Melatonin for prevention of delirium in advanced cancer

TITLE:	Randomised, double-blind, placebo-controlled phase III trial of oral melatonin for the prevention of delirium in hospital in people with advanced cancer
PROTOCOL NUMBER	035/16 v 1.1
STUDY MEDICINE	Melatonin prolonged release 2mg, oral Placebo, oral
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DATE OF PROTOCOL	29th September 2016
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Confidentiality Statement

Information in this protocol should not be disclosed, other than to those involved in the execution or ethical review of the study, without written authorisation from the Palliative Care Clinical Studies Collaborative.

Regulatory Statement

All study procedures will be conducted within ICH GCP guidelines (TGA annotated version) and all other regulatory requirements.

Protocol Preparation

This protocol has been prepared in conformance of the CONSORT Guidelines[Error! Reference source not found.] and Jadad scores.[Error! Reference source not found.] It complies with Guidelines for Good Clinical Practice in clinical research.[Error! Reference source not found.]

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1.0	25/06/2016	Meera Agar	New protocol from draft
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Protocol Approval			
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1.0	25/06/2016	Meera Agar	
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TRIAL SUMMARY

Background:

Delirium is a highly prevalent, medical emergency in advanced cancer. Despite being preventable in many cases, two thirds of people with advanced cancer will have a delirium episode at some point whilst in hospital. Delirium causes additional medical complications, excess mortality, high levels of patient and caregiver distress, and significant increases in health care costs. Delirium adversely affects cognition, awareness and communication ability at a critical time when being mentally aware and interacting with loved ones is crucial for quality of life.

Recent randomised controlled trial (RCT) data has demonstrated that pharmacological therapy with antipsychotics has limited success in managing symptoms of delirium in palliative care patients once they occur. Hence, we believe the urgent priority in advanced cancer should be on delirium prevention, given the wide reaching improvements in health outcomes that could be achieved. Delirium prevention strategies include complex multicomponent non-pharmacological interventions; however the inclusion of cognitive and exercise based strategies make adherence unachievable for many advanced cancer patients suffering fatigue and functional decline.

Alternative strategies for preventing delirium in advanced cancer are therefore needed, with robust evaluation via RCTs. A supplemental pharmacological approach with an acceptable adverse effect profile is an attractive alternative; and melatonin shows particular promise. Clinical and laboratory data identify low melatonin levels and circadian desynchrony in delirium, and 3 RCTs have demonstrated support for melatonin as a safe preventative agent in the hospitalised elderly. The team completed a phase II RCT (n=30) and established feasibility of trial methods and demonstrated potential for increase in delirium-free days and lower delirium incidence rate.

Study design:

A prospective, randomised, double-blind, placebo-controlled parallel-arm, multicentre phase III trial of oral prolonged release melatonin 2mg versus placebo taken each night during inpatient oncology or palliative care admission.

Objectives:

The **primary objective** is to determine if oral prolonged release melatonin compared to placebo can increase the number of delirium-free days during hospitalisation for advanced cancer patients.

Secondary objectives are to determine if oral prolonged release melatonin can:

1. reduce delirium severity and duration for those who develop a delirium episode;
2. reduce delirium incidence;
3. cause adverse effects, in particular sedation;
4. positively influence adverse events associated with delirium episodes, including:

i. length of hospital stay and inpatient resource utilisation;
ii. benzodiazepine and antipsychotic use (delirium or non-delirium indication);
iii. in-hospital complications (pressure areas, falls, thromboembolism, pneumonia, functional decline);
iv. days spent in coma and survival;
v. Patient and family distress;

5. provide other symptom benefits in the form of improved sleep quality.

Treatment schedule: Oral melatonin prolonged release (2mg) or placebo taken at 2000 hours. Intervention will be commenced within 48 hours of admission and continued until delirium occurrence, discharge or three weeks if patient remains in hospital (e.g. while awaiting long-term care placement) after any acute medical issues imparting a delirium risk have been resolved.

Assessments: Delirium Rating Scale – Revised – 98 (DRS-R-98);[1] Nursing Delirium Screening Scale (NuDESC);[2] Delirium Etiology Checklist (DEC);[3] Short Blessed Test (SBT);[4] Insomnia Severity Index (ISI); [5] Charlson Comorbidity Index;[6] Richmond Agitation-Sedation Scale (RASS);[7]; EQ-5D-5L[8], Australian Karnofsky Performance Status (AKPS);[9] 15ml blood will be drawn at baseline and any delirium events.

Definition of response: no delirium defined as DR-R-98 [1] (total score <17.75) for entire admission.

Primary endpoint: Delirium-free days (which occur before delirium onset for any participant who develops delirium).

Analysis: Intention-to-treat analysis will be used for all statistical comparisons. For the primary outcome, comparisons between groups for delirium-free days, with adjustment to the length of stay and other potential covariates using a general linear model approach will be undertaken. For the secondary outcomes, time-to-event analysis, such as survival analysis will be used to determine differences in time to first episode of delirium. Delirium precipitants, which occur at variable times and for different durations during the study period are time-dependent covariates and proportional logistic regression modelling will be used. The incidence rate of delirium, will also be calculated and compared between the treatment and control groups. Two planned interim analyses will be conducted independently and reviewed by the independent data and safety monitoring committee after about 33% and 66% of patients have been enrolled. The primary outcome and adverse events will be compared between groups with $p<0.001$ required as the threshold of stopping the trial for significant evidence of benefit or harm in either one of the treatment arms.

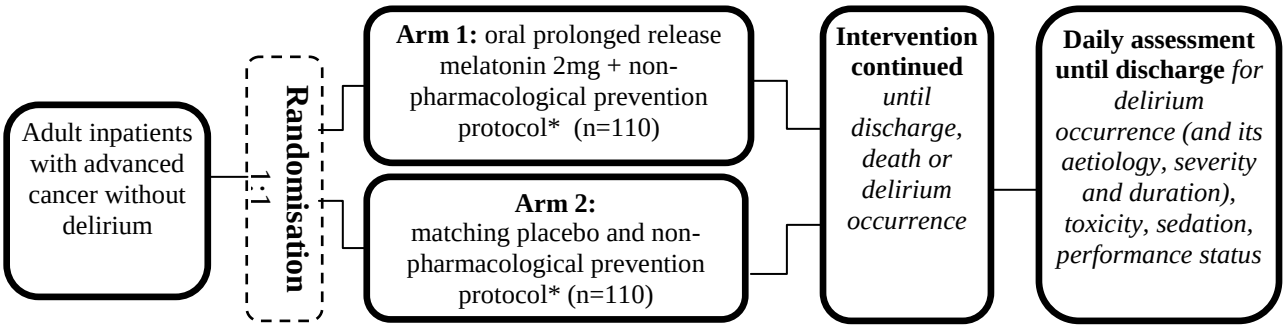
Economic analysis:
The within-study cost-effectiveness will estimate incremental costs, effects and net benefit of prolonged release melatonin relative to placebo from participant level data collected over 21 days of follow up (survival to 21 days or death whichever is shorter) for the following:

- resource use:

    - bed days spent in hospital for inpatient admissions (index admission and readmissions);
    - within-hospital resource use; health care professional time (particularly nursing time), diagnostic & investigational services;
    - professional community support utilised at home if discharged from hospital, including general practitioner and palliative care service visits,
    - concomitant medication use; and
- effects:
    - days of survival without delirium,
    - toxicity,
    - adverse events,
    - health related quality of life

Bootstrapping of patient costs and effects data will be used to model decision - making uncertainty related to the net benefit and value for money of prolonged release melatonin relative to placebo.

Study diagram



*Standardardised non-pharmacological prevention protocol in both arms: for reducing delirium risk (targeting sleep preservation, mobility, orientation and sensory deficit minimisation) and to standardise light exposure at night.

Table of study measures

	Eligibility	Baseline	Daily	Delirium occurrence	Discharge	Follow-up[#]
Investigations						
Liver function	*			*		
Electrolytes	*			*		
Full blood count	*			*		
Measures						
Medical file review						
Demographics	*					
Diagnosis	*					
Con meds	*	*	*	*	*	*
Prn medications		*	*			
Specific medications: Anticholinergics, corticosteroid and benzodiazepines CYP1A2 inhibitors (quinolones, carbamazepine, rifampicin, fluvoxamine) Warfarin		*	*	*		*
Vital signs		*	*	*		
Admission data		*				
Preventative care non-pharm measures		*	*	*		
Survival					*	*
Falls			*		*	*
Pressure areas			*		*	*
Pneumonia			*		*	*
Length of stay					*	
Health services utilisation					*	*
In hospital resource utilisation			*		*	
Patient measures						
Vision	*					
Hearing	*					
AKPS	*	*		*	*	*
Short Blessed Test		*			*	
Insomnia Severity Index		*	Every five days			
Quality of life (EQ-		*			*	*

	Eligibility	Baseline	Daily	Delirium occurrence	Discharge	Follow-up[#]
5D-5L)						
Medical assessment	*		*			
Delirium Experience Questionnaire					* (only if delirium occurred)	* (only if delirium occurred)
Clinician assessed						
Toxicity		*	*	*		*
Charlson Comorbidity Index		*				
Sedation (RASS)		*	*			
DRS- R-98	*		Daily for 7 days.	*		
NuDESC	*	*	* each shift			
Delirium Etiology Checklist		*		*		
Carer measure						
Delirium Experience Questionnaire				*		* (only if delirium occurred in participant)
Carer Experience Scale		*		*		*

[#] Measured up to death or 21 days after ceasing study medication (whichever is the shorter period) by weekly phone call.

CONTENTS

LIST OF ABBREVIATIONS

µg	microgram
AE	Adverse Event
AIN	Assistants in Nursing.
AKPS	Australia – modified Karnofsky Performance Status
AMH	Australian Medicines Handbook
BD	Twice daily
BPI	Brief Pain Inventory
BT	Breakthrough
CADSS	Clinician Assessed Dissociative States Scale
CAM	Confusion Assessment Method
CIRS	Cumulative Illness Rating Scale
CRF	Case Report Forms
DRG	Diagnosis Related Group
DRS	Delirium Rating Scale
DSM III R	Diagnostic and Statistical Manual of Mental Disorders. Third edition – revised
DSM IV R	Diagnostic and Statistical Manual of Mental Disorders. Fourth edition - revised
ECOG	Eastern Co-operative Oncology Group
EORTC-QLQ- C	European organization for Research and Treatment of Cancer- Quality of Life Questionnaire- core
EPS	extrapyramidal side effects
ESRS	Extrapyramidal Symptom Rating Scale
FACIT-PAL	Palliative care quality of life instrument used in this protocol
FDA	Food and Drug Administration
HIC	Health insurance commission
HREC	Human Research Ethics Committee
ICH GCP	International Conference on Harmonisation, Good Clinical Practice
ICU	Intensive Care Unit
ID	Identification number
IQCODE	Short informant Questionnaire on Cognitive Decline in the Elderly
IVI	Intra Venous Injection
kg	Kilogram

LANSS	Leeds Assessment of Neuropathic Symptoms and Signs
MA	Medicare Australia
MDAS	Memorial Delirium Assessment Scale
mg	milligram
ml	millilitre
N/saline	Normal saline
NCI	National Cancer Institute
NMDA	N-methyl-D-aspartate
NRS	Numeric Rating Scale
NSAID	Non steroidal anti-inflammatory drug
NuDesc	Nursing Delirium Screening Scale
O2	Oxygen
PaCCSC	Palliative Care Clinical Studies Collaborative
PBS	Pharmaceutical Benefits Scheme
PS	Performance status
QALY	Quality adjusted life years
QOL	Quality of life
QT Interval	The relationship between two conduction points on an electrocardiograph (ECG)
RASS	Richmond Agitation Sedation Scale
RCT	Randomised controlled trial
SAE	Serious Adverse Event
SC	Subcutaneous
SCN	suprachiasmatic nucleus
SOP	Standard Operating Procedure
TGA	Therapeutic Goods Administration
VAS	Visual Analogue Scale

1.0 BACKGROUND AND RATIONALE

1.1 Review of the literature

Prevalence and incidence of delirium in advanced cancer

Delirium is a complex neuropsychiatric syndrome with fluctuating symptoms and multifactorial aetiology, characterized by a disturbance in cognition, arousal and attention occurring in the presence of an underlying medical condition.[10] Delirium is associated with a spectrum of distressing symptoms (for example disorientation, sleep wake disturbance, hallucinations, delusions, agitation, paranoia, and worsening physical function).[11,12]

The prevalence of delirium in patients with advanced cancer in both oncology and palliative care settings is significantly higher than that seen in other settings, including geriatrics.[13] Delirium prevalence on admission to hospital in advanced cancer patients has been shown in several studies to range between 28% - 48%, and up to 90% in the days and hours before death.[14] The reported incidence of new episodes of delirium during admission ranges between 20% and 45%.[14,15] This means that two thirds of patients with advanced cancer may have a delirium episode at some point during an inpatient stay. The Australian Institute for Health and Welfare projected the number of deaths due to cancer in 2015 to be 46,570, so it is predicted at least 30,000 advanced cancer patients would have experienced delirium before their death.

There are multiple independent variables mediating this higher risk, such as advanced age, prior episode of delirium and cognitive impairment which all predispose to delirium in other settings; and also cancer-related factors such as hypoalbuminaemia, renal and hepatic impairment, bone and liver metastases, haematological malignancies, and use of opioids, corticosteroids and/or benzodiazepines.[16,17] On average a person with cancer and delirium will have at least three contributing precipitants for delirium at any one time.[15] When treated, delirium is reversible only in up to half of cases in advanced cancer.[15,18]

Delirium is associated with significant morbidity and mortality

Delirium is one of the most significant medical complications in advanced cancer. Work by this team has confirmed that delirium is associated with increased mortality regardless of underlying illness.[19] This risk is increased if patients receive treatment with an antipsychotic,[20] and extends after discharge even if delirium has resolved.[21,22] Even if detected and treated, delirium is associated with significant morbidity and economic cost arising from longer length of hospital stay, increased risk of functional and cognitive decline which often leads to a need for institutional care.[22,23] There is convincing evidence that people who experience delirium are aware of their symptoms and are highly distressed by the recollection of this when the delirium resolves.[24] Delirium reduces mental awareness, when being mentally aware is highly valued by people with advanced cancer.[25] Witnessing delirium is also highly distressing for families and health professionals.[24] Treatment with

antipsychotics does not offer relief of symptoms in this setting, and delirium symptoms worsen after three days of treatment with either risperidone or haloperidol compared to placebo in a recent trial completed by this group.[20] Hence to make the most impact on outcomes delirium prevention is the key.

Current strategies for delirium prevention

Pharmacological; multicomponent non-pharmacological interventions; and proactive geriatric consultation have been evaluated for their potential to reduce the risk of delirium during hospital admission in at-risk patients outside the oncology setting.[26] [27] Despite the significance of delirium in cancer, there are no studies available to inform specific guidance for the cancer setting.

Pharmacological strategies have included anticholinesterases, atypical and typical antipsychotics, tested in heterogeneous post-operative settings.[27] Comparators for these agents have been placebo or, in one study, proactive geriatric consultation.[26] Antipsychotics may reduce delirium incidence and duration[28], but further trials are necessary before clinical recommendations can be made due to heterogeneity of populations, doses and agents studied, and methodological concerns in some studies (incomplete follow-up, poor delirium case identification, underpowered).[27]

Non-pharmacological strategies (e.g. physical and cognitive exercise) for delirium prevention have been explored in eleven interventional studies.[29] A recent meta-analysis (n=4,267) of randomized or matched trials showed significant reduction in delirium incidence, with the odds of delirium 53% lower in the group receiving non-pharmacological interventions compared with controls (odds ratio 0.47, 95% confidence interval 0.38-0.58, $p<0.001$).[29] However, less than a third of the included studies were RCTs, blinding was difficult to achieve due to the nature of the interventions, and many of the included studies had small sample sizes.[29] A RCT of proactive physician-led geriatric consultations following hip fractures also showed reduced delirium incidence.[30,31]

The challenge is that 'one size' does not fit all, with components of cognitive and exercise interventions not feasible for many patients with advanced cancer, who experience high levels of fatigue and/or functional decline. Advanced cancer patients are therefore unlikely to sustain the intervention over time as cancer progresses, corresponding to the period of highest probability of delirium. A less challenging multicomponent intervention developed for advanced cancer patients failed to demonstrate a difference in the incidence of delirium between two palliative care centres that received the intervention and seven that did not.[32] There are also significant issues in translating multi-component interventions into practice that require substantive administrative changes,[33] as well as comprehensive and ongoing clinician education; with upfront additional costs estimated as AUS$800/patient (though a delirium episode can cost the healthcare system up to AUS$90K (2005 figures)).[34]

1.2 Existing evidence

Melatonin Physiology and pharmacokinetics

Melatonin (*N-acetyl-5-methoxytryptamine*) is a hormone produced by the pineal gland and secreted in response to darkness. High levels of melatonin are present at night whilst it is almost absent during the daytime. Night-time production of melatonin is driven by the hypothalamic suprachiasmatic nucleus (SCN) and a feedback system to this internal clock results in sleep onset/sleepiness. This chronobiotic property of melatonin and light/dark exposure maintains circadian rhythms and regulates the sleep–wake cycle.[35] Melatonin is metabolised from serotonin, which is derived from trypophan. [36] Tryptophan is first converted to 5 – hydroxytryptophan by tryptophan hydroxylase, and then decarboxylated to serotonin which is then metabolised to melatonin by two enzymes located in the pineal gland (arylalkylamine *N*-acetyltransferase and hydroxyindole-*O*-methyltransferase) [37]

Evidence for the role of melatonin in delirium prevention

Current theory of delirium pathophysiology: Though it was previously believed delirium was mediated by dopamine and cholinergic abnormalities alone, many neurotransmitter pathways are now implicated.[38] There are complex interactions between the circadian system and the other pathways involved in causing delirium – namely the cholinergic, dopamine, GABAergic systems and hypothalamic-pituitary-adrenal axis.[39] Inflammatory mechanisms also play a significant role in delirium, with delirium believed to be an outward expression of potentially reversible brain inflammation triggered by peripheral immune stimulation. The SCN also exerts a circadian influence on the inflammatory response via melatonin.[39]

Evidence of melatonin deficiency in delirium*:* Chemical or inflammatory processes in delirium may disrupt signalling pathways and function of the SCN and pineal gland. Changes in hepatic enzyme activity and reduced oral intake may also stimulate enterochromaffin cells to produce melatonin, contributing to raised levels occurring at the wrong time, leading to circadian desynchrony.[40-43,44,45] Tryptophan depletion also occurs in illness, which can lead to melatonin deficiency ("Tryptophan dysregulation model").[13,38,46-47] Low tryptophan levels are seen postoperatively[48], and low melatonin levels have been reported in both postoperative and intensive care units (ICU) setting where delirium is also prevalent.[42,43] Lack of circadian rhythm rise with persistently low serum melatonin levels has been reported in ICU patients with delirium.[43] Finally, it is possible that melatonin regulation is altered by psychoactive medications commonly used in palliative care. Opioids increase melatonin secretion, benzodiazepines may impair light induced phase shifts of circadian rhythms and corticosteroids have a suppressive effect.[42 39]

1.3 Rationale for intervention

Clinical evidence for efficacy of melatonin in delirium prevention:

Preliminary work supports the need to explore the role of melatonin in delirium prevention further, particularly in cancer or palliative populations where no data exist. Three investigator-led RCTs in elderly populations and a phase II RCT by this team in cancer patients demonstrate preliminary evidence for a role for melatonin in delirium prevention, with all studies showing a positive effect on preventing delirium or reducing its duration, as well as encouraging safety profile. A RCT of elderly patients admitted to hospital through emergency (n=145) found daily 0.5 mg melatonin over 14 days prevented delirium (OR 0.29 (95% CI: 0.11–0.74)).[49] Only two adverse events were reported, and neither were directly attributed to melatonin.[49]

A RCT of 300 participants aged >65 years undergoing hip arthroplasty under spinal anaesthesia randomized to one of 4 groups: Group 1 (control) received no sedation; Group 2 (melatonin) received 5 mg melatonin at bedtime and 5mg melatonin 90 minutes preoperatively; Group 3 (midazolam) received 7.5 mg midazolam 90 minutes preoperatively and Group 4 (clonidine) received 100 mcg clonidine at sleep time and another 100mcg 90 minutes preoperatively.[50] There was a significant reduction in postoperative delirium defined as Abbreviated Mental Test Score <8 in those administered melatonin (event rate 5/53 melatonin (2% of all delirium episodes) versus 16/49 control (9% of all delirium episodes)), with a non-statistically significant increase in delirium in clonidine (event rate 19/51, 11 of all delirium episodes) and midazolam (22/50, 14% of all delirium episodes) groups. Patients from any group in this RCT who developed postoperative delirium (62/300) went on to a further trial to evaluate melatonin for delirium treatment. These patients received 5 mg of melatonin at 9 pm for three successive days in a trial to treat delirium, and in this group treatment was deemed successful in 58% of cases, though the treatment success definition was not described.[50] These results are limited by a cognitive test rather than validated delirium instrument being used for the primary outcome, adverse effects not reported, being underpowered and lack of a response definition.

A RCT of melatonin (3mg for five consecutive days from 24 hours of admission) for the prevention of delirium in elderly hip fracture patients in the Netherlands (n=452), observed no effect on delirium incidence, however demonstrated a reduction in delirium duration, with fewer patients in melatonin group experiencing a delirium episode lasting for over two days (25% vs 54%, p=0.02).[51] Another near–complete Canadian study is underway of melatonin (5mg) for 5 postoperative days (n=302) in patients undergoing elective vascular or cardiac surgery (NCT01198938).

The melatonin agonist, ramelteon 8mg/day, has also shown benefit in the elderly medically unwell (n=69) with lower risk of delirium (3% compared with 32% in placebo group, p=0.003, which was still seen even after controlling for other risk factors (odds ratio 0.07, 95% CI 0.008-0.54, p=0.01)[52] Melatonin, bright light therapy

and melatonin agonists have also been used successfully to treat delirium, further supporting a benefit.[39]

Melatonin offers promising potential as a safe pharmacological agent for preventing delirium. Due to the differing baseline risk factors, multiple clinical precipitants and the higher prevalence in cancer it is important to evaluate whether similar effects are seen in this setting.

A randomised, double-blind placebo-controlled pilot phase II study[53] of oral prolonged release melatonin 2mg in hospital inpatients with advanced cancer (n=30) was conducted at five sites in New South Wales and Victoria demonstrating feasibility of ethical approval, recruitment, randomisation, study procedures and outcome measurement. Mean delirium-free days in the melatonin arm was 20.0 days (standard deviation (SD) 3.7) and control arm was 17.9 (SD 6.4) over a three week period. Five of the 20 patients (25%) developed delirium, 4 of whom were in the placebo arm and 1 in the treatment. The times to delirium from baseline were 2 (2 cases), 9 and 18 days in placebo arm and 7 days in the melatonin arm. The pilot was powered for feasibility, but demonstrated a lower incidence rate of about 4.5/1,000 population-days in melatonin. The pilot demonstrated the importance of capturing delirium events on weekends by qualified research personnel. The intervention was extremely well tolerated with only 4 adverse events unrelated to melatonin observed in the intervention arm. Inclusion criteria were refined as a direct result of this pilot (liver function criteria refined, percutaneous gastrostomies/nasogastric tubes excluded).

1.4 Conclusions and aims

This is the first trial of its kind in cancer care, aiming to prevent delirium, or reduce its duration and severity to stall the cascade of functional and cognitive decline, morbidity, mortality and resultant health care costs. Melatonin use could be rapidly translated into practice, given the formulation already has Therapeutics Goods Administration registration for another indication.

1.5 Rationale and significance

Delirium is one of the most significant medical complications in advanced cancer. Work by this team has confirmed that delirium is associated with increased mortality in advanced cancer,[19] a risk that is increased if patients receive treatment with an antipsychotic,[20] and extending after discharge even if delirium has resolved.[21,22] Even if detected and treated, delirium is associated with significant morbidity and economic cost arising from longer length of hospital stay, increased risk of functional and cognitive decline which often leads a need for institutional care.[22,23] People with cancer who experience delirium are aware of their symptoms, are highly distressed at the time and when recalling after delirium resolves.[24] Delirium reduces mental awareness, when being mentally aware is highly valued by people with advanced

cancer.[25] Witnessing delirium is also highly distressing for families and health professionals.[24] Treatment with antipsychotics does not offer relief of symptoms in this setting, with delirium symptoms worse after three days of treatment with either risperidone or haloperidol compared to placebo in a recent trial completed by this group.[20]

2.0 STUDY OBJECTIVES

2.1 Aim

The principal aim of this investigator-initiated, cooperative group trial is to determine the effectiveness of melatonin in preventing delirium; by increasing the number of delirium-free days during hospital admission, achieved by reducing overall delirium occurrence, or reducing duration and severity of delirium if it occurs.

2.2 Objectives

2.2.1 Primary objective

The primary objective is to determine if oral prolonged release melatonin when compared to placebo can increase the number of delirium-free days during a hospitalisation for advanced cancer patients.

2.2.2 Secondary objectives

Secondary objectives are to determine if oral prolonged release melatonin can:

1. reduce delirium severity and duration for those who develop a delirium episode;
2. reduce delirium incidence;
3. cause adverse effects, in particular sedation;
4. positively influence adverse events associated with delirium episodes, including:
    vi. length of hospital stay and inpatient resource utilisation;
    vii. benzodiazepine and antipsychotic use (delirium or non-delirium indication);
    viii. in-hospital complications (pressure areas, falls, thromboembolism, pneumonia, functional decline);
    ix. days spent in coma and survival;
    x. Patient and family distress;
5. provide other symptom benefits in the form of improved sleep quality.

2.3 Null Hypothesis

The null hypothesis is that oral prolonged release melatonin 2mg will not result in an increased number of delirium-free days for people with advanced cancer compared to placebo during an inpatient stay, when used in conjunction with non-pharmacological preventative strategies.

3.0 STUDY POPULATION

3.1 Target population

Adult advanced cancer patients admitted to hospital without delirium

3.2 Inclusion criteria

- Aged 18 years or older
- English speaking or availability of a health care interpreter.
- Diagnosis of advanced cancer (histological or clinical diagnosis) defined by the intent of treatment no longer being curative
- Admission to an acute or sub-acute inpatient facility
- participant is able to give fully informed written consent

3.3 Exclusion criteria

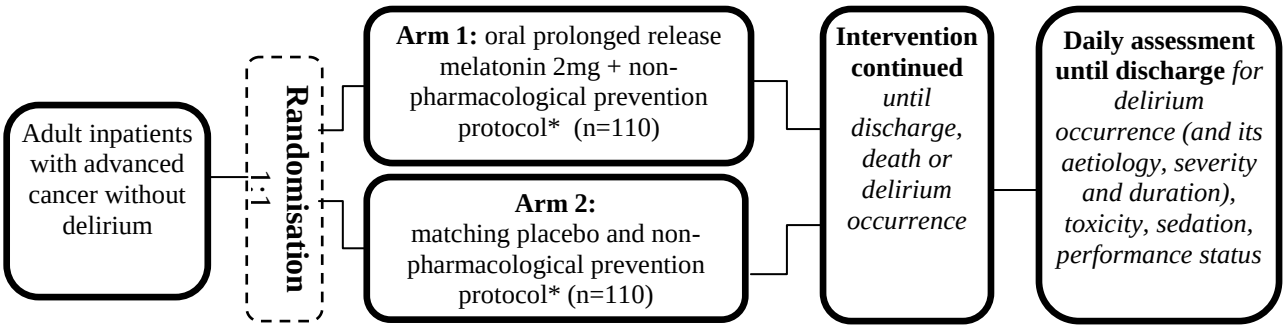
- Inability to take medications orally
- Delirium on admission as defined the cut off score on the delirium rating scale DRS-R-98[54] ≥17.75 indicative of delirium
- Australian Karnofsky Performance Status (AKPS) score less than 30 at the beginning of the study;
- A known allergy to melatonin or placebo content
- Active seizure disorder defined as seizure within last one month, or seizure disorder not on anticonvulsants
- Concomitant cimetidine use (CYP2D Inhibitor increases melatonin levels by 1.7 fold)
- Current history alcohol abuse (alcohol reduces melatonin levels);
- In people taking warfarin, a markedly nontherapeutic international normalized ratio (< 1 or > 4)
- Moderate to severe dementia as defined by clinical diagnosis of dementia and a Short Blessed Test (SBT) score of ≥10
- Severe hepatic impairment (defined as bilirubin ≥2.5 times upper limit of normal; alkaline phosphatase, aspartate transaminase and/or alanine transaminase > 3 times upper limit of normal clinically determined to be due to hepatic impairment)
- Current use of melatonin for other indication, melatonin use within last 14 days
- Currently taking agomelatine, or use of agomelatine in the past 7 days
- Pregnant or breastfeeding

4.0 INVESTIGATIONAL PLAN

4.1 Study design

A prospective, randomised, double-blind, placebo-controlled parallel-arm, multicentre phase III trial of oral prolonged release melatonin 2mg versus placebo taken each night during inpatient oncology or palliative care admission.

4.2 Study diagram



*Standardardised non-pharmacological prevention protocol in both arms: for reducing delirium risk (targeting sleep preservation, mobility, orientation and sensory deficit minimisation) and to standardise light exposure at night.

5.0 INTERVENTIONS

5.1 Study medication

Arm 1: Oral melatonin prolonged release 2mg (Neurim Pharmaceuticals Ltd) taken at 2000 +/-hours. Intervention will be commenced within 48 hours of admission and continued until delirium occurrence, discharge or for a maximum of three weeks if patient remains in hospital (e.g. while awaiting long-term care placement) after any acute medical issues imparting a delirium risk have been resolved.

Arm 2: Oral placebo tablet containing identical ingredients except the active ingredient melatonin

5.2 Dosing schedule

All study drug will be prescribed as a daily dose to be taken at 2000 (+/- one hour) of each day of the intervention period.

Rationale for dose and timing of administration:

The optimal timing of melatonin is two hours before bedtime, with this timing used in prior studies. [49 51] Doses used in prior delirium prevention studies ranged from 0.5 to 5mg. [49 50 51]

Lower doses provide sufficient increment of serum melatonin levels, and higher doses are associated with sustained daytime supra-physiological melatonin levels with a study in critical care demonstrated that a 10mg dose is excessive.[55] Oral melatonin 2mg prolonged release is the only Therapeutics Goods Administration (TGA) approved formulation in Australia, the dose proposed is within the range of prior studies. This dose and timing has demonstrated a signal of effect in our pilot phase II study.

5.3 Method of assigning participants to treatment groups

At each centre, people referred to the study will be sequentially allocated an ID number. This ID number will be used for all subsequent study documentation for that participant. The procedures outlined in the Allocation of ID number Standard Operating Procedure (*5.5.5 Allocation of ID number*) are to be followed.

Randomisation schedules will be developed for each site using random number tables, generated at an independent central registry. Randomisation will be conducted using permuted block randomization with a block size between 3 and 6. The randomization will be conducted using a computer algorithm. The central registry will supply site randomisation schedules to each site pharmacy. There will be no stratification at the randomisation level for this study.

On notification of a participant, the pharmacist at each site will consult the supplied randomization schedule and will allocate the next code available. The participant ID, allocation code, dates of request, preparation, and dispensing will be recorded in a log maintained by the pharmacist and supplied to the central registry on each randomisation.

At all times, from eligibility screening to completion of the study, all study staff are unaware of the treatment allocation. Allocation is concealed from the investigator at the time of the participant inclusion in the trial; the allocation is determined by contacting the site pharmacy.

5.4 Blinding

The study drug and placebo will be manufactured by an external facility and supplied to each site pharmacy in pre-prepared and coded bottles. Each bottle will be numbered according to the pre-determined allocation code and labeled as:

> *Study number 035/16 Melatonin prolonged release (2mg)/ placebo. Take one tablet every night at 2000 hours after food during admission.*

Treatment allocation will not be disclosed to study staff, treating clinicians or investigators. The code will only be broken in cases of extreme emergency. Such situations only include where knowledge of the code will have consequences for clinical decision making in consultation with the Lead Chief Investigator.

5.5 Method of administration

The pharmacists at the study sites will dispense the study medication. All medications must be dispensed in accordance with the delivery system used within the study site.

The intervention will be delivered at 2000 hours (±1 hour). At each dose, the individually labeled bottle will be opened and the prescribed dose taken out. The clinical nurse will observe the participant while the participant swallows the tablet whole, and then record the administration in the medicine record.

5.6 Drug accountability

All active medicine must be stored in a locked medicine cabinet at or below 25°C within the site pharmacy. The pharmacy will maintain accountability records, in addition to the study allocation records. On dispensing to the inpatient unit, the medicine will be stored within a locked medicine cabinet appropriate to state regulations. The medicine will be checked and recorded by an appropriately qualified nurse on administration to the patient.

5.7 Drug supply

The medicine will be supplied in the following manner;

1. Oral melatonin 2mg prolonged release (Neurim Pharmaceuticals Ltd)
2. Oral placebo tablet containing identical ingredients except the active ingredient melatonin (amino methacrylate co-polymer, lactose, silicon dioxide, talcum and magnesium stearate) to ensure matching taste, size, shape and colour.

5.8 Drug destruction

All unused study drug will be destroyed on completion of the study. Unused and empty bottles in the inpatient unit will be delivered back to the pharmacy, using the established practice within the hospital.

All unused bottles returned to pharmacy will be destroyed in a manner consistent with the applicable regulations governing destruction in each state. The pharmacy Standard Operating Procedures and state regulations are to be referred to and adhered to at all times.

5.9 Concurrent treatments

Trial patients are to continue their current medicine regimen. Any changes in concomitant medications must be documented in the Case Report Form.

Benzodiazepine and antipsychotic as concurrent treatments: regular use and administration of 'as required' doses of all benzodiazepine and antipsychotics will be recorded daily, including the clinical indication. This will capture whether there is a reduced need for nocturnal sedation due to concurrent melatonin use and benzodiazepines/antipsychotic administration for delirium symptoms.

5.9.1 Non-pharmacological strategies for delirium risk

Components of inpatient care that may influence delirium risk will be standardised across centres via an evidence – based non-pharmacological protocol in domains of sleep preservation, mobility, orientation and sensory deficit minimisation, for which study staff will receive training.

This will include assessment of the patient's readiness for mobility and exercise, and to encourage and coordinate passive or active range of motion exercises, sitting out of bed and/or ambulation as appropriate. The study staff will also ensure that participants who need hearing aids and glasses have them to use, sleep preservation techniques are followed where feasible for the individual participant (noise reduction, normal day night illumination, promoting comfort and relaxation), and provide reorientation conveying day, date, place and reason for hospitalisation, and having clock and calendar visible. [56]

5.10 Rescue medications

There are no specific rescue medications, however as required benzodiazepines and antipsychotics will be recorded.

5.11 Dose modification

There are no dose modifications of the study medication allowed.

5.12 Cessation of study drug

- Participant request
- Unacceptable side effects from study medications (defined by National Cancer Institute Common Criteria for Adverse Events; CTCAE version 4.0).
- Participants who in the opinion of the investigator are not well enough to continue the study (Specific reasons for withdrawal need to be documented in the Case Report Form)
- Treatment deemed ineffective by treating clinician, who wishes to use alternative therapy.
- Occurrence of delirium (completion of study)
- Can no longer swallow
- Discharge from Hospital (completion of study)
- The participant withdraws their consent, with or without consent to use already collected data.
- It is inappropriate to continue the study medication for whatever reason

5.13 Post study treatments

All participants will be followed by their clinician for continuing care, irrespective of the point at which they exit the study.

Treatment continuation: Melatonin will only be available for currently approved indications (primary insomnia) if the participants meets that indication, after study completion (on discharge). The treatment available to reduce delirium risk after discharge will be determined by the treating clinician, and can include individualised strategies to reduce risk of delirium including regular exercise as tolerated, maintaining vision and hearing or using aids, regular reorientation and non-medication methods to improve sleep (quiet room, relaxation for example).

In all study participants, regardless of above choices, secondary outcomes and collection of data for will occur until the end of the inpatient admission after randomization, unless consent is withdrawn

5.14 Follow-up

During the follow-up phase frequency of adverse events, delirium (based on medical record), quality of life, medication and health service usage will be measured up to death or 21 days after ceasing study medication (whichever is the shorter period). These data will be collected via a weekly telephone call to the participant if they have been discharged home. Carer experience will also be captured using the Carer Experience Scale.

We will record the date of death for all participants where possible, including post recruitment. The census date will be 28 days after recruitment of the last participant to the study.

Economic evaluation

Limited evidence suggests that interventions to prevent delirium or reduce its duration in hospital are cost effective,[57,58] with the majority of cost offsets from longer term care savings.[57] Estimating cost offsets over shorter time frames is crucial given advanced cancer has limited prognosis, and in prior cost-effectiveness studies, patients with terminal illness were excluded.[34] The cost-effectiveness sub-study will evaluate the within-study incremental resource use, cost and consequences of melatonin relative to placebo for preventing delirium in advanced cancer patients from randomisation to study end or death (whichever is sooner). The analysis will include efficacy (delirium-free days), toxicity, survival and resource data (intervention costs, hospital length of stay, health professional time, medication use and investigations). Sampling and parameter uncertainty will be estimated by bootstrapping on participants' costs and effect pairs to maintain covariance in re-sampling with replacement across 10,000 replicates. Cost-effectiveness acceptability curves, sensitivity and scenario analyses will be undertaken.

6.0 OUTCOMES AND MEASURES

6.1 Primary outcome and measure

Delirium-free days (which occur before delirium onset for any participant who develops delirium).

6.2 Secondary outcomes

The secondary endpoints provide a profile of delirium risk and precipitants, measure toxicities, inform the health economic analysis; and explore the collateral benefits in sleep. The severity and duration of delirium, and its impacts will be evaluated if it occurs. Days in coma will also be measured as this may occur in severe irreversible delirium prior to death. Sleep quality will require participant involvement, measured every five days only to minimize participant burden.

Delirium profile: DRS-R-98 cut off score ≥17.75 will diagnose delirium and as a continuous variable will assess severity.

Toxicity: Sedation will be rated daily by observation using the Richmond Agitation-Sedation Scale - Palliative (RASS - Pal). This has modified the intensity of verbal or physical stimuli required to avoid additional discomfort in the palliative population, and has good correlation with the original RASS (interclass correlation coefficient 0.83 – 0.98). It is 10-point scale using observation, verbal stimulation, and physical stimulation, differentiating between different potency of stimulation (verbal versus physical), and also examines constructs related to delirium (agitation, sedation, inattention as measured by eye contact). It will also assess days in coma defined as RASS-Pal score of -4 or -5.[59] Other adverse effects will be assessed using the National Cancer Institute Common Terminology Criteria. [60]

Benzodiazepine and antipsychotic use: regular use and administration of 'as required' doses of all benzodiazepine and antipsychotics will be recorded daily, including the clinical indication. This will capture whether there is a reduced need for nocturnal sedation due to concurrent melatonin use and benzodiazepines/antipsychotic administration for delirium symptoms.

Delirium risk factors: will be recorded at baseline: age (>65 and >80 years of interest), cognitive impairment defined as SBT score >4, visual impairment, presence of infection, and use of physical restraint.[26] Risk factors which have uncertain/contradictory evidence will also be collected to advance the science for future work: primary or secondary brain malignancy, benzodiazepines (oral diazepam equivalents), corticosteroids (oral dexamethasone equivalents), opioids (oral morphine equivalents), hearing impairment, comorbidities (Charlson Comorbidity Index), diagnosis of depression, use of indwelling bladder catheter, number of room/bed changes during admission, multiple medications (number of medications), and high blood urea/creatinine ratio (>18).

Delirium precipitating factors: The Delirium Etiology Checklist (DEC) will be completed at time of delirium occurrence. The DEC is a structured tool that utilizes clinical information from all sources, and then applies a weighted approach to each category of potential delirium precipitants.[3] Each category is rated as ruled out (0), present and apparently not contributory (1), present and possibly contributory (2), likely cause (3), or definite cause (4). It can document multiple concurrent causes.

In-hospital complications: Falls, pneumonia, thromboembolism, pressure areas, changes in performance status (AKPS[61]) and survival will be documented, complications which increase if delirium occurs.

Family distress (Delirium experience questionnaire): The Delirium Experience Questionnaire is a face-valid, brief instrument that assesses recall of the delirium experience and distress related to the delirium episode in patients, spouses/caregivers, and nurses, and has been used in cancer patients.[24]

Sleep quality: will be measured using the Insomnia Severity Index at baseline and every 5 days during the admission, which has established psychometric properties in cancer. The ISI is a 7-item scale that characterizes the type of sleep problem (difficulty falling asleep, staying asleep or waking up too early), and assesses impact (sleep satisfaction, associated distress and impact on others).

Inpatient resource utilisation: variables include duration of admission (days), daily medications, investigations (blood tests, imaging, urine cultures), and level of nursing required for transfers or care (independent, standby assistance, one or two assistants) and use of one to one nursing (hours).

7.0 STUDY ASSESSMENTS

7.1 Laboratory measures

Liver function tests, serum electrolytes, INR (for participants on warfarin only) and full blood count will be taken to ensure eligibility is met and at delirium occurrence to assess contributing factors to the aetiology of the delirium episode.

7.2 Medical and physical measurements

The study assessments are tabulated in *8.1 Study Procedures*. The study period will be until discharge or death.

7.3 Demographics

1. Age
2. Gender
3. Availability of primary caregiver:
    a. lives with carer;
    b. lives alone but carer available;
    c. lives with non-carer;
    d. lives alone, no carer
4. Postcode
5. Language spoken at home
6. Aboriginal or Torres Strait Islander status
7. Ethnicity

7.4 Main clinical diagnosis

The following clinical data will be collected:

i. Tumour stage
ii. Sites of metastases (especially if known cerebral metastases).

7.5 Performance status

7.5.1 Australia - modified Karnofsky Performance Status

The Australia - modified Karnofsky Performance Status is a validated variant of the Karnofsky Performance Status.[Error! Reference source not found.] The Australian version has criteria that can be applied in either the inpatient or outpatient setting, which is more appropriate to the population seen in palliative care. This objective measure has high inter-rater reliability and is sensitive to changes in function over time. A score of 0 to 100 (in increments of 10) is assigned to participants based on their ability to undertake a range of daily tasks. The score gives an indication of the participant condition (in terms of physical ability) and can assist in prognostication. The tool will be used in this study to assist

investigators to determine participant condition and possible prognosis, together with any measurable improvements in functional status as a result of the intervention.

7.6 Quality of Life

Quality of life of participants for the economic evaluation will be measured using the EQ-5D-5L™. It is a standardised instrument for use as a measure of health outcome.[8] Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status. EQ-5D-5L is primarily designed for self-completion by participants and is ideally suited for use in postal surveys, in clinics and face-to-face interviews. It is cognitively simple, taking only a few minutes to complete. Instructions to participants are included in the questionnaire.

The EQ-5D-5L will be completed at baseline, on study exit by participants and during the follow up stage.

7.7 Delirium occurrence

7.7.1 Delirium Rating Scale – Revised 98:

The Delirium Rating Scale – Revised 98 (DRS-R-98) will be used to confirm delirium presence and delirium severity. The DRS-R-98 is a 16-item scale with 13 severity and 3 diagnostic items. It has high inter-rater reliability, sensitivity and specificity for detecting delirium in mixed neuropsychiatric and other hospital populations [54]), It has also demonstrated high sensitivity and adequate internal consistency (Cronbach's alpha = 0.70) and factor validity in cancer patients [62], and has been used in palliative care inpatient populations extensively [18,63]. Each item is rated 0 (absent/normal) to 3 (severe impairment) with descriptions anchoring each severity level. Severity scale scores range from 0 to 39 with higher scores indicating more severe delirium. The DRS-R-98 can be further divided into a cognitive subscale (sum of items 9– 13: attention, orientation, short-term memory, long-term memory, visuospatial function) and a non-cognitive subscale (sum of items 1– 8: sleep-wake cycle disturbances, perceptual disturbances, delusions, thought process abnormalities, language difficulties, affective lability, psychomotor agitation, psychomotor retardation) for phenomenologic analyses. Participants will be assessed daily for delirium occurrence, risk factors and precipitants. For those who have a delirium episode: severity, duration, symptoms, time to occurrence and time to resolution from commencement of study intervention; delirium-free days after the episode and related adverse events will be assessed. For the rest of the admission DRS–R-98 will be completed every three days, and whenever daily screening with the Nursing Delirium Screening Scale (NuDESC) [2] registers a score of 2, there is a clinical suspicion or diagnosis of delirium, a potential delirium precipitant occurs, or if antipsychotic and/or benzodiazepine medications are administered for symptoms which may be due to delirium.

7.7.2 Delirium screening:

To ensure no episodes of incident delirium are missed delirium screening will occur on each of the three 8-hour shifts by the ward nurses, using the Nursing Delirium Screening Scale (NuDESC) which is a validated and highly recommended screening tool. The NuDESC is an observational five-item scale that can be completed quickly. The psychometric properties were studied in 146 consecutive hospitalized patients from a prospective cohort study, and compared NuDESC assessment by bedside nurses with 59 blinded Confusion Assessment Method (CAM) ratings made by research nurses and psychiatrists [2.]. Analysis of these data showed that the Nu-DESC is psychometrically valid and has a sensitivity and specificity of 85.7% and 86.8%, respectively [2].

7.8 Sedation

Sedation will be rated daily by observation using the Richmond Agitation-Sedation Scale (RASS-Pal). This has modified the intensity of verbal or physical stimuli required to avoid additional discomfort in the palliative population, and has good correlation with the original RASS (interclass correlation coefficient 0.83 – 0.98). It is a 10-point scale using observation, verbal stimulation, and physical stimulation, the last used only to assess the two (out of five) deepest levels of sedation. It has been selected because it gives clear descriptors for assigning scores, differentiates between different potency of stimulation (verbal versus physical), includes agitation and sedation, and also looks at constructs related to delirium (inattention as measured duration of eye contact). It will also assess days in coma defined as RASS-Pal score of -4 or -5.[59] Other adverse effects will be assessed using the National Cancer Institute Common Terminology Criteria. [60]

7.8.1 Benzodiazepine and antipsychotic use:

Regular use and administration of 'as required' doses of all benzodiazepine and antipsychotics will be recorded daily, including the clinical indication. This will capture whether there is a reduced need for nocturnal sedation due to concurrent melatonin use and benzodiazepines/antipsychotic administration for delirium symptoms.

7.8.2 Delirium risk factors:

These risk factors will be recorded at baseline: age (over 65 and over 80 years are categories of interest), prior cognitive impairment defined as defined as SBT score >4, visual impairment, presence of infection, and use of physical restraint [26]. Risk factors which have uncertain/contradictory evidence will also be collected to take the science forward for future work: cerebral primary or secondary cancer, use of benzodiazepine use (oral diazepam equivalents), corticosteroids (oral dexamethasone equivalents), opioids (oral morphine equivalents), anticholinergic load (Clinician rated anticholinergic scale [64]), hearing impairment, comorbidities (Charlson Comorbidity Index > 3 [6] diagnosis of depression from medical record, presence of indwelling bladder catheter, multiple medications (number of medications at baseline), and high blood urea to creatinine ratio (above 18).[26,65] The number of room /bed changes during the admission will be recorded [26].

7.8.3 Delirium precipitating factors:

The delirium etiology checklist (DEC) will be completed at time of incident delirium, in conjunction with the participants treating physician. The DEC is a structured tool that utilizes clinical information from all sources, and then applies a weighted approach to each category of potential delirium precipitants.[3] Each category is rated by treating physician as ruled out (0), present and apparently not contributory (1), present and possibly contributory (2), likely cause (3), and definite cause (4). It can document multiple concurrent causes of delirium, which is important in cancer patients where the average number of precipitants is 3 or more.[15] This checklist will also be completed during the study period if new precipitants are identified. Day of resolution of prior precipitant will also be recorded. If a new potential precipitating factor occurs after day 7 of the study period the DRS-R-98 will be re-administered.

7.8.4 Sleep quality:

Sleep quality will be measured using the Insomnia Severity Index (ISI) at every 5 days during admission, which has established psychometric properties in cancer. The ISI is a 7 item scale which characterizes the type of sleep problem (difficulty falling asleep, staying asleep or waking up too early), and assesses impact (sleep satisfaction, associated distress and impact on others).[5] The psychometric properties of the ISI in cancer patients are well established, with a cut-off of 8 having optimal sensitivity and specificity.

7.8.5 Inpatient resource utilization:

Variables include duration of admission (days), daily medications, investigations (blood tests, imaging, urine cultures), and level of nursing required for transfers or care (independent, standby assistance, one or two assistants) and use of one to one nursing (hours).

7.8.6 Carer assessments

The Carer Experience Scale[66] will be used to evaluate carer experience to inform the economic analysis, given the important impact delirium occurrence has on carers. This scale is a brief instrument, and has been validated in palliative care informal carers[67], and the responses can be used to calculate a 'QALY-type' measure. This will be measured at baseline, delirium occurrence if it occurs and at followup.

The Delirium Experience Questionnaire (DEQ) is a face-valid, brief instrument that assesses recall of the delirium experience and the degree of distress related to the delirium episode in patients, spouses/caregivers, and nurses. [68] It has been used to describe delirium experience in 154 hospitalised cancer patients, however its psychometric properties have

not been established. There is however no other available instrument to measure distress hence it has been chosen for this study. The scale consists of several yes/no questions plus two five point Likert scale questions (for the patient), one Likert scale question for the carer and nurse versions, as well as an open question in each version to allow qualitative analysis of the experience.

The carer version will be utilized at delirium occurrence and in followup (for those participants where delirium occurred) and for participants in followup if delirium occurred and has now resolved.

7.9 Safety assessment

Safety assessments are made at all participant contacts as described earlier. All safety assessments are made before efficacy assessments. If burden, side effects or safety issues are identified, continuation in the study will be stopped.

In the event of an adverse event clinicians will manage the event according to best medical practice.

Further, the research nurse who visits the participants and their carers will also ask about any other unexpected adverse outcomes. The study investigators will oversee this research nurse. All serious adverse events will be reported to the Research and Ethics Committee within 24 hours (see section *9.0 Adverse Events*). Other adverse events will be described in the Annual Report to the Committee.

Serious adverse events will be followed until documentation of resolution or the successful initiation of relevant management strategies.

7.10 Assessments for economic analysis

Economic analyses undertaken alongside clinical trials as part of processes of health technology assessment have the potential to improve and enrich evidence-based decision making in at least three ways:

- consider current uncertainty (net clinical benefit and net benefit) in decision making to inform optimal (efficient) trial design;
- provide evidence of relative joint effects and resource use of alternative approaches to participant care in defined participant populations;
- translate evidence of effects and resource use to model impacts on practice, and absolute incremental costs and outcomes from policy making in a given jurisdiction given current practice, population, prices and incentives.

Each of these forms of economic analyses are planned to be used to aid the melatonin randomised control trial in improving evidence based decision making for palliative care participant populations in Australia.

Life-time estimates of incremental costs and consequences of increasing delirium-free days, weeks of survival, weeks of survival out of institutional care at home) will also estimated based on data collected on survival, medications (hospital formulary use) and length of stay within hospital, and extrapolating resource use conditional on events and management

within trial and consequent expected patterns of care beyond trial where necessary. Sensitivity analysis will be undertaken on ranges of uncertainty of treatment effect observed within trial, and in varying assumptions made to extrapolate observed treatment effects beyond the follow-up period. Estimates of within trial and lifetime cost effectiveness will also be undertaken in sub-groups of participants by major risks factors.

In informing decision making in bodies such as the Pharmaceutical Benefit Advisory Committee it is important to establish evidence on the relative effects on health care resource use, costs (preparation administration and follow up effects) and consequences (time in hospital, home and other, side effects) of the expected use of melatonin in practice in palliative care populations.

Decision trees are useful in systematically formalising practice patterns and their expected costs and outcomes in defined participant populations, both currently and how this is expected to change with new strategies. In considering management of participants with cancer related pain in a palliative care setting decision makers and stakeholders for current practice include: the participant; the clinician(s); the carer; hospital formularies and the Pharmaceutical Benefit Advisory Committee. Current practice varies across institutions and prescribers. Understanding the factors that determine current practice will allow better use to be made of strategies to change current practice as a consequence of the trial evidence and any changes in funding that might follow. For example, if the evidence from the clinical trial suggests that melatonin is no more effective than standard therapy and placebo alone, it is likely to change current practice by clinicians who currently prescribe melatonin. Alternatively, if melatonin is shown to be effective and cost effective, practice within hospitals will change with substantial additional cost to hospitals in its delivery. Furthermore, if melatonin is shown to prevent delirium or increase delirium free days, by reducing the delirium, will this impact on total length of hospital stay. It is also possible that improved management of delirium, having presented to hospital will increase the participants' ability to move to care at home. Finally, if melatonin is shown to be effective in prevention of delirium or increasing delirium free days would expected incremental benefits (cost and outcome) from administration outside of hospital (in the community) be greater than incremental costs from increased risk of use off licence?

The main objective of the health economics study is to determine the incremental costs and consequences of melatonin relative to placebo prevention of delirium in patients with advanced cancer in hospital. This will be accomplished by:

- estimating the effectiveness of melatonin compared to placebo in terms of increasing delirium-free days without diminished survival time and time spent out of institutional care (at home).
- estimating the resource usage associated with melatonin compared to placebo;
- a within-trial analyses will estimate the incremental costs, effects and cost-effectiveness (incremental cost per additional delirium-free day) of melatonin (compared with placebo) over the 21 days of the efficacy study.

Palliative care has multiple domains of effect, such as symptom management, psycho-social support and care giver effects, which should be jointly considered alongside health related quality of life, in comparing alternative palliative care strategies. Consideration by decision

makers of the incremental costs and effects of alternative palliative care strategies therefore requires a robust framework for comparing costs and multiple effects of care.

Using current conventional methods such cost consequences analysis has been restricted in allowing for the interaction of consequences and their joint consideration under uncertainty.[Error! Reference source not found.] This restriction has been primarily a result of the inability to consider more than one effect in comparing strategies on the incremental cost effectiveness plane. The absence of radial properties on the incremental cost effectiveness plane (performance not improving in contracting to a vertex) results in comparison being restricted to cost and one generic measure of effect framed from a utility bearing perspective (survival, reduction in morbidity, life years, Quality Adjusted Life Years).

However, Eckermann[Error! Reference source not found.] and Eckermann, Briggs and Willan[Error! Reference source not found.,Error! Reference source not found.] have demonstrated that reframing effects from a disutility perspective (mortality, morbidity, reduction in life years or QALYs) and comparing strategies on the cost-disutility plane does allow radial properties. Hence the cost-disutility plane can, for example, consider the interaction and uncertainty between participant symptoms, participant functioning, side effects of strategies, psychosocial effects on the participant and family of place of care and care giver burden. The cost disutility plane allows natural and intuitive modeling of the interaction between such multiple effects as well as consideration of decisions region across multiple effects over which a strategy is preferred.

In practice, evidence will be prospectively collected from participants in each arm of the study on costs and consequences of participant symptom relief, functioning, capabilities and psychosocial support in the defined palliative care population of interest, as described in sections 1 and 2. These participant level data allows within trial modeling using bootstrapping methods[Error! Reference source not found.] of replicates for costs and consequences of strategies with multiple outcomes, allowing for covariance between costs and effects. Chance differences in prognostic factors can be minimised in linking replicates comparing strategies following Eckermann and Kirby.[Error! Reference source not found.] Such bootstrapped distributions for costs and consequences across strategies can then be mapped onto the cost-disutility plane to compare strategies and inform decision making.

Mapping distributions on the cost disutility plane allows natural use of efficiency methods in comparing multiple strategies with multiple outcomes under uncertainty[Error! Reference source not found.] at all potential relative decision making values for consequences. Consequently, following Eckermann, Briggs and Willan[Error! Reference source not found.] the net loss acceptability frontier can be estimated to simultaneously identify at potential threshold values for effects:

- which strategy maximises expected net benefit across the distribution of incremental net benefit
- the expected potential value of future research.

This best informs joint policy questions of whether to reimburse and whether further research is required.[Error! Reference source not found.,Error! Reference source not found.]

8.0 STUDY PROCEDURES

8.1 Table of study measures

	Eligibility	Baseline	Daily	Delirium occurrence	Discharge	Follow-up[#]
Investigations						
Liver function	*			*		
Electrolytes	*			*		
Full blood count	*			*		
Measures						
Medical file review						
Demographics	*					
Diagnosis	*					
Con meds	*	*	*	*	*	*
Prn medications		*	*			
Specific medications: Anticholinergics, corticosteroid and benzodiazepines CYP1A2 inhibitors (quinolones, carbamazepine, rifampicin, fluvoxamine) Warfarin		*	*	*		*
Vital signs		*	*	*		
Admission data		*				
Preventative care non-pharmacological measures		*	*	*		
Survival					*	*
Falls			*		*	*
Pressure areas			*		*	*
Pneumonia			*		*	*
Length of stay					*	
Health services utilisation					*	*
In hospital resource utilisation			*		*	
Patient measures						
Vision	*					
Hearing	*					

	Eligibility	Baseline	Daily	Delirium occurrence	Discharge	Follow-up[#]
AKPS	*	*		*	*	*
Short Blessed Test		*			*	
Insomnia Severity Index		*	Every five days			
Quality of life (EQ-5D-5L)		*			*	*
Medical assessment	*		*			
Delirium Experience Questionnaire					* (only if delirium occurred)	* (only if delirium occurred)
Clinician assessed						
Toxicity		*	*	*		*
Charlson Comorbidity Index		*				
Sedation (RASS)		*	*			
DRS- R-98	*		Daily for 7 days.	*		
NuDESC	*	*	* each shift			
Delirium Etiology Checklist		*		*		
Carer measure						
Delirium Experience Questions				*		* (only if delirium occurred in participant)
Carer Experience Scale		*		*		*

[#] Measured up to death or 21 days after ceasing study medication (whichever is the shorter period) by weekly phone call.

8.2 Referrals

All people with advanced cancer admitted to hospital can be referred to the study. The study nurse will ask the consultant in charge for permission to approach potentially eligible participants. This referral will be recorded within both the Case Report Form and the participant's clinical file.

8.3 Consent process

Obtaining consent for this study will be a process of information exchange between the study staff, the potential participant and any other person the potential participant believes should be included in the discussion. The participant information sheet will be used as a basis for the discussion, which will cover all procedures, benefits, burdens and side effects expected of possible during the study. The participant will be given opportunity (in time and physical capacity) to consider the study and formulate questions. Any questions will be addressed and answered fully.

Prior to study commencement, during the site initiation visit, the study nurse, site coordinator and the investigator will be trained in consent procedures for this study, with the opportunity to role play scenarios and develop a consent script to ensure all information is fully covered. The consent form is completed by the study nurse in accordance with the requirements of the institutional ethics committee. The form is signed and dated by the participant in front of the witness. The witness can be anyone who observes the participant signing the consent form, and is able to say that the participant was signing of their own free will, but cannot be the researcher.

The completed consent form is copied (at the time of signing or on return to the study office)

- one copy is to be given to the patient
- one copy is to be inserted into the medical file (with research sticker on file if required)
- one copy is to be filed in study file.

8.4 Screening for eligibility

A Participant Master Index (an excel file to track participant names, ID numbers, and progress through the study, developed and maintained at each site) will be kept of all potentially eligible participants including the reasons for non-entry. Participants suitable for entry who are approached about the study and who have given consent for the study nurse to obtain information about them, will undergo a review of eligibility criteria and complete the eligibility screening as per the Eligibility Case Report Form

- Some items will be obtained while in discussion with the potential participant
- Specific items will require intervention or assessments that are specific for the purposes of research and can only be completed after specific consent to participate in the study has been obtained
    - those items are to be left until it appears that the person is likely to be eligible
    - obtain consent prior to conducting the interventional assessments
- Other items will be completed by referring to the person's clinical file or medical record
- The plan of management will be checked with treating team (ie ensure no planned or likely change in management during the study period)

The completed Case Report Form will be discussed with the Site Investigator. The CRF will be entered into the online data base to enable the Project Officer at the coordinating centre to monitor eligibility of those enrolled in the study and cross reference with the randomisation process. This data entry will occur within 24 hours of CRF completion. If eligibility is confirmed proceed to baseline investigations and randomisation. The study will commence the following day (start Day 1).

8.5 Re-Screening

In some cases it is possible that potential participants will need to be re-screened, for example:

- If a person consents to participate, meets the eligibility criteria but there is a delay in starting due to a change in situation (family issues, individual request for attending private matter, etc);
- If the person previously failed eligibility due to an acute event that has now resolved; or
- Medications have now stabilised

In these situations, if randomisation has not occurred;

- A new Eligibility Case Report Form is used
- A new ID number is assigned to the participant
- The participant is flagged as having been re-screened on both the Case Report Form and the site master list
- The Eligibility Case Report Form is completed as if being fully screened, data is not copied form one form to the next, but completed using the current clinical situation as documented within the patient clinical notes.

It is not appropriate to re-screen a person if they have previously failed to meet the eligibility criteria and there have been no further changes or treatments that would now indicate that the patient may be suitable.

More detail is provided within the Standard Operating Procedure for re-screening (*6.5.2, Re-screening*).

8.6 Procedure to request randomisation

Pharmacy will be contacted whenever a person is under-going the screening process to warn them of a potential trial candidate. This will be followed up by a confirmatory call as soon as the person's eligibility has been confirmed. The randomisation request will take the form of the prescription of the study drugs.

The site clinical trials pharmacist will identify the study drugs for the participant according to the allocation determined in the supplied schedule, and label the bottles providing the details as described above.

The allocation will be recorded on the schedule along with the date of allocation, the signature of the pharmacist preparing the syringe and the patient ID number.

Participant randomisation will be registered with the coordinating site. PaCCSC has a Standard Operating Procedure for Randomisation (*4.7.1, Randomisation*), this procedure is to be followed. In summary, the procedure outlines that on randomisation of a participant, the site pharmacy is to fax a notification to the coordinating site. This notice will be monitored alongside the participant eligibility as entered onto the on-line data base from Eligibility CRF.

Participants will not be randomised twice. Participation during a previous admission will exclude any future participation.

8.7 Prescription of study drugs

All prescriptions for the use of investigational products for clinical trials must be:

- Completed by a person authorised to do so
    - the principle site investigator
    - sub/co investigators
    - those medically authorised to prescribe the specific product under investigation
- Completed on a hospital prescription form and detail full description of the
    - participant details
    - study protocol number
    - medicine (this will be melatonin/placebo)
    - dose (this will specify the dose level/s)
    - frequency
    - route

In this study the prescription will therefore read:

Melatonin prolonged release (2mg)/ placebo. Take one tablet (whole) every night at 2000 hours during admission. Supply 7 tablets.

The medication will be dispensed to the ward, with up to one week supply at a time dependent on the ward procedures. Smaller numbers of tablets can be dispensed if preferred.

8.8 Treatment commencement

All baseline assessments will be undertaken as soon as eligibility is confirmed, and treatment initiated as soon as practicable.

All baseline assessments will be undertaken immediately before the first study dose on day 1, treatment will be then initiated on the first night at 2100 hours ($\pm$ one hour). Local hospital procedures are to be followed regarding checking of study medicine.

8.9 Daily assessments

Participants will be visited daily by the study nurse in the inpatient unit, at the same time in the morning of each day. Prior to reviewing the participant, the study nurse will check with the unit nursing staff regarding the participant's condition, and any recent events.

During the visit, the study nurse will take the measures and assessments as outlined in the table of study measures and record the visit in the Case Report Form for that time point. This visit will also be recorded within the participant clinical file, along with any instructions or changes regarding the infusion.

8.10 Exit assessments

Participants will be visited in the morning following the last dose of the study intervention prior to discharge (last day of data collection, or when treatment is ceased, if earlier cessation occurs) for collection of exit data. During the visit, the study nurse will take the measures and assessments as outlined in *8.1 Table of study measures* and record the visit in the CRF. This visit will also be recorded within the participant clinical file, along with any instructions or changes regarding ongoing management.

8.11 Withdrawal assessments

If participants are to be withdrawn, a 'Withdrawal Case Report Form' will be completed by the study nurse on instruction from the investigator. The assessments and reason for withdrawal will be recorded. Withdrawal will be initiated if the participant meets any of the withdrawal criteria as described in section *5.13 Cessation of study medicine*. All associated

documents will be completed (Serious Adverse Event report, adverse event assessment score etc).

8.12 Follow-up phase assessments

Participants will enter a follow-up phase irrespective of their place of care until death or 21 days after ceasing the study medication (whichever is the shorter period); or if withdrawal of consent occurs. During the follow-up phase frequency of adverse events, delirium (based on medical record), quality of life, performance status, medication and health service usage will be collected.

Follow-up data will be collected by the study nurse weekly by telephone for up to 21 days. A medication list will be updated at each contact to record actual prescribed and taken medications since the preceding visit.

8.13 Economic evaluation

The data collected in the follow-up phase (8.12) will inform the economic evaluatiuon, and includes longer term clinical and economic outcomes.

9.0 ADVERSE EVENTS

9.1 Reporting of adverse events

All adverse events will be reported via an online reporting system to enable study wide reporting. The Palliative Care Clinical Studies Collaborative (PaCCSC) has a Standard Operating Procedure for Adverse Event reporting (5.17, Adverse Event Reporting) that will operate at all study sites. In addition there will be specific events and reporting mechanisms required due to the nature of the study medicine. This is described below.

9.2 Criteria for assessing severity

Severity of adverse events will be assessed according to Good Clinical Practice guidelines [69] and National Institutes of Health Common Terminology Criteria for Adverse Events[70].

9.2.1 Adverse events

Adverse events are defined as any untoward or unexpected occurrence in a patient or clinical investigation participant where the occurrence does not necessarily have a causal relationship with the study intervention.

There are circumstances where adverse events will not be reported. Examples are;

- An expected side effect from a study intervention, such as constipation unless the side effect required additional treatment or assessment
- Signs or symptoms associated with the disease or disorder under study, unless they are more severe than expected.
- Social admission to hospital

9.2.2 Serious adverse events

Serious Adverse Events are any untoward medical occurrence that meets one or more of the following criteria/outcomes;

- death
- life-threatening (i.e. at immediate risk of death)
- in-patient hospitalisation or prolongation of existing hospitalisation
- persistent or significant disability/incapacity
- congenital anomaly or birth defect
- other medically relevant condition judged as serious

The expected study population have an underlying disease that is expected to significantly shorten life expectancy, they are already termed palliative and are expected to die within a short period of time.

The conditions recognised as being excluded from SAE reporting are as follows:

- Where participants are admitted as a planned admission due to respite, family or social issues, or for pre-planned treatment
- Where participants are admitted (or admission is prolonged) due to a documented expected deterioration in their condition due to the underlying disease process, or where the admission is prolonged for this reason
- Where participants die due to a well documented decline in their condition due to the underlying disease process

"Life threatening" means that the participant was at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more serious form, might have caused death.

"Requires inpatient hospitalisation" is defined as hospital admission for treatment of the adverse event. Hospital admission for scheduled elective surgery would not be a serious adverse event.

"Other medically relevant condition judged as serious" is where medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse. A diagnosis of a new cancer during the course of the treatment should be considered as medically important.

Progression of a participant's underlying condition leading to one of the above should always be reported as a serious (but expected) adverse event, which is unrelated to protocol treatment, or caused by failure of the anticipated therapeutic effect of the study drugs.

In all other cases, serious adverse events will be reported according to the requirements of the local Hospital Ethics Committee.

9.3 Criteria for assessing causality

The site investigator will assess each event for relatedness or causality of the intervention and the event. A guide to grading the degree of certainty about such a relationship is available at www.niaid.nih.gov/ncn/sop/adverseevents.htm. A summary of the grading is as follows:

Unrelated Where the adverse event is clearly not related

Unlikely Where the adverse event does not have a clear relationship to the intervention

Possible Where the adverse event follows a known pattern of response

Probable Where the adverse event reduces or ceases with withdrawal of the intervention

Definite Where the adverse event ceased with withdrawal of the intervention and recurs with re-exposure

9.3.1 Time period for assessing AE's and SAE's

At each visit, the participants are encouraged to mention any problems since the last visit. In addition, the following standard questions should be asked;

1. Have you had any medical problems since the last visit or study assessment?
2. Have you started any new medications, other than given to you in this study, since the last visit or assessment?

For all randomised participants all AE's, irrespective of causality, will be assessed and recorded as per the standard operating procedures. The time period includes the time from randomisation, the inpatient treatment period and the 4 week extension phase (by telephone).

For patients who meet the eligibility criteria and then do not proceed to randomisation, any AE's detected during that window of time, should be reported. If an AE is the reason that a person does not proceed to randomisation, this should be recorded within the CRF, adverse event report and in the clinical record, irrespective of causality or seriousness.

9.3.2 National Cancer Institute, Common Terminology Criteria for Adverse Events.V4.0

These criteria [70] have been used to determine adverse events likely to occur during the study period and will be used to determine adverse event reporting and study progress. Criteria specific to the expected events know to be associated with melatonin have been listed below. This is administered by study staff

Symptoms will be identified during each visit using criteria established by the National Cancer Institute, and will be graded accordingly.
Specifically, for this study, the symptoms of interest will be;

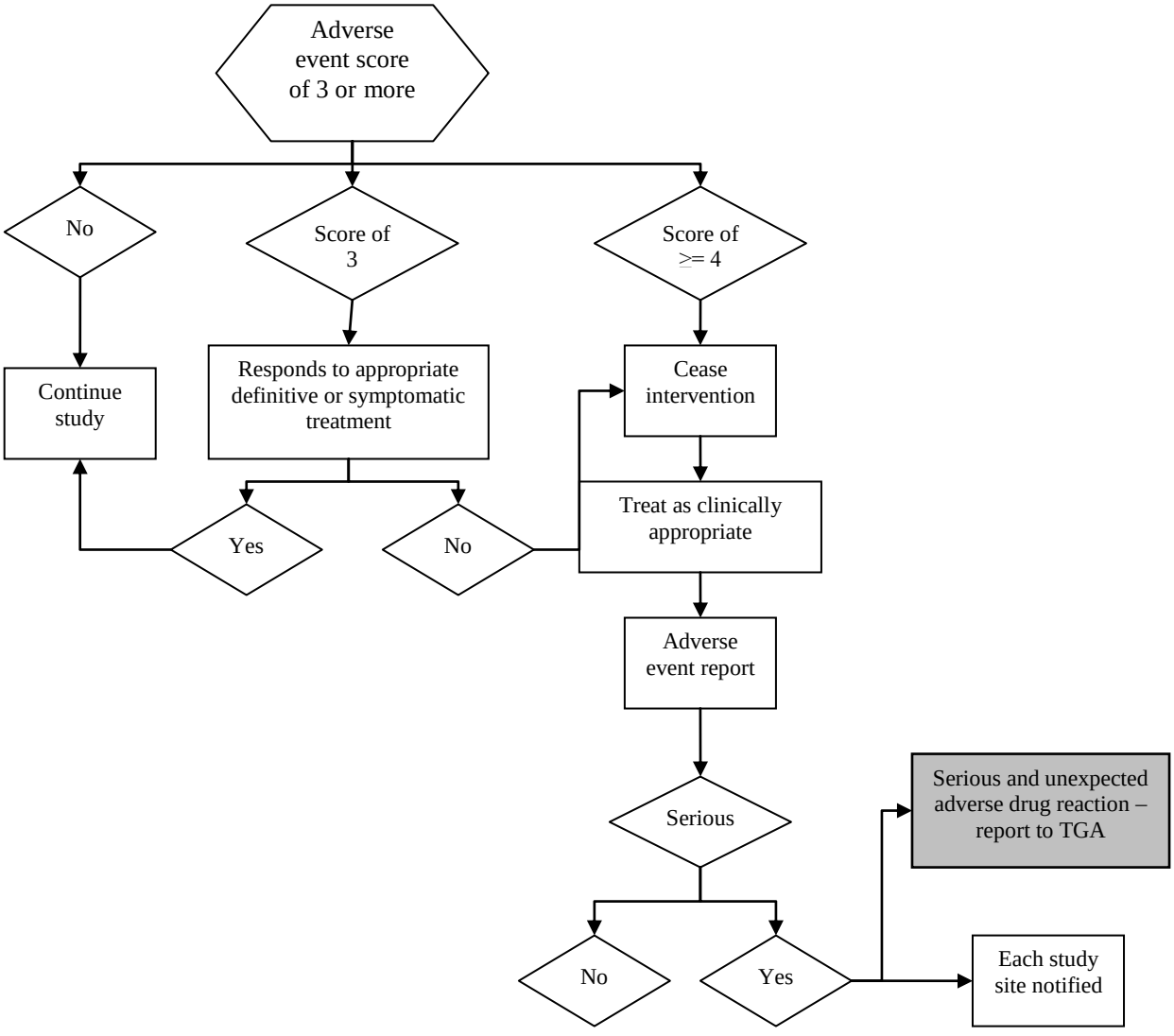
- Sedation
- Dizziness
- Seizure
- Agitation
- Anxiety
- Increased INR

- Depression

A grade of 3 (that has not responded to symptomatic treatment instituted by the treating physician according to local protocols) or 4 will activate cessation of study intervention and an adverse event report.

All adverse events will be collated by the project officer, and reported to the executive committee on a monthly basis. Adverse event rates will form part of the Key Performance Indicators for the study and will be reported on a regular basis to the Trial Steering Committee and the ethical review boards of the participating sites.

9.4 Adverse Event Assessment Diagram



Serious Adverse Events will be reported by the study site, to the local Hospital Research Ethics Committee and to the study coordinating site for study wide reporting. This will occur within 24 hours of first knowledge of the event unless death or life threatening which must be immediate. In addition, events deemed to be both serious and unexpected, and related to the study intervention, will be reported by the coordinating site to the Therapeutic Goods Administration using a 'Blue Form'.

In addition, PaCCSC has a Standard Operating Procedure that describes the reporting of adverse events in detail. The on-line reporting is to be used to enable reporting between sites, local forms of reporting are also to be used for reporting to local sites.

9.5 Follow-up of AE's and SAE's

After the initial report, investigators are required to follow-up each adverse event and provide further information both to the coordinating centre and the local HREC. All events reported as ongoing are to be reviewed at subsequent visits or appointments in order to report progress and resolution.

All events are to be followed until:

- resolution;
- the condition of the participant stabilises;
- the event can be explained;
- the participant is lost to follow-up;
- death.

Reports are to contain details of follow-up investigations, result reports or reports from other consultations, and are to be updated in a report to the coordinating centre and the local HREC.

9.5.1 Post study AE's and SAE's

A post study event is defined as any event that occurs outside of the time period described in section 9.3 of the protocol. Investigators are required to report any events they become aware of if;

- the event occurs at any time after study participation has ceased, and
- the event is assessed as being reasonably related to the study intervention.

Investigators are not obliged to actively seek events that occur after the study period defined in 9.3.

9.6 Unblinding

In cases of medical need, where urgent medical decisions will be influenced by knowledge of the treatment assignment, the Lead Investigator will have access to the sealed unblinding envelopes and must be contacted in the first place. Clinical staff will be able to discuss the clinical situation with the Lead Investigator to determine the urgency and need for unblinding, and will be informed by the Lead Investigator of the assignment based on these discussions.

In the case of not being able to contact the Lead Study Investigator, the designed staff from PaCCSC should be contacted.

PaCCSC has a Standard Operating Procedure for unblinding (*4.7.2, Unblinding*), and is to be referred to in the occurrence of unblinding. The PaCCSC coordinating centre will monitor real time unblinding frequency by collecting CRF withdrawal data and unblinding reporting from the Lead Study Investigator.

9.7 Stopping rules

The study will be stopped if new literature indicates findings that can be applied to this question in terms of benefit or side effects, or if reporting of adverse events indicate that review of the study protocol is required, for either or both of the study drugs, or rescue medicine. Two planned interim analyses will be conducted independently and reviewed by the independent data and safety monitoring committee after about 33% and 66% of patients have been enrolled. The primary outcome and adverse events will be compared between groups with $p<0.001$ required as the threshold of stopping the trial for significant evidence of benefit or harm in either one of the treatment arms.

10.0 TRIAL MONITORING

10.1 Adverse events and efficacy

Adverse events and efficacy for the entire study will be reviewed via a number of mechanisms.

10.1.1 Adverse events

In line with the PaCCSC Standard Operating Procedure for Adverse Events (*5.17 Adverse Event Reporting*), reports of serious adverse events will be sent to the Trial Management Committee, all participating site Hospital Ethics Review Committees (see Table below) and the Data Safety Monitoring Committee within 24 hours of knowledge of the event, while adverse events will be reported as summary reports as stipulated in the table below.

10.1.1.1 The Trial Management Committee

Each meeting of the Trial Management Committee will receive from the coordinating centre a summary report of the adverse events reported by the investigators. Each summary report will be generated from the on-line entry of adverse event reports by PaCCSC sites. This summary report will be reviewed for reporting compliance, trends in events, and outstanding events that require specific attention. All Trial Management Committee discussions will be minuted, with actions detailed, and reviewed at the subsequent meeting. The chairperson's report to the Scientific Committee will contain a summary of the discussions of the adverse event report and the agreed outcomes. The Trial Management Committee will not have access to unblinded reports of adverse events.

10.1.1.2 Hospital Ethics Review Committees

Adverse events and serious adverse events are to be reported to site HRECs and where appropriate the DSMC in the format and timeframe stipulated by each individual committee.

10.1.2 Efficacy

This study has been adequately powered using available data to ensure a primary efficacy end point that will address the null hypothesis. Interim unblinded analysis is not planned for this study given the impact that this will have on the sample size calculation. An unblinded analysis is likely to increase the need for recruitment and potentially delay the availability of results without addressing the secondary outcomes particularly if the study were to be prematurely closed.

10.2 Data Safety Monitoring Committee

This study will have a contracted independent Data Safety Monitoring Committee (DSMC). The primary role of the DSMC will be to monitor adverse and serious adverse events. All adverse and serious adverse event reports will be reviewed at 6 monthly intervals, as agreed by the DSMC. In addition, any emerging safety issues will be reviewed by the DSMC on an ad hoc basis if required.

The Data Safety Monitoring Committee (DSMC) will be established to:

- review data from an ethical standpoint, with patient rights, safety and wellbeing being paramount
- consider data from interim analysis where such an analysis is planned
- report on trial continuation

Reports will be provided to the PaCCSC Management Advisory Board and Scientific Committee.

The Data Safety Monitoring Committee (DSMC) will consist of:

- experts in field
- a clinical trials statistician
- a trial pharmacist
- an experienced palliative care physician.

Specifically, the DSMC will receive serious adverse events as part of the established reporting mechanism (email notification of the report from the coordinating site within 24 hours) if the event is unexpected and related to the study intervention. In addition, the DSMC will receive a summary report of all adverse events, these will be discussed as a standing agenda item, with the discussions, actions and outcomes recorded. The DSMC will also receive an updated literature summary at each meeting, which will address new published literature that may have an impact on the study.

11.0 STATISTICS

11.1 Null hypotheses to be tested

In people with advanced cancer admitted to hospital there is no difference in delirium-free days with the addition of prolonged release melatonin when compared with placebo

11.2 Statistical analysis of efficacy primary outcome

Intention-to-treat analysis will be used for all statistical comparisons. For the primary outcome, comparisons between groups for delirium-free days, with adjustment to the length of stay and other potential covariates using a general linear model approach will be undertaken. For potential missing data, multiple imputation technique will be applied to handle the missing data. A proper multiple imputation method will be employed that based on various models of assumption including missing completely at random (MCAR), missing at random (MAR), and missing not at random (MNAR). Sensitivity analysis will apply to examine the effects of these different assumptions on the imputed data structure in order to ascertain the most reliable approach.

11.3 Statistical analysis of secondary end points

For the secondary outcomes, time-to-event analysis, such as survival analysis will be used to determine differences in time to first episode of delirium. Delirium precipitants, which occur at variable times and for different durations during the study period are time-dependent covariates and Cox proportional hazard modelling will be used.

The incidence rate of delirium will also be calculated and compared between the treatment and control groups. For possible toxicity of the medication, incidence of adverse event will be calculated and reported.

11.4 Health economic analyses

Limited evidence suggests that interventions to prevent delirium or reduce its duration in hospital are cost effective,[57,58] with the majority of cost offsets from longer term care savings.[57] Estimating cost offsets over shorter time frames is crucial given advanced cancer has limited prognosis, and in prior cost-effectiveness studies, patients with terminal illness were excluded.[34] The cost-effectiveness sub-study will evaluate the within-study incremental resource use, cost and consequences of melatonin relative to placebo for preventing delirium in advanced cancer patients from randomisation to study end or death (whichever is sooner). The analysis will include efficacy (delirium-free days), toxicity, survival and resource data (intervention costs, hospital length of stay, health professional time, medication use and investigations). Sampling and parameter uncertainty will be

estimated by bootstrapping on participants' costs and effect pairs to maintain covariance in re-sampling with replacement across 10,000 replicates. Cost-effectiveness acceptability curves, sensitivity and scenario analyses will be undertaken.

11.5 Power and sample size

Sample size was calculated based on the information obtained in the pilot study on the primary outcome, namely delirium-free days during a 3 week study period, and an analytical approach of comparing the mean delirium-free days between groups. It has been estimated that a sample size of 110 in each arm (n=220 in total) would provide 90% power to reject the null hypothesis with a 5% type I error rate to detect an increase of 2 delirium-free days allowing for 30% drop out or loss to follow-up and 5% for possible adjustments for covariates.

11.6 Interim analyses

Two planned interim analyses will be conducted independently and reviewed by the independent data and safety monitoring committee after about 33% and 66% of patients have been enrolled. The primary outcome and adverse events will be compared between groups with $p<0.001$ required as the threshold of stopping the trial for significant evidence of benefit or harm in either one of the treatment arms.

12.0 ETHICS

12.1 Benefit anticipated from the study

At present, there is no medicine specifically approved for the treatment of delirium despite this symptom being relatively common in the palliative care setting, and the cause of considerable distress to patients, care givers and clinical staff.

This study therefore proposes to validate the use of a treatment that could provide significant improvement in symptom control where current treatments are not efficacious. The results of this study will provide evidence for the use of melatonin in this population, and if positive, may provide information to enable this medication to be submitted for approval by the Therapeutic Goods Administration and for listing on the Pharmaceutical Benefits Scheme for use in the community. If negative, given this is an adequately powered study that will help to inform clinical practice.

12.2 The possibility of physical stress or discomfort

Each of the study measures have been carefully selected to ensure they provide the best possible data with the least impact on the participant, and have been validated. As much as possible, the study measures are non-invasive in order to minimise physical stress.

Participants will be asked to provide a blood sample for baseline physiological measures. The taking of blood is uncomfortable, but short term. This is the only invasive procedure during the study period.

The study protocol is carefully planned to ensure that each participant's symptoms can be responded to by either increasing the study medication, and/or providing rescue medication that is currently used in clinical practice.

Side effects will be carefully monitored to ensure any anticipated discomfort is detected and treated in a timely manner.

12.3 The possibility of psychological stress or discomfort

Some participants may experience stress associated with completing some of the study measures. This is a vulnerable population, where sensitive issues about ability to continue to function, quality of life and other questions may raise broader issues of psychological distress.

Emotional distress caused by any of the questions in the quality of life measures will be dealt with by members of the palliative care team who would be involved either directly or in consultation with the care of the people under those circumstances. Although there may be acute distress, the weight of evidence is that such 'prompt' questions are in fact an avenue to open up discussions, which are well regarded by people despite their initial potential distress on occasion.

There will be no deception of participants at any stage of the project. Each participant interaction will be undertaken by carefully selected and trained study staff. This training will initially be undertaken in conjunction with investigators and senior research personnel, who have been trained in Good Clinical Practice, to ensure that staff are able to detect and monitor participant distress. Ongoing site monitoring will provide ongoing training opportunities.

12.4 Research on people in dependent relationships

The nature of doctor-participant relationships dictates that participants may feel that they are in the dependent position. The investigators and their designees will work to minimise any concern of inappropriate influence—the presentation of the study will be as unbiased as possible, the information sheet and consent forms will be clear, and participants will be able to withdraw from the study at any time. A person not directly involved in the clinical care of the participant will obtain consent. Each site will employ a recruitment nurse who will approach participants for permission to present the study. Each recruitment nurse will be trained in presenting the study in such a way that clinical care is separated.

12.5 Separation of research and clinical responsibilities

There are many distressing symptoms faced by participants with a life limiting illness and there is very little research to support many of the interventions that palliative medicine doctors provide daily around the world. Although research in this area poses its own unique dilemmas, the ethics of not conducting research into the best management of the dying participants is untenable. Importantly, participants will be cared for as individuals with specific needs; the needs of research will come second. Research staff, (medical or nursing), will clearly identify themselves and the purpose of their visit at their contact with the participant as being part of the research process. Training at the site initiation visit will provide an opportunity for study staff to determine appropriate ways of dealing with clinical situations that might arise during their research visits.

12.6 Method and nature of recruitment and advertising

Participants will be recruited on admission to the palliative care service and during initial screening in the participating clinics at each site. Advertising brochures will not be provided, only the information sheet and a verbal explanation. Any participant who is approached to take part in this study has the right of refusal. Refusal to take part in this study will not adversely affect the provision or quality of care provided to any participant in any way.

12.7 Protection of privacy and preservation of confidentiality

The participants will be allocated a unique ID number. The master list linking identifying participant information and ID number will be maintained in a locked cabinet, separate from the participant database. Form tracking will be via participant ID number only. There will be master lists held at each participating site and at the coordinating site at Flinders University in South Australia. The participant database will be stored on a password-

protected hard drive maintained by the study investigators. Data will be analysed by ID number only.

12.8 Restriction of use of data

Investigators will have access to data by ID number only for the purposes of data monitoring and analysis. The Project Officer will have access to all study data for the purposes of data checking, monitoring and preparation for analysis. Study project officers and site coordinators will have access to the local site Case Report Forms and the data contained within for the purposes of data collection, data entry and data query resolution. The Data Safety Monitoring Board will have access to de-identified data for safety and efficacy assessments. Study auditors will have access to Case Report Forms (by ID number only) and study files in order to audit the study. Site research ethics committees will have access to local data for audit purposes.

12.9 Use of personal information

Only enough personal information to give a general demographic and disease profile of the participant will be collected. The participant responses collected are limited to those that will address the study's primary and secondary aims.

12.10 Estimated time of retention of personal information and planned disposal

Records from the study will be maintained for 15 years after study completion in secure archiving facilities. Once the 15 year waiting period is complete, the files will be erased from the database hard-drive and any paper copies shredded, including the master list linking participant name and treatment number.

The data will be retained in accordance with good clinical practice recommended by the NHMRC National Statement and the CGP guidelines, and in a form that is at least as secure as the sources from which it was obtained.

13.0 STUDY ADMINISTRATION

13.1 Data handling and record keeping

The Palliative Care Clinical Studies Collaborative (PaCCSC) has a number of Standard Operating Procedure that will apply to all sites for the management of study data. Specifically the following Standard Operating Procedures apply;

- 5.5.1 Electronic Data Handling
- 5.23.2 CRF completion
- 8.0 Essential documents
- 8.4.1 Archiving of research/project materials
- 8.42 Record destruction

13.1.1 Direct access to source data:

A statement of permission to access source data for regulatory and audit purposes is included within the participant consent form with explicit explanation about this given as part of the consent process. Specifically, access will be required by study staff (including investigators, site coordinators and study nurses), Hospital Research Ethics Committees (HRECs), Data Safety Monitoring Committee (DSMC) and the PaCCSC data management team (National Project Officer and Administrative Officer) In addition de-identified data will be made available for meta-analysis and where requested by journals for publication purposes.

Case Report Forms will include:

- CRF – Eligibility
- CRF – Baseline
- CRF – Intervention
- CRF – Treatment Cessation
- CRF - Withdrawal
- CRF – Follow-up
- Medical Assessment and Screening Form

13.1.2 Data collection

Data will be sourced from the following;

Measure	**Source**	**Completed by:**
General demographic details	Clinical file	Study nurse
General Medical information	Clinical file	Medical officer
Concurrent medications	Clinical file	Medical officer
Pathology results	Pathology report	Pathology service
Vital signs	Clinical file	Study nurse
DRS-R-98	scale	Study nurse
DSM-V	CRF	Study nurse
NuDesc	scale	Study nurse
Insomnia Severity Index	scale	participant
RASS - Pal	CRF	Study nurse

13.1.3 Electronic recording

Study data will be recorded in a number of files for both the administration of the study and collection of participant data.

1. A master index will contain confidential participant contact information and will be the only link between individual participants and the ID number. This will be an Excel spreadsheet (Master patient index.xls).

2. The Forms Tracking index will be identified by ID number only. It will be used to track the data collection forms for each participant for auditing of data collection. It will contain dates of when each form is due, entered and finalised. (Forms tracking index.xls).

3. The Data file will be held and administered in the coordinating site, and will contain all the participant data as downloaded from the web site data forms. This data will then be transferred to the data set for analysis.

13.1.4 Data entry

Data will be entered from each site into a web-based interface specifically developed for this study. This password protected interface is protected behind a 'Ciskopix' firewall which helps prevent unauthorised access. No personally identifying information will be entered on this interface. The coordinating site will download the data on a regular basis as a comma delimited file.

On completion of data entry for each form, the study site will 'submit' the data, generating an automatic email sent to the project manager as part of the auditing process. The original form will be sent to the coordinating site for verification and then filed.

13.1.5 Data querying

Data will be checked according to the Data Management Standard Operating Procedure (*5.5.1, Electronic Data Handling*). Data errors detected during the data checking procedures will be queried to the study site when a data report form will be raised. The data report form will be sent to the site, recording the details of the query, and the correction and resolution instructions. The data base will be updated according to the instructions, again generating an automatic email providing an audit trail of data changes.

The coordinating site will maintain a register of data checks for monitoring purposes. The register will record the date of data entry and checking, the date of return to the study site for correction, the date of return of correction, and the date of resolution. A log will be maintained detailing the corrections required for each data form.

13.1.6 Data storage

All data collected at each site for each participant will be kept in a participant file (identified by ID number only) which will contain the Case Report Forms, any corrected and amended data, copies of adverse event reports, file notes etc. All data will be stored at each study site in a locked filing cabinet with all identifying information removed, away from the administrative files for the study. All study files will be stored in accordance with Good Clinical Practice guidelines

All identifiable data (consent forms, pathology reports, etc) will be de-identified and filed with the study documents during the recruitment period. At completion of the study, all Case Report Forms will be sent to the coordinating site by registered mail, for collation and archiving. All participant files will be reconciled and stored along with all study materials – both hard copy and electronic – consistent with the regulations of the Government of South Australia regarding the retention and disposal of participant records.

13.2 Quality control

13.2.1 Training procedures:

The following training procedures will be conducted to ensure quality control.

Person trained	Description	Assessed by
All site staff	ICH Good Clinical Practice training	National manager (PaCCSC)
Study nurse	Blood sampling	Pathology department
Study nurse	Eligibility assessment	Site investigator
Study nurse	Consent procedure	Study coordinator
Investigator, sub investigators	ICH Good Clinical Practice training Protocol	National manager (PaCCSC) Chief investigator
Study nurse, investigators	Data management	National manager (PaCCSC)
Medical staff	Prescription	Site investigator
Clinical trials pharmacist	Randomisation, medication preparation procedures	National manager (PaCCSC) Chief investigator

Competency will be recorded at the study coordinating site with a copy filed in each study site.

13.2.2 Blood collection

Venous blood samples will be drawn for eligibility screening. In some instances blood samples, checked in the preceding 7 days, will be used for eligibility if the clinical situation is otherwise unchanged. The results will be held in the participant study file as source data.

Each study site will keep a copy of the pathology service guidelines for obtaining, transporting and storing blood samples.

13.2.3 Peer review and site visits

Each study site will be visited by the PaCCSC Project Officer prior to recruitment commencement, when the site coordinator and study nurse will be assessed as appropriate, and trained in the data collection, data entry, and filing and other trial procedures in order to comply with Good Clinical Practice. Peer review will be undertaken via regular study nurse telephone links and ongoing assessment by the study investigator. The assessment will be recorded and a copy sent to the study site.

13.2.4 Pharmacy training

At the site initiation visit the pharmacy will be visited by the coordinating site Project Officer. At this time the pharmacy procedures will be clarified, the protocol reviewed in detail and a pharmacy manual provided. The manual has been prepared with the input and advice of experienced trial pharmacists during the protocol development, and reviewed by 2 other pharmacists prior to finalisation.

13.2.5 Monitoring visits

Internal monitoring of the study is described in detail in the Monitoring Standard Operating Procedure (*5.18, Monitoring*).

Briefly, each study site will be visited by staff from the coordinating site at initiation, mid recruitment and study closure where all study procedures, recording, reporting and maintenance will be checked, including the pharmacy records. This will include data quality, protocol violations, adverse event reporting, participant existence and eligibility, and other aspects to determine Good Clinical Practice compliance.

In addition, auditing may take place by an external agency. This agency will be entirely independent of PaCCSC and will audit all study procedures including the pharmacies and coordinating site. External auditing will be conducted on completion of study recruitment, and when monitoring indicates the need for independent audit. The audit report will be provided to the Management Advisory Board of PaCCSC.

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15.0 APPENDICES

15.1 Assessment tools

Delirium Rating Scale - 98 – Revised (DRS-R-98) [1]

DELIRIUM RATING SCALE-R-98 (DRS-R-98)

This is a revision of the Delirium Rating Scale (Trzepacz et al. 1988). It is used for initial assessment and repeated measurements of delirium symptom severity. The sum of the 13 item scores provides a severity score. All available sources of information are used to rate the items (nurses, family, chart) in addition to examination of the patient. For serial repeated ratings of delirium severity, reasonable time frames should be chosen between ratings to document meaningful changes because delirium symptom severity can fluctuate without interventions.

DRS-R-98 SEVERITY SCALE

1. Sleep-wake cycle disturbance
Rate sleep-wake pattern using all sources of information, including from family, caregivers, nurses' reports, and patient. Try to distinguish sleep from resting with eyes closed.

0. Not present
1. Mild sleep continuity disturbance at night or occasional drowsiness during the day
2. Moderate disorganization of sleep-wake cycle (e.g., falling asleep during conversations, napping during the day or several brief awakenings during the night with confusion/behavioral changes or very little nighttime sleep)
3. Severe disruption of sleep-wake cycle (e.g., day-night reversal of sleep-wake cycle or severe circadian fragmentation with multiple periods of sleep and wakefulness or severe sleeplessness.)

2. Perceptual disturbances and hallucinations
Illusions and hallucinations can be of any sensory modality. Misperceptions are "simple" if they are uncomplicated, such as a sound, noise, color, spot, or flashes and ''complex'' if they are multidimensional, such as voices, music, people, animals, or scenes. Rate if reported by patient or caregiver, or inferred by observation.

0. Not present
1. Mild perceptual disturbances (e.g., feelings of derealization or depersonalization; or patient may not be able to discriminate dreams from reality)
2. Illusions present
3. Hallucinations present

3. Delusions
Delusions can be of any type, but are most often persecutory. Rate if reported by patient, family or caregiver. Rate as delusional if ideas are unlikely to be true yet are believed by the patient who cannot be dissuaded by logic. Delusional ideas cannot be explained otherwise by the patient's usual cultural or religious background.

0. Not present
1. Mildly suspicious, hypervigilant, or preoccupied
2. Unusual or overvalued ideation that does not reach delusional proportions or could be plausible
3. Delusional

4. Lability of affect
Rate the patient's affect as the outward presentation of emotions and not as a description of what the patient feels.

0. Not present
1. Affect somewhat altered or incongruent to situation; changes over the course of hours; emotions are mostly under self-control
2. Affect is often inappropriate to the situation and intermittently changes over the course of minutes; emotions are not consistently under self-control, though they respond to redirection by others
3. Severe and consistent disinhibition of emotions; affect changes rapidly, is inappropriate to context, and does not respond to redirection by others

5. Language
Rate abnormalities of spoken, written or sign language that cannot be otherwise attributed to dialect or stuttering. Assess fluency, grammar, comprehension, semantic content and naming. Test comprehension and naming nonverbally if necessary by having patient follow commands or point.

0. Normal language
1. Mild impairment including word-finding difficulty or problems with naming or fluency
2. Moderate impairment including comprehension difficulties or deficits in meaningful communication (semantic content)
3. Severe impairment including nonsensical semantic content, word salad, muteness, or severely reduced comprehension

6. Thought process abnormalities
Rate abnormalities of thinking processes based on verbal or written output. If a patient does not speak or write, do not rate this item.

0. Normal thought processes
1. Tangential or circumstantial
2. Associations loosely connected occasionally, but largely comprehensible
3. Associations loosely connected most of the time

7. Motor agitation
Rate by observation, including from other sources of observation such as by visitors, family and clinical staff. Do not include dyskinesia, tics, or chorea.

0. No restlessness or agitation
1. Mild restlessness of gross motor movements or mild fidgetiness
2. Moderate motor agitation including dramatic movements of the extremities, pacing, fidgeting, removing intravenous lines, etc.
3. Severe motor agitation, such as combativeness or a need for restraints or seclusion

8. Motor retardation
Rate movements by direct observation or from other sources of observation such as family, visitors, or clinical staff. Do not rate components of retardation that are caused by parkinsonian symptoms. Do not rate drowsiness or sleep.

0. No slowness of voluntary movements
1. Mildly reduced frequency, spontaneity or speed of motor movements, to the degree that may interfere somewhat with the assessment.
2. Moderately reduced frequency, spontaneity or speed of motor movements to the degree that it interferes with participation in activities or self-care
3. Severe motor retardation with few spontaneous movements.

9. Orientation
Patients who cannot speak can be given a visual or auditory presentation of multiple choice answers. Allow patient to be wrong by up to 7 days instead of 2 days for patients hospitalized more than 3 weeks. Disorientation to person means not recognizing familiar persons and may be intact even if the person has naming difficulty but recognizes the person. Disorientation to person is most severe when one doesn't know one's own identity and is rare. Disorientation to person usually occurs after disorientation to time and/or place.

0. Oriented to person, place and time
1. Disoriented to time (e.g., by more than 2 days or wrong month or wrong year) or to place (e.g., name of building, city, state), but not both
2. Disoriented to time and place
3. Disoriented to person

10. Attention
Patients with sensory deficits or who are intubated or whose hand movements are constrained should be tested using an alternate modality besides writing. Attention can be assessed during the interview (e.g., verbal perseverations, distractibility, and difficulty with set shifting) and/or through use of specific tests, e.g., digit span.

0. Alert and attentive
1. Mildly distractible or mild difficulty sustaining attention, but able to refocus with cueing. On formal testing makes only minor errors and is not significantly slow in responses
2. Moderate inattention with difficulty focusing and sustaining attention. On formal testing, makes numerous errors and either requires prodding to focus or finish the task
3. Severe difficulty focusing and/or sustaining attention, with many incorrect or incomplete responses or inability to follow instructions. Distractible by other noises or events in the environment

11. Short-term memory
Defined as recall of information (e.g., 3 items presented either verbally or visually) after a delay of about 2 to 3 minutes. When formally tested, information must be registered adequately before recall is tested. The number of trials to register as well as effect of cueing can be noted on scoresheet. Patient should not be allowed to rehearse during the delay period and should be distracted during that time. Patient may speak or nonverbally communicate to the examiner the identity of the correct items. Short-term deficits noticed during the course of the interview can be used also.

0. Short-term memory intact
1. Recalls 2/3 items; may be able to recall third item after category cueing
2. Recalls 1/3 items; may be able to recall other items after category cueing
3. Recalls 0/3 items

Nurses Delirium Screening Scale (NuDESC) [2]

Date today; _____/_____/_____ Day of study (circle one) 1 2 3

Features and descriptions	**SYMPTOM RATING 0 - 2**		
Symptom/time period	Midnight – 8am	8am – 4pm	4pm - midnight
DISORIENTATION: Verbal or behavioural of not being orientated to time or place or misperceiving persons in the environment			
INAPPROPRIATE BEHAVIOUR: Behaviour inappropriate to place and/or for the person e.g pulling at tubes or dressings, attempting to get out of bed when that is contraindicated and the like			
INAPPROPRIATE COMMUNICATION: Communication inappropriate to place and/or for the person e.g incoherence, non-communicativeness, nonsensical or unintelligible speech			
ILLUSIONS/HALLUCINATIONS: Seeing or hearing things that are not there, distortion of visual objects.			
PSYCHOMOTOR RETARDATION: Delayed responsiveness, few or no spontaneous actions/words e.g when patient is prodded, reaction is deferred and/or the patient is unrousable			
TOTAL SCORE (out of 10)			

Any score of 1 or more

- Contact investigator
- Dose modification schedule as per protocol
- Rescue medications as per protocol

GUIDE TO SCORING:

0 = Behaviour **not present** during shift/assessment period.
1 = Behaviour **present at some time** during shift/assessment period, but **mild**
2 = Behaviour **present at some time** during shift/assessment period, and **pronounced**

Insomnia Severity Index (ISI) [5]

Insomnia Severity Index (ISI)

Please Rate the Current (i.e. Last Week) Severity of your Insomnia Problem(s):

		none < 30 min	mild 30 - 45 min	modarate 45 - 90 min	severe 90 - 120 min	very > 120 min
1.	Difficulty falling asleep:	○	○	○	○	○
2.	Difficulty staying asleep:	○	○	○	○	○
3.	Problem waking up too early:	○	○	○	○	○

		none 0	mild 1	modarate 2	severe 3
4.	How SATISFIED/dissatisfied are you with your current sleep pattern?	○	○	○	○
5.	To what extent do you consider your sleep problem to INTERFERE with your daily functioning (e.g. daytime fatigue, ability to function at work/daily chores, concentration, memory, mood, etc.)?	○	○	○	○
6.	How NOTICEABLE to others do you think your sleeping problem is in terms of impairing the quality of your life?	○	○	○	○
7.	How WORRIED/distressed are you about your current sleep problem?	○	○	○	○

Score = {{insomnia.score = 1*insomnia.falling + 1*insomnia.staying + 1*insomnia.waking + 1*insomnia.satisfaction + 1*insomnia.interference + 1*insomnia.noticable + 1*insomnia.worried}}

Richmond Agitation-Sedation Scale (RASS) [7]

Procedure

1. Observe patient.
    a. Patient is alert, restless or agitated — Score 0 to +4
2. If not alert, state the patients name and say 'open yours eyes and look at me'
    a. Awakens with sustained eye opening and eye contact — Score -1
    b. Awakens with eye opening and contact, but not sustained — Score -2
    c. Any movement in response, but no eye contact — Score -3
3. When no response to verbal stimulation, physically stimulate by shaking shoulder and/or rubbing sternum
    a. Patient has any movement to stimulation — Score -4
    b. Patient has no response to any stimulation — Score -5

Score	Term	Description
+4	Combative	Overtly combative, violent, immediate danger to sta
+3	Very agitated	Pulls or removes tubes or catheters, aggressive
+2	Agitated	Frequent nonpurposeful movement, fights ventilator
+1	Restless	Anxious but movements not aggressive or vigorous
0	Alert and calm	
-1	Drowsy	Not fully alert, but has sustained awakening
-2	Light sedation	Briefly awakens with eye contact to voice
-3	Moderate sedation	Movement or eye opening to voice but no eye conta
-4	Deep sedation	No response to voice, but movement or eye opening physical stimulation
-5	Unarousable	No response to voice or physical stimulation.
___	**Score**	

Delirium Etiology Checklist (DEC) [3]

This checklist accounts for the multifactorial etiologies in causing delirium by allowing a weighted approach for documenting the range of potential inputs in any single case. Therefore, raters may indicate multiple categories as contributing toward reaching the threshold for delirium. The relative importance of history, examination, and tests in supporting the significance of any particular causative factor will vary among cases so that the certainty of causation will depend on the judgement of the clinician involved based on all available information. Specific disorders assigned to categories are noted on the reverse side of this page.

Please "X" a box for each row as appropriate.

	[1]Definite Cause	[2]Likely Cause	[3]Present and Possible Contributory	[4]Present but Apparently not Contributory	[4]Ruled Out/Not Present/ Not Relevant
[1]**Drug Intoxication**					
[2]Drug Withdrawal					
[3]Metabolic/Endocrine Disturbance					
[4]Traumatic Brain Injury					
[5]Seizures					
[6]Infection (intracranial)					
[7]Infection (systemic)					
[8]Neoplasm (intracranial)					
[9]Neoplasm (systemic)					
[10]Cerebrovascular					
[11]Organ Insufficiency					
[12]Other CNS					
[13]Other					

See other side for a more detailed list of conditions grouped under each of the above categories and please check each one you considered as a contributory (definite, likely, or possible) factor.

Drug Intoxication

1θ Alcohol
2θ Sedative - hypnotic
3θ Opiate
4θ Psychostimulant
5θ Hallucinogenic
6θ Prescribed drug _____
7θ Other _____
8θ OTC _____

Drug Withdrawal

1θ Alcohol
2θ Sedative-hypnotic
3θ Prescribed drug _____
4θ Other drug _____

Metabolic/Endocrine Disturbance

1θ Volume depletion
2θ Volume overload
3θ Acidosis
4θ Alkalosis
5θ Hypoxia
6θ Uremia
7θ Anemia
8θ Avitaminosis _____
9θ Hypervitaminosis _____
10θ Hypoglycemia
11θ Hyperglycemia
12θ Hypoalbuminemia
13θ Hyperalbuminemia
14θ Bilirubinemia
15θ Hypocalcemia
16θ Hypercalcemia
17θ Hypokalemia
18θ Hyperkalemia
19θ Hyponatremia
20θ Hypernatremia
21θ Hypomagnesiemia
22θ Hypermagnesiemia
23θ Hypophosphatemia
24θ Hypothyroidism
25θ Hyperthyroidism
26θ Hypoparathyroidism
27θ Hyperparathyroidism
28θ Cushing's Syndrome
29θ Addison's Disease
30θ Other _____ _____

θ Traumatic Brain Injury

θ Seizures

Intracranial Infection

1θ Meningitis
2θ Encephalitis
3θ Abscess
4θ Neurosyphilis
5θ HIV
6θ Other _____

Systemic Infection

1θ Bacteremia
2θ Sepsis
3θ Fungal
4θ Protozoal
5θ Viral
6θ Respiratory
7θ Urinary
8θ Other _____

Intracranial Neoplasm

1θ Primary
Histology _____
2θ Metastasis
Site _____
3θ Meningeal Carcinomatosis

Extracranial Neoplasm

Site of primary lesion _____
θ Paraneoplastic Syndrome

Cerebrovascular Disorder

1θ Transient Ischemic Attack
2θ Subarachnoid Hemorrhage
3θ Stroke
4θ Subdural Hemorrhage
5θ Cerebral Edema
5θ Intraparenchymal hemorrhage
6θ Cerebral Vasculitis
7θ Other _____

Organ Insufficiency

1θ Cardiac
2θ Pulmonary
3θ Hepatic
4θ Renal
5θ Pancreatic
6θ Other _____

Other CNS

1θ Parkinson's Disease
2θ Huntington's Disease
3θ Multiple Sclerosis
4θ Wilson's Disease
5θ Hydrocephalus
6θ Other _____

Other Systemic

1θ Heat stroke
2θ Hypothermia
3θ Radiation
4θ Post-operative state
5θ Immunosuppressed
6θ Other _____
7θ Fractures

Short Blessed Test [4]

"Now I would like to ask you some questions to check your memory and concentration. Some of them may be easy and some of them may be hard."

	Correct	Incorrect
1. What year is it now?	0	1
2. What month is it?	0	1

Please repeat this name and address after me:
John Brown, 42 Market Street, Chicago
John Brown, 42 Market Street, Chicago
John Brown, 42 Market Street, Chicago
(underline words repeated correctly in each trial)
Trials to learn _____ (if unable to do in 3 trials = C)

"Good, now remember that name and address for a few minutes."

3) Without looking at your watch or clock, tell me what time it is.
(If response is vague, prompt for specific response

Within one hour Correct (0) Incorrect (1)

4) Count aloud backwards from 20 to 1 0 1 2 Errors
Mark correctly sequenced numerals. If subject starts counting forward or forgets the task, repeat instructions and score one error
20 19 18 17 16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1

5) Say the months of the year in reverse order 0 1 2 Errors
If the tester needs to prompt with the last name of the month of the year, one error should be scored – mark correctly sequenced months.
D N O S A JL JN MY AP MR F J

6) Repeat the name and address you were asked to remember.
John Brown, 42 Market Street, Chicago 0 1 2 3 4 5 Errors

___ _____ __ _____ _____

Check Correct Items ("street" not required)

SCORING

Item # Final	Errors (0 - 5)	Weighting Factor	Item Score
1		X 4	
2		X 3	
3		X 3	
4		X 2	
5		X 2	
6		X 2	
		Sum Total = (Range 0 – 28)	

INTERPRETATION
0-4 = normal cognition
5-9 = questionable impairment
≥ 10 = Impairment consistent with dementia

Charlson Comorbidity Index [6]

Assigned weights for diseases	***Conditions***
1	Myocardial infarct Congestive cardiac failure Peripheral vascular disease Cerebrovascular disease Dementia Chronic pulmonary disease Connective tissue disease Ulcer disease Mild liver disease Diabetes
2	Hemiplegia Moderate or severe renal disease Diabetes with end organ damage Any tumour Leukaemia Lymphoma
3	Moderate or severe liver disease
6	Metastatic solid tumour AIDS

Assigned weights for each condition and total equals the score

Score - ____

Australian Karnofsky Performance Status (AKPS) [9]

***Australia - Modified Karnofsky Performance Status**

- ○ 100=Normal; no complaints; no evidence of disease.
- ○ 90 = Able to carry on normal activity; minor signs or symptoms.
- ○ 80 = Normal activity with effort; some signs or symptoms of disease.
- ○ 70 = Cares for self; unable to carry on normal activity or to do active work.
- ○ 60 = Requires occasional assistance but is able to care for most of his needs.
- ○ 50 = Requires considerable assistance and frequent medical care
- ○ 40 = In bed more than 50% of the time.
- ○ 30 = Almost completely bedfast.
- ○ 20 = Totally bedfast and requiring extensive nursing care by professionals and/or family.
- ○ 10 = Comatose or barely rousable.
- ○ 0 = Dead.
- ○ Not collected

Carer experience scale[66]

Carer Experience Scale

PLEASE TICK ONE BOX FOR EACH GROUP to indicate which statement best describes your current caring situation.

1.Activities outside caring *(Socialising, physical activity and spending time on hobbies, leisure or study)*

You can do most of the other things you want to do outside caring ……. ☐1
You can do some of the other things you want to do outside caring ……. ☐2
You can do few of the other things you want to do outside caring …….. ☐3

2. Support from family and friends (*Personal help in caring and/or emotional support from family, friends, neighbours or work colleagues)*

You get a lot of support from family and friends …… ☐1
You get some support from family and friends …… ☐2
You get little support from family and friends …….. ☐3

3. Assistance from organisations and the Government *(Help from public, private or voluntary groups in terms of benefits, respite and practical information)*

You get a lot of assistance from organisations and the Government …….. ☐1
You get some assistance from organisations and the Government …… ☐2
You get little assistance from organisations and the Government …….. ☐3

4. Fulfilment from caring *(Positive feelings from providing care, which may come from: making the person you care for happy, maintaining their dignity, being appreciated, fulfilling your responsibility, gaining new skills or contributing to the care of the person you look after)*

You mostly find caring fulfilling …….. ☐1
You sometimes find caring fulfilling …… ☐2
You rarely find caring fulfilling …… ☐3

5. Control over the caring *(Your ability to influence the overall care of the person you look after)*

You are in control of most aspects of the caring …… ☐1
You are in control of some aspects of the caring …… ☐2
You are in control of few aspects of the caring …… ☐3

6. Getting on with the person you care for *(Being able to talk with the person you look after, and discuss things without arguing)*

You mostly get on with the person you care for …… ☐1
You sometimes get on with the person you care for …… ☐2
You rarely get on with the person you care for …… ☐3

15.2 Protocol amendments

15.3 Amendment Number - 1

Date of amendment – 29th September 2016

Statement of intent – Response to Human Research Ethics Committee review and PaCCSC Scientific Committee Review

List of specific changes

Change #1

- Section 5.1 Study medication
  - Reason for change – to clarify duration of treatment is a maximum of three weeks
    - Original text
      - Discharge or three weeks
    - New text
      - discharge or for a maximum of three weeks

- Section 5.14 Follow-up
  - Reason for change – inclusion of carer experience scale
    - New text
      - During the follow-up phase frequency of adverse events, delirium (based on medical record), quality of life, medication and health service usage will be measured up to death or 21 days after ceasing study medication (whichever is the shorter period). These data will be collected via a weekly telephone call to the participant if they have been discharged home. Carer experience will also be captured using the Carer Experience Scale.

- Section 7.7.1 Delirium Rating Scale – Revised 98
  - Reason for change – clarification of use of this measure
    - New Text - The Delirium Rating Scale – Revised 98 (DRS-R-98) will be used to confirm delirium presence and delirium severity.

- Section 7.8.6 Carer assessments
  - Reason for change – given impact of delirium on family carers it was deemed important to include carer measures in economic evaluation.
    - New text - The Carer Experience Scale[66] will be used to evaluate carer experience to inform the economic analysis, given the important impact delirium occurrence has on carers. This scale is a brief instrument, and has been validated in palliative care informal carers[67], and the responses can be used to calculate a 'QALY-type' measure. This will be measured at baseline, delirium occurrence if it

occurs and at followup. The Delirium Experience Questionnaire (DEQ) is a face-valid, brief instrument that assesses recall of the delirium experience and the degree of distress related to the delirium episode in patients, spouses/caregivers, and nurses. [68] It has been used to describe delirium experience in 154 hospitalised cancer patients, however its psychometric properties have not been established. There is however no other available instrument to measure distress hence it has been chosen for this study. The scale consists of several yes/no questions plus two five point Likert scale questions (for the patient), one Likert scale question for the carer and nurse versions, as well as an open question in each version to allow qualitative analysis of the experience. The carer version will be utilized at delirium occurrence and in followup (for those participants where delirium occurred) and for participants in followup if delirium occurred and has now resolved.

- Section 8.12 – Followup phase assessments
  - Reason for change – improve clarity of followup assessments
    - New text: Participants will enter a follow-up phase irrespective of their place of care until death or 21 days after ceasing the study medication (whichever is the shorter period); or if withdrawal of consent occurs. During the follow-up phase frequency of adverse events, delirium (based on medical record), quality of life, performance status, medication and health service usage will be collected.

15.4 Information sheets and consent forms

Patient Information sheet and consent form

15.5 Product information and investigator brochure