a permuted block randomization method. We notified sites of allocation after local governance approvals.

### **Ethical procedures**

Hospital and university Human Research Ethics Committees approved the trial (HREC/17/LPOOL/224 and ETH17-1697). One person per site with requisite authority gave cluster-level consent to participate. Patients and family were informed about the trial via posters and verbal communication, including that they could opt out.

### **Intervention and control conditions**

All sites instituted delirium screening and diagnostic assessment of enrolled patients for the first seven days of admission. Nurses completed the Nursing Delirium Screening Scale (Nu-DESC)<sup>23</sup> each eight-hour shift. Within 24 hours of a positive Nu-DESC (score  $\geq 2$ ) for patients not already diagnosed as delirious, physicians applied Diagnostic and Statistical Manual of Mental Disorders, Fifth edition (DSM-5) diagnostic criteria for delirium<sup>1</sup> and the Delirium Rating Scale-Revised-1998 (DRS-R-98).<sup>24</sup> Except for one site that mandated the Nu-DESC for the first three days of admission, structured delirium screening and diagnostic assessment were new processes and therefore additional to usual care.

The intervention had six domains (eating and drinking, sleep, exercise, reorientation, vision and hearing, and family partnership) containing 36 strategies overall (4-12 per domain) (supplementary file 1). We asked team members to enlist family and volunteers and tailor the intervention to patients' needs and wishes. Team members documented delivered strategies on a checklist designed for data collection, plus their designation and reason for non-delivery: 'not required', 'patient choice', 'not clinically appropriate', 'not possible with current resources', and 'other'.<sup>19</sup>

A two-month site engagement and training period, guided by customized information manuals (available on request), preceded control and intervention conditions. Sites formed working groups of interested team members to plan implementation in line with their resources and systems. University-based researchers attended working group meetings to ensure intervention fidelity, trial integrity and timely progress [AH, RA, JH, JW]. Sites shared meeting records whenever researchers could not attend in person.

We designed and conducted training via four discrete 30-40 minute sessions (i.e. Introduction to the study; Delirium screening using the NuDESC; Delirium assessment and diagnosis; Multicomponent delirium prevention intervention) using Biggs' educational model<sup>25</sup> [AH, RA, JH, JW, site investigators, clinical educators, nursing managers], delivered multiple times for broadest reach. Learning outcomes were clinicians' understanding of the study processes relevant to their role and achievement of target adherence to study measures. Control sites received information about delirium prevention strategies when they transitioned to the intervention phase, along with a summary of learnings from intervention sites about optimizing trial processes. A key message was that the checklist was not the intervention *per se*, but essential to measuring the primary outcome of adherence.

### **Data collection**

Site research nurses recorded delirium measures, intervention delivery and adverse events during enrolled patients' first seven days of admission on Case Report Forms and Excel spreadsheets and uploaded data into REDCap.<sup>26</sup> Project staff obtained site-level patient demographics and functional status for all patients admitted during study periods from Palliative Care Outcomes Collaboration datasets.<sup>27</sup>

The schedule of study measures is presented in supplementary file 2.

### **Blinding**

The cluster design and nature of the intervention precluded blinding of site teams and data collectors. To minimize ascertainment bias, sites teams provided patients and family caregivers with

information about clinical aspects of the trial but not design or site allocation. We used standardized data collection tools and training to limit measurement bias.

## Outcomes

The primary outcome was intervention adherence at intervention and waitlisted sites, according to checklist documentation of each strategy at least once daily for the first seven days of admission. *A priori*, 60% or more patients having full adherence (delivery of all required strategies within at least four domains for at least five days) was considered minimum evidence that the intervention was feasible without major modification. Partial adherence to the intervention was defined as at least one strategy in at least four domains daily for at least five days.

Secondary outcomes were:

1. Delivery of care: i) Sample feasibility (percentage of patients with data collected, reasons for non-inclusion, time to achieve sample); ii) Coverage (proportion eligible patients receiving intervention, reasons for non-delivery, weekend coverage); iii) Compliance with study measures; iv) Methods, areas and levels interdisciplinary delivery; and v) Sustainability (adherence to delirium measures and prevention strategies at sites six months after intervention);
2. Delirium-related: i) Proportion of patients with a positive Nu-DESC at least once each 24-hours; ii) Delirium incidence (first meeting DSM-5 delirium diagnostic criteria within 24-hours of a positive Nu-DESC); and iii) Delirium severity (DRS-R-98 at first onset);
3. Adverse events: Falls, deaths, other, according to National Cancer Institute Common Terminology Criteria for Adverse Events<sup>28</sup> and complaints; reported as numbers, rates and descriptively, overall and intervention-related.

## Sample size

To obtain a sufficient sample size for a pilot study of at least 9% of the sample of the planned phase III trial, we enrolled four sites and 40 patients (10 per site), then 20 patients at waitlisted sites (10 per site).<sup>29</sup>

## Statistical analysis

Adherence to the delirium prevention strategies and by whom was computed using conditional counting techniques. Secondary outcomes were summarized using frequency and percentage for categorical variables, and mean and standard deviation or median and range for continuous variables. Independent sample t-tests, Chi-square tests and Fisher's Exact Test were used to measure differences between patients' demographic and delirium status across control, intervention and

waitlist sites. Data were managed using Microsoft Excel 2016 and Statistical Package for Social Sciences version 25.

## Results

During enrolment periods, the four sites admitted 90 patients and screened all for eligibility (figure 2). Seventy-two patients were eligible according to the protocol, with 68 considered eligible by site investigators. Four eligible patients were not enrolled due to: 'distress on admission', 'patient admitted for terminal care', 'patient unable to communicate well', with no reason given for the fourth. Non-enrolment of three patients considered eligible by site investigators was because two patients requested withdrawal and one 'other'.

We collected and analyzed data for 65 patients (90% of protocol-eligible patients, 96% according to site investigators). Of these, 38 patients (58%) had seven days of data collected. Twenty patients died within seven days (31%), four were discharged (6%), one control site patient was considered not well enough to continue, and two patients had data collection ceased before seven days for other, non-specified reasons.

Patient enrolment took an average of 20 days per site (range 8-36) and the overall sample was achieved in five months (May-September 2018).

### Site-level patient characteristics

During study periods, just over half (56%) of all admitted patients were male. Most were aged 70 years or over (59%), with a primary diagnosis of cancer (90%), born in Australia (56%) and had English their primary language (92%). Few were Aboriginal or Torres Strait Islander (n=2, 1%). There were no significant differences in patients' baseline characteristics at control sites compared to intervention or waitlist sites (table 1).

### Adherence to the intervention

Overall, 40 patients received the intervention for an average (SD) of  $5.8 \pm 1.8$  days. Of these, fourteen died (35%) and two (5%) were discharged within seven days of admission.

There was full adherence for 5% patients at intervention sites, 25% at waitlist sites. Percentages of patients having partial adherence was 25% at intervention sites, 45% at waitlist sites (figure 3).

Per domain, highest adherence was to exercise (59%), then eating and drinking (54%), reorientation (52%), and sleep, vision and hearing and enabling family (each 41%) (table 2). There was higher delivery of every strategy at waitlist sites. Overall, nurses delivered most strategies (67%), followed by medical staff (16%), allied health (8.4%), family caregivers (7%), volunteers (0.5%), with patients themselves recording 1.1%. There was minimal documentation of reasons for non-delivery: 'not

required' (1.4%), 'not appropriate' (1%), 'patient choice' (0.7%), 'not possible' (0.4%), and 'other' (n=1).

### **Delirium measures**

Nurses completed the Nu-DESC at least once per day for 373/379 patient days (98%). Physicians applied the DSM-5 diagnostic criteria and DRS-R-98 within 24-hours of a first positive Nu-DESC for 24/31 occasions (77.4%). There was no significant difference between weekday and weekend completion of delirium measures.

Eight patients developed delirium in the first seven days of admission at control sites (32%) compared with four patients each at intervention (20%) and waitlist sites (20%) ( $p=0.5$ ). Mean (SD) delirium severity (DRS-R-98) was  $16.8 \pm 12.0$  for patients at control sites compared with  $18.4 \pm 8.2$  at intervention sites ( $p=0.6$ ) and  $18.7 \pm 7.8$  at waitlist sites ( $p=0.5$ ) (table 3).

### **Adverse events**

Forty-five patients (69%) experienced a total of 162 adverse events: 15 (60%) control, 14 (70%) intervention and 16 (80%) waitlist sites (supplementary table 3). Site investigators attributed no adverse events to the intervention. Two (8%) control site patients fell, compared with one each at intervention and waitlist sites (5%). Six (24%) patients died within seven days of admission at control sites compared to seven (35%) at both intervention and waitlist sites.

### **Sustainability (at six months)**

Of 20 consecutively admitted patients (five per site), two patients (10%) died within five days, leaving 97 patient days for analysis. In these, there were five instances of delirium screening using the NuDESC and one using the Confusion Assessment Method (6%).<sup>30</sup> There was no DRS-R-98 or DSM-5 diagnostic criteria for delirium documented. Adherence to the delirium prevention strategies was not full for any patient and partial for six (30%). Almost every strategy was less frequently documented than during the intervention (table 2).

## **Discussion**

Despite site engagement and training and higher intervention adherence at waitlist sites, the trial did not achieve its primary feasibility outcome. In contrast, secondary outcomes demonstrated feasibility of the sample and delirium measures, no adverse effects, and a non-statistically significant decrease in the proportion of patients with delirium in the first week of admission when sites delivered the intervention. Adherence was higher at waitlist sites, likely due to the more staged implementation (i.e. delirium measures then prevention strategies), in conjunction with giving waitlist site teams more explicit information about importance of documenting the intervention.



Post-intervention, measurement of usual care demonstrated higher adherence to strategies occurred within-trial. Taken together, results support the ongoing investigation of delirium prevention in patients with advanced cancer through non-pharmacological means. However, as higher delivery of multicomponent non-pharmacological delirium prevention interventions is associated with greater effectiveness, modifications to optimize adherence in a phase III trial will be required.<sup>14, 31</sup>

Next steps in this staged research program are to integrate qualitative findings with trial results to inform modification of the intervention. Strategies to be retained will be those with highest overall evidence, delivered with higher adherence or under-delivered due to resolvable barriers in this trial, and considered essential by those involved.

An intervention with fewer strategies will also facilitate more precise dose measurement. In this feasibility trial, it was sufficient to measure intervention *frequency* (24 hours) and *duration* (one week), whereas determining dose/efficacy ratios will also require measuring the *amount* patients receive each time.<sup>32</sup> Full dose measurement will require *a priori* consideration of equivalent strengths of intervention parts and whether to measure these at the domain or strategy level.

Other factors important to consider for dose potency are who delivers the strategy and how, because fundamental care strategies are delivered through highly interpersonal interactions. Such interactions serve not only visible objectives (e.g. to help the person drink a glass of water) but also to communicate caring, compassion and respect for an ill person. *How* fundamental care is delivered is instrumental to maintenance of psychological well-being during advanced illness and dying in hospital and therefore worthy of closer attention in future delirium research in palliative care contexts.<sup>33, 34</sup>

We explicitly sought to include patients near the end of life in this trial and so it was not surprising that almost one-third of enrolled patients died within seven days of admission. Endeavouring to develop and trial non-pharmacological delirium interventions in the last weeks of life is justifiable, because patients with terminal illness value maintaining cognition and connection with others<sup>35, 36</sup> and both delirium and customary pharmacological treatments disrupt this potential.<sup>8, 37</sup> However, it is not possible to diagnose delirium in an unresponsive person.<sup>1</sup> Therefore, collateral measurement of psychomotor activity and awareness would inform a primary trial outcome of days without delirium or coma, as successfully evaluated in studies in intensive care.<sup>12, 14</sup> This would be a clinically meaningful palliative care outcome, as it would help determine the extent to which non-pharmacological delirium interventions enable patients to remain more alert and able to attend to important undertakings with those they love in the last days of life.<sup>38</sup>

### **Limitations and strengths**

Limitations include lack of blinding, inherently difficult in multicomponent non-pharmacological interventions and a source of bias in this field of delirium research.<sup>7</sup> The small sample was appropriate for a phase II trial but precluded definitive determination of intervention effectiveness in reducing delirium incidence or severity. While patients who became delirious continued to receive the intervention, we did not examine delirium treatment or resolution. Strengths include the cluster RCT design, which promoted enrolment of almost all eligible patients and reduced the risk of selection bias. The waitlisted arm facilitated multisite recruitment and engagement. Systematic adverse event measurement ensured close monitoring of enrolled patients for potential harms and was an advancement upon previous similar studies.<sup>7</sup>

### **Generalisability**

The study informs future research in delirium prevention in patients with advanced cancer in palliative care units. The study population was representative of Australian palliative care inpatients and sites typified the varyingly resourced units across metropolitan Australia. Intervention strategies addressed fundamental human needs, and prior implementation in many settings underscores their universal relevance for hospitalized patients.<sup>15-17</sup> However, results may not be generalized to other geographical regions, health care systems or patients with other advanced illnesses.

### **Conclusion**

A multicomponent intervention to optimize eating and drinking, sleep, exercise, reorientation, vision and hearing and family partnership to prevent delirium in patients with advanced cancer was piloted in four palliative care units. Outcomes indicate a phase III trial will be feasible in this patient population and setting if the intervention is modified. Next steps are to integrate qualitative findings with trial results to inform modification of the intervention, and determine dose and outcome measures most fitting for patients with advanced cancer in palliative care units, including those in the last weeks and days of life.

## **Acknowledgements**

The authors gratefully acknowledge the contributions of patients, family caregivers, clinicians and volunteers at the four participating sites and the Palliative Care Outcomes Collaboration team who provided site level data.

The trial was funded 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](mailto:info@nbcf.org.au), W: <https://nbcf.org.au/>. The NBCF had no role in the study design, data collection, management, analysis, interpretation or publication of results.

The trial sponsor was the Palliative Care Clinical Trials Collaborative (PaCCSC) (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](mailto:paccsc@uts.edu.au), W: [uts.edu.au/paccsc](http://uts.edu.au/paccsc)). PaCCSC supports optimal trial governance through standard operating procedures for electronic data handling, completion of case report forms, monitoring, dissemination, archiving of research materials, and record destruction, and trial infrastructure through Trials Management and Scientific Committees.

## **Author Disclosure Statement**

Drs. Hosie, Phillips, Lam, Kochovska, Cheah, Green and Agar and Ms Brown, Fazekas Edwards, Hunt, Attwood, Assen, Garcia and Wilcock report a grant from the National Breast Cancer Foundation during the conduct of the study. Dr Hosie also reports personal fees from Medtronic, outside the submitted work. Dr. Caplan reports grants from Bionomics Pty Ltd, outside the submitted work. Dr. Ely reports personal fees from Masimo, grants from VA/NIH, personal fees from Pfizer/Orion and grants from Koheler, outside the submitted work. All remaining authors have no disclosures to report.

## **Authors' contributions**

AH, MA, JP co-led the trial and AH is corresponding author. MA, JP, AH developed the intervention in consultation with an expert working group.<sup>19</sup> MB, BN provided consumer insights into trial rationale and the intervention. AC advised on alignment of the intervention and delirium measures with the Australian Commission on Safety and Quality in Health Care's Delirium Clinical Care Standard. LL devised the statistical analysis and randomization process. JMD and ML provided insights into the waitlist design. AH, MA, JMD, ML, CP, SW, KH, SMcA, KJ, CP, LK, JK, JH, RA, TA, MG, JW co-designed processes for site engagement, training and intervention implementation. SK, GC, RC, BL, EWE, PL, SB contributed clinical and research expertise into study design, process, measures and/or analysis. LB, BF, AG, SLC, LE contributed to processes for data collection, adverse event reporting entry, storage and/or analysis. All authors have approved manuscript submission.

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**Table 1: Site-level patient characteristics on admission**

	Control sites (n=2)	Intervention sites (n=2)	Waitlisted sites (n=2)
<b>Patient n (%)</b>	n = 37**	n = 56**	n = 50**
Age in years, mean (SD)	70.5 (15.5)	76.0 (11.2)	68.1 (12.5)*
Aged >70	19 (51)	41 (73)	24 (48)*
Male sex	24 (65)	23 (41)	33 (66)*
<b>ATSI status</b>			
Not ATSI	34 (92)	56 (100)	48 (96)
ATSI	1 (3)	0	1 (2)
Not documented	2 (5)	0	1 (2)
<b>Country of Birth</b>			
Australia	23 (62)	28 (50)	29 (58)
Elsewhere	11 (30)	27 (48)	21 (42)
Not documented	3 (8)	1 (2)	0
<b>Primary language</b>			
English	33 (89)	50 (89)	49 (98)
Other than English	2 (5.5)	6 (11)	1 (2)
Not documented	2 (5.5)	0	0
<b>Primary diagnosis</b>			
Malignant	36 (97)	48 (86)	45 (90)
Non-malignant	1 (3)	8 (14)	5 (10)
<b>AKPS</b>			
70	1 (3)	1 (2)	1 (2)
60	6 (16)	7 (12)	1 (2)
50	5 (14)	13 (23)	10 (20)
40	3 (8)	15 (27)	15 (30)
30	4 (11)	11 (20)	5 (10)
20	16 (43)	8 (14)	16 (32)
10	2 (5)	1 (2)	2 (4)
<b>Total RUG-ADL</b>			
4	7 (19)	9 (16)	3 (6)
4-18	16 (43)	31 (55)	37 (74)
18	14 (38)	16 (29)	10 (20)

AKPS Australian-modified Karnofsky Performance Scale ATSI: Aboriginal or Torres Strait Islander RUG-ADL Resource Utilisation Group Activities Daily Living

\* With Bonferroni adjustment for familywise corrections ( $p=0.05/3=0.0167$ ), independent sample t-test revealed statistical significant difference for mean ages ( $p=0.001$ ), and Chi-square tests revealed statistical significant differences for Age>70 (0.008) and genders (0.01) between the intervention and waitlisted sites.

\*\* **Site-level data includes ALL patients admitted during study periods**

**Table 2: Adherence and interdisciplinary delivery of the intervention**

Domain (%)	Strategy (%)	I n=20	W n=20	Overall n=40	Delivered by (%)	Post- trial n=20
<b>Exercise (59)</b>	Minimize physical restraints e.g. bed rails, lock-in chair tables	55	70	63	Nursing (63.2), allied health (P, D)* (18.6), medical (14.9), family (2.6), patient (0.7)	45
	Minimize tethers e.g. IV, IDC, drain, oxygen tubing	55	65	60		49
	Encourage and assist physical activity	50	60	55		77
<b>Eating &amp; drinking (54)</b>	Encourage oral fluids	55	70	63	Nursing (69.2), family (13.4), medical (10.1), allied health (D, OT, PC, SP)* (5.5), patient (1.6), volunteer (0.3)	41
	Drinking aids	40	65	53		9
	Respond to reversible causes of poor oral intake	35	70	53		21
	Volunteer assist with set up	40	65	53		7
	Physical assistance with meals and drinks	40	60	50		22
<b>Reorientation (52)</b>	Greet patient by name	55	70	63	Nursing (66.4), medical (20.6), allied health (D, PC, P, SW, OT)* (8.6), family (3.4), volunteer (0.8), patient (0.2)	73
	Introduce self	55	70	63		74
	Refer to person, time and place	55	70	63		75
	Remains in allocated room	55	70	63		53
	Discuss current events	55	70	63		55
	Encourage patient to reminisce and talk	55	70	63		42
	Clock or watch in room	50	70	60		99
	Daily update of in-room whiteboards	45	70	58		0
	Access to cognitively stimulating activities	35	55	45		22
	Translation aids	15	50	33		5
	Interpreter	15	45	30		1
	Cognitively stimulating activities in care plan	10	40	25		0
<b>Sleep (41)</b>	Lights off or minimized at night	55	70	63	Nursing (75.6), medical (10.9), allied health (D, PC, OT, P)* (7), family (4.7), patient (1.6), volunteer (0.2)	41
	Curtains/blinds open in day	55	70	63		49
	Uninterrupted sleep during night	35	55	45		42
	Time spent outside during day	30	45	38		31
	Avoid caffeine after 4pm	30	45	38		11
	Eye shades	5	40	23		0



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	Ear plugs	5	40	23		0
<b>Vision &amp; hearing (41)</b>	Use visual aids	35	65	50	Nursing (64.6), medical (16.5), family (10.7), allied health (D, P, PC, OT, SW, SP)* (5.1), patient (2.4), volunteer (0.7)	24
	Assess hearing	30	65	48		4
	Assess vision	20	60	40		4
	Use hearing aids	25	50	38		0
	Ear wax clearing	15	40	28		0
<b>Enabling Family (41)</b>	Ask about patient's baseline cognition	30	65	48	Nursing (46.6), medical (43.5), allied health (5.3), family (4.6)	15
	Invite participation in prevention strategies	25	60	43		1
	Verbally inform about delirium risk and prevention strategies	20	55	38		1
	Give delirium brochure	20	55	38		0

\* Codes for allied health staff and rate of their participation in overall delivery of the delirium prevention intervention: D=Dietician (4.2%), P=Physiotherapist (2.3%), PC=Pastoral care (1.1%), OT=Occupational therapist (0.4%), SW=Social worker (0.3%), SP=Speech pathologist (0.1%) I: Intervention sites, WI: Waitlist sites

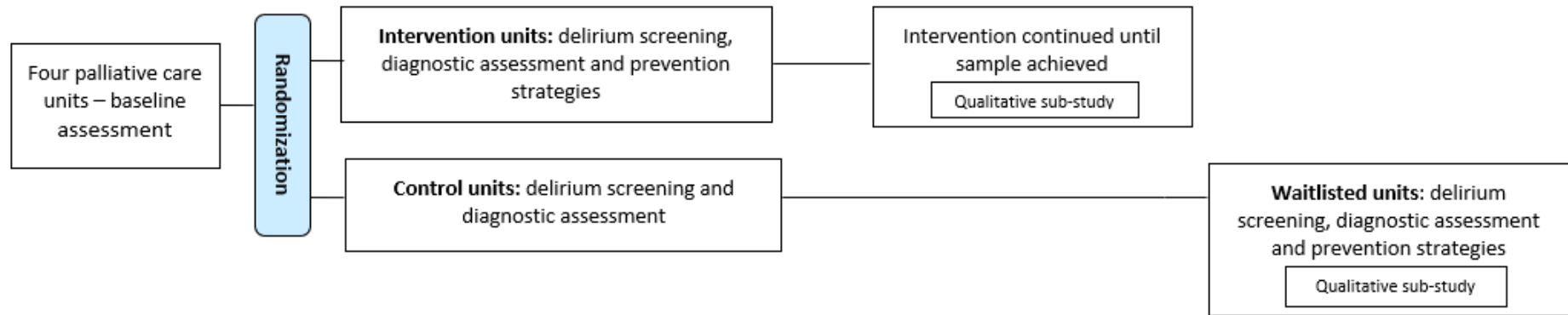
NB all figures are percentages of patients receiving intervention elements

**Table 3: Delirium incidence and severity**

<b>Delirium measure n (%)</b>	<b>Control sites (n=25)</b>	<b>Intervention sites (n=20)</b>	<b>Waitlisted sites (n=20)</b>
<b>Nu-DESC <math>\geq 2</math></b>	13 (52)	6 (30)	12 (60)
<b>Delirium incidence (DSM-5)</b>	8 (32)	4 (20)	4 (20)
<b>Delirium severity (DRS-R-98) Mean (Range; SD)</b>	16.8 (2-36; 12.0)	18.4 (5-24; 8.2)	18.7 (10-31, 7.8)

Fisher's Exact Test and Independent sample t-test found no statistically significant differences for any delirium measure across study sites  
SD: Standard Deviation

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**Figure 1: Study Diagram**

Standardized delirium screening and diagnostic assessment at all units + delirium prevention strategies at intervention units (May-Jun 2018); control units were waitlisted to the intervention (Aug-Sep 2018)

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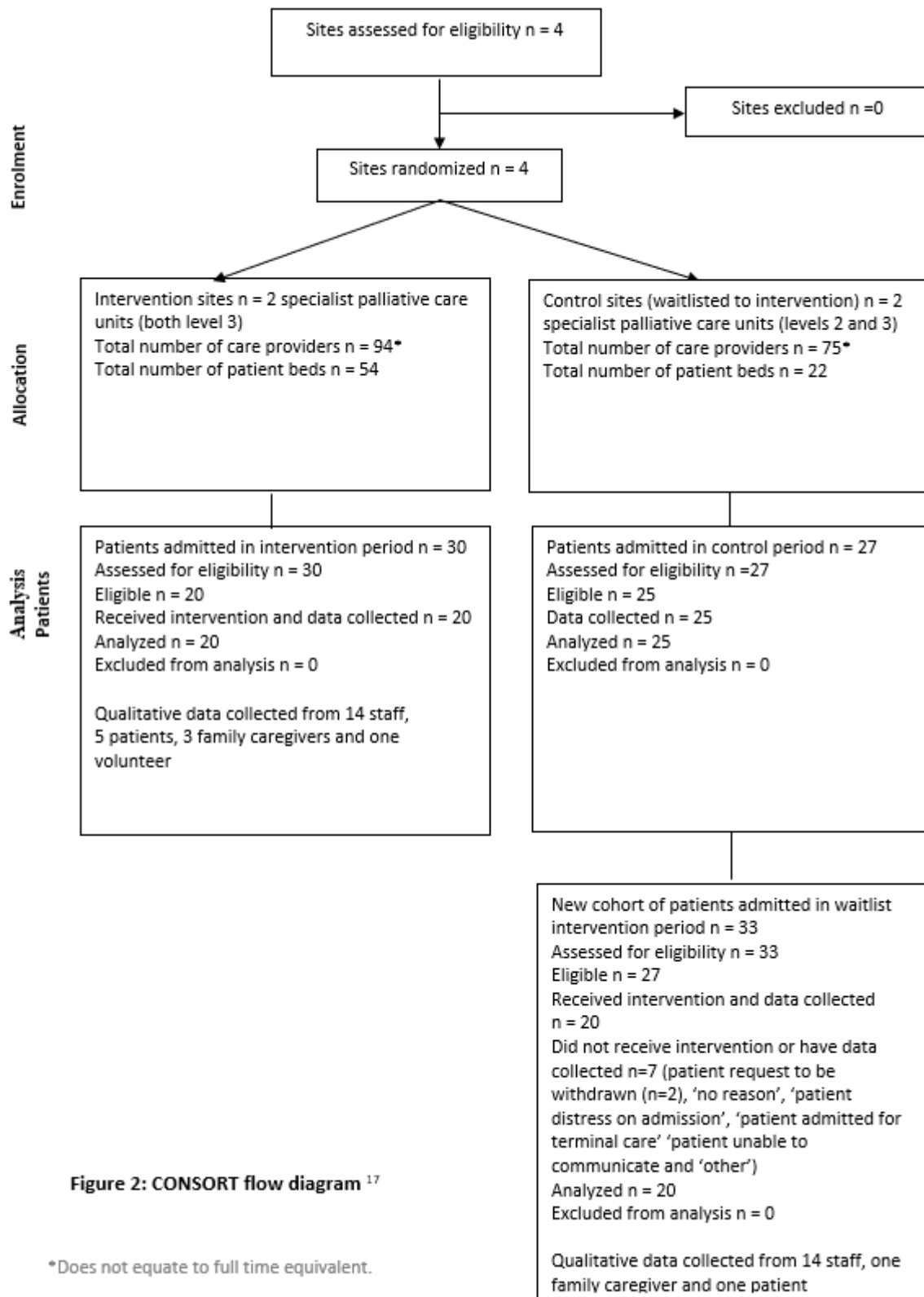
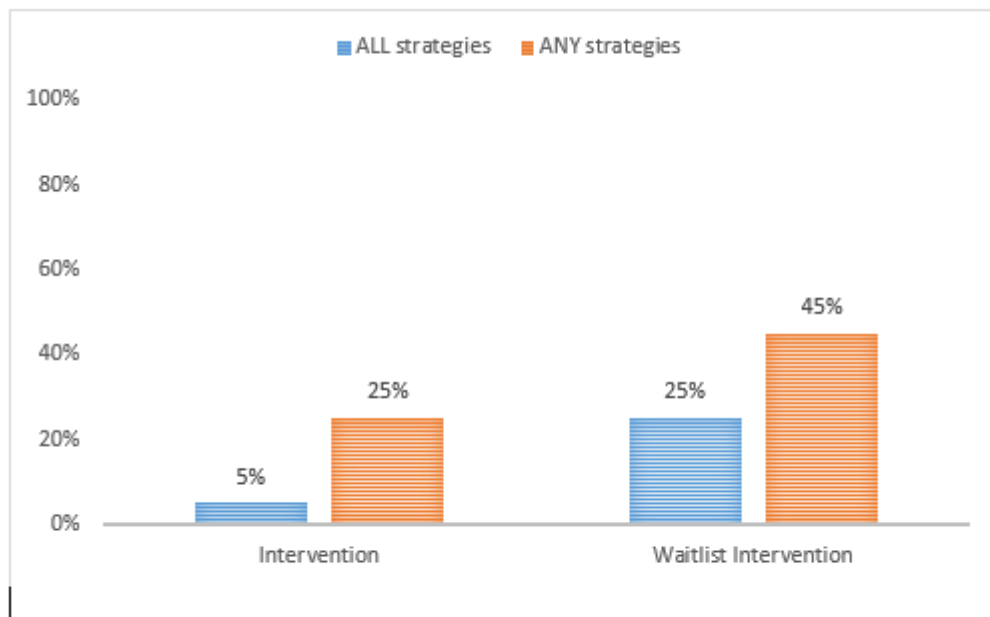


Figure 2: CONSORT flow diagram <sup>17</sup>

\*Does not equate to full time equivalent.



**Figure 3: Adherence to delirium prevention intervention at intervention and waitlisted sites, calculated as either *all* strategies or *any* strategy  $\geq 4$  domains for  $\geq 5$  days.**

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**Supplementary file 1: Elements of the intervention**

Domains	Strategies	Implementation
<p><b>1.</b> Preserve natural sleep</p>	<ul style="list-style-type: none"> <li>• Offer ear plugs to patients who have low risk of falls</li> <li>• Offer eye shades to patients who have low risk of falls</li> <li>• Reduce noise outside patient rooms during 21:00-06:00</li> <li>• Normal day-night variation in room and unit lighting</li> <li>• Exposure to natural light during daylight hours</li> <li>• Schedule care activities to allow uninterrupted sleep during the night</li> <li>• Avoid caffeine after 4pm</li> </ul>	<ul style="list-style-type: none"> <li>• The patient wears ear plugs at night</li> <li>• The patient wears eye shades at night</li> <li>• Room curtains/blinds are open during the day</li> <li>• Room lights are off or minimised at night</li> <li>• The patient spends time outside during the day</li> <li>• The patient drinks no caffeinated tea, coffee or cola after 4pm</li> <li>• The patient reports night-time sleep uninterrupted by noise or care activities</li> </ul>
<p><b>2.</b> Maintain optimal sensory perception</p>	<ul style="list-style-type: none"> <li>• Hearing:                             <ul style="list-style-type: none"> <li>○ Assess hearing</li> <li>○ Assist with and re-inforce use of hearing aids and special communication techniques</li> <li>○ Ear wax clearing as needed</li> </ul> </li> <li>• Vision:                             <ul style="list-style-type: none"> <li>○ Assess need for visual aids (glasses, magnifying lenses)</li> <li>○ If needed, ask family to provide for the patient</li> <li>○ Assist with and re-inforce use of visual aids</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• The patient hearing was assessed</li> <li>• The patient has ear wax cleaning</li> <li>• The patient wears functioning hearing aids</li> <li>• The patient has their vision assessed</li> <li>• The patient wears their glasses appropriately</li> <li>• The patient uses visual aids</li> </ul>
<p><b>3.</b> Optimize hydration</p>	<ul style="list-style-type: none"> <li>• Encourage oral fluids</li> <li>• Physical assistance with drinks and meals, as required</li> <li>• Drinking aids, as required</li> <li>• Be alert and respond to reversible causes of poor oral intake within 24 hours e.g. nausea, vomiting, drowsiness, sore mouth.</li> </ul>	<ul style="list-style-type: none"> <li>• The patient is encouraged to drink</li> <li>• The patient is assisted with meals</li> <li>• Drinking aids are provided e.g. straws, cup holders, cups with lids, spouts, handles or grips</li> <li>• Intervention for reversible causes of poor oral intake are in place</li> </ul>
<p><b>4.</b> Stimulate communication, orientation and cognition</p>	<ul style="list-style-type: none"> <li>• Communication:                             <ul style="list-style-type: none"> <li>○ Interpreter and translation for people with non-English speaking background</li> </ul> </li> <li>• Orientation:                             <ul style="list-style-type: none"> <li>○ Greet the patient by name</li> <li>○ Introduce self by name and role</li> <li>○ Refer to person, time and place when talking with the patient</li> <li>○ Time aids in room e.g. watch, personal or wall clock; wall, desk or electronic calendar</li> <li>○ Update in-room whiteboards daily with date, day, place, reason for admission, team member names, schedule</li> <li>○ Minimize number of transfers to other beds or rooms within the unit</li> </ul> </li> <li>• Cognition:                             <ul style="list-style-type: none"> <li>○ Discuss current events with the patient</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Interpreter is available and utilized</li> <li>• Orientating information is translated into the patient's native language</li> <li>• The patient can see the time in their room</li> <li>• The patient can see the day, date and month in their room</li> <li>• The patient remains in the same bed location within the unit</li> <li>• The patient discusses current events</li> <li>• The patient reminisces and/or talks about their life and family</li> <li>• The patient spends time in cognitively stimulating activities e.g. reading, puzzles, games, knitting, music</li> <li>• Cognitive stimulating activities are in the patient's care plan</li> </ul>

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	<ul style="list-style-type: none"> <li>○ Encourage the patient to reminisce and talk</li> <li>○ Encourage the patient to engage in cognitively stimulating activities</li> </ul>	
5. Optimise mobility	<ul style="list-style-type: none"> <li>• Minimize use of tethers e.g. intravenous line, indwelling catheter, drain, oxygen</li> <li>• Minimize use of physical restraints e.g. bed rails, lock-in chair tables, vest restraints, limb restraints</li> <li>• Encourage and/or assist the patient to undertake physical activity throughout the day according to their capacity:               <ul style="list-style-type: none"> <li>○ Level 0: No activity planned (state reason):</li> <li>○ Level 1: Active range of movement exercises in bed and/or sitting position in bed (e.g. regular bed adjustment, assistance with re-positioning)</li> <li>○ Level 2: Assistance to sit on the side of the bed</li> <li>○ Level 3: Sitting out of bed in a chair, standing</li> <li>○ Level 4: Walking (marching in place, independent or assisted walking around room and unit)</li> <li>○ Level 5: Attend inpatient gym, walking outside of unit</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• The patient is free of tethers</li> <li>• The patient is free of physical restraint</li> <li>• The patient moves and/or exercises to their optimal capacity</li> </ul>
6. Family partnership	<ul style="list-style-type: none"> <li>• Ask family about the patient's baseline cognition</li> <li>• Inform the patient and family about delirium risk</li> <li>• Inform the patient and family about delirium prevention strategies and invite participation</li> </ul>	<ul style="list-style-type: none"> <li>• Family are asked about the patient's baseline cognition on admission</li> <li>• Delirium information brochure is provided to the patient and family</li> <li>• Patients and family are verbally informed about delirium</li> <li>• Patients and family are informed about delirium prevention strategies and invited to participate</li> </ul>

**Supplementary file 2: Schedule of study measures and time points**

Measure	Study arm/period							
	Control and intervention					Intervention only		
	Baseline	O/A	Daily (1-7)	Nu-DESC $\geq 2$	Study end	Daily (1-7)	Intervention completion	
						Immediately after	Six months after	
<b>Site level</b>								
Geographical location	x							
Type and level of service provision	x							
Number of beds	x							
Team composition	x							
Clinical documentation method	x							
Routine delirium process and measures	x							x
Patient demographics, function (AKPS, RUG-ADL), palliative care phase*					x			
<b>Patient level</b>								
Primary diagnosis*		x						x
Nu-DESC			x					x
DSM-5 diagnostic criteria for delirium				x				x
DRS-R-98				x				x
Adherence to delirium prevention strategies						x		x
<b>Sub-study</b>								
Semi-structured interviews with patients, family, staff and volunteers							x	

\*Collected via Palliative Care Outcomes Collaborative (PCOC) routine measures for ALL admitted patients for study periods

AKPS: Australian-modified Karnofsky Performance Status; DRS-R-98: Delirium Rating Scale-Revised-1998; DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth edition; Nu-DESC: Nursing Delirium Screening Scale; O/A: On admission; RUG-ADL: Resource Utilisation Groups—Activities of Daily Living



**Supplementary file 3: Adverse events**

<b>Patient/event</b>	<b>Control sites</b> (n=25)	<b>Intervention sites</b> (n=20)	<b>Waitlisted sites</b> (n=20)
Patient n (%)	15 (60)	14 (70)	16 (80)
<b>Category of adverse event n (%)</b>			
Falls *	2 (8)	1 (5)	1 (5)
Complaints *	0	0	1 (5)
Death *	6 (24)	7 (35)	7 (35)
Other †	12 (48); 48 (4)	11 (55); 38 (3.5)	15 (75); 51 (3.4)
Serious ††	11 (44); 15 (1.4)	6 (30); 33 (5.5)	6 (30); 33 (5.5)
<b>Relatedness to intervention**</b>			
Unlikely	0	3 (1 patient)	0
Unrelated	30 (15 patients)	85 (12 patients)	54 (14 patients)

\* Reported as number (percentage) of patients who experienced the adverse event

† Reported as number (percentage) of patients who experienced an adverse event other than falls, complaints or death; and overall number of other adverse events (mean number per patient)

†† Reported as number (percent) of patients who experienced a serious adverse event; and overall number of serious adverse events (mean number per patient)

\*\*Other categories were Possible/Probably/Definite/Not possible, for which there were none