*DELI*rium in *I*ntensive care: reducing the incidence and duration among adults admitted to intensive care.

Short Title: The ***DELI*** study:

LIST OF INVESTIGATORS AND PARTICIPATING INSTITUTIONS

Principal Investigators:

Joan Lynch[1-3], Leanne Hunt[1-3], Kathleen Brennan[1,4,5], Sharon Shunker[3], David Sanchez[1,7], Evan Alexandrou[1-5], Mariepaz Hazell[3], Martin Christensen[1,2,6], and Steve Frost[1-3,5-6]

[1] Critical Care Research in Collaboration and Evidence Translation (CCRICET)

[2] School of Nursing and Midwifery, Western Sydney University

[3] Intensive Care Unit Liverpool Hospital

[4] Intensive Care Bankstown Hospital

[5] South Western Sydney Clinical School, UNSW

[6] Centre for Applied Nursing Research, SWSLHD

[7] Intensive Care Unit Campbelltown Hospital

SITE INVESITGATORS/COORDINATORS

Sharon Shunker	CNC, Intensive Care Unit Liverpool Hospital
Kathleen Brennan	NP, Intensive Care Unit Bankstown Hospital
David Sanchez	CNC, Intensive Care Unit Campbelltown Hospital
Masar E Sayfe	CNE, Intensive Care Unit Fairfield Hospital

Australian New Zealand Clinical Trials Registry (ANZCTR): ACTRN12618000411246p

2. SYNOPSIS (*The synopsis is similar to an abstract and should be about 200-250 words. It is a stand-alone summary of the study and includes background, objectives and study plan)*

Background

Delirium is an acute neurocognitive disorder that is characterised by a fluctuating level of consciousness with impaired attention and cognition. Delirium has been estimated to occur in approximately 30% of adults admitted the intensive care [1-3]. Delirium is associated with poor outcomes which include longer stay in intensive care unit, longer stay in hospital by 10 days and experience a prolonged duration of mechanical ventilation [4, 5]. The longer-term outcomes include long-term cognitive impairment, dependency in activities of daily living and 2-3 times higher mortality rates [4-10]. The restlessness and agitation experienced by patients leads to increasing workload of ICU nurses who need to stay continually by the bedside to ensure the patients safety, thereby requiring one-to-one nursing care. This increases the financial burden of delirium on the Intensive Care unit as well as the hospital.

Objectives

This study will evaluate the impact of a nursing-led delirium-prevention protocol ('the intervention') that is aimed at reducing the incidence, severity, and duration of delirium among adults admitted to ICU. The Delirium Prevention Nursing Protocol targets the risk factors for delirium which includes visual and hearing impairment, to prevent or treat sensory deprivation and ultimately the loss of orientation; sleep deprivation, cognitive impairment to (re)orientate patients with regard to time, place and person to prevent or minimize decline; and immobility, to improve patients' functional mobility in the ICU and to stimulate patients' cognition.

Study Plan

This study will be conducted using a multicentre stepped wedge cluster randomized controlled trial [11]. The intervention will be implemented in four Intensive Care Units

across the South Western Sydney Local Health District in a stepped process where each unit will move from a control unit to training unit to intervention unit, over a 12-month period.

3. RATIONALE / BACKGROUND

This should provide an introduction to the study, what is already known (brief literature review), what is missing, what the study is going to find out, how this is going to be achieved and what impact the study will have.

Delirium is a serious disorder that results in the acute disturbance of neurocognition, leading to fluctuating levels of awareness, attention and cognition. Delirium occurs in approximately 30% of critically ill adults [1-3, 8, 12] but in some populations such patients who stay more than 2-days, older male trauma patients and patients undergoing mechanical ventilation the incidence has been reported over 60% [10, 13-15].

Delirium is independently associated with worse outcomes among adults admitted to intensive care. Hospital mortality has been reported 2-3 times higher in patients who experience delirium [4, 6, 16]. Studies also report longer length of stay in the ICU and hospital [4, 10], longer time spent on the ventilator [4], higher incidence of cognitive impairment at hospital discharge [4, 9] and dependency in activities of daily living [6]. Delirium is associated with serious consequences, thus reducing or preventing delirium in critical care will have significant impacts on outcomes in these patients.

The risk factors for delirium have been extensively studied [3, 5, 10, 15]. The risk factors include primary risk factors (i.e., brain damage, dementia, and cognitive impairment due to stroke), physical factors (i.e., visual and auditory disorders, fluid and electrolyte imbalance, metabolism disorders, emergency hospitalization, hypoperfusion, pain, fracture, hypertension,

alcoholism, high severity of illness at admission, and infection) [17], and frequently, combinations of several factors (i.e., combination of sleep deprivation, use of a restraint, and exposure to noise) [7]. Therefore, a multidisciplinary and multi-component intervention approach is recommended for delirium prevention [18]. Recent studies that have used a non-pharmacologic multi component intervention programs to prevent delirium have shown promise in reducing the burden of delirium, mortality and length of stay in ICU. Their effectiveness though has been hampered by lack of rigorous design, insufficient sample size and problems with data collection [1, 2, 19]. Further research that has adequate sample size from multiple ICU's and rigorous study design is required.

4. AIMS / OBJECTIVES / HYPOTHESES

Provide a clear and concise statement of primary and secondary objectives and a clearly defined hypothesis (where relevant).

The primary objective of this study is to determine the effectiveness of introducing a nurse led delirium-prevention protocol in reducing the incidence and severity of delirium among adults admitted to intensive care. The **Primary Outcomes** of interest being: (1) incidence of delirium among adults admitted to the ICU; and (2) the number of delirium free day, while in the ICU.

Secondary Outcomes: (1) ICU and hospital mortality rates; (2) ICU length of stay; (3) Duration of mechanical ventilation; (4) among those receiving mechanical ventilation, re-intubation rates; and, (5) hospital length of stay.

Our hypothesis being that a tailored non-pharmacological approach to prevent delirium among adults admitted to intensive care will significantly reduce the incidence and duration

of delirium. Consequently, longer-term use of this protocol should reduce the length of stay within the ICU and hospital, and the risk of in-hospital mortality.

5. PARTICIPATING SITES

The intervention will be implemented across SWSLHD including the Intensive care/ High dependency units (average no. of monthly admissions):

1. Liverpool Hospital, ICU (250)
2. Bankstown Hospital, ICU (120)
3. Campbelltown Hospital, ICU (120)
4. Fairfield Hospital, ICU (80)

6. RESEARCH PLAN / STUDY DESIGN

Describe the type of study, the source of participants, datasets or collections to be accessed.
Describe the sample size, sample size calculation or justification of numbers, outcome measures used.
Provide details of the linkage and analysis variables used and why they are required and what study comparisons are being made.
Describe the process of how records are linked and whether the datasets are held in the CHeReL Master Linkage key.
Provide an analysis plan of how the aims will be met, the statistical methods to be used and who will be carrying out the analysis.
Suggested sub-headings are as follows:

6.1 Type of study (prospective study or involving access to data or data linkage as relevant)

A multicentre stepped wedge cluster randomized controlled trial will be used [11, 20, 21]. Four Intensive Care Units from the SWSLHD will participate. A cluster stepped wedge design was chosen due to the risk associated with randomization at the patient level may result in contamination between patients in the intervention group and patients in the control group [11]. This contamination could possibly result in a diluted effect of the program including risk for a false-negative outcome. Importantly, based on current evidence these

interventions have demonstrated their safety and effectiveness [2], so therefore 'de-implementation' of the intervention at the end of the study is not required.

At baseline, all ICUs will simultaneously start with the control period. The order in which an ICU will move to the intervention period will be randomized. Every month the intervention will be implemented in an additional ICU. From that point on the intervention will be part of the standard care in that ICU. In each ICU two months of staff training will be provided, after which the ICU moves from control to intervention (Fig. 1). All of the ICU's will participate for the entire study period.

Figure 1 Timeline and Randomisation.

	Study period (months)											
Study Site	1	2	3	4	5	6	7	8	9	10	11	12
1	C	C	C	T	I	I	I	I	I	I	I	I
2	C	C	C	C	T	I	I	I	I	I	I	I
3	C	C	C	C	C	T	I	I	I	I	I	I
4	C	C	C	C	C	C	T	I	I	I	I	I

Note: C = control; T = training, and, I = intervention periods.

6.2 Data sources/Collection

Cognitive Screening

Cognitive screening will involve overall assessment of consciousness, which involves two steps. Firstly, assessment of level of consciousness is done using the Richmond Agitation-

Sedation Scale (RAAS) [22]. This scale is currently used as standard practice in most ICU's. For patients who are in a coma or stupor (RAAS -4 or -5) do not undergo further assessment and referred to as 'unable to assess'. Those who are rousable (RAAS -3 or greater) go on for delirium assessment.

The second step involves delirium assessment and requires assessment of 'content of consciousness. This is done by the Confusion Assessment Method (CAM)-ICU. The CAM-ICU has been validated as a rapid, reliable (kappa = 0.96; 95%CI 0.91-0.99) and valid (sensitivity 93% and specificity 98%) tool for diagnosing delirium in the Intensive Care Unit setting [23]. The CAM-ICU will be the assessment tool that will be used throughout the study in all ICUs.

The CAM-ICU and RAAS (see appendix 2) will be collected each shift by the bedside nurse - this screening is part of routine ICU care. Patients will be diagnosed as delirious when they have at least one positive delirium screening (confusion assessment method (CAM)-ICU) [23] during their complete ICU stay or when they are treated for delirium with haloperidol (without a positive CAM-ICU screening). The duration of delirium is defined as time from the first positive CAM-ICU or treatment with haloperidol, until the beginning of two consecutive days of negative delirium screenings. A delirium-coma-free day is defined as a nondelirious day with a RASS greater than -3/-4 or -5.

Nurse led delirium prevention protocol

The intervention will incorporate a nurse led delirium prevention protocol, targeting risk factors for delirium: (1) visual and hearing impairment - nurses will ensure glasses, or hearing aids are used among patients when needed; (2) to prevent and treat sensory deprivation,

cognitive impairment, and loss of orientation - all patients will be re-orientated to place, person, and time; (3) Sleep deprivation will be minimised, and avoided where possible; and, (4) lack of mobility - staff will attempt to improve functional mobility while in the intensive care, and stimulate cognition.

Patient Characteristics

The baseline characteristics are incidentally collected and part of the ANZICS database by administration officers in each Intensive Care Unit.

The following patient characteristics will be retrieved:

Date and time of admission	Admission source	Admission source
Age	Mechanical ventilation	Comorbidities
Sex	Duration of MV	SOFA score
DOB	Reason for admission	Discharge status
APACHE II-III	Principle diagnosis	Length of stay (ICU and Hospital)

Primary Outcomes of Interest

Incidence of delirium and delirium-coma-free days will be calculated from the CAM-ICU. The duration of delirium is defined as time from the first positive CAM-ICU or treatment with haloperidol, until the beginning of two consecutive days of negative delirium screenings. For ICU patients this is defined as a negative CAM-ICU screening. Reoccurrence of delirium, defined as a new delirium episode occurring after a minimum of 48 h of negative delirium scores, will be documented. Delirium-coma-free days is defined as the number of days a patient is not delirious and not in coma in 28 days starting from the day of inclusion in the study. A delirium-coma-free day is defined as a non-delirious day with a RASS [22] greater than -3/-4 or -5.

Secondary outcomes measures

- Mortality

ICU and hospital mortality will be collected from ANZICS database.

The following variables will be extracted from the ANZICS database:

- ICU length of stay
- Hospital length of stay
- duration of mechanical ventilation
- incidence of re-intubation or restart of mechanical ventilation in case of tracheostomy patients
- incidence of ICU re-admission
- *unplanned removal of tubes/catheters*
- *the use of physical restraints*
- *the use of antipsychotics/benzodiazipines*

Add data collection point to CAM-ICU form

6.3 Population/Sample size

The sample size of the study is based on the two main outcomes of interest: (1) a clinically relevant effect on the incidence of delirium; and, (2) a reduction in the number of delirium-coma-free days. The Delirium-Prevention Nursing Protocol is considered to be effective if the incidence of delirium is reduced by 10% (30% to 20%) [2, 18], four clusters of 50 patient admission each month, before and after the intervention will provide a power of greater than 0.85, and this sample size will have over 0.9 power to detect a reduction of delirium free days by 2 (22 versus 20, among control and intervention periods, respectively). All Type I error rates set at 0.05 [21, 24]. The four ICUs are participating in the study currently admit between 80 and 250 (largest ICU) patients each month (average 120 admission each month).

6.4 Expected duration of study and start times

The study is expected to run for 12-months, beginning March 2019.

6.5 Text and Flow chart of data linkage process*

Not applicable.

6.6 Statistical analysis

Characteristics of adult patients admitted to prior, and post implementation of the nurse-led delirium protocol will be presented as descriptive statistics. All outcomes of interest will be assessed using 'intention to treat' analysis. Binary and continuous outcomes will be compared between pre- and post-intervention period using logistic or linear mixed models, clustered at the ICU level [21].

7. ETHICAL CONSIDERATIONS

Provide information on where, when, how participants will be recruited, what the inclusion /exclusion criteria are. Identify and justify any dual relationships, coercion or inducement.
Describe how voluntary informed consent will be sought or if a waiver of consent is being sought. Identify and justify any waiver of consent.
Describe how confidentiality, anonymity and the identity of participants will be maintained, who is undertaking the data linkage, whether identifying information will be provided to researchers and a rationale for this.
What security steps are in place for the transfer of data, where and how the data will be stored.
Identify and justify any non-negligible risk or burden.
Suggested sub-headings are as follows:

7.1 Recruitment and selection of participants*

All patients admitted to the ICU who meet the eligibility criteria will undergo cognitive assessment and be screened for their risk for delirium as part of standard care and receive the Delirium-Prevention Nursing Protocol.

Assignment of interventions

The Delirium-Prevention Nursing Protocol used in this study will become standard treatment in all participating ICUs upon entering the intervention phase. These ICUs will be assigned to the intervention based on cluster randomisation, following a 3-month baseline period, each month for 4-months a study site will be randomised to the commence the teach and then intervention period (Figure 1). After 7-months of the study all study sights be have taken up the intervention, and remain so until the end of 12-month study period.

7.1.1 Inclusion and exclusion criteria

Inclusion criteria

- Aged 18+ years
- RAAS > -3 s
- Expected to survive, or stay more than 24-hours

Exclusion criteria

- Delirious on admission
- Stay < 24 hours
- if reliable assessment for delirium is not possible due to sustained coma during complete ICU stay defined as Richmond agitation sedation score (RASS) of -4 to -5
- inability to understand English
- severely mentally disabled
- serious receptive aphasia

7.2 Informed consent

A waiver for individual consent is being sought. As this study is a cluster-randomised trial-hence allocation to the intervention will be as a "cluster" rather than at the level of the individual patient; therefore consent to the interventions cannot occur at an individual level [25]. Equally, because the intervention in a cluster trial, and delivered at a unit rather than an individual level, there is little or no scope for any patient to opt out without jeopardising the internal validity of the study [26]. In addition, the nature of the intervention constitutes that of *good quality nursing care,* and will become standard care within the participating ICUs in

the LHD, and carries no risk to participants. Therefore, the benefits from the research justify any risk of harm associated with not seeking consent. We believe that even if the participants were asked there is no known or likely reason for thinking that participants would not have consented anyway.

Data collection for this study includes data that is routinely collected. All patient data outcomes will be collected from the ANZICS database. As we will be using data that is routinely collected, a waiver for use of patient information is also being sought.

All patients and their families (next of kin) upon admission to the ICU will be provided with information regarding the research project. This information will detail the nursing delirium prevention protocol. Empowering family members to be active participants in this project will be instrumental to its success. The role of the families will be pivotal to this project, for example by telling the time of day and date, assisting in maintaining a day/night routine, and participating in normal activities with the patient such as reading the newspaper.

7.3 Confidentiality and Privacy

Confidentiality and privacy of study participants, and study sites will be ensured through various steps, namely: (1) study participant data will be limited to that needed to address the main hypothesis of the study (see data collection for specifics), identifying data that will be collected will be limited to Medical Record Number (MRN), date of birth (for calculation of age), and sex of study participants; (2) specific data collection forms that will be used at each site to collect data will remain at the site; (3) all study data will be placed in password protected study specific database (residing on the SWSLHD network); (4) when reporting the results of the study, specific study participants, and study sites will not be identified; and, (5) access to study data will be limited to the research team (listed in this ethics application, all of whom are employees of the SWSLHD).

7.4 Data storage and Record retention

As mentioned above, all study data will be entered into a password protected database, that will reside on the SWSLHD network. Hardcopy data collection forms will remain at the specific study site in a locked filing cabinet in the ICU department. In accordance with SWSLHS HREC guidelines study data will be retained for 7-years. And, study data will be destroyed as recommend by the SWSLHD HREC.

** To help the reader understand complex studies, it is very often useful to include a flow chart illustrating exactly what happens (and when) to participants as they pass through recruitment, consent and follow-up.*

8. OUTCOMES AND SIGNIFICANCE

The current outcomes of patients who experience delirium in ICU are poor; associated with high mortality, extended hospital stays and poor cognitive function at hospital discharge. A significant proportion of ICU patients, at least 30% will experience delirium during their ICU stay. The frequency of occurrence in combination with poor outcomes makes improving care of these patients a nursing imperative.

The prevention of delirium, early detection through regular assessment, and prompt interventions are essential components of delirium management. This study aims to deliver multi-component tailored intervention that will improve the outcomes and quality of care to patients who have delirium. The interventions include; regular cognitive assessment and with orientation, assessing and correcting visual and auditory function, ensuring nutritional needs are met, night time routine, early mobilisation/ambulation, avoiding when administering medications, such as anti-cholinergic, narcotic, and/or sedative hypnotic drugs, monitor for signs of infection, limiting urinary catheter use, avoid hypoxia and controlling pain. Implementation of non-pharmacological multi-component interventions have shown to reduce the risk of in-hospital mortality, length of stay and incidence of delirium. This highlights the importance of the role of nurses in the care of patients as bedside healthcare providers

responsible for 24-h patient care, nurses may be situated to prevent delirium, perform early delirium detection, and provide early intervention.

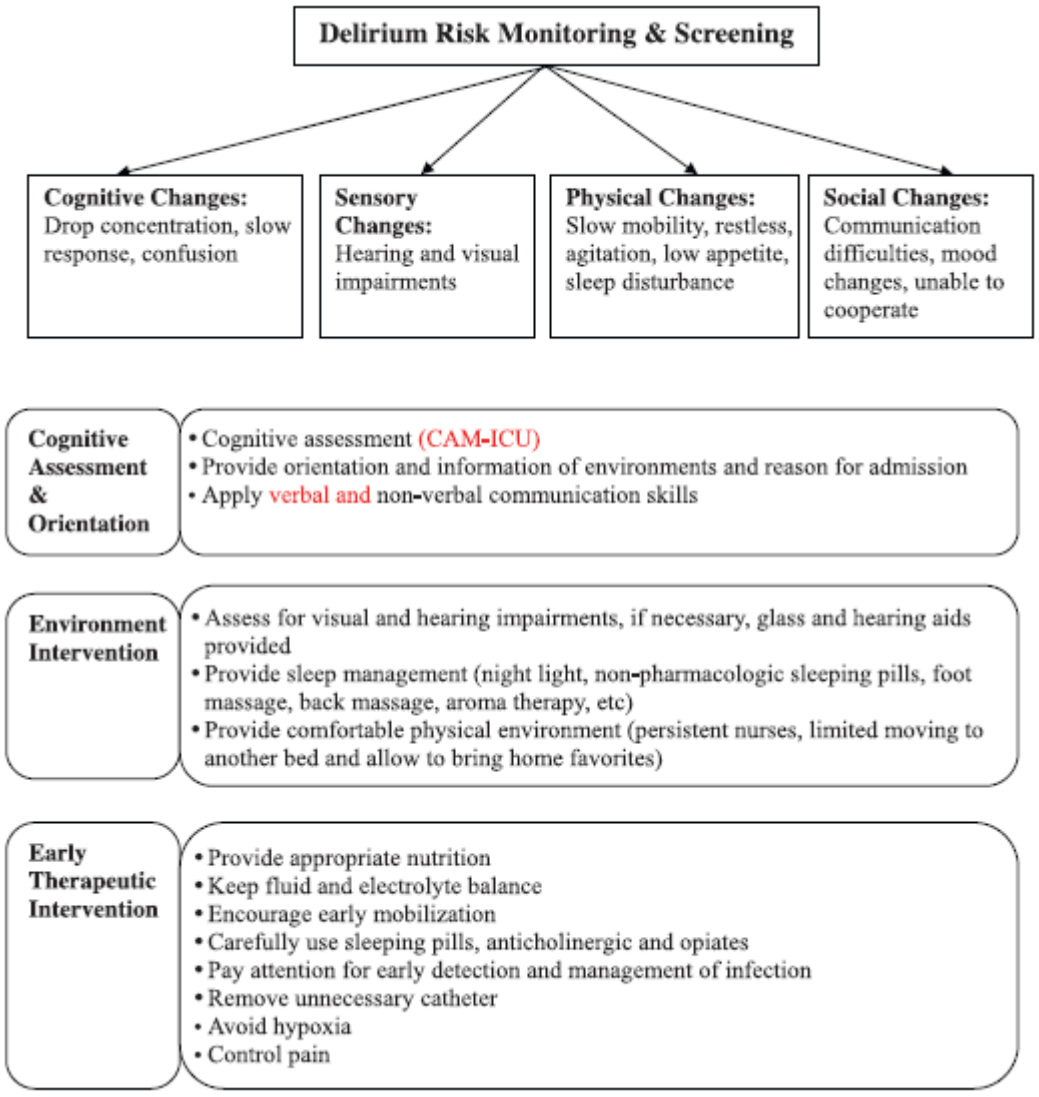
9. TIMELINES / MILESTONES

November to December 2017	Successful Ethics approval, and finalisation of training material for nurse-led delirium intervention
January to December 2018	All sites begin as controls, all patients admitted to ICU's undergo cognitive assessment
March 2019	Each Study site enters training phase (1-month) and then intervention phase
April to December 2020	Analysis of data and preparation of manuscript for publication.

10. PUBLICATION POLICY

APPENDIX 1- THE DELIRIUM PREVENTION PROTOCOL

Delirium Risk monitoring and key interventions (from Moon and Lee, 2015)



APPENDIX 2

Assessing Consciousness: Linking Level of Consciousness & Delirium Monitoring

Step 1 Level of Consciousness: RASS*

Scale	Label	Description	
+4	COMBATIVE	Combative, violent, immediate danger to staff	
+3	VERY AGITATED	Pulls to remove tubes or catheters; aggressive	
+2	AGITATED	Frequent non-purposeful movement, fights ventilator	
+1	RESTLESS	Anxious, apprehensive, movements not aggressive	
0	ALERT & CALM	Spontaneously pays attention to caregiver	
-1	DROWSY	Not fully alert, but has sustained awakening to voice (eye opening & contact >10 sec)	VOICE
-2	LIGHT SEDATION	Briefly awakens to voice (eyes open & contact <10 sec)	VOICE
-3	MODERATE SEDATION	Movement or eye opening to voice (no eye contact)	VOICE

If RASS is ≥ -3 proceed to CAM-ICU (Is patient CAM-ICU positive or negative?)

-4	DEEP SEDATION	No response to voice, but movement or eye opening to physical stimulation	TOUCH
-5	UNAROUSABLE	No response to voice or physical stimulation	TOUCH

If RASS is -4 or -5 → STOP (patient unconscious), RECHECK later

[3]Sessler, et al. AJRCCM 2002; 166:1338-1344.
[4]Ely, et al. JAMA 2003; 289:2983-2991.
*For RASS equivalents to other sedation-agitation scales see FAQs page 20-21.

Step 2 Content of Consciousness: CAM-ICU

Feature 1: Acute change or fluctuating course of mental status

And

Feature 2: Inattention

And

Feature 3: Altered level of consciousness

Or

Feature 4: Disorganized Thinking

[6]Inouye, et. al. Ann Intern Med 1990; 113:941-948.
[7]Ely, et. al. CCM 2001; 29:1370-1379.
[8]Ely, et. al. JAMA 2001; 286:2703-2710.

11. REFERENCES

1. Foster, J. and M. Kelly, *A pilot study to test the feasibility and effectiveness of a nonpharmacologic intervention for prevention of delirium in medical intensive care unit.* Clinical Nurse Specialist: The Journal for Advanced Nursing Practice, 2013. **27**(5): p. 231-8.
2. Moon, K.J. and S.M. Lee, *The effects of a tailored intensive care unit delirium prevention protocol: A randomized controlled trial.* Int J Nurs Stud, 2015. **52**(9): p. 1423-32.
3. Salluh, J.I., et al., *Delirium epidemiology in critical care (DECCA): an international study.* Crit Care, 2010. **14**(6): p. R210.
4. Ely, E.W., et al., *Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit.* JAMA: Journal of the American Medical Association, 2004. **291**(14): p. 1753-1762.
5. Ouimet, S., et al., *Incidence, risk factors and consequences of ICU delirium.* Intensive Care Medicine, 2007. **33**(1): p. 66-73.
6. Abelha, F.J., et al., *Outcome and quality of life in patients with postoperative delirium during an ICU stay following major surgery.* Critical Care, 2013. **17**(3): p. R257-R257.
7. Andrews, L., et al., *Delirium monitoring and patient outcomes in a general intensive care unit.* American Journal of Critical Care, 2015. **24**(1): p. 48-56.
8. Balas, M.C., et al., *Delirium in older patients in surgical intensive care units.* Journal of Nursing Scholarship, 2007. **39**(2): p. 147-154.
9. Hideaki, S., et al., *Severity of delirium in the ICU is associated with short term cognitive impairment. A prospective cohort study.* Intensive & Critical Care Nursing, 2015. **31**(4): p. 250-257.
10. Mehta, S., et al., *Prevalence, risk factors, and outcomes of delirium in mechanically ventilated adults*.* Critical Care Medicine, 2015. **43**(3): p. 557-566.
11. Eccles, M., et al., *Research designs for studies evaluating the effectiveness of change and improvement strategies.* Quality and Safe Health Care 2003. **12**(1): p. 47-52.
12. Mohammadi, M., et al., *Cyproheptadine for the Prevention of Postoperative Delirium: A Pilot Study.* Annals of Pharmacotherapy, 2016. **50**(3): p. 180-187.
13. Bounds, M., *Effect of ABCDE bundle implementation on prevalence of delirium in intensive care unit patients.* American Journal of Critical Care, 2016. **25**(6): p. 535-544.
14. Kamdar, B.B., et al., *The effect of a quality improvement intervention on perceived sleep quality and cognition in a medical ICU.* Critical Care Medicine, 2013. **41**(3): p. 800-809.
15. Bryczkowski, S.B., et al., *Risk factors for delirium in older trauma patients admitted to the surgical intensive care unit.* Journal of Trauma & Acute Care Surgery, 2014. **77**(6): p. 944-951.
16. Caruso, P., et al., *ICU architectural design affects the delirium prevalence: a comparison between single-bed and multibed rooms*.* Critical Care Medicine, 2014. **42**(10): p. 2204-2210.
17. Barr, J., et al., *Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit.* Crit Care Med, 2013. **41**(1): p. 263-306.

18. Wassenaar, A., et al., *Multinational development and validation of an early prediction model for delirium in ICU patients.* Intensive Care Med, 2015. **41**(6): p. 1048-56.
19. Rivosecchi, R.M., et al., *The implementation of a nonpharmacologic protocol to prevent intensive care delirium.* J Crit Care, 2016. **31**(1): p. 206-11.
20. Brown, C. and R. Lilford, *The stepped wedge trial design: a systematic review.* BMC Medical Research Methodology, 2006. **6**: p. 54.
21. Hussey, M. and J. Hughes, *Design and analysis of stepped wedge cluster randomized trials.* Contemporary Clinical Trials, 2007. **28**(2): p. 182-191.
22. Sessler, C., et al., *The Richmond Agitation-Sedation Scale: vadlidity and reliability in adult intensive care unit patients.* American Journal of Respiratory and Critical Care Medicine, 2002. **166**(10): p. 1338-1344.
23. Ely, E.W., et al., *Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU).* JAMA: Journal of the American Medical Association, 2001. **286**(21): p. 2703-2746.
24. Moerbeek, M. and S. Teerenstra, *Power analysis of trials with multilevel Data.* CRC, 2015.
25. Sim, J. and A. Dawson, *Informed Consent and Cluster-Randomized Trials.* American Journal of Public Health, 2012. **102**(3): p. 480-485.
26. Giraudeau, B., et al., *Participant Informed Consent in Cluster Randomized Trials: Review.* PLOS ONE, 2012. **7**(7): p. e40436.