Risperidone and haloperidol for delirium

TITLE: Randomised control trial of oral risperidone, oral haloperidol, and oral placebo with rescue subcutaneous midazolam in the management of delirium in palliative care inpatients.

PROTOCOL NUMBER 002/07 V1.4.8

STUDY DRUG
- Oral risperidone solution 1mg/ml
- Oral haloperidol solution 2mg/ml

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DATE OF PROTOCOL 30th October 2014

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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 to conform with the CONSORT Guidelines1 and allow easy assessment for Jadad scores2. It complies with Guidelines for Good Clinical Practice in clinical research.

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<table>
<thead>
<tr>
<th>Name</th>
<th>Faculty/Department</th>
<th>Telephone</th>
<th>Qualifications</th>
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<tbody>
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<tr>
<th>Name</th>
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08 8275  
2859 |
|                            | B. Maths (Hons)  
M. Math  
PhD |
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<td>M Agar</td>
<td>New protocol from draft</td>
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## Protocol Approval

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TRIAL SUMMARY

Background: Delirium is prevalent in patients with advanced cancer and in the palliative care setting, and is associated with significant and distressing symptomatology and poor prognosis. Antipsychotics are considered by most clinicians as first line pharmacotherapeutic agents for delirium despite limited level 2 evidence for management of delirium in any health care setting, including palliative care. The few studies that exist explore post treatment efficacy in relation to total delirium score reduction, and do not guide management of target symptomatology. There has been no systematic evaluation of toxicity profile in relation to delirium management with typical or atypical antipsychotics, in particular extrapyramidal toxicity and degree of sedation. There is need for randomized control trial evidence of the efficacy of antipsychotics to control targeted delirium symptoms, and also to consider broader implications on caregiver and patient distress.

Study design: A randomised double blind placebo controlled phase III study to compare the effectiveness and toxicity of oral risperidone, oral haloperidol, and oral placebo with rescue subcutaneous midazolam in the management of palliative care patients with “Diagnostic and Statistical Manual of Mental Disorders – IV edition revised” (DSM IV – R) defined Delirium.

Objectives: Primary Objective: To compare the efficacy of oral Risperidone solution and control (oral placebo solution with subcutaneous midazolam rescue). Secondary Objectives: To compare oral Haloperidol solution and control; and oral Risperidone solution and oral haloperidol solution in control of targeted delirium symptoms at 72 hours from treatment commencement.

Treatment schedule: Commencing doses will be a loading dose of 0.5mg ((0.25mg in > 65yrs)., then 0.5 mg bd (0.25mg bd in > 65 yrs) in both haloperidol and risperidone arms, with 12 hourly increments based on target delirium symptom(s) score. Maximum dose will be 4mg, and 2 mg in those > 65 years. Rescue protocol commences at 2.5mg subcutaneously midazolam 2 hourly based on targeted delirium symptom(s) score, with titration protocol if ineffective.

Assessments: Delirium will be assessed using Nursing Delirium Screening Scale and Memorial Delirium Assessment Scale. Comorbidity burden, medication, and prior cognitive impairment will be assessed. Toxicity will be measured using validated scales - Extrapyramidal Symptom Rating Scale and Richmond Agitation Sedation Scale. Patient, caregiver and nurse rated distress due to delirium symptoms will be measured.

Primary endpoint: Change in sum of scores on Nursing Delirium screening scale (NuDesc) items 2 (inappropriate behaviour), 3 (inappropriate communication), and 4 (illusions/hallucinations) from baseline and follow-up (on day 3), where baseline is the average of the eligibility score on entry to the trial and the score obtained before the first dose is given, and follow up is the average of the last morning and evening scores on the third day.

Clinical response: A one-unit change between baseline and follow up scores.

Analysis: A total sample size of 110 patients (55 risperidone, 55 control) will provide 80% power to detect a difference in change of NuDesc score of 1 unit assuming a baseline Standard deviation of 1.92 units, and a correlation of at least 50% between baseline and follow-up scores. The change in sum of NuDesc scores (item 2, 3 and 4) between baseline and follow-up between arms will be evaluated as the group effect (coded 0/1) from the regression of the average of follow up scores on the average of baseline scores and group. Intention to treat analysis will be used.

Economic analysis: The economic evaluation will estimate incremental costs (resource use); patient effects; and caregiver and health professional consequences in comparisons of Risperidone, Haloperidol and placebo from patient level data collected over 28 days of follow up. Patient level resource use data collected to inform for this analysis will include: days spent in hospital (index admission and readmissions), in hospital use of nursing assistants, non hospital institutional bed days, medication use, general practitioner visits, home care palliative care team review visits. Data on

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effects and consequences collected to inform this analysis will include patient efficacy (Nursing delirium scale scores), toxicity, and medical complications and caregiver and health professional impact/distress.

Study diagram
Dose schedule timeline

Under 65 years

<table>
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<tr>
<th>Time point</th>
<th>Dose 1</th>
<th>Dose 2</th>
<th>Dose 3</th>
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<td>0</td>
<td>12 hrs</td>
<td>24 hrs</td>
<td>36 hrs</td>
<td>48 hrs</td>
<td>60 hrs</td>
<td>72 hrs</td>
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Maximum dose possible at that time point*

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<th>Volume (1mg/4ml)</th>
<th>1mg includes loading dose and first dose</th>
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Data point

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Data point

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Over 65 years

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Maximum dose possible at that time point*

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Data point

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* dose titration only occurs based on NuDesc score. At anytime point if NuDesc score < 1 on items 2,3,4 no titration will occur and patient will remain on prior dose level unless adverse events.

Table of study measures.

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| Measures | Medical file review |  |  |  |  |  |  |
|----------|---------------------|---|---|---|---|---|
| Demographics | * |  |  |  |  |  |
| Diagnosis | * |  |  |  |  |  |
| Barthel index | * | * | * | * | * | * |
| Con meds | * | * | * | * | * | * |
| Rescue medications |  | * |  |  | * |  |
| Anticholinergic scale | * | * |  |  |  | * |
| Admission data |  | * |  |  |  |  |
| Complications |  |  |  |  |  |  |
| **Patient measures** |  |  |  |  |  |  |
| Vision | * |  |  |  |  |  |
| Hearing | * |  |  |  |  |  |
| AKPS | * | * | * | * | * | * |
| MMSE |  | * |  |  | * |  |
| Pulse oximetry | * | * |  |  | * |  |
| Patient rated distress | * |  |  |  |  |  |
| EORTC QLQ – C30 or C15) |  |  | * |  |  |  |
| FACIT – Pal |  |  |  | * |  |  |
| Medical assessment | * |  | * |  |  |  |
| **Clinician assessed** |  |  |  |  |  |  |
| Toxicity | * | * |  |  |  |  |
| Cumulative illness rating scale | * |  |  |  |  |  |
| Charlson comorbidity index | * |  |  |  |  |  |
| Sedation | * | * |  |  |  |  |
| ESRS |  | * |  |  |  |  |
| MDAS | * |  | * |  |  | * |
| NuDESC |  | * |  | * | * | * |
| IQCODE |  |  |  |  |  |  |
| Nursing rated distress |  | * |  | * |  |  |
| Caregiver distress | * | * |  | * |  |  |
| Supportive measures | * | * |  | * |  |  |
| Survival |  |  |  |  | * |  |
| Date of death |  |  |  |  | * |  |
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<th>Description</th>
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<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>AIN</td>
<td>Assistants in Nursing</td>
</tr>
<tr>
<td>AKPS</td>
<td>Australia – modified Karnofsky Performance Status</td>
</tr>
<tr>
<td>AMH</td>
<td>Australian Medicines Handbook</td>
</tr>
<tr>
<td>BD</td>
<td>Twice daily</td>
</tr>
<tr>
<td>CAM</td>
<td>Confusion Assessment Method</td>
</tr>
<tr>
<td>CIRS</td>
<td>Cumulative Illness Rating Scale</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Forms</td>
</tr>
<tr>
<td>DRS</td>
<td>Delirium Rating Scale</td>
</tr>
<tr>
<td>DSM III R</td>
<td>Diagnostic and Statistical Manual of Mental Disorders. Third edition – revised</td>
</tr>
<tr>
<td>DSM IV R</td>
<td>Diagnostic and Statistical Manual of Mental Disorders. Fourth edition – revised</td>
</tr>
<tr>
<td>EPS</td>
<td>extrapyramidal side effects</td>
</tr>
<tr>
<td>EORTC QLQ C</td>
<td>European organization for Research and Treatment of Cancer-Quality of Life Questionnaire- core</td>
</tr>
<tr>
<td>ESRS</td>
<td>Extrapyrmal Symptom Rating Scale</td>
</tr>
<tr>
<td>FACIT-PAL</td>
<td>Functional Assessment of Cancer Therapy scale - Palliative care</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>HREC</td>
<td>Hospital Research Ethics Committee</td>
</tr>
<tr>
<td>ID</td>
<td>Identification number</td>
</tr>
<tr>
<td>IQCODE</td>
<td>Short informant Questionnaire on Cognitive Decline in the Elderly</td>
</tr>
<tr>
<td>IVI</td>
<td>Intra Venous Injection</td>
</tr>
<tr>
<td>MDAS</td>
<td>Memorial Delirium Assessment Scale</td>
</tr>
<tr>
<td>NuDesc</td>
<td>Nursing Delirium Screening Scale</td>
</tr>
<tr>
<td>PaCCSC</td>
<td>Palliative Care Clinical Studies Collaborative</td>
</tr>
<tr>
<td>QT Interval</td>
<td>The relationship between two conduction points on an electrocardiograph (ECG)</td>
</tr>
<tr>
<td>RASS</td>
<td>Richmond Agitation Sedation Scale</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>SOP</td>
<td>Standard Operating Procedure</td>
</tr>
<tr>
<td>TGA</td>
<td>Therapeutic Goods Administration</td>
</tr>
</tbody>
</table>
1.0 Background and rationale

1.1 The importance of randomised control trial evidence in for use of risperidone in management of delirium:

Prevalence, morbidity and mortality:

Delirium is prevalent in patients with advanced cancer and in the palliative care setting (3, 4). It is associated with significant and distressing symptomatology and poor prognosis (3, 4). Delirium has been reported to occur on admission to hospital in patients with advanced cancer in 28% - 48%, and up to 90% in the hours to days before death (3). The incidence of new episodes of delirium during admission has been reported as ranging between 20 and 45% (5). In the advanced cancer population occurrence of delirium is an independent predictor of mortality (6-8).

Several studies have shown an association between an episode of delirium and increased length of hospital stay, postoperative complications, increased risk of institutionalisation, mortality and functional and cognitive decline (9-17). In cancer patients delirium is an independent predictor of mortality, but information about functional and cognitive outcomes is lacking (6-8).

More recent focus has been on psychological morbidity experienced by patients, caregivers, and/or health care providers (18). Maintaining lucidity at the end of life has been identified by patients and their families as very important, however is less likely to be identified by their treating physicians (19, 20). It can be extrapolated that mental awareness can also be a crucial component in allowing patients to achieve the other significant goals at the end of life such as communication with their physician regarding decision making, achieving a sense of completion and preparation for death (19, 20).

Patient and Caregiver impact:

It is often assumed that the majority of patients are unable to recall a delirium episode, however case reports and emerging data contradict this (21, 22). A prospective cohort study of 154 hospitalised cancer patients meeting DSM IV criteria for delirium demonstrated that in the 101 patients with delirium resolution, 53.5% recalled their delirium experience (18). The presence of delusions was the most significant predictor of patient distress, the performance status of the patient predicted spouse/caregiver distress, and presence of perceptual disturbance predicted nurse distress (18). Distress occurred for both hyperactive and hypoactive delirium, with 43% of patients with hypoactive subtype and 66% of hyperactive subtype recalling the experience (18).

Similarly, a study of bereaved family members who were asked to rate frequency and level of distress for 12 delirium related symptoms; showed that more than two thirds found all delirium symptoms other than somnolence distressing (23). The symptoms families recalled their family member experiencing were physical restlessness and mood lability (62%), hallucinations and delusions (35%), somnolence (92%) and cognitive symptoms (72%) (23).
A qualitative study exploring the impact on families of delirium, described families perception was emotionally and physically distressing to patients, a powerful sense it was related to multidimensional suffering, and disappointment in lack of ability to have meaningful conversation (24). In regard to pharmacological management family members were ambivalent, expressing on one hand they did not wish their loved one to suffer, but that it also that it distanced them and reduced ability to say goodbye, or communicate (24). Some expressed their belief medication were used so “they didn’t bother anyone” (24).

**1.2 Patho-physiological abnormalities in delirium and rationale for intervention:**

Delirium is conceptualised as a disorder of “arousal and cognition”, however its pathophysiology is poorly defined (4, 25). The dominant theory is of central neurotransmission abnormality with cholinergic deficiency, serotonin deficiency and/or dopaminergic excess, either absolute or relative to each other (26-32). Cholinergic transmission is relevant to many aspects of arousal, sleep, attention and memory, and cholinergic failure is a postulated mechanism of delirium (33). The cholinergic system has been implicated due to propensity of anticholinergic medications to cause delirium, and impairment of this system in ageing and dementia which also are predisposing factors for delirium (33-35).

Antipsychotics have become the pharmacological agent of choice for delirium management, extrapolated from the evidence that dopamine and serotonin antagonists reduce psychotic symptoms in other disorders such as schizophrenia (36). Haloperidol is thought to block positive psychotic symptoms (hallucinations, delusions) by blocking dopaminergic D2 activity in the mesolimbic pathway, however this same action in nigrostriatal pathway results in extrapyramidal symptoms (37). It also blocks anticholinergic (muscarinic), histamine (H1) and noradrenergic (α1) receptors leading to other adverse effects (sedation, blurred vision, dry mouth, orthostatic hypotension, dizziness) (37). The atypical antipsychotics (in particular risperidone, olanzapine, and quietiapine) have gained popularity given their specific pharmacological property of serotonin 2A-dopamine 2 (5HT2A/D2) antagonism, a property that theoretically leads to less toxicity, in particular extra-pyramidal side effects (36, 37).

**1.3 Role of neuronal apoptosis and serum marker of neuronal injury:**

The sequelae of delirium are also uncertain, however direct neuronal injury is likely in some cases, and may be related to the long term outcomes (32). Serum markers that detect neuronal injury may be relevant in delirium onset, delirium persistence and adverse cognitive sequelae; and have been studied in situations of direct neuronal injury (stroke, head trauma, subarachnoid haemorrhage, post cardiac surgery) where relationships to degree of damage sustained have been seen (32, 38). These markers also may provide an indicator for the impact of pharmacotherapeutics in patho-physiological mechanisms, and hence potential to improve/impact long term outcomes. S 100 beta is a serum protein that can be assayed using enzyme linked immunosorbent assay methods using arterial or venous serum (32, 39). The role of protein S-100B is not yet fully understood, however it seems to have intracellular and extracellular neurotropic as well as neurotoxic function (39). At nanomolar levels, S-100B stimulates neurite outgrowth and enhances survival of neurons (39). However, at micromolar levels it stimulates the expression of inflammatory cytokines and induces apoptosis (39). Other markers which have been studied include Cytochrome C, Caspase 3 and Neuron Specific Enolase, and these also have a role in neuronal cell death (40-43).
1.4 Existing evidence for pharmacological management of delirium.

Antipsychotics are considered by most clinicians as first line pharmacological agents for delirium despite limited randomized double blind controlled evidence for management of delirium in any health care setting, including palliative care (44). These studies explore post treatment efficacy simplistically, in relation to total delirium score reduction. There has been no systematic evaluation of toxicity profile in relation to delirium management with typical or atypical antipsychotics. These studies also were not adequately powered to detect predetermined efficacy outcomes.

The initial randomized study was in 30 hospitalized AIDS patients with DSM III R defined delirium, comparing haloperidol, chlorpromazine and lorazepam (45). This study showed delirium rating scale (DRS) scores significantly reduced to below the threshold for diagnosis of delirium in the haloperidol and chlorpromazine arms within 24 hours, with little or no further improvement after day 2, but not in lorazepam arm (45). All six patients in the lorazepam arm had treatment limiting adverse events (sedation, increased confusion, ataxia and disinhibition) leading to discontinuation of the drug (45).

There has only been one randomised double blind trial of risperidone versus haloperidol, in 28 oncology, general medical and intensive care patients with DSM IIIR defined delirium (46). This study did not rigorously assess for adverse events, or assess more complex outcomes such as health service utilisation (46). The results of this study was reduced Memorial Delirium Assessment Scale (MDAS) total scores in both groups, with no significant difference in mean scores between groups, and group by-time effect not significant (46). One patient had severe sedation with haloperidol, and one patient mild akathisia (46). The average time to response was 4.22 days in haloperidol arm, and 4.17 days in risperidone arm (46).

There have been several case reports, three open label prospective studies, and one retrospective study exploring the role of risperidone in delirium in palliative care patients (47-52). These studies have supported the hypothesis that risperidone may be efficacious in controlling delirium symptoms, and may have less extrapyramidal side effects. Horikawa et al reported use of oral risperidone in 10 medical and surgical inpatients (0.5mg/day titrated by 0.5 m/day until DRS score 50% of baseline). The average dose used in this study was 1.7mg/day; and in 8 of the 10 patients moderate to marked improvement in DRS score was reported (53). Mittal et al did a similar study using risperidone 0.5 mg bd, and used a fixed titration schedule until DRS score < 12, and demonstrated that DRS scores improved from day 1 and remained improved up to day 6, with mean extrapyramidal symptom rating scale scores low and decreased by day 6 (50). A larger study of 64 hospitalised medical patients with DSM- IV R defined delirium used mean daily doses of 2.6mg (± 1.3mg), had 90% of participants achieve DRS scores less than 13 within 72 hours of treatment, with two patients experiencing drowsiness (54).

A more recent prospective open label flexible dose study (n=10) measured plasma concentrations of risperidone, 30 minutes after administration of the first 0.5mg dose of risperidone oral solution (55). The plasma concentrations varied between 0.3 – 14.60 ng/ml. The two patients who had the highest concentrations experienced daytime somnolence, whereas the patient with the lowest plasma level did not achieve remission of delirium.
symptoms (defined as Delirium rating scale – Japanese version score less than 12). This study however did not measure steady state concentrations.

1.5 Conclusions and aims:

Delirium is a significant clinical problem in palliative care, from both a clinical and consumer perspective. There is currently limited evidence in the understanding of patho-physiology processes involved and no adequately powered randomized evidence to guide pharmacotherapeutic options.

Following review of the data available from clinical trials it was concluded that additional data is required in order to justify the use of either risperidone or haloperidol in the treatment of delirium in the palliative care setting. Risperidone is currently not approved for use for this indication despite current clinical use. There are currently no drugs approved for the treatment of delirium. The most appropriate study design is to compare risperidone and haloperidol against a placebo (56).

A placebo controlled arm can be justified as (a) there is no currently approved medication (b) there are short and long term side effects of medications in both active arms that may outweigh any benefit of the study medications, if the clinical benefits are marginal (c) there are accepted non-pharmacological approaches to mild delirium that may be of equal or greater benefit than medications.

The haloperidol arm has been included in this study as it is currently in wide clinical use for this symptom. There are sparse outcome data for this medication in the treatment of delirium, although there are clinical practice guidelines suggesting that it may be of some use. The extent of benefit has not been quantified, nor the population most likely to benefit from this intervention.

The primary aim is to compare the efficacy of regular oral risperidone solution and oral placebo solution, for treatment of delirium, and the incidence of adverse effects in particular extrapyramidal side effects.

The secondary aim is to compare efficacy of regular oral haloperidol solution and oral placebo solution; and oral haloperidol and oral risperidone; for treatment of delirium, and the incidence of adverse effects in particular extrapyramidal side effects.

The other secondary aims are to consider the economic implications; patient, caregiver and health professional rated distress in relation to delirium episode, and to explore pathophysiological correlates of delirium management.

1.6 Rationale and significance:

Current practice for the pharmacological management of delirium is limited to anti-psychotics, most commonly haloperidol, and little empirical evidence of its efficacy. Risperidone is also used in the clinical setting, with similar limitations, and has the potential of equal efficacy, but lower incidence of extrapyramidal effects associated with the typical antipsychotics (e.g
Haloperidol). This adequately powered study will help guide clinical practice for the control of delirium, in particular in relation to targeted delirium symptomatology.
2.0 STUDY OBJECTIVES

2.1 Aim:

To improve the pharmacological management of delirium in palliative care patients.

2.2 Objectives

2.2.1 Primary objective:

To compare the efficacy of oral risperidone solution and control (oral placebo solution with subcutaneous midazolam rescue), in control of targeted delirium symptoms at 72 hours from treatment commencement.

2.2.2 Secondary objectives:

A: Efficacy:
1. To compare the efficacy of oral haloperidol solution and control (oral placebo solution with subcutaneous midazolam rescue); in control of targeted delirium symptoms at 72 hours from treatment commencement.
2. To compare the efficacy of oral haloperidol solution and oral risperidone solution; in control of targeted delirium symptoms at 72 hours from treatment commencement.
3. To describe time profile of delirium in the three treatment arms (delirium duration, severity, subtype, cognitive impairment and resolution).
4. To describe:
   - Patient reported distress on delirium resolution.
   - Caregiver and health professional rated distress.
   - Improvement in cognition.
   - Requirement for usage of rescue midazolam protocol.
   - Dosage and length of administration.

B: Toxicity:
To compare the toxicity of oral risperidone solution, oral haloperidol solution versus control (oral placebo solution and subcutaneous midazolam rescue), in terms of:

   - Extrapyramidal side effects.
   - Sedation.

C: Pathophysiology:

To explore the pathophysiological correlates (serum marker of neuronal apoptosis (S 100 beta and other serum markers) over time in patients treated with oral risperidone solution, oral haloperidol solution and oral placebo solution with rescue midazolam, and compare associations with outcomes.

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D: Health outcomes and health services utilisation:

To compare the incremental effectiveness and costs of risperidone in comparison to placebo; and haloperidol in comparison to placebo in terms of:

- Age care facility admissions
- Medical complications (Pressure ulceration, thromboembolism, Pneumonia, falls, incontinence) [while inpatient]
- Usage of Assistants in Nursing (hours).
- Persistent Cognitive impairment.
- Functional decline.
- Survival. [time as a total]
- Survival time outside of institutional care
- Acute care hospital or palliative care unit admissions.
- Readmission for second episode of delirium.
- Inpatient Medication use
- General practitioner use
- Quality of life

2.3 Null Hypothesis

2.3.1 Primary null hypothesis:
There is no difference between change between baseline and follow up in the sum of scores on Nursing Delirium screening scale (NuDesc) items 2 (inappropriate behaviour), 3 (inappropriate communication), and 4 (illusions/hallucinations) in the oral risperidone (delivered in oral solution with dose titrated to effect – dose range of 0.5 mg/24 hours to 4mg/24 hours) and oral placebo solution arms.

2.3.2 Secondary null hypotheses:

1. There is no difference between change between baseline and follow up in sum of scores on Nursing Delirium screening scale (NuDesc) items 2 (inappropriate behaviour), 3 (inappropriate communication), and 4 (illusions/hallucinations) in the oral haloperidol (delivered in oral solution with dose titrated to effect – dose range of 0.5 mg/24 hours to 4mg/24 hours) and oral placebo solution arms.

2. There is no difference between change between baseline and follow up in sum of scores on Nursing Delirium screening scale (NuDesc) items 2 (inappropriate behaviour), 3 (inappropriate communication), and 4 (illusions/hallucinations) in the oral risperidone (delivered in oral solution with dose titrated to effect – dose range of 0.5 mg/24 hours to 4mg/24 hours) and oral haloperidol solution (delivered in oral solution with dose titrated to effect – dose range of 0.5 mg/24 hours to 4mg/24 hours) arms.
3.0 STUDY POPULATION

Palliative care inpatients with incident or prevalent delirium as defined by:

- DSM IVR criteria for diagnosis of delirium.
- Memorial Delirium Assessment Scale (MDAS) score ≥ 7.

3.1 Inclusion criteria:

- Diagnosis of Delirium as defined by DSM IVR criteria for delirium and MDAS score ≥ 7.
- Score on Nursing Delirium screening scale items 2 (inappropriate behaviour), and/or item 3 (inappropriate communication), and/or item 4 illusions /hallucinations) ≥1 (items 1 and 5 are not targeted symptoms in this study and will not be used in this assessment)
- Age ≥ 18.
- English speaking or access to health care interpreter
- Proxy written informed consent.
- Cancer or non-cancer life limiting illness.
- Able to take oral medication in solution formulation.

3.2 Exclusion criteria:

- Delirium due to alcohol or other withdrawal syndrome where more specific treatment is indicated.
- Current or past history of neuroleptic malignant syndrome.
- Regular antipsychotic use within past 48 hours. A single ‘as required’ (PRN) dose of haloperidol, prochlorperazine or levomepromazine is allowed if
  - administered more than 24 hours previously
  - the dose was at or below the study dose for the age group
  - prescribed for a non delirium indication
- Maintenance on antipsychotic required for other diagnosis.
- Previous adverse reaction to any of the study medications.
- Established Parkinson’s disease or other extrapyramidal disorder.
- Documented prolonged QT syndrome (greater than 0.43sec for males, 0.45 for females).
- Clinician predicted survival less than seven days.
- Cerebrovascular accident with in the last month.
- Seizure within the last month.
- Pregnant or breastfeeding.
4.0 INVESTIGATIONAL PLAN

4.1 Overall study design:

A randomised double blind placebo controlled phase III study to compare the effectiveness and adverse events of oral risperidone, oral haloperidol, and oral placebo with rescue midazolam in the management of palliative care patients with “Diagnostic and Statistical Manual of Mental Disorders – IV edition revised” (DSM IV – R) defined Delirium and Memorial Delirium Assessment Scale score ≥ 7.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Intervention</th>
<th>Study phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delirium</td>
<td>Medication: oral risperidone solution and rescue midazolam protocol</td>
<td>Phase III</td>
</tr>
<tr>
<td></td>
<td>Medication: oral haloperidol solution and rescue midazolam protocol</td>
<td></td>
</tr>
</tbody>
</table>

Patients with cancer or non-cancer life limiting illness and who develop symptoms of delirium during their inpatient admission will be asked to participate. Those who provide consent (via a proxy consent process) will be randomised to receive either risperidone, haloperidol or placebo as an oral solution over 72 hours; with a rescue midazolam protocol in all arms.

4.2 Treatment arms:

Arm I: RISPERIDONE: Risperidone oral solution with rescue protocol for 72 hours
Arm II: HALOPERIDOL: Haloperidol oral solution with rescue protocol for 72 hours
Arm III: CONTROL: Placebo oral solution with rescue protocol for 72 hours

All participants in the three arms of the study will receive active non medication measures for management of delirium (including assessment for and interventions for potentially reversible precipitants where clinically indicated; and non-pharmacological measures such as attention to hydration, sensory deprivation (vision and hearing aids), presence of familiar family and reorientation). Due to the individual nature of precipitants the non-medication management will be decided by treating clinician.

The product information for each treatment is attached.
4.3 Study diagram

- Palliative care inpatient
  - Consent and Screening on delirium development
    - Incident delirium
    - Prevalent delirium
      - Randomisation
        - Risperidone oral solution + rescue protocol
        - Haloperidol oral solution + rescue protocol
        - Placebo oral solution + rescue protocol
          - 72 hours Safety and efficacy assessments
            - Study exit
              - Follow-up, weekly for 3 weeks by telephone and one visit at one month.
5.0 INTERVENTIONS

5.1 Study medication:

1. Oral risperidone solution 1mg/4 ml.
   a. Twenty ml of risperidone oral solution 1mg/ml will be diluted with 60mls of placebo solution containing;
      i. Lactic acid B.P
      ii. Comp. hydroxybenzoate solution A.P.F
      iii. Sodium hydroxide 2%
      iv. Water for irritation

2. Oral haloperidol solution 1mg/4 ml.
   a. Ten ml of haloperidol oral solution 2mg/ml will be diluted with 70mls of placebo solution containing;
      i. Lactic acid B.P
      ii. Comp. hydroxybenzoate solution A.P.F
      iii. Sodium hydroxide 2%
      iv. Water for irrigation

3. Oral placebo solution.
   a. Placebo solution will be manufactured in 100ml batches of;
      i. Lactic acid B.P 1.1g
      ii. Comp. hydroxybenzoate solution A.P.F 1ml
      iii. Sodium hydroxide 2% for pH adjustment
      iv. Water for irrigation to a volume of 100ml


5.2 Dosing schedule

If 65 years or less, participants will be given a loading dose of 0.5mg together with the first dose of 0.5mg (total dose 1.0mg), then 12 hours later commenced on maintenance dose (first dose level 0.5mg BD). The dose will be adjusted in increments of 0.25mg (every 12 hours for first 24 hours) after assessment at 8am and 5pm each day. The dose can be titrated from first 12th hourly dose. At or after 24 hours if symptoms persist/recur dose can be adjusted by increments of 0.5 mg every 12 hours.

If over 65 years, participants will be given a loading dose of 0.25mg together with the first dose of 0.25mg (total dose 0.5mg), then 12 hours later commenced on maintenance dose (first dose level 0.25mg BD). The dose will be adjusted in increments of 0.25mg (every 12 hours for first 24 hours) after assessment at 8am and 5pm each day. The dose can be titrated from first 12th hourly dose. At or after 24 hours if symptoms persist/recur dose can be adjusted by increments of 0.5 mg every 12 hours.

Dose titration only occurs based on the NuDesc score. At anytime point if the NuDesc score is < 1 on the sum of items 2, 3, and 4 no titration will occur and patient will remain on prior dose level unless there is evidence of adverse events or symptoms in which case the dose can be reduced to the previous dose. If the NuDesc score on the sum of items 2 (inappropriate behaviour), 3 (inappropriate communication), and 4
(illusions/hallucinations) is ≥1 the dose can be titrated up according to the following tables.

<table>
<thead>
<tr>
<th>Age</th>
<th>Loading dose</th>
<th>Starting dose given with loading dose</th>
<th>Titration at dose 2</th>
<th>All other titrations</th>
<th>Titration Down</th>
<th>Maximum 24 hourly dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 65</td>
<td>0.25 mg*</td>
<td>0.25 mg</td>
<td>0.25 mg</td>
<td>0.5 mg</td>
<td>0.25 mg</td>
<td>2 mg/24 hrs</td>
</tr>
<tr>
<td>≤ 65</td>
<td>0.5 mg*</td>
<td>0.5 mg</td>
<td>0.25 mg</td>
<td>0.5 mg</td>
<td>0.25 mg</td>
<td>4 mg/24 hrs</td>
</tr>
</tbody>
</table>

* first dose increase is on commencement dose of 0.5 mg (or 0.25 mg if > 65 years) not inclusive of loading dose
Dose modification applies for either risperidone, haloperidol, or placebo arms.

Standard dosing times will be 8am and 8pm. NuDesc scores will be taken at the end of each nursing shift (8 hourly intervals). The 8 am dose will be determined by 8 am NuDesc score and 8 pm dose determined by 4 pm NuDesc score; however if there is a change in the patient condition between the time of the afternoon NuDesc score and the evening study dose, the NuDesc is to be repeated. If at this point, the NuDesc indicates a change in the patient condition, the site investigator is to be called so that the evening study dose can be reviewed.

The maximum duration of the study will be 72 hours (or 12 hours after the 6th dose). Patients who show a response and or side effects can increase or decrease the dose from one dose to the next at the same incremental levels as described above.

Where-ever possible the loading dose should be given at same time as first dose. If the time to first dose is long loading dose can be given initially, prior to first dose which will be given at scheduled time after discussion with investigator.
5.3 Dose schedule diagram.

Over 65 Years

> 65 years

- Loading dose 0.25mg
- Commencement dose 0.25 mg BD
- Toxicity Assessment
  - None
  - ≥1 on sum of items 2, 3, and 4
    - Increase dose to 0.5 mg BD
    - ≥1 on sum of items 2, 3, and 4
      - Increase dose
    - < 1 on sum of items 2, 3, and 4
      - NuDesc Prior to dose 3 (8-9am)
      - Remain on current dose
    - NuDesc Prior to dose 2 (4-5pm)
      - < 1 on sum of items 2, 3, and 4
      -Reduce dose
      - Adverse events or clinically indicated
- Toxicity grade as per page 39
- Withdraw
Under 65 Years

≤ 65 years

- Loading dose 0.5mg
- Commencement dose 0.5 mg BD

Toxicity Assessment

- Toxicity grade as per page 39
- None

- ≥1 on sum of items 2, 3, and 4
- NuDesc Prior to dose 2 (4-5pm)
- < 1 on sum of items 2, 3, and 4
- Increase dose to 0.75 mg BD
- Remain on 0.5mg

- NuDesc Prior to dose 3 (8-9am)
- ≥1 on sum of items 2, 3, and 4
- < 1 on sum of items 2, 3, and 4

- Increase dose
- Remain on current dose
- Reduce dose

Continuation

Continue to assess twice daily and increase dose based on NuDesc, or decrease dose based on adverse events

Yes

- Delirium resolution (MDAS <7 for 48 hours)
- Remain on blinded study medication for 2 days while reducing dose

No

- Cease study medication and treat as clinically indicated
5.4 Dose schedule (maximum possible titrations) timeline

Under 65 years

<table>
<thead>
<tr>
<th>Time point</th>
<th>Dose 1</th>
<th>Dose 2</th>
<th>Dose 3</th>
<th>Dose 4</th>
<th>Dose 5</th>
<th>Dose 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1mg</td>
<td>0.75</td>
<td>1.25</td>
<td>1.75</td>
<td>2.0</td>
<td>2.0</td>
</tr>
<tr>
<td>12 hrs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 hrs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>36 hrs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>48 hrs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60 hrs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>72 hrs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum dose possible at that time point*</td>
<td>includes loading dose and first dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Volume (1mg/4ml) | 4 | 3 | 5 | 7 | 8 | 8 | - |

<table>
<thead>
<tr>
<th>Data point</th>
<th>0830</th>
<th>1600-1700</th>
<th>0830</th>
<th>1600-1700</th>
<th>0830</th>
<th>1600-1700</th>
<th>0830 (study exit)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data point</td>
<td>0830</td>
<td>1600-1700</td>
<td>0830</td>
<td>1600-1700</td>
<td>0830</td>
<td>1600-1700</td>
<td>0830 (study exit)</td>
</tr>
<tr>
<td>CRF point</td>
<td>Baseline</td>
<td>Daily visit 1</td>
<td>Daily visit 2</td>
<td>Daily visit 3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Over 65 years

<table>
<thead>
<tr>
<th>Time point</th>
<th>Dose 1</th>
<th>Dose 2</th>
<th>Dose 3</th>
<th>Dose 4</th>
<th>Dose 5</th>
<th>Dose 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.5mg</td>
<td>0.5</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>12 hrs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 hrs</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>36 hrs</td>
<td></td>
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<tr>
<td>48 hrs</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60 hrs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>72 hrs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum dose possible at that time point*</td>
<td>includes loading dose and first dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Volume (1mg/4ml) | 2 | 2 | 4 | 4 | 4 | 4 | - |

<table>
<thead>
<tr>
<th>Data point</th>
<th>0830</th>
<th>1600-1700</th>
<th>0830</th>
<th>1600-1700</th>
<th>0830</th>
<th>1600-1700</th>
<th>0830 (study exit)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data point</td>
<td>0830</td>
<td>1600-1700</td>
<td>0830</td>
<td>1600-1700</td>
<td>0830</td>
<td>1600-1700</td>
<td>0830 (study exit)</td>
</tr>
<tr>
<td>CRF point</td>
<td>Baseline</td>
<td>Daily visit 1</td>
<td>Daily visit 2</td>
<td>Daily visit 3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* dose titration only occurs based on NuDesc score. At anytime point if NuDesc score < 1 on the sum of items 2, 3, and 4 no titration will occur and patient will remain on prior dose level unless adverse events.

5.5 Method of assigning participants to treatment groups

Over the course of the study, participants will be allocated a series of identifying numbers. A two digit study number, a two digit site number, and a sequential three digit screening number will be allocated on referral to the study. This ID number will be used
for all subsequent study documentation for that participant. The procedures outlined in
the Standard Operating Procedures (5.5.5 Allocation of ID Number) are to be followed. 
In addition, a 3 digit randomisation number will be allocated on randomisation of the
participant. The full number sequence will be unique to that participant and will not be
reassigned.

Randomisation schedules will be developed for each site using random number tables,
generated at an independent centre (central registry). Treatment for each patient will be
allocated according to a block randomisation (blocks of 6) schedule held by the central
registry in a 1:1:1 ratio. Block randomisation will ensure even allocation to each code in
each site. The central registry will supply the schedule tables to each site pharmacy. 
This is described in more detail within the Randomisation Standard Operating 
Procedure (4.7.1 Randomisation).

The pharmacist at each site will allocate the next lowest code available according to the
supplied schedule and prepare the active or inactive drug delivered in a labeled opaque 
screw top bottle. The participant ID, allocation code, dates of request, preparation, and
dispensing will be recorded in a log maintained by the pharmacist.

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 lead investigator following the unblinding procedures.

5.6 Blinding

All medication bottles will be prepared by the site clinical trial pharmacist according to
the randomisation schedule. Each bottle will be numbered according to the pre-
determined allocation code and labeled as 002/07 study – risperidone (1mg/4ml
containing 80ml) / haloperidol (1mg/4ml containing 80ml) / placebo (80 ml) oral
solution. All opaque bottles will look identical in volume and colour to preserve the
blinding irrespective of the contents. The 80 ml volume will contain the entire study
drug needs for the patient over the study timeframe of 72 hours, allowing for the
maximum allowable doses.

Treatment allocation will not be disclosed to patient and their proxy, 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.

5.7 Method of administration

The pharmacist will locate the appropriate solution according to the randomisation
schedule immediately prior to dispensing the study medication. All medications must be
prepared in pharmacy and dispensed as a 80 ml volume in a screw top, opaque bottle.
The intervention will be delivered as oral solution. At each dose, the individually labeled bottle will be opened and the prescribed dose drawn into a 5 or 10 ml terumo or BD syringe (dependant on the dose to be administered), in order to accurately check the dose volume for administration to the patient. The clinical nurse will observe the participant while the participant drinks the entire contents of the syringe, and then record the administration in the medication record.

5.8 Drug accountability
All active drug must be stored undiluted in a locked drug 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 drug will be stored within a locked drug cabinet appropriate to state regulations. The drug will be checked and recorded by an appropriately qualified nurse on administration to the patient.

5.9 Drug supply
All study drug will be manufactured by an external facility and supplied to each site pharmacy in pre-prepared and coded bottles. The drug will be supplied in the following manner;

1. Risperidone 1mg/ml will be diluted with inactive solution base (see Section 5.1) to a concentration of 1mg/4ml and be supplied as a 80 ml volume within an opaque screw top bottle. This volume will enable accurate measurement of the regular (0.5mg) and incremental doses (0.25mg to 0.5mg) with a maximum dose available to the participant of 2 mg bd (8 ml volume). Allowing for slight measurement differences, this will make a maximum of 80mls available to the participant over the total 6 doses assuming the maximal titration rate. Once manufactured, an expiry date of 28 days will apply.

2. Haloperidol 2mg/ml will be diluted with inactive solution base (see Section 5.1) to a concentration of 1mg/4ml and be supplied as a 80 ml volume within an opaque screw top bottle. This volume will enable accurate measurement of the regular (0.5mg) and incremental doses (0.25mg to 0.5mg) with a maximum dose available to the participant of 2 mg bd (8 ml volume). Allowing for slight measurement differences, this will make a maximum of 80mls available to the participant over the total 6 doses assuming the maximal titration rate. Once manufactured, an expiry date of 28 days will apply.

3. Placebo. An inactive solution base (as described in section 5.1) will be supplied in a screw top, opaque bottle containing 80 ml. Once manufactured, an expiry date of 28 days will apply.

5.10 Drug destruction
Unused syrup in the inpatient unit, as well as any empty bottles, will be delivered back to the pharmacy, using the established practice within the hospital.

All unused syrup and empty bottles returned to pharmacy will be stored until study monitoring and then 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.

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

5.12 Rescue medications
Rescue medications are available for administration throughout the 72 hour intervention period. The medication can be initiated at the time of first treatment if the indications below are met.
5.12.1 Rescue dose diagram

Toxicity symptoms

Uncontrolled delirium symptoms

NuDesc score 2 (Inappropriate behaviour Or Illusions/hallucinations)

Yes

Dose level 1
Midazolam 2.5mg sc 2 hrly prn

No Response

Dose level 2
Midazolam 5mg sc 2hrly prn

No Response

Crisis dose
5mg sc stat

Laryngeal spasm

Dyspnoea, laryngeal stridor, patient may grab throat or chest, respiratory distress.

Yes

Stop study drugs.
Urgent medical attention required.
Attention to airway, breathing and circulation.
IVI benzotropine 1 – 2 mg.

No

Continue current dose

Dystonic reaction

Intermittent, sustained, often painful muscular spasms, Dysphagia, mandibular dislocation or laryngeal obstruction in severe events.

Yes

Stop study drugs.

No

Severe sedation

Multifactorial aetiology delirium symptomatology or patient entering terminal phase of their illness. Consideration of the temporal relationship

Yes

Clinician decision based on assessment of aetiology

5.12.2 Uncontrolled delirium symptoms:

Any NuDesc scores of 2 on one or more of the items listed below, that requires immediate intervention for patient and or staff safety, or due to patient distress can result in the following rescue midazolam doses in consultation with the investigator.

2. 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

4. ILLUSIONS/HALLUCINATIONS:

Seeing or hearing things that are not there, distortion of visual objects.

<table>
<thead>
<tr>
<th>Dose level of intervention</th>
<th>Dosing of midazolam rescue</th>
<th>frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose Level 1:</td>
<td>2.5mg subcutaneous</td>
<td>Q2h prn</td>
</tr>
<tr>
<td>Dose level 2:</td>
<td>5mg subcutaneous</td>
<td>Q2h prn</td>
</tr>
<tr>
<td>Can be increased by treating clinician if no response to dose level 1 on two repeated doses.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crisis dose</td>
<td>5mg subcutaneous</td>
<td>stat</td>
</tr>
</tbody>
</table>

Benzodiazepines for Sleep disturbance, dyspnoea or seizure control are allowed as clinician prescribes and will be calculated as diazepam dose equivalents:

In event of non response to crisis dose further therapy is at the discretion of the treating physician.

Midazolam administered for symptoms other than delirium symptoms are to be ordered separately on the prescription orders, clearly prescribing the indication for administration.

5.12.3 Laryngeal spasm:
Symptom cluster: Dyspnoea, laryngeal stridor, patient may grab throat or chest, respiratory distress. Dystonic reactions may be present in other parts of the body e.g head, neck, pharynx. Differential diagnosis is acute anaphylaxis or airway obstruction from other causes.

Immediate cessation of study drugs. Urgent medical attention is required and attention to airway, breathing and circulation. IVI benzotropine 1 – 2 mg.

5.12.4 Dystonic reaction
Symptom cluster: typically intermittent or sustained, often painful muscular spasms, producing twisting and abnormal postures of the eyes, jaw, face, neck, limbs or axial structures. Severe events can produce dysphagia, mandibular dislocation or laryngeal obstruction.

Immediate cessation of drug. IVI benzotropine 1 – 2 mg. These reactions respond well to treatment and cessation of drug.
5.12.5 Severe sedation:
Richmond Agitation and Sedation Score of -3 to -5. Consideration of multifactorial aetiology given fluctuating level of consciousness may be part of delirium symptomatology or patient entering terminal phase of their illness. Consideration of the temporal relationship to dose titration is important.

Clinician decision whether drug cessation or dose reduction is required will be dependant on individual clinical circumstances.

5.13 Dose modification for reduction or cessation (toxicity or resolution)
The study drug dose can be increased or decreased according to participant response as described in the table below:

<table>
<thead>
<tr>
<th>Measure</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose decrease at 12 hourly dosing.</td>
<td>If adverse events occurred</td>
</tr>
<tr>
<td></td>
<td>Reduce by 0.25 mg at each 12 hourly dosing.</td>
</tr>
<tr>
<td></td>
<td>If delirium symptoms re-appear then the participant is to have</td>
</tr>
<tr>
<td></td>
<td>treatment ceased (retitration is not possible due to prior adverse</td>
</tr>
<tr>
<td></td>
<td>events).</td>
</tr>
<tr>
<td>Discontinuation of therapy for</td>
<td>If delirium resolution - MDAS score &lt; 7 for 48 hours and Sum of</td>
</tr>
<tr>
<td>delirium resolution – Dose reduction</td>
<td>Nudesc items 2 (inappropriate behaviour), and 3 (inappropriate</td>
</tr>
<tr>
<td>protocol</td>
<td>communication), and 4 (illusions/hallucinations) &lt; 1 for 48 hours</td>
</tr>
<tr>
<td></td>
<td>Reduce by 0.25mg at each 12 hourly dosing</td>
</tr>
<tr>
<td></td>
<td>At dose level that symptoms reappear – increase by 0.25 mg bd</td>
</tr>
<tr>
<td></td>
<td>(if occurs after 72 hours clinician can decide to change to</td>
</tr>
<tr>
<td></td>
<td>alternative treatment of choice and stop study drug).</td>
</tr>
<tr>
<td></td>
<td>Reduce dose again when definition for delirium resolution next met.</td>
</tr>
<tr>
<td>Measure</td>
<td>Dose</td>
</tr>
<tr>
<td>---------</td>
<td>------</td>
</tr>
<tr>
<td>Discontinuation of therapy for symptom resolution – Dose reduction protocol</td>
<td>Reduce by 0.25mg at each 12 hourly dosing. At dose level that symptoms reappear – increase by 0.25 mg bd (if occurs after 72 hours clinician can decide to change to alternative treatment of choice and stop study drug). Reduce dose again when definition for delirium resolution next met.</td>
</tr>
<tr>
<td>Sum of Nudesc items 2 (inappropriate behaviour), and 3 (inappropriate communication), and 4 (illusions/hallucinations) &lt; 1 for 48 hours</td>
<td></td>
</tr>
<tr>
<td>Discontinuation for patients who symptoms don’t improve</td>
<td>Continue therapy (including further titration if required as per section 5.2) for a total of five days if no adverse effects as efficacy may occur after 72 hours. Clinician may decide to add or change to alternative therapy. This is not an indication for unblinding. At end of 5 days if patient does not meet criteria for discontinuation (symptom resolution or delirium resolution) study drug should be stopped and clinician can change to alternative therapy of choice.</td>
</tr>
<tr>
<td>Unacceptable adverse effects as assessed by clinician. In event of dystonic reaction, neuroleptic malignant syndrome, severe sedation (RASS -3 to -5) or laryngeal spasm.</td>
<td>Stop study drug. Immediate withdrawal of treatment if dystonic reaction, neuroleptic malignant syndrome, severe sedation (RASS -3 to -5) or laryngeal spasm.</td>
</tr>
</tbody>
</table>

*For dose increments (titration) refer to section 5.2 Dosing schedule*
5.14 Cessation of study drug

5.14.1 Treatment failure
- Adverse events related to the study drug unacceptable to participant/carer or clinician in charge
- Treatment deemed ineffective by treating clinician, who wishes to use alternative therapy.

5.14.2 Cessation for reasons other than treatment failure:
- Participants who in the opinion of the investigator are not well enough to continue the study drug
- It is inappropriate to continue the study drug for whatever reason
- The participant or proxy withdraws their consent, with or without consent to use already collected data.

5.15 Post study treatments
After 72 hours participants will enter the follow-up phase of the study. The treating clinician can chose depending on the following scenarios:

<table>
<thead>
<tr>
<th>RESPONSE (NUDESC SCORE)</th>
<th>ABILITY TO SWALLOW ORAL SOLUTION</th>
<th>Lack of efficacy (no response or partial response)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom resolution* or delirium resolution# (see table 5.13)</td>
<td>Can swallow</td>
<td>Continue on study protocol blinded using dose reduction schedule as section 5.13 or Further therapy decided by treating clinician</td>
</tr>
<tr>
<td>Option to remain on study protocol for five days. At end of 5 days if patient does not meet criteria for discontinuation (symptom resolution or delirium resolution) study drug should be stopped and clinician can change to alternative therapy of choice. or Further therapy decided by treating clinician</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Can’t swallow

| Further therapy decided by treating clinician | Further therapy decided by treating clinician |

*Symptom resolution defined as Sum of Nudesc items 2 (inappropriate behaviour), and 3 (inappropriate communication), and 4 (illusions/hallucinations) < 1 for 48 hours

*Delirium resolution defined as MDAS score < 7 for 48 hours

When change to agent of clinician choice and ceasing study drug, the clinician remains blinded to whether patient received active antipsychotic or not and will institute new agent with re-titration as will not have information of whether active agent was received and its dose level. Rapid retitration within 24 hours is possible with appropriate access to as required doses.

In all study participants, regardless of above choices, secondary outcomes and collection of data for economic evaluation will occur unless consent has been withdrawn.
6.0 Outcomes and measures

6.1 Primary outcome and measure:
Change in sum of scores on Nursing Delirium screening scale - items 2 (inappropriate behaviour), 3 (inappropriate communication), and 4 (illusions/hallucinations) between baseline and follow-up.

6.2 Secondary outcomes:

6.2.1 Efficacy:
1. Time to discontinuation of therapy (hours):
   a. lack of efficacy following an appropriate titration protocol or
   b. lack of tolerability – extrapyramidal toxicity or other toxicity (Global measure of effectiveness - integrated outcome of clinician, participant and caregiver efficacy, safety and tolerability).
2. Time to first rescue midazolam dose (hours).
3. Number/total dosage of midazolam rescue usage
4. Memorial Delirium Assessment Scale score < 7 at 72 hours.
5. Percentage of participants who did not require rescue dosage within 72 hours.
6. Percentage of participants who have delirium recurrence after 48 hours of MDAS < 7.
7. Time profile using random effects mixed models of Memorial Delirium Assessment Scale scores, adjusted for baseline covariates (performance status, prior cognitive impairment, comorbidity burden (cumulative illness rating scale scores), opioid dose in oral morphine equivalents, benzodiazepine dosage (oral diazepam equivalents), life limiting illness type).
8. Participant reported recall after delirium resolution (48 hours after MDAS < 7)  
9. Participant rated distress after delirium resolution using the Delirium Experience Questionnaire, Patient
10. Caregiver rated distress using the Delirium Experience Questionnaire, Caregiver
11. Nursing staff rated distress using the Delirium Experience Questionnaire, Nursing staff

6.2.2 Toxicity:
1. Extrapyramidal toxicity:
   • Extrapyramidal symptom rating scale (ESRS) score

2. Sedation:
   • Richmond Agitation Sedation scale.

3. Adverse events:
Adverse events and serious adverse events will be elicited by direct questioning and observation by the investigator and their delegates. The adverse events will be reported using NCI common terminology criteria for adverse events v 3.0.

Specific adverse events include:
  - Neuroleptic malignant syndrome.
  - Cerebrovascular accident.
  - Laryngeal spasm
  - Acute dystonia.
  - Survival

6.2.3 Health service utilisation and long term outcomes:

1. Medical complications during admission (falls, pressure ulceration, thromboembolism, pneumonia, incontinence).
2. Death.
3. Cognitive impairment (defined as abbreviated short mental status score ≤ 7), after delirium resolution and at last follow-up.
4. Functional decline.
5. Usage of Assistants in Nursing (hours) during delirium episode.
7. Length of admission in palliative care unit (days).
8. Survival outside of institutional care (days).

6.2.4 Serum apoptosis marker levels:

1. S100B
2. Cytochrome C
3. Caspase 3
7.0 STUDY ASSESSMENTS

7.1 Laboratory measures

7.1.1 Metabolic factors:
Liver function tests, serum electrolytes, full blood count will be taken on eligibility and on delirium resolution to assess precipitating factors of delirium according to definitions described below. If blood samples from the previous 3 days are available these results will be used.
Those participants who are diabetic are vulnerable to increased blood sugar levels when administered antipsychotics. In this group, daily BSL will be taken.

7.1.2 Serum apoptosis markers:
S 100 beta is a serum protein that can be assayed using enzyme linked immunosorbent assay methods using venous blood sampling. (32, 39).

Ten ml of blood will be collected from a consenting subset of participants, and dispatched to Dept of Cell Biology, University of New South Wales. Serum will be stored at – 80 degrees and analysed in batches. Assays will apply Enzyme-Linked Immunosorbent Assay (ELISA) analysis initially for the S100B serum marker, and subsequently a selected series of potential delirium serum indicators (Cytochrome C, Caspase 3 and Neuron Specific Enolase).

7.2 Medical and physical measurements
The study assessments are tabulated in 8.1 Study Procedures. The study period will be for 72 hours from randomisation, and follow – up phase for the duration of admission until death; or if discharged, follow-up will be weekly for 3 weeks by telephone, then a visit at 1 month.

Though some studies have demonstrated mean time for delirium resolution is an average of 4 days, this study has outcomes of targeted symptom control. The time period of 72 hours was determined as the clinically significant time period in which target symptom resolution should occur for these therapies to be effective, especially in a palliative care population where rapid control of distressing symptoms is important, even in the setting where delirium resolution does not occur.

7.3 Demographics:
1. Age
2. Gender
3. Availability of primary caregiver
4. Aboriginal or Torres Strait Islander status
5. Language spoken at home
6. Post code

7.4 Main Clinical Diagnosis:
The following clinical data will be collected:
1. Main life limiting illness:
   i. Tumour stage
2. For cancer life limiting illness:
   ii. Sites of metastases (especially if known cerebral metastases).
3. Reason for admission to palliative care unit: symptom control/respite/terminal care.
4. Other central nervous system pathology.

### 7.5 Performance status:
The AKPS has been developed for use in palliative care populations, and is designed to use descriptors more suited to palliative care populations. Preliminary data has shown this provides a measure that is more applicable to palliative care patients, in comparison to the standard Karnofsky performance status measure in palliative care (57). 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 patients based on their ability to undertake a range of daily tasks. The score gives an indication of the patient condition (in terms of physical ability) and can assist in prognostication. The tool will be used in this study to provide a global measure of level of impairment.

### 7.6 Barthel index:
The Barthel index will be used to assess impairment of activities of daily living, to further delineate functional domains affected by delirium. It has established psychometric properties (58-60). This tool will be used in this study to provide a measure of specific impairment.

### 7.7 Comorbidity burden:
A scale for measuring comorbid illness is also crucial in a study of delirium, to attempt to quantify the body systems involved and the severity.

#### 7.7.1 The Cumulative Illness Rating Scale (CIRS)
The Cumulative Illness Rating Scale (CIRS) rates 13 conceptually valid body systems on a five point pathophysiologic severity scale, and is valid and reliable (61). It is useful in the palliative care setting as it is structured relating to body systems and gives a clinical severity rating, both which correspond well with clinical practice (61). It is scored based on clinical judgment, and was studied in populations including cancer patients (61). CIRS does not require invasive physiological measures such as arterial pH or oxygenation, which are not appropriate to perform routinely in many patients with advanced cancer.

#### 7.7.2 The Charlson Comorbidity index
The Charlson Comorbidity index will also be calculated, which is a valid and reliable tool, and has shown relationships with mortality, disability and length of stay (61, 62).

### 7.8 Vulnerability factors:
A series of factors will be recorded in order to describe the study population in terms of delirium vulnerability.

#### 7.8.1 Vision:
If possible visual acuity will be assessed by whether or not the participant requires reading glasses or glasses for vision at all times will be documented.

#### 7.8.2 Hearing:
Hearing impairment will be defined as wearing of hearing aid, or participant/caregiver assessment of a hearing impairment.

#### 7.8.3 Malnutrition/cachexia:
Serum albumin level less than 30 g/L occurring during hospitalization.
7.8.4 Prior cognitive impairment:
The IQCODE will be used to define the presence or absence of prior cognitive impairment. See section 7.14.1.

7.9 Precipitating factors
The following factors will be assessed according to protocol used by Lawlor et al (5) which evaluated each potential precipitating factor for delirium for:

1. Evidence of presence from specific clinical, laboratory, or radiological findings
2. Temporal association with the course of delirium consistent with a potential precipitating role.
3. Changes in the severity of delirium in association with similar changes in the precipitating factor.

Reversibility will be assessed in view of delirium improvement (at least a 25% reduction in MDAS score) or reversal corresponding to evidence of improvement or resolution of the precipitating factor as previously defined by Lawlor et al (5). If MDAS scores failed to decrease or even increased with clinical or other evidence of unsuccessful treatment or progression of the putative precipitating factor this will be defined as irreversible as previously defined by Lawlor et al (5).

The specific factors that will be considered are:

7.9.1 Infection
Definition - Presence of Intercurrent infection: Pneumonia, Urinary tract infection, or wound infection.

7.9.2 Psychoactive medication:
Patient received a psychoactive medication known to cause delirium; and delirium improvement or reversal occurs after at least 25% reduction in dose; or drug cessation.

7.9.3 Hypoxia
Oxygen saturation < 90% on room air, or requiring an oxygen flow of 2l/min or more.

7.9.4 Metabolic factors
1. Persistent creatinine level of greater than 150 µmol/L (1.70 mg/dL) (renal insufficiency);
2. Glucose level of less than 4 mmol/L (72.0 mg/dL) (hypoglycemia); magnesium level of less than 0.7 mmol/L (1.75 mg/dL) (hypomagnesemia);
3. Aspartate aminotransferase levels of greater than 40 U/L,
4. Alanine aminotransferase levels of greater than 50 U/L,
5. Bilirubin levels of greater than 20µmol/L (1169.6 mg/dL) (hepatic impairment).
6. Hypercalcemia was recorded if calcium levels (corrected for albumin level) were greater than 2.6 mmol/L (10.4 mg/dL).

7.9.5 Cessation or reduction of nicotine or alcohol intake.
The nicotine intake will be documented as cigarettes per day, and duration (days) or reduced or ceased intake recorded. Whether or not nicotine replacement therapy is needed will be recorded. Alcohol intake will be documented in standard drinks per day and...
duration (days) or reduced or ceased intake recorded. Whether or not alcohol withdrawal
needed benzodiazepine therapy will be recorded.

**7.10 Nursing delirium Screening Scale:**
For a continuous assessment measure to assess delirium fluctuation, and targeted delirium
symptoms being measured as the primary outcome over 24 hours the Nursing Delirium
Screening Scale (Nu-DESC) will be used (63). The Nu-DESC 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 be bedside nurses with 59 blinded Confusion Assessment Method (CAM)
ratings made by research nurses and psychiatrists (63). DSM-IV criteria and the Memorial
Delirium Assessment Scale (MDAS) were rated along with CAM assessments. 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 (63). These values are comparable to those of
the MDAS.

The NuDesc will be obtained in order to determine the dose titration and will be obtained
and recorded at 8am, 4pm and 12 am daily; and be scored based on the prior 8 hours. The
4pm score will be obtained by the study nurse and will be discussed with the site
investigator in order to determine the study drug dose for that evening.

The investigators recognize that delirium often becomes more apparent later in the day and
into the evening. An increase in the symptoms of delirium may potentially occur after the
NuDesc score at 4pm, and before the evening study dose. To avoid mistakes with the study
protocol, study dose prescribing has been kept within working hours when investigator and
study nurse are both still on site. The NuDesc score is an assessment of the presence and
intensity of symptoms since the last recording so all fluctuations during that period will be
captured. If there is a change in the patient condition between the time of the afternoon
NuDesc score and the evening study dose, the NuDesc is to be repeated. If at this point, the
NuDesc indicates a change in the patient condition, the site investigator is to be called so
that the evening study dose can be reviewed.

Whenever possible the overnight nurses will be requested to complete at the 12am NuDesc.

**7.11 Memorial Delirium Assessment Scale:**
Several delirium evaluation instruments exist, however for the purpose of this study, a tool
which allowed repeated assessments and measured change in severity over time is needed
(64, 65).

The Memorial Delirium Assessment Scale is a brief, valid and reliable tool for assessing
delirium severity in advanced cancer patients, and is easy to use for repeated assessment
(64, 66). The MDAS was developed to be consistent with DSM IV criteria (64). Using a cut
off score of 13 in a population including AIDS and cancer patients it shows a sensitivity of
70.6% and a specificity of 93.7% for discriminating delirious from nondelirious patients;
and using a cut off score of 7 in acute palliative care inpatients a sensitivity of 98% and
specificity of 96% was obtained (64). Only a validated Italian version is available for use in
non English speaking background patients (67). Internal consistency using Cronbach alpha
coefficient was 0.9 (64). Interrater reliability varies depending on scale item with intraclass
correlation coefficient r = 1 for disorientation and impaired digit span, and lowest for
reduced attention (r = 0.69) (66). Five out of ten MDAS items have inter-rater correlation
coefficients above 0.8, and 8 are above 0.7 (64).
It is a continuous severity measure, and hence can identify subsyndromal delirium, which also has been associated with poor outcomes (68). MDAS has been validated in cancer populations and it allows repeated assessments which is necessary in this study (64).

The MDAS can classify for hypoactive and hyperactive delirium using item 9 “decreased or increased psychomotor activity, and each is rated on severity from 0 – mild to 3 - severe (68). Differentiation between hyperactive and hypoactive subtypes has shown positive correlation between delirium severity and functional outcome so is important to include (65). The percentage agreement between rater’s for psychomotor classification was high at 93.8% (66). Delirium severity can be categorized by use of MDAS scores, with "mild" delirium reflected by MDAS scores <=15, "moderate" severity delirium by MDAS scores of 16–22, and "severe" delirium as MDAS scores of 23–30.

The Memorial delirium assessment scale (MDAS) will be performed at eligibility and daily in conjunction with information provided by treating medical and nursing team, between 8 am and 12 midday (because of known variation of delirium symptoms within a 24 hour period.) The MDAS will be scored based on the prior 24 hour period. An initial training session will occur for staff so observations required are known.

7.12 Extrapyramidal symptom rating scale (ESRS):
The Extrapyramidal Symptom Rating Scale has been developed to assess the extrapyramidal side effects of psychoactive medications (69), and has been widely used as a research tool in psychiatry and in pharmacological studies of psychoactive medications. The scale identifies four drug-induced movement disorders – Parkinsonism, akathisia, dystonia, and tardive dyskinesia. The incidence of these movement disorders in palliative care patients has not been described, however the ESRS measurement of drug-induced EPS is valid and discriminative from psychiatric symptoms in other populations (69). The scale consists of an objective (observational) component based on a standardised clinician neurological assessment, and a component of the subjective experience of the symptoms, addressed with a few simple questions. In participants with a sedation score of -3 or less, only the objective measures will be used. In participants who are judged to be too unwell for the complete standardised examination, a minimal examination will be performed to assess muscle tone, facial movements, and presence or absence of dystonias or dyskinesias.

7.13 Sedation
The three aspects of consciousness that need measurement are 1) arousal (a state of responsiveness to sensory stimulation); 2) alertness (a condition of being mentally quick, active, and keenly aware of the environment) i.e. orientation and communication, and 3) appropriate voluntary motor activity (70). There are no studies of psychometric properties sedation assessment scales in palliative care settings (70).

7.13.1 The Richmond Agitation-Sedation Scale (RASS)
The Richmond Agitation-Sedation Scale (RASS) has been validated in the intensive care setting in patients on mechanical ventilation (71, 72). 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) and also looks at constructs related to delirium (inattention as measured duration of eye contact) (71).
7.14 Cognition:

7.14.1 IQCODE
The IQCODE questionnaire for caregivers has high reliability and measures a single general factor of cognitive decline (73-75) in the participant. It has had its validity tested against conventional cognitive screening tests, predicts incident dementia, and correlates with a wide range of cognitive tests. It is relatively unaffected by education and pre-morbid ability or by proficiency in the culture's dominant language. Its disadvantages are that is by informant characteristics (for example depression and anxiety in the informant) and the quality of the relationship between the informant and the subject. This instrument has been used in prior outcomes studies of delirium in other populations to define prior cognitive impairment (76, 77). The introduction has been modified to make sure caregiver understands it is in relation to weeks prior to delirium episode as the comparator.

7.14.2 Minimental status examination
The Mini Mental Status Examination is used in this study to determine higher cognitive function (78).

7.15 Medication:

7.15.1 Opioid dose equivalents:
Daily opioid dose will be calculated using oral morphine equivalents/24 hours, according to a conversion table. (79).

7.15.2 Benzodiazepine usage:
Daily Benzodiazepine dose will be calculated as oral diazepam /24 hours, according to conversion table. Benzodiazepines for sleep disturbance, dyspnoea and/or seizure control are allowed as clinician prescribes and will be calculated as diazepam dose equivalents. Benzodiazepine usage for delirium is as per benzodiazepine rescue protocol.

7.15.3 Rescue midazolam usage:
Daily rescue midazolam usage will be calculated and the time for first rescue, and time between rescue doses recorded.

7.15.4 Number of medication added:
The number of medications added to the participants medication regimen will be calculated for each 24 hour period.

7.15.5 Clinician rated anticholinergic scale:
All current medications will be documented, and scored on the clinician rated anticholinergic scale – modified version, which is the best available measure for calculating anticholinergic activity of medication (80-82). Daily alteration to medication regimes will be noted. As required (prn) medication will be included, only if a dose has been administered within 24 hours.

7.16 Patient, caregiver and nurse distress:

7.16.1 Delirium Experience Questionnaire
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 (18). 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.

Participant distress and recall will be assessed at delirium resolution (MDAS < 7 for 48 hours), at discharge; and week 4.

Nurse distress will be assessed at recruitment, and at 72 hours and delirium resolution if occurs.

Caregiver distress will be assessed at recruitment and at 72 hours, at delirium resolution if it occurs, and at 4 weeks following discharge (study nurse visit).

7.16.2 Quality of Life
Quality of life assessment will be undertaken in participants who have delirium resolution only.

Quality of life of patients will be measured using the EORTC QLQ-C30 and in participants who are able with the FACIT - PAL (83, 84). There is currently no gold standard instrument for measuring quality of life in palliative care populations. However, the EORTC QLQ-C30 is the most widely used cancer-specific quality of life measure. It has been found valid for use in a wide variety of cancer populations, including patients undergoing palliative care (85-87). A large amount of published data is available for comparison purposes. A palliative specific EORTC-QLQ (88, 89) has been developed with 15 key questions, recognising that palliative patients become fatigued quickly. These 15 questions are included in the C30 version, we will be shading the 15 questions, if it is clear that the patient is fatigued, the study nurse will administer the 15 shaded questions only, instead of the 30 questions.

A large amount of published data is available for comparison purposes. In addition, we intend to collect data for the validation of the FACIT-PAL, which shows promise as a palliative care-specific measure and includes items concerned with existential issues that are absent from the QLQ-C30. The FACIT-PAL includes the FACT-G (91), the second most widely used cancer-specific quality of life measure. Performance on questionnaires from the EORTC and FACIT collections of questionnaires has been compared in a number of different cancer populations (89-94); collecting data on the QLQ-C30 and FACT-G in the palliative care population will enable us to validate conversion of scores between the two questionnaires in this group. The capacity to convert scores would enable meta-analysis of data from studies reported in the literature. Unlike the QLQ-C30, the FACT-G allows all items to be summed to give an overall quality of life score of superior precision. This score will be used in the economic analysis for this study. The FACIT-PAL will only be completed in patients who are not fatigued and have been able to complete EORTC QLQ without problems.
### 7.17 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.

Each participant will be a current inpatient, under the care of palliative care clinical teams. In the event of an adverse outcome, expertly trained palliative clinicians and other necessary specialists will manage the event according to the participant and his/her carer’s wishes.

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. Other adverse events will be described in the Annual Report to the Committee.

Serious adverse events will be followed until documentation of resolution, assessment that the event is not related to the intervention, or clinical opinion in that the event is an ongoing clinical problem with active intervention.

### 7.18 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:

1. Consider current uncertainty (net clinical benefit and net benefit) in decision making to inform optimal (efficient) trial design;
2. Provide evidence of relative joint effects and resource use of alternative approaches to patient care in defined patient populations;
3. 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 Risperidone randomised control trial in improving evidence based decision making for palliative care practice in Australia.

### 7.18.1 Comparative cost and effect:

With limited health care resources, a new therapy must be shown not only to be effective but also to provide any benefits at a reasonable cost to the community. Consequently, information on economic outcomes is becoming necessary in the evaluation of any new treatment (the Australian Pharmaceutical Benefit Scheme requires such analyses for new submissions).

This study will undertake economic analyses alongside the Risperidone study, a randomised double-blind controlled multi-centred trial of Risperidone in management of delirium in palliative care inpatients. The study plans to recruit 165 patients from 6 palliative centres in Australia, who will be randomised to either oral risperidone (55), oral Haloperidol (55) or oral placebo (55), in each case with rescue subcutaneous Midazolam. Study participants will be followed up in detail for 72 hours and then with routine data collection in consenting patients for a further 3 months. Information on inclusion and exclusion criteria, selection procedures, dose modifications and side effects, statistical
considerations regarding sample size, and the managerial structure for the study are contained in the Clinical Study Protocol.

The main objective of the clinical study is to determine the effect of Risperidone relative to Haloperidol and active treatment relative to Placebo, with rescue Midazolam in each case, on delirium symptoms and extrapyramidal side effects of medication. However, in informing decision making in bodies such as the Pharmaceutical Benefits advisory Committee (PBAC) in a palliative care setting it is also important to establish evidence on

(i) the relative effects on patient, family and carer psychosocial effects
(ii) health care resource use, costs (preparation administration and follow up effects) and consequences (time in hospital, home, side effects).

Issues of translating evidence from a trial setting to the expected use of Risperidone for delirium management in palliative care populations in practice will also be considered.

The expected value of the proposed randomised control trial evidence is in reducing uncertainty of the net clinical benefit and net benefit of Risperidone use in palliative care settings. The value of information in informing decision making by bodies such as the PBAC is expected to be substantial given the current paucity of robust evidence and hence significant uncertainty in decision making. The trial is broadly designed following the principle of maximising the expected value to decision making from the available research funding in increasing the evidence base to inform clinical and policy decisions around use of Risperidone in palliative care (95, 96).

This section details the economic evaluation designed to run in parallel and conjunction with the main Risperidone clinical study to collect this data. The clinical study will collect data on:

- Delirium symptom duration/severity/resolution;
- Patient reported distress on delirium resolution;
- Caregiver, family and health professional rated distress;
- Australia – modified Karnofsky performance status, Barthel’s index;
- Cognition, and;
- Rescue protocol use.

Additional data for the economic evaluation will include information on:

- Utility from health related quality of life
- Survival time outside of institutional care to 3 months
- Index hospital admission health care professional time (specifically assistants in nurses, use of restraints, and hoists,
- Follow up hospital admissions – from telephone follow-up
- Medication use (CRF and telephone follow-up)
- GP use (telephone follow-up)
- Age care facility admissions – discharge summary and community/ palliative care service/telephone follow up
- Complications of delirium treatment including pressure ulcerations, thromboembolism, pneumonia and incontinence – within initial hospital admission
- Carer time at home

The prices associated with specific resources will be determined from sources outside the Risperidone study. Table 1 provides a summary of the planned data collection to inform economic evaluation from the Risperidone study.
Table 1: Summary of Economic Evaluation

<table>
<thead>
<tr>
<th>Treatment Effectiveness</th>
<th>Source of Data</th>
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<tbody>
<tr>
<td>Resolution of delirium @ 72 hrs</td>
<td>All study patients (165)</td>
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<tr>
<td>Memorial delirium assessment scale</td>
<td>All study patients (165)</td>
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<tr>
<td>Time to response</td>
<td>All study patients (165)</td>
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<td>Probability of lucidity (able to conduct affairs) with response</td>
<td>Patients with delirium resolution (165)</td>
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<tr>
<td>Quality of Life</td>
<td>All study patients (165)</td>
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<tr>
<td>Global deficit Australian modified Karnofsky Performance Status index; Barthel index</td>
<td>All study patients (165)</td>
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<tr>
<td>Survival time</td>
<td>All study patients (165)</td>
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<td>Survival time in community (free from hospital, aged care and other institutional care)</td>
<td>All study patients (165)</td>
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<tr>
<td>Side effects - sedation score, extrapyramidal score</td>
<td>All study patients (165)</td>
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<tr>
<td>Carer and family impact</td>
<td>All study patient carers and families</td>
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<td>Distress</td>
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<td>Resource Use Within Hospital</td>
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<tr>
<td>Risperidone doses</td>
<td>All Risperidone arm patients (55)</td>
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<td>Risperidone costs of preparation and administration</td>
<td>Substudy at one site</td>
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<tr>
<td>Haloperidol doses</td>
<td>All Haloperidol arm patients (55)</td>
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<td>Haloperidol costs of preparation and administration</td>
<td>Substudy at one site</td>
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<tr>
<td>Midazolam (rescue medication) doses</td>
<td>All patients (165)</td>
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<tr>
<td>Midazolam costs of preparation and administration</td>
<td>Hospital formulary in index admission</td>
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<tr>
<td>Hospital Inpatient stays and length of stay (bed days)</td>
<td>All study patients (165)</td>
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</table>

Data on resource use and cost within hospital relevant to the economic evaluation will be collected within study. Data on return to hospital and use of other institutional care is also planned to be collected as part of follow-up contact with palliative care physicians and next of kin.

7.18.2 Objectives of health economics study

Comparative effect and cost

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The main objective of the health economics study is to determine the costs and consequences of oral Risperidone compared to Haloperidol management and active compared to placebo management of palliative care patients with delirium. This will be accomplished by:

1. Estimating the effectiveness of Risperidone compared to Haloperidol and active management versus placebo in terms of reductions in delirium scores, increase in survival time and survival time out of institutional care (at home) and impact on family and carers.

2. Estimating the resource usage associated with Risperidone compared to Haloperidol and active management versus placebo with particular reference to determining whether incremental study medication procurement, preparation and administration costs are somewhat offset by lower costs associated with any better management of delirium.

3. A within-trial analyses will estimate the incremental costs and improvement in delirium management with Risperidone compared with Haloperidol and with active over placebo control over a 72 hour follow-up period. This analysis will enable best evidence for an acute within study estimate of incremental cost per improvement in nursing delirium screening scale (additional delirium resolution) at 72 hours. Longer term incremental costs and consequences (time to delirium resolution, weeks of survival, weeks of survival out of institutional care at home, impacts on family and carers) will also be estimated based on data collected over a further 3 months of less intensive study follow. Sub-studies of medication use (dosage, preparation, and administration) and costs, distress in patients, families and carers and carer burden are also planned.

Sensitivity analysis will be undertaken on ranges of uncertainty of treatment effect observed within the trial follow up period and extended 3 month

Cost–Consequences methods
Palliative care has multiple domains of effect, such as delirium management, psycho-social support and carer 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 (97). 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, QALYs).

However, Eckermann et al 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 (98-100). Hence the cost-disutility plane can, for example, consider the interaction and uncertainty between patient delirium symptoms, patient functioning, side effects of strategies, psychosocial effects on
the patient and family of place of care and carer burden. The cost disutility plane allows natural and intuitive modelling 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 patients in each arm of the study on costs and consequences of patient symptom relief, functioning, capabilities and psychosocial support in the defined palliative care population of interest. This patient level data allows within trial modelling using bootstrapping methods (97) 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 (101). 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 at all potential relative decision making values for consequences (98). Consequently the net loss acceptability frontier can be estimated to simultaneously identify at potential threshold values for effects (99):

(i) which strategy maximises expected net benefit across the distribution of incremental net benefit

(ii) the expected potential value of future research.

This best informs joint policy questions of whether to reimburse and whether further research is required (95, 96).

In summary current conventional economic analysis under uncertainty in health technology assessment (HTA) undertaken on the incremental cost effectiveness plane restricts analysis to consideration of a single measure of effect. Conversely, the current conventional method for considering multiple effects of cost-consequences analysis has been applied without consideration of their joint effects under uncertainty. Consequently, current conventional methods of economic analysis in HTA do not enable robust consideration of many relevant domains of effect in palliative care.

However, a recently developed method enables joint consideration of evidence from multiple domains (e.g. functioning, delirium management, psychosocial support) and decision making under uncertainty (96, 97). This is suggested to have significant value in palliative care in allowing informed decision making under uncertainty across multiple domains by bodies such as the PBAC and by palliative care clinicians in practice.
# 8.0 STUDY PROCEDURES

## 8.1 Table of study measures.

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<tr>
<th>Eligibility</th>
<th>Baseline</th>
<th>Day 1-3</th>
<th>Cessation</th>
<th>Resolution/withdrawal</th>
<th>Discharge</th>
<th>Follow up</th>
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</tbody>
</table>

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### 8.2 Patient referrals

All new in-patients under the care or shared care of the palliative care team will be screened by the study nurse for their suitability to enter the study in consultation with the treating clinician and nursing staff. The principle investigator (medical practitioner) will ask the clinician in charge for permission to approach potentially eligible participants. This referral will be recorded within both the CRF and the participant clinical file.

### 8.3 Consent process

#### 8.3.1 Proxy consent:

It is critically important to improve the evidence base for management of delirium in palliative care due to the significance of maintaining lucidity at the end of life, and also due to the associated significant distress, morbidity and mortality.

By definition delirium is a disorder associated with cognitive impairment, though the severity of this can be variable and fluctuate. Hence it is not possible to obtain written informed consent from the participant in this population.

Obtaining consent for this study will be a process of information exchange between the study staff, the potential proxy and any other person the potential proxy believes should be included in the discussion (a health care interpreter can be used). The information sheet will be used as a basis for the discussion, which will cover all procedures, benefits, burdens and side effects expected as possible during the study. The proxy will be given opportunity (in time and physical capacity) to consider the study and formulate questions, any questions will be addressed and answered fully. An actual time period is not specified as this will be determined in part by conditions at the time, but the proxy will be given the time to consult with others and to ask questions. The study nurse will specifically ask if the proxy has been given enough time and opportunity to consider the study.

Written informed proxy consent will be obtained from a person responsible. No information collected for this study will be released to the proxy consent person.

This study will be submitted for approval through the approval of clinical trials process, to the Guardianship Tribunal or appropriate body in each state, after Human research Ethics Approval has been obtained.

#### 8.3.2 Summary of Australian State requirements for proxy consent process.

**Queensland**

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Legislation – Schedule 2, Section 66 of the Guardianship and Administration Act 2000. The clinical trial is to be approved by the relevant ethics committee and then an application made to the Guardianship and Administration Tribunal for approval of the trial as clinical research.

- Summary of the protocol
- Proposed information sheet and consent forms
- Ethics approval from relevant committee
- Application form

Once approved as clinical research the Statutory Health Attorney can then be approached for individual consent for the study.

Statutory Health Attorney is defined as (in order of preference)
- Advanced health directive
- Tribunal appointed guardian
- Enduring power of attorney
- Patient spouse (if the relationship is close and continuing)
- Patient primary carer, but not paid carer
- A close adult friend or relative
- The Adult Guardian as a last resort
  - For this to be approved, the investigator needs to telephone the Office of the Adult Guardian for individual consent

NSW.
Legislation – Part 4a Medical and Administration Act 1986.
The trial must be approved the NSW Guardianship Tribunal. This is achieved by;
- Final ethics approval (from all hospitals in NSW where the study will be conducted)
- Apply to the tribunal
  - Proposal must cover
    - Only those with condition to be included
    - No substantial risk to patient, or no greater risk than existing treatments
    - Treatment is appropriate and available to use in those who cannot consent to own treatment.
    - Treatment is approved by ethics committee
    - Relevant guidelines complied with
    - Best interest to take part in trial
  - Covering letter
  - Protocol
  - Information sheets and consent forms
  - Correspondence from the ethics committees
  - IB
    - A hearing date is set and approval is provided/withheld depending on considerations, and the tribunal delegates the decision making to the person responsible (investigator and applicant are expected to attend
    - Investigator receives an order approving the trial, and delegating responsibility

- Identify the person responsible for each patient considered for the study (hierarchical)
  - a guardian (including an enduring guardian) who has the function of consenting to medical, dental and health care treatments, or, if there is no guardian:

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the most recent spouse or de facto spouse with whom the person has a close, continuing relationship. 'De facto spouse' includes same sex partners; or, if there is no spouse or de facto spouse:

- an unpaid carer who is now providing support to the person or provided this support before the person entered residential care, or, if there is no carer:
- a relative or friend who has a close personal relationship with the person
- If there is no person identified individual applications can be made to the Tribunal.

- Obtain their consent.

**Victorian Legislation – Guardianship and Administration Act 1986, Version No. 070; Part 4a Medical and other treatment.**

The person responsible is to be approached for consent. The order of those responsible is hierarchical:

1. An agent, appointed by the patient under enduring power of attorney (medical treatment)
2. A person appointed by VCAT to make decisions about the proposed treatment
3. A guardian appointed by VCAT with health powers
4. An enduring guardian appointed by the patient with health care powers
5. A person appointed by the patient in writing to make decisions about medical and dental treatment, including the proposed treatment
6. The patient spouse or partner
7. The patient’s primary carer, including those in receipt of carers payment, excluding paid carers
8. Patient nearest relative (in order – son/daughter [oldest], father/mother, brother/sister [including adopted, or step], grandparent, grandchild, uncle/aunt, nephew/niece)

If one of the above is not willing to make the decision, the next person on the list can be approached (seek reason for why decision not possible first).

If there is no one identified, a section 42T certificate can be completed and faxed to the Office of the Public Advocate for consideration and approval or not.

**SA Legislation – Section 59 of the Guardianship and Administration Act 1993.**

If a patient is possibly suitable for the planned clinical trial, and is not able to provide their own informed consent due to delirium an Advance Directive is to be checked if in place.

If there is – the named guardian is to be approached for consent, they can then consent as a proxy in the knowledge of the patient expressed wishes, or known likely wishes. If the public advocate is the guardian, individual consent would need to be obtained direct from the office.

If there is not – an informal guardian can be approached, such as spouse, daughter/son, parent, or someone who has day to day care and decision making. They all have equal ranking, so if there is conflict over consent or not, the investigators will not go ahead with the consent process given the nature of the population and study, but it is possible for any dispute to be put to the Office of the Public Advocate. The benchmark is where this person would have reasonable knowledge of the patient wishes and views, and is able to decide based on this knowledge.
These people may be:
- Named guardian
- Spouse/partner
- Parent
- Child
- Person responsible for day to day care (for example, director of nursing home)
- Sibling.

(Note – South Australia does not recognize hierarchy in guardianship, all persons listed have equal status. If the person approached for proxy consent does not provide that consent the study will not seek alternative consent from another person who meets the definition of guardian for the purposes of obtaining proxy consent.)

WA
Legislation – Section 119 of the Guardian and Administration Act 1990

If a guardian has been appointed this person must be approached for consent. Check patient notes and other documents to locate this person. If the Public advocate is the guardian, an application for consent must be provided in writing, presenting the trial and case for consent.

If a guardian has not been appointed, an informal guardianship arrangement is used. There is a hierarchy of persons who can act in this capacity, if one refuses consent, the next person cannot be approached.

- Spouse or defacto partner
- A person who, or a regular basis, provides or arranges for domestic services and support but does not receive remuneration for doing so [the eldest child is the next closest relative who should be approached]
- The nearest relative (other than the spouse) and who maintains a close personal relationship
- Any other person who maintains a close personal relationship
- A person prescribed in the regulations

8.3.3 Consent for serum sample:
Separate proxy consent will be obtained to participate in the serum marker study, so that participants who do not wish to have blood tests can still participate in the main study. If at time of blood collection patient refuses to have specimen collected they will be withdrawn from this sub-study.

8.3.4 Nurse and caregiver consent:
Written informed consent will be obtained from nursing staff and caregiver, to participate in the study in relation to caregiver and nursing distress. If caregiver or nurse does not wish to participate in rating distress, this does not exclude the participant from study participation.

8.3.5 Participant consent:
Participant consent will be obtained at the time of symptom resolution in order to record participant recall of distress. Where possible this consent will be obtained within the presence of the person who gave the proxy consent for the study, and will be carefully scripted and practised by study staff in order to reduce burden and potential conflict over
the initial consent. A health care interpreter may be used if appropriate. If the participant withdraws consent for their participation in the main study when they regain capacity they will be withdrawn from the study intervention and will be asked specifically if data already collected can be retained.

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 patient signing the consent form, and is able to say that the patient was signing of their own free will. The witness can be the study nurse if this meets local requirements.

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 person signing the consent (participant, proxy, caregiver, nurse)
- 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**

A screening log will be kept of all potentially eligible patients including the reasons for non entry.

All participants will be seen while inpatient. After checking with the clinical team to make sure the patient is feeling well enough to be seen, the study nurse will introduce themselves to the patient and undertake the following;

1. Explain the study.
2. Complete the eligibility screening as per the CRF-A
   - Some items will be obtained while in discussion with the participant
   - Other items will be completed by referring to the participant clinical file
   - Further items of an investigational or interventional nature will not be confirmed until after the consent of the proxy has been obtained
3. Check to confirm the proxy has signed the consent form
4. Request permission to obtain blood samples if required

The screening process may take up to 3 days to determine if eligibility criteria are met (such as blood results, confirming proxy presence or medical review). At the 3 day limit, the participant either proceeds to participate or is deemed ineligible. Three day screening is appropriate due to the variability of the symptoms of delirium. Symptoms may be evident and then subside again within a short time frame. Taking a NuDesc score each day for three days will ensure that the main measure of the symptom is captured. No score meeting the eligibility criteria within 3 days is a screen failure.

The completed CRF-A will be discussed with the Site Investigator, and approval to proceed to randomisation will be obtained.
8.5 Re-Screening
In some cases it is possible that patients will need to be re-screened, such as consent to participate is given, the eligibility criteria are met and then there is a delay to start due to change in situation (family issues, patient request for attending private matter, etc). In these situations:

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

More detail is provided within the standard operating procedure for re-screening (6.5.2 Re-screening).

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

- Completed by a person authorised to do so
  - The site investigator
  - Sub investigators
  - Those medically authorised to prescribe the specific product under investigation (medically registered clinician)
- Completed on a hospital prescription form and detail full description of the
  - Patient details
  - Study protocol number
  - Drug (this will be Risperidone/haloperidol/placebo) 1mg/4ml
  - Dose (this will specify the dose level, 0.5mg)
  - Frequency (bd and 12hourly prn)
  - Route (oral)

The investigators recognise that once patients are eligible to participate and consent has been obtained, it is very important to commence study intervention as quickly as possible. For this reason randomisation numbers will be used.

The site clinical trials pharmacist will pre-prepare a number of bottles containing the study drug according to the randomisation schedule kept by the pharmacist. On commencement of the study, the study staff will allocate the next randomisation number available from the bottles already prepared to the participant, and record this both on the CRF and in a communication to the pharmacist (by fax). The bottle will contain the drug as scheduled, and will be already available for the participant to commence as soon as all the baseline and eligibility data points have been confirmed.

The participant details will be recorded on the randomisation schedule by the pharmacist on notification and new replacement bottles will be prepared according to the next available allocations on the randomisation table.

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

Patient randomisation will be registered with the coordinating site. PaCCSC has a Standard Operating Procedure (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 patient eligibility as entered onto the on-line data base from CRF A.

8.7 Treatment
All baseline assessments will be undertaken immediately before the first study dose on day 1, treatment will be then initiated on the first 12 hourly dosing. Local hospital procedures are to be followed regarding checking of study drug.

The regular dosing will be commenced in the morning of day one if prior to midday, at which time the morning dose will be given, or the evening of day 1 if after midday at which time the evening dose will be given. Rescue medication can be used prior to the first study dose if immediate control of symptoms required (as per criteria on rescue protocol).

8.8 Daily assessments
Participants will be visited daily 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 condition, and any recent events.

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 for that time point. This visit will also be recorded within the participant clinical file, along with any instructions or changes regarding the dosing schedule. The NuDesc will be recorded, and will form the basis of the morning study dose prescription.

The evening NuDesc will be recorded between 4 and 5pm each day of the study, to give the study staff the opportunity to have the dose reviewed by the site investigator and new prescription orders written.

8.9 Exit assessments
Participants will be visited 12 hours following the last dose of the study intervention (morning of day 4) 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.

8.10 Withdrawal assessments
If participants are to be withdrawn from study treatment, a ‘Withdrawal CRF’ 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 patient meets any of the withdrawal criteria as described in 5.15 Cessation of study drug Section. All associated documents will be completed (SAE report, NuDesc score, etc).

8.11 Follow-up Phase Assessments
Any participant completing the study or who is withdrawn from the study at any stage is to be treated according to the treating clinician’s discretion. The options for clinicians are outlined in section 5.18. Unblinding of the drug received will only occur in emergency situations or if crucial to further clinical care of the participant following discussion with the lead investigator.

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Participants will enter a follow-up phase irrespective of their place of care or delirium status. Follow-up data will be collected by the study nurse weekly for 3 weeks by telephone, then to the place of care at month 1. A medication list will be updated at each contact to record actual prescribed and taken medications since the preceding visit.

**8.12 Extension phase for economic evaluation:**

The objective of the economic evaluation is to estimate and compare costs and consequences for oral risperidone, oral haloperidol and oral placebo in the management of delirium, in each case with midazolam rescue.

The economic evaluation will utilize within study data on treatment effectiveness and resource use. Resource use within study is planned to be collected for: days spent in hospital, palliative care clinician and nursing time, time to readmission, number of inpatient admissions to death, community support (GP visits, home care palliative care team review) caregiver impact/distress, concomitant medications and drug compliance and treatment effectiveness: efficacy, toxicity, and medical complications.

In an economic sub study undertaken at one PaCCSC site only, a full economic evaluation will be undertaken of the cost of risperidone and haloperidol purchase, preparation and delivery.
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 drug. This is described below.

9.2 Criteria for assessing severity
Severity of adverse events will be assessed according to Good Clinical Practice guidelines (ICH GCP).

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;
- results in death
- is life-threatening
(These events require very rapid reporting)
- results in attempted suicide
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity,
- requires ongoing medical or professional attention
- are judged to represent significant hazard

In this study, a number of serious adverse events are expected. 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 due to a documented deterioration in their condition due to the underlying disease process
- Where participants die due to an well documented decline in their condition due to the underlying disease process

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

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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 National Cancer Institute, Common Terminology Criteria for Adverse Events.V3

These criteria have been used to determine likely adverse events 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 risperidone have been listed. This is administered by study staff. (102).

Adverse events will be identified during each visit using criteria established by the National Cancer Institute Common Terminology Criteria for Adverse Events (V3.0), participant symptoms will be graded accordingly.

Specifically, for this study, the adverse events of interest have been identified as those being related to the study intervention, and will be:
- Anorexia
- Cardiac Arrhythmia, tachycardia
- Cognitive disturbance *
- Cerebral-vascular accident
- Constipation *
- Diarrhea
- Dysphagia
- Dyspnoea
- Edema (peripheral)
- Gait/walking *
- Hypertension
- Hypotension
- Hyperthermia
- Hypoxia
- Insomnia
- Involuntary movement/tremor
- Laryngeal nerve dysfunction
- Nausea
- Neuroleptic Malignant syndrome

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• Mood alteration; agitation/anxiety (specify)
• Mucositis, symptomatic - thirst
• Musculo-skeletal – rigidity (lead pipe)
• Prolonged QT interval
• Seizures
• Somnolence *
• Sweating
• Vomiting

*. These symptoms may be present as baseline due to the general condition of the likely participants. These symptoms will be reported as an AE if there is a change from baseline.

Cessation of study intervention and an adverse event report in all cases (of any severity) of:
• Neuroleptic malignant syndrome.
• Laryngeal spasm
• Acute dystonia.
• Prolonged QT interval.
• Cerebrovascular accident.

A grade of 3 or 4 will activate cessation of the study intervention and an adverse event report for the following:
• Seizures.
• Cardiac arrhythmia, tachycardia.
• Hyperthermia.

9.4 Adverse Event Assessment Diagram
9.5 Reporting of SAEs

SAEs will be reported by the study site, to the local HREC and to the coordinating site for study wide reporting. This will occur within 48 hours of first knowledge of the event. 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’.

All adverse events will be collated by the PaCCSC National Manager, and reported to the Trial Management Subcommittee on a monthly basis. Event rates will form part of the Key Performance Indicators for the study and will be reported on a regular basis to the PaCCSC Trials Management Committee and the ethical review boards of the participating sites.

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.

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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 medication.
10 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 a summary report from the coordinating centre 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 three monthly 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 in the format and timeframe stipulated by each individual committee. Reporting requirements for site HRECs as of 1st May 2008 are:

Summary of reporting requirements

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<tr>
<th>Site</th>
<th>Reporting timeframe adverse events</th>
<th>Reporting timeframe serious adverse events</th>
<th>Specific form required</th>
<th>Other requirements</th>
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</thead>
<tbody>
<tr>
<td>Repatriation General Hospital, Daw Park, SA</td>
<td>Monthly summary report</td>
<td>72 hours</td>
<td>Yes</td>
<td>Adverse events from other sites to be summarised monthly in specific form</td>
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<tr>
<td>Flinders Medical Centre, Bedford Park, SA</td>
<td>In collated form in annual report</td>
<td>When they occur</td>
<td>Yes</td>
<td>Does not require reports from other sites unless appropriate</td>
</tr>
<tr>
<td>Curtin University, WA</td>
<td>Immediate</td>
<td>None specified</td>
<td>No</td>
<td>Suspend recruitment until reviewed</td>
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<tr>
<td>Braeside (Hope Healthcare), Wetherill, NSW</td>
<td>None specified</td>
<td>None specified</td>
<td>No</td>
<td>Report to NSW lead ethics committee</td>
</tr>
<tr>
<td>Peter MacCallum Cancer Centre, East Melbourne, Vic.</td>
<td>As early as possible</td>
<td>None specified</td>
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</tr>
</tbody>
</table>

Victorian Managed Insurance Authority also need to be notified of events due to indemnity implications (use specific form).
Requires all serious and unexpected reports from other sites.

<table>
<thead>
<tr>
<th>Mater Health</th>
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<tbody>
<tr>
<td>Delirium study 002/07 V1.4.8</td>
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</tbody>
</table>
10.1.1.3 Data Safety Monitoring Committee

The overall management of the trial requires aggregation of serious adverse events, which will be prepared by the coordinating centre and reviewed at regular intervals by the Data Safety Monitoring Committee (DSMC). Adverse events and serious adverse events are crucial to the safe conduct of the study. (See 10.2 Data Safety Monitoring Committee). The DSMC will have access to unblinded adverse event data if necessary. Following review of the trial safety reports, the DSMC may make a recommendation to the Trial Management Committee that a study be terminated.

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) managed through the Mater Health Service, Brisbane. The primary role of the DSMC will be to monitor adverse and serious adverse events. All serious adverse events will be sent to the DSMC within 7 days for review while adverse event reports will be reviewed at 3 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
  - Report back to the PaCCSC 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 STATISTICS

11.1 Null hypotheses to be tested:

Statistical analyses will test the following three null hypotheses:

Primary null hypotheses:

(i) Effect of risperidone = Effect of control

Secondary null hypotheses:

(ii) Effect of haloperidol = Effect of control
(iii) Effect of risperidone = Effect of haloperidol

The null hypothesis will be rejected if p < 0.05.

11.2 Statistical analysis of primary null hypothesis:

The change in sum of NuDesc scores (item 2, 3 and 4) between baseline and follow up will be evaluated as the group effect (coded 0/1) from the regression of the average of follow up scores on the average of baseline scores and group. Intention to treat analysis will be used. For patients with missing values at any of the 4 time points that comprise the primary endpoint, NuDesc scores will be imputed using multiple imputation with 50 resamples, with predictive mean matching using age, gender, eligibility delirium symptoms score (NuDesc score item 2, 3, 4), AKPS, CIRS, baseline oral morphine and diazepam equivalents, prior cognitive impairment and life limiting illness.

11.3 Statistical analysis of secondary null hypotheses:

Secondary null hypotheses will be tested by will be evaluated as the group effect (coded 0/1) from the regression of the average of follow up scores on the average of baseline scores and group.

11.4 Statistical analysis of Toxicity outcomes:

ESRS and RASS scores during the treatment period will be determined for each patient, and analysed using random effects mixed modelling (see section 11.7).

Survival will be modelled using a Cox regression frailty model, clustering over site, after verifying that the proportional hazards assumption is met.

11.5 Statistical analysis of other efficacy outcomes:

Proportions of patients with MDAS scores < 7 at follow-up, proportions who did not require rescue dosage within 72 hours, and proportions with delirium recurrence after 48 hours of MDAS < 7 will be compared by chi square tests. For participants who die during the 72 and do not have a further MDAS score after baseline, their delirium episode will be classified as not resolved.
11.6 Time-to-event analysis:

Time to resolution of delirium or withdrawal due to toxicity will be analyzed jointly using competing risks methodology, with all cause death taken to be the competing risk. Patients withdrawn for reasons unrelated to treatment (e.g reaching end of study period) will be considered as censored. Fine and Gray’s method will be used to compare crude cumulative incidences (103).

Time to first rescue medication will be analyzed by Cox’s proportional hazards regression. Should the proportional hazards assumption be violated, the treatment period will be divided into intervals within which the proportional hazards assumption holds.

11.7 Random effects mixed models

Daily MDAS scores, NuDesc, RASS, and ESRS scores will be analyzed using random effects mixed models. Covariates will include baseline measurements of performance status (AKPS score), opioid dose in oral morphine equivalents, benzodiazepine dosage (oral diazepam equivalents), comorbidity burden (cumulative illness rating scale scores), life limiting illness type (cancer, non-cancer), and prior cognitive impairment (yes/no).

All multivariable secondary analyses will control for the same variables used to impute in the primary analysis. Participants and time will be entered as random effects. Study site will be entered as a higher order random effect, given significant model improvement. For all continuous outcomes, time will be reparametrized by adding a time-squared term. For delirium symptom scores and MDAS, a time-squared by group interaction will be entered into the model to improve fit. Mixed models will be validated by examining the residuals visually for normality, homoscedasticity and independence using quantile normal and scatter plots.

11.8 Power and sample size

A total sample size of 110 patients (55 risperidone, 55 control) will provide 80% power to detect a difference in change of NuDesc score of 1 unit assuming a baseline standard deviation of 1.92 units, and a correlation of at least 50% between baseline and follow-up scores.

Prior to study close blinded checks of the standard deviations in each arm will be conducted to review the sample size required to provide 80% power.

11.9 End points

Change in sum of scores on Nursing Delirium screening scale items 2 (inappropriate behaviour), 3 (inappropriate communication), and 4 (illusions/hallucinations) between baseline and follow up.
12 ETHICS

12.1 Benefit anticipated from the study

At present, there is no medication 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 is aimed at determining if any of the currently used drugs have any documented benefit for targeted symptoms of delirium.

There may be benefit for the patient and their family, if the study drug relieves the symptoms of delirium. The study is not designed to specifically provide such benefit. The study is designed to provide benefit to future clinical decision making and care.

12.2 The Possibility of Physical Stress or Discomfort

The symptoms of delirium are distressing; this study has been carefully designed using measures that cause as little additional burden as possible, while still ensuring that the study outcomes can be met.

Participants will be asked to provide a blood sample for baseline physiological measures and repeated on day 3. The taking of blood is uncomfortable, but short term. This is the only invasive procedure during the study period.

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. The study measures ask caregivers to rate their distress at the delirium in the person for whom they provide care. This level of distress will be monitored by the study nurse closely. Each study nurse will have close contact with the clinical team, any distress in the caregiver can be reported to the clinical team, once confirmed by the caregiver, in order that clinical care of the caregiver can take place.

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 patient distress. Ongoing site monitoring will provide ongoing training opportunities.

12.4 Research on people in dependent relationships

The nature of doctor-patient relationships dictates that participants may feel that they are in the dependent position. The investigators and study staff with designated study related duties will work to eliminate 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 patients will be able to withdraw from the study at any time. All study procedures (with the exception of the morning NuDesc scores), including eligibility, baseline assessment and other data collection points, will be performed by a person not involved in the clinical care of the participant.
12.5 Separation of research and clinical responsibilities
There are many distressing symptoms faced by patients with a life limiting illness and there is very little research to support many of the interventions that palliative medicine clinicians provide. Although research in this area poses its own unique dilemmas, the ethics of not conducting research into the best management of the dying patients is untenable. Importantly, patients 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 patient 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
Patients will be recruited on admission to the palliative care service and during initial screening in the participating clinics at each site. We will not provide advertising brochures, only the information sheet and a verbal explanation. Any patient 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 patient 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 patient ID number only. There will be master lists held at each participating site and at the co-ordinating site at Flinders University in South Australia. The participant database will be stored on a password-protected hard drive maintained by the study investigators. We will analyse data by ID number only.

12.8 Restriction of use of data
Only study investigators, study nurses, the Project Officer, and members of the Research and Ethics Committees (for auditing purposes) will have access to participant data. In addition, the study auditors will have access to the participant data.

12.9 Use of personal information
We plan to collect only enough personal information to give a general demographic and disease profile of the participant. The participant responses collected are limited to those that will address our 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, we will erase the files from the database hard-drive and shred any paper copies, including the master list linking patient 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 Study administration

13.1 DATA HANDLING AND RECORD KEEPING

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.

Case Report Forms will include:
- CRF A – Eligibility
- CRF B – baseline
- CRF C1-3 - daily visit
- CRF D – Resolution visit
- CRF E Discharge visit
- CRF F1-5 – Extension
- CRF G - Withdrawal form
- Baseline medical assessment
- Medical review form

13.1.2 Data collection
Data will be sourced from the following:

<table>
<thead>
<tr>
<th>Measure</th>
<th>Source</th>
<th>Completed by:</th>
</tr>
</thead>
<tbody>
<tr>
<td>General demographic details</td>
<td>Clinical file</td>
<td>Study nurse</td>
</tr>
<tr>
<td>General Medical information</td>
<td>Clinical file</td>
<td>Medical officer</td>
</tr>
<tr>
<td>Concurrent medications</td>
<td>Clinical file</td>
<td>Medical officer</td>
</tr>
<tr>
<td>Pathology results</td>
<td>Pathology report</td>
<td>Pathology service</td>
</tr>
<tr>
<td>Vital signs</td>
<td>Clinical file</td>
<td>Study nurse</td>
</tr>
<tr>
<td>Mini Mental Status Examination</td>
<td>CRF</td>
<td>Study nurse</td>
</tr>
<tr>
<td>Quality of Life</td>
<td>CRF</td>
<td>Study nurse</td>
</tr>
<tr>
<td>Medical assessments</td>
<td>CRF</td>
<td>Medical officer</td>
</tr>
<tr>
<td>Efficacy</td>
<td>CRF</td>
<td>Study nurse</td>
</tr>
<tr>
<td>Side effects, safety</td>
<td>CRF</td>
<td>Study nurse</td>
</tr>
</tbody>
</table>

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., including data resolution (Forms tracking index.xls).
3. The Data file will be held and administered in the co-ordinating 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 co-ordinating site will download the data on a regular basis as a text file, and store the data in an SPSS file for analysis.

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 co-ordinating site for verification and then filed.

**13.1.5 Data querying**

Data will be checked according to the 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 co-ordinating site will maintain a register of data checks for monitoring purposes. The database 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 patient 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 the Trail Master File index (Trial Master File index.xls).

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 co-ordinating site by registered mail, for collation and archiving. All patient 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 patient records.
13.2 Quality control

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

<table>
<thead>
<tr>
<th>Person trained</th>
<th>Description</th>
<th>Assessed by</th>
</tr>
</thead>
<tbody>
<tr>
<td>All site staff</td>
<td>ICH GCP training</td>
<td>National manager (PaCCSC)</td>
</tr>
<tr>
<td>Study nurse</td>
<td>Blood sampling</td>
<td>Pathology department</td>
</tr>
<tr>
<td>Study nurse</td>
<td>Eligibility assessment</td>
<td>Site investigator</td>
</tr>
<tr>
<td>Study nurse</td>
<td>Consent procedure</td>
<td>Study coordinator</td>
</tr>
<tr>
<td>Investigator, sub investigators</td>
<td>ICH GCP training Protocol Medical</td>
<td>National manager (PaCCSC) Lead</td>
</tr>
<tr>
<td>Study nurse, investigators</td>
<td>Data management</td>
<td>National manager (PaCCSC)</td>
</tr>
<tr>
<td>Medical staff</td>
<td>Prescription</td>
<td>Site investigator</td>
</tr>
<tr>
<td>Clinical trials pharmacist</td>
<td>Randomisation, drug preparation</td>
<td>National manager (PaCCSC) Lead</td>
</tr>
</tbody>
</table>

Competency will be recorded at the study co-ordinating site with a copy filed in each study site.

13.2.2 Blood collection.
Venous blood samples will be drawn for eligibility screening and on delirium resolution. In some instances blood samples, checked in the preceding 3 days, will be used this if the clinical situation is otherwise unchanged. The results will be held in the patient 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.

13.3.4 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 advise 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 Standard Operating Procedure (5.18 Monitoring). Briefly, each study site will be visited by staff from the co-ordinating 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 GCP compliance.

In addition, auditing will 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 auditor will report to the Management Advisory Board of PaCCSC and will refer to the Standard Operating Procedure (5.19 Auditing).


70. Dean M. Monitoring of sedation at end of life, and supportive care for families. 2007.


15 APPENDICES

15.1 Protocol amendments

15.1.1 Amendment 1

Date of amendment – 16th November 2007

Statement of intent – This amendment is to align the protocol with standard formatting, clarify sections after review by the scientific committee, refer to standard operating procedures where applicable, and to review the statistics section.

List of General changes

Standard Operating Procedures apply to PaCCSC studies, reference to these have now been made where appropriate.

General typing errors and terminology have been corrected.
Patient and subject, where the person is now enrolled in the study, has been changed to participant throughout.
Investigator has been clarified, the lead investigator is the investigator of the study (M Agar), site investigators are those investigators who will hold responsibility for the study at each participating site.
Syrup has been amended to read solution throughout.

List of specific changes

Change #1
The protocol now has section numbers

Change #2
The study title has been amended to reflect the study design.

Original text
Randomised control trial of oral risperidone versus oral haloperidol versus oral placebo with rescue subcutaneous midazolam in the management of delirium in palliative care inpatients.

New text
Randomised control trial of oral risperidone, oral haloperidol, and oral placebo with rescue subcutaneous midazolam in the management of delirium in palliative care inpatients.

Change #3
1.5 New paragraph inserted to describe the rationale for the study drugs, and the choice of study design.

Change #4
5.2 The timing of the NuDesc in relation to the review of the evening study dose has been explained more fully, with the rationale for this inserted.
Change #5
5.5 Method of assigning participants to treatment groups
This section has been amended to more clearly describe the process.

Original text
At each site, patients will be sequentially allocated a patient number of referral to the study. This ID number will be used for all subsequent study documentation for that participant.

Amended text
Over the course of the study, participants will be allocated a series of identifying numbers. A two digit study number, a two digit site number, and a sequential three digit screening number will be allocated on referral to the study. This ID number will be used for all subsequent study documentation for that participant. In addition, a 4 digit randomisation number will be allocated on randomisation of the participant. The full number sequence will be unique to that participant and will not be reassigned.

Change #6
5.14. Patient withdrawal criteria have been redefined. Participants will have the study drug stopped given the situations listed within the protocol, but will not be withdrawn from the study.

Original text
Subject withdrawal criteria

Amended text
Cessation of study drug

Change #7
9.0 All references to Common Toxicity Criteria have been changed to Common Terminology Criteria for Adverse Events, all references to toxicity have been amended to now read adverse events in order to better reflect the assessment process. This section has now been moved to the adverse events section (9.0)

Change #8
10.0 The statistical analysis section has been reviewed and more detail inserted to explain the analysis.

Original text
10.3 Statistical analysis of secondary efficacy outcomes: Secondary null hypotheses will be tested by analysis of variance. Linear contrasts will be constructed comparing risperidone and haloperidol groups, and haloperidol and control groups.

Amended text
10.3 Statistical analysis of secondary null hypotheses: Secondary null hypotheses will be tested by analysis of variance. Linear contrasts will be constructed comparing risperidone and haloperidol groups, and haloperidol and control groups. Additional statistical analyses will be conducted to test the primary and secondary null hypotheses, using data from only those subjects with NuDesc scores at both baseline and 72 hours.

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10.5 Statistical analysis of other efficacy outcomes:
Proportions of patients with MDAS scores < 10 at 72 hours, proportions who did not require rescue dosage within 72 hours, and proportions with delirium recurrence after 48 hours of MDAS < 10 will be compared by chi square tests.

Amended Text
10.5 Statistical analysis of other efficacy outcomes:
Proportions of patients with MDAS scores < 10 at 72 hours, proportions who did not require rescue dosage within 72 hours, and proportions with delirium recurrence after 48 hours of MDAS < 10 will be compared by chi square tests. For patients who die during the 72 hour period the last recorded MDAS will be used in the analysis. In those participants who do not have a further MDAS score after baseline, they will be classified as delirium not resolved.
15.1.2 Amendment 2

Date of amendment – 5th February 2008

Statement of intent – This amendment is to further clarify sections after review by the scientific committee and respond to questions following ethical review.

List of General changes
The abbreviation list has been updated to include new scales and other abbreviations not included in earlier versions.

The reference list has been amended to ensure references within text are in the correct order.

List of specific changes

Change #1
A new compliance statement has been inserted on the title page.

This protocol has been prepared to conform with the CONSORT Guidelines\(^1\) and allow easy assessment for Jadad scores\(^2\). It complies with Guidelines for Good Clinical Practice in clinical research.

The reference list has been amended accordingly.

Change #2
3.1 A new inclusion criteria has been inserted to ensure only suitable participants are enrolled.

- New criteria
  - Able to take oral medications in solution formulation

Change #3
4.3 Study diagram. The diagram has been corrected to ensure the follow-up phase describes follow-up weekly for 3 weeks, then a final visit at one month.

Change #4
5.1 Study drug. The manufacture procedure has been detailed. The placebo solution is described as follows.

1. Oral risperidone solution 1mg/4 ml.
   a. Ten ml of risperidone oral solution 1mg/ml will be diluted with 30mls of placebo solution containing:
      i. Benzoic acid solution B.P
      ii. Comp. hydroxybenzoate solution A.P.F
      iii. Water for irrigation
2. Oral haloperidol solution 1mg/4 ml.
   b. Five ml of haloperidol oral solution 2mg/ml will be diluted with 35mls of placebo solution containing:
      i. Benzoic acid solution B.P

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ii. Comp. hydroxybenzoate solution A.P.F
iii. Water for irrigation

3. Oral placebo solution.
   c. Placebo solution will be manufactured in 100ml batches of;
      i. Benzoic acid solution B.P 2ml
      ii. Comp. hydroxybenzoate solution A.P.F 1ml
      iii. Water for irrigation to a volume of 100ml


Change #5
5.2 Dosing schedule. The time of the NuDesc scores has been further clarified to ensure that the scores are recorded evenly over any 24 hour period during the study intervention, and that the next study dose is adjusted according to a suitable NuDesc score.

- Old text
  o Standard dosing times will be 8am (with 8am NuDesc recording) and 8pm (based on a 5pm NuDesc recording). If there is a change in the patient condition between the time of the afternoon NuDesc score and the evening study dose, the NuDesc is to be repeated.

- New text
  o Standard dosing times will be 8am and 8pm. NuDesc scores will be taken at 8am, 4pm and 12am (8 hourly intervals). The 8 am dose will be determined by 8 am NuDesc score and 8 pm dose determined by 4 pm NuDesc score; however if there is a change in the patient condition between the time of the afternoon NuDesc score and the evening study dose, the NuDesc is to be repeated.

Change #6
5.12.2 Uncontrolled delirium symptoms.

- New text has been inserted to further clarify clinical management of non response to the study intervention.
  o In event of non response to crisis dose further therapy is at the discretion of the treating physician.

Change #7
5.12.5 Severe sedation. New text has been inserted to further clarify clinical management of sedation.

- Old text
  o Clinician decision whether drug cessation is required will be dependant on individual clinical circumstances.

- New text
  o Clinician decision whether drug cessation or dose reduction is required will be dependant on individual clinical circumstances.

Change #8
5.15 Post study treatments. This section has been reviewed and amended in order to ensure that clinical management after participants have completed the study intervention.

- Old text
After 72 hours participants will enter the follow-up phase of the study. The treating clinician can chose:
1. Partial or complete response:
   a. participant remains on study protocol and follows the dose reduction schedule.

2. Participant no longer can swallow:
   a. continue on rescue subcutaneous midazolam only.
   b. change to dose equivalent of subcutaneous haloperidol based on level of
dosing/24 hours of active agent (risperidone and haloperidol 1:1
clorpromazine equivalence).
   c. Change to antipsychotic or other agent of clinician choice.

3. Lack of efficacy:
   a. continue on rescue subcutaneous midazolam only.
   b. change to dose equivalent of subcutaneous haloperidol based on level of
dosing/24 hours of active agent (risperidone and haloperidol 1:1
clorpromazine equivalence).
   c. Change to antipsychotic or other agent of clinician choice.

   • New text.

# In event of lack of efficacy at 72 hours:

• Continue current dose of study medication if patient can swallow for five days.
  Clinician may choose to add an additional agent on regular or prn basis. The clinical
  scenario may be that some response has occurred and further improvement may
  occur with continuation of study drug. This would be appropriate in setting a
  benzodiazepine was being added, or the clinician felt the agent chosen could be
  added to risperidone or haloperidol.

• Change to agent of clinician choice; and cease study drug (clinician remains blinded
to whether patient received active antipsychotic or not and will institute new agent
with re-titration as will not have information of whether active agent was received
and its dose level). Rapid retitration within 24 hours is possible with appropriate
access to as required doses.

• Unblinding so clinician knows if patient received active agent or not and dose level –
to allow clinical decision of ongoing therapy.

Choices for clinicians if lack of efficacy occurs prior to 72 hours and for clinical
reasons they wish to withdraw the patient from the study protocol:

• Continue current dose of study medication if patient can swallow for five days.
  Clinician may choose to add an additional agent on regular or prn basis. The clinical
  scenario may be that some response has occurred and further improvement may
  occur with continuation of study drug. This would be appropriate in setting a
  benzodiazepine was being added, or the clinician felt the agent chosen could be
  added to risperidone or haloperidol.

• Change to agent of clinician choice; and cease study drug – benzodiazepine or
  antipsychotic (clinician remains blinded to whether patient received active
  antipsychotic or not and will institute new agent with re-titration as will not have
  information of whether active agent was received and its dose level). Rapid
  retitration within 24 hours is possible with appropriate access to as required doses.

• Unblinding so clinician knows if patient received active agent or not and dose level –
to allow clinical decision of ongoing therapy.
Where-ever possible options that do not include unblinding need to be considered.

**Change #9**

6.2.2 Toxicity: Adverse events. Two additional dot points have been inserted to provide clarity got he specific adverse events that indicate toxicity to the study intervention and require clinical action.

- **Old text.**
  - Specific adverse events include:
    - Neuroleptic malignant syndrome.
    - Cerebrovascular accident.
- **New text**
  - Specific adverse events include:
    - Neuroleptic malignant syndrome.
    - Cerebrovascular accident.
    - Laryngeal spasm
    - Acute dystonia

**Change #10**

7.1.2 Serum apoptosis markers. This section now specifies that only participants in New South Wales will have these blood assays drawn. See also Section 8.3.3 Consent for serum sample.

**Change #11**

7.2 Medical and physical assessments. This has been amended to be consistent with change #3 above, the follow-up will be via telephone for 3 weeks, then a final visit at 1 month.

**Change #12**

7.5 Performance status. More information has been inserted to further explain this data collection point.

- **Old text.**
  - The AKPS has been developed for use in palliative care populations, and is designed to use descriptors more suited to palliative care populations. Preliminary data has shown this provides a measure that is more applicable to palliative care patients, in comparison to the standard Karnofsky performance status measure in palliative care (57).
- **New text**
  - The AKPS has been developed for use in palliative care populations, and is designed to use descriptors more suited to palliative care populations. Preliminary data has shown this provides a measure that is more applicable to palliative care patients, in comparison to the standard Karnofsky performance status measure in palliative care (57). 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 patients based on their ability to undertake a range of daily tasks. The score gives an indication of the patient condition (in terms of physical ability) and can assist in prognostication. The tool will be used in this study to provide a global measure of level of impairment.

**Change #13**

Deli-rium study 002/07 V1.4.8 93 of 117 30th October 2014
7.6 Barthel index. More information has been inserted to further explain this data collection point.

- Old text.
  - The Barthel index will be used to assess impairment of activities of daily living, to further delineate functional domains affected by delirium. It has established psychometric properties (58-60).

- New text
  - The Barthel index will be used to assess impairment of activities of daily living, to further delineate functional domains affected by delirium. It has established psychometric properties (58-60). This tool will be used in this study to provide a measure of specific impairment.

Change #14
7.9.2 Psychoactive medications. This section has been added to the protocol to ensure that the influence of these medications are accounted for during the study period.

- New text
  - Patient received a psychoactive medication known to cause delirium; and delirium improvement or reversal occurs after at least 25% reduction in dose; or drug cessation.

Change #15
7.10 Nursing delirium screening scale. New text has been inserted to be consistent with the changes made in Section 5.2.

- New text
  - If there is a change in the patient condition between the time of the afternoon NuDesc score and the evening study dose, the NuDesc is to be repeated. If at this point, the NuDesc indicates a change in the patient condition, the site investigator is to be called so that the evening study dose can be reviewed. Whenever possible the overnight nurses will be requested to complete a 2400 hrs NuDesc.

Change #16
7.11 Memorial Delirium Assessment Scale. New text has been inserted to clarify the MDAD score referring to the previous 24 hour period.

- New text
  - The MDAS will be scored based on the prior 24 hour period.

Change #17
7.14.2 Mini Mental Status Examination. New text has been inserted to be consistent with the intended use of the tool.

- Removed text
  - The Mini Mental Status Examination is used in this study to assist the screening eligibility for the study

Change #18
7.16.2 Quality of life. In addition to the EORTC QLQ C30, a complimentary scale will also be administered in participants who are able. The Facit-Pal is a tool to provide an extra
dimension to the quality of life measures for this study, and will give greater depth to the existential issues specific to the palliative care setting.

- New text
  - A large amount of published data is available for comparison purposes. In addition, we intend to collect data for the validation of the FACIT-PAL, which shows promise as a palliative care-specific measure and includes items concerned with existential issues that are absent from the QLQ-C30. The FACIT-PAL includes the FACT-G (99), the second most widely used cancer-specific quality of life measure. Performance on questionnaires from the EORTC and FACIT collections of questionnaires has been compared in a number of different cancer populations (100 - 104); collecting data on the QLQ-C30 and FACT-G in the palliative care population will enable us to validate conversion of scores between the two questionnaires in this group. The capacity to convert scores would enable meta-analysis of data from studies reported in the literature. Unlike the QLQ-C30, the FACT-G allows all items to be summed to give an overall quality of life score of superior precision. This score will be used in the economic analysis for this study. The FACIT – pal will only be completed in patients who are not fatigued and have been able to complete EORTC QLQ without problems.
  - This has been added to the table of study measures (Section 8.1)

Change #19
8.3.2 Summary of Australian State requirements for proxy consent process. New text has been inserted for the Queensland requirements to clarify that an application form is to be used when applying to the Guardianship Tribunal, Statutory Health Authority is renamed to Statutory Health Attorney, and the preference listing for Statutory Health Attorney.

- Old text
  - Patient spouse (if the relationship is close and continuing
  - Patient primary carer, but not paid carer
  - A close adult friend or relative
  - The Adult Guardian as a last resort
    - For this to be approved, the investigator needs to telephone the Office of the Adult Guardian for individual consent

- New text
  - Advanced health directive
  - Tribunal appointed guardian
  - Enduring power of attorney
  - Patient spouse (if the relationship is close and continuing
  - Patient primary carer, but not paid carer
  - A close adult friend or relative
  - The Adult Guardian as a last resort
    - For this to be approved, the investigator needs to telephone the Office of the Adult Guardian for individual consent

Change #20
8.11 Follow-up phase assessments. Text has been changed to reflect clinical decision making after study intervention ceases.

- Old text
  - Any participant completing the study or who is withdrawn from the study at any stage is to be treated according to the treating clinician’s discretion. The options for clinicians are outlined in the dosing schedule table. Unblinding of
the drug received will only occur in emergency situations following discussion with the lead investigator.

- New text.
  - Any participant completing the study or who is withdrawn from the study at any stage is to be treated according to the treating clinician’s discretion. The options for clinicians are outlined in section 5.18. Unblinding of the drug received will only occur in emergency situations or if crucial to further clinical care of the participant following discussion with the lead investigator.
  - This section has also been amended to be consistent with sections 4.3 and 7.2 above.

**Change #21**

9.3.1 Serious adverse events, Common Terminology Criteria. In addition to the adverse events being identified during the study intervention, two new sections have been added to clarify the process of AE reporting and study cessation for the more serious events.

- New text.
  - Cessation of study intervention and an adverse event report in all cases (of any severity) of:
    - Neuroleptic malignant syndrome.
    - Laryngeal spasm
    - Acute dystonia.
    - Prolonged QT interval.
    - Cerebrovascular accident.

  - A grade of 3 or 4 will activate cessation of the study intervention and an adverse event report for the following:
    - Seizures.
    - Cardiac arrhythmia, tachycardia.
    - Hyperthermia.

**Change #22**

10.5 Statistical analysis of other efficacy outcomes. Slight wording change for grammatical reasons.
15.1.3 Amendment 3

Date of amendment – 11th March 2008

Statement of intent – This amendment is to further clarify sections after review by the scientific committee and respond to questions following ethical review.

List of specific changes

Change # 1

5.2 Dosing schedule. Following ethical review a loading dose has been incorporated into the dosing schedule.

- Old Text.
  - Participants will be commenced on 0.5mg BD.

- New Text.
  - Participants will be given a loading dose of 1mg, then 12 hours later commenced on maintenance dose (first dose level 0.5mg BD).

The Dose table and the Dose Schedule Diagram have been amended accordingly.

Table: dose schedule timeline has been amended to include loading dose, and row 3 amended to **Maximum dose possible at that time point** plus a footnote:

“dose titration only occurs based on NuDesc score. At anytime point if NuDesc score < 1 on items 2,3,4 no titration will occur and patient will remain on prior dose level unless adverse events”

Change # 2

5.10 Drug destruction. This text has been expanded to clarify the return, storage and destruction. The text now reads;

Unused syrup in the inpatient unit, as well as any empty bottles, will be delivered back to the pharmacy, using the established practice within the hospital. All unused syrup and empty bottles returned to pharmacy will be stored until study monitoring and then 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.

Change # 3

5.31 Dose Modification. The table has had a footnote added.

- **first dose increase is on commencement dose of 0.5 mg (or 0.25 mg if > 65 years not loading dose)**
15.1.4 Amendment 4

Date of amendment – 28th April 2008

Statement of intent – This amendment is to further clarify sections after further ethical review and to correct further minor typographical and grammatical errors.

List of specific changes

Change # 1

1.4. Health outcome evaluation. Following ethical review this section has been clarified to ensure that both active arms are compared to placebo in line with section 7.18.2.

- Old Text.
  - To compare the incremental effectiveness and costs of risperidone in comparison to placebo in terms of:

- New Text.
  - To compare the incremental effectiveness and costs of risperidone in comparison to placebo; and haloperidol in comparison to placebo in terms of:

Change # 2

2.2.2 Health outcome evaluation. Following ethical review this section has been clarified to ensure that both active arms are compared to placebo in line with section 7.18.2.

- Old Text.
  - To compare the incremental effectiveness and costs of risperidone in comparison to placebo in terms of:

- New Text.
  - To compare the incremental effectiveness and costs of risperidone in comparison to placebo; and haloperidol in comparison to placebo in terms of:

Change # 3

4.1 Overall study design. Following ethical review this section has been clarified to ensure that both active arms are described with rescue midazolam.

- Old Text.
  - Those who provide consent (via a proxy consent process) will be randomised to receive either risperidone, haloperidol or placebo as an oral solution over 72 hours.

- New Text.
  - Those who provide consent (via a proxy consent process) will be randomised to receive either risperidone, haloperidol or placebo as an oral solution over 72 hours; with a rescue midazolam protocol in all arms.

Change # 4

Deltirium study 002/07 V1.4.8 98 of 117 30th October 2014
5.3. Dose schedule diagram. Following ethical review this diagram has been amended slightly to fully describe the items to be assessed for dose adjustments.

Change # 5

10.2. Statistical analysis. Following ethical review this heading has been changed to be more consistent with other heading in section 10.

- Old Text.
  - Statistical analysis of efficacy primary outcome.

- New Text.
  - Statistical analysis of primary null hypothesis.

Change # 6

10.5. Statistical analysis of other efficacy outcomes. Following ethical review this section has been clarified to be consistent with section 6.2.1.

- Old Text.
  - Proportions of patients with MDAS scores < 10 at 72 hours, proportions who did not require rescue dosage within 72 hours, and proportions with delirium recurrence after 48 hours of MDAS < 10 will be compared by chi square tests.

- New Text.
  - Proportions of patients with MDAS scores < 7 at 72 hours, proportions who did not require rescue dosage within 72 hours, and proportions with delirium recurrence after 48 hours of MDAS < 7 will be compared by chi square tests.

- Removed text.
  - Time to first rescue medication will be analysed by Mann Whitney U test.
15.1.5 Amendment 5

Date of amendment – 28\textsuperscript{th} July 2008

Statement of intent – This amendment is to further clarify sections after further ethical review, to correct further minor typographical and grammatical errors, clarify the dosing schedules, and the study monitoring.

List of general changes
All Standard Operating Procedures have details of the SOP number and SOP title inserted.

List of specific changes

Change # 1

4.2 Treatment arms. New text has been inserted to clarify the usual care for patients irrespective of the treatment arm.

- New Text.
  - All participants in the three arms of the study will receive active non medication measures for management of delirium (including assessment for and interventions for potentially reversible precipitants where clinically indicated; and non-pharmacological measures such as attention to hydration, sensory deprivation (vision and hearing aids), presence of familiar family and reorientation). Due to the individual nature of precipitants the non-medication management will be decided by treating clinician.

Change # 2

5.1 Study medication. This section has been updated to further clarify the expiants used in the manufacture process. This study will use central manufacture, communications with the company has determined a slightly different formulation in order to maintain pH and stability of the study medication. This section has also been amended to reflect an 80ml volume of study medication, all subsequent sections have been amended accordingly.

1. Oral risperidone solution 1mg/4 ml.
   d. Twenty ml of risperidone oral solution 1mg/ml will be diluted with 80mls of placebo solution containing:
      i. Lactic acid B.P
      ii. Comp. hydroxybenzoate solution A.P.F
      iii. Sodium hydroxide 2%
      iv. Water for irrigation

2. Oral haloperidol solution 1mg/4 ml.
   a. Ten ml of haloperidol oral solution 2mg/ml will be diluted with 70mls of placebo solution containing:
      i. Lactic acid B.P
      ii. Comp. hydroxybenzoate solution A.P.F
      iii. Sodium hydroxide 2%
      iv. Water for irrigation

3. Oral placebo solution.
   a. Placebo solution will be manufactured in 100ml batches of;
i. Lactic acid B.P 1.1g
ii. Comp. hydroxybenzoate solution A.P.F 1ml
iii. Sodium hydroxide 2% for pH adjustment
iv. Water for irrigation to a volume of 100ml


**Change # 3**

5.2 Dosing schedule. This has had minor wording changes to clarify the incorporation of the loading dose and to ensure that the dose titration is clarified taking into account the loading dose. The Dose schedule diagram has also been amended to reflect the larger first dose, and the dose schedule timeline has been updated accordingly.

- **Old Text.**
  - Participants will be given a loading dose of 1mg, then 12 hours later commenced on maintenance dose (first dose level 0.5mg BD). The dose will be adjusted in increments of 0.25mg (every 12 hours for first 24 hours) after assessment at 8am and 5pm each day. The dose can be titrated from first 12th hourly dose. After 24 hours if symptoms persist dose can be adjusted by increments of 0.5 mg every 12 hours.

- **New Text.**
  - This section has been expanded to explain the dosing for those participants 65 years and under, and those over 65 years.
  - New tables have been inserted in order to make the dose titration schedule clear.
  - Refer to sections
    - 5.2
    - 5.3
    - 5.4

**Change # 4**

5.12.2. Uncontrolled delirium symptoms. New text has been inserted in order to clarify that midazolam is to be administered in consultation with the investigator. While midazolam can also be administered for other reasons, the indication for administration is to be specified within the prescription orders.

- **New Text.**
  - Midazolam administered for symptoms other than delirium symptoms are to be ordered separately on the prescription orders, clearly prescribing the indication for administration.

**Change # 5**

5.13. Dose modification. The table has been adjusted in order to clarify to dose modification schedule according to different assessments during the study period.

**Change # 6**

Delirium study 002/07 V1.4.8 101 of 117 30th October 2014
5.15. Post study treatments. A minor editorial correction has been made to the paragraphs describing clinician choices for treatment post study intervention.

- Old Text.
  - This would be appropriate in setting a benzodiazepine was being added.

- New Text.
  - This would be appropriate in the setting of a benzodiazepine being added.

Change # 7

6.2.1 Efficacy outcomes. The efficacy outcomes for distress have been expanded to describe the instrument used to measure this outcome.

Change # 8

7.3 Demographics. Two new data points have been inserted in order to more clearly define general demographics of the participant population.

- New Text.
  - Language spoken at home
  - Postcode

Change # 9

8.1 Table of study procedures. This has had minor changes better reflect data collection points and prevent repetition of data collection. Discussion with investigators has now reduced the number of measures taken at the daily visits, and a number of measure have been reduced where possible to reduce the burden on the assessing medical staff, without effecting the study outcomes or safety assessments. A Treatment cessation timepoint has been introduced to ensure that certain data are collected at the point at which study intervention is cease, irrespective of the day of intervention. Some of these data were previously collected during the day 3 visit.

Change # 10

8.2 Patient referrals. A minor correction has been made to clarify the process by which potential participants are approached.

- Old Text.
  - All new in-patients under the care or shared care of the palliative care team will be screened by the study nurse for their suitability to enter the study in consultation with the treating clinician and nursing staff. The study nurse will ask the clinician in charge for permission to approach potentially eligible participants. This referral will be recorded within both the CRF and the participant clinical file.

- New Text.
  - All new in-patients under the care or shared care of the palliative care team will be screened by the study nurse for their suitability to enter the study in consultation with the treating clinician and nursing staff. The principle investigator (medical practitioner) will ask the clinician in charge for
permission to approach potentially eligible participants. This referral will be recorded within both the CRF and the participant clinical file.

**Change # 11**

8.12. Extension phase for economic evaluation. This section has been corrected. Participants will only be followed up by telephone and visit for 4 weeks following study intervention, reference to monthly telephone contact for 12 months has been removed. Long term survival data will be obtained using date of death data.

- **Old Text.**
  - Participants will enter a follow-up phase irrespective of their place of care or delirium status. Follow-up data will be collected by the study nurse weekly for 3 weeks by telephone, then to the place of care at month 1, then monthly for 12 months by telephone. A medication list will be updated at each contact to record actual prescribed and taken medications since the preceding visit.

- **New Text.**
  - Participants will enter a follow-up phase irrespective of their place of care or delirium status. Follow-up data will be collected by the study nurse weekly for 3 weeks by telephone, then to the place of care at month 1. A medication list will be updated at each contact to record actual prescribed and taken medications since the preceding visit.

**Change # 12**

9.3.1 NCI Common Terminology for Criteria for Adverse Events. The list of symptoms likely to be related to the study intervention has been amended as follows.

- Constipation *
- Gait/walking *
- Somnolence *

*. These symptoms may be present as baseline due to the general condition of the likely participants. These symptoms will be reported as an AE if there is a change from baseline.

**Change # 13**

10 Study monitoring. A new section has been inserted in order to clarify the activities associated with study wide monitoring. This text replaces previous text referring to the Data Safety Monitoring Board, and clarifies the reporting and monitoring relationships.
15.1.6 Amendment 6

Date of amendment – 3rd November 2008

Statement of intent – This amendment is to include specific detail about the substudy for neuronal markers, as this can now be undertaken outside of NSW. Each site outside NSW will submit a new information sheet and consent form in order for participants of the main study to also separately participate in the substudy.

In addition, minor changes have been made to clarify the supply and manufacture of the study drug.

List of general changes
All Standard Operating Procedures have details of the SOP number and SOP title inserted.

List of specific changes

Change #1

5.2 Dosing schedule
This section has been further amended following a study site workshop where protocol uncertainties were clarified, and protocol changes made as a result.
The table explaining the dosing and titration between the age groups has been amended to the following.

<table>
<thead>
<tr>
<th>Age</th>
<th>Loading dose</th>
<th>Starting dose given with loading dose</th>
<th>Titration at dose 2</th>
<th>All other titrations</th>
<th>Titration down</th>
<th>Maximum 24 hourly dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 65</td>
<td>0.25 mg</td>
<td>0.25 mg</td>
<td>0.25 mg</td>
<td>0.5 mg</td>
<td>0.25 mg</td>
<td>2 mg/24 hrs</td>
</tr>
<tr>
<td>≤ 65</td>
<td>0.5 mg</td>
<td>0.5 mg</td>
<td>0.25 mg</td>
<td>0.5 mg</td>
<td>0.25 mg</td>
<td>4 mg/24 hrs</td>
</tr>
</tbody>
</table>

Change # 2

5.7 Method of administration and 5.9 Drug supply.
These two sections have been amended to correct inconsistencies in the volume of the bottles for administration. The bottles will contain an 80 ml volume to ensure that each participant has enough study drug supplied to account for maximal dose increases and clinical choice to continue treatment for a further 2 days. In addition, the process of study drug supply has now been finalized. All study drug will be manufactured by an independent manufacturing facility and will be supplied to each pharmacy on order in a coded manner. All references to both of these items have been amended.

Change # 3

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8.4 Screening.
This section has been amended slightly to ensure that only measures of an investigational or interventional nature are collected after consent to participate has been provided by the proxy. As much screening as possible is to be undertaken prior to the obtaining of consent in order to avoid unnecessary consent when potential participants are not eligible on very easily measured criteria.

- **Old Text.**
  - All participants will be seen while inpatient. After checking with the clinical team sure the patient is feeling well enough to be seen, the study nurse will introduce themselves to the patient and undertake the following;
    - Explain the study.
    - Check to confirm the proxy has signed the consent form
    - Complete the eligibility screening as per the CRF-A
    - Some items will be obtained while in discussion with the participant
    - Other items will be completed by referring to the participant clinical file
    - Request permission to obtain blood samples if required

- **New Text.**
  All participants will be seen while inpatient. After checking with the clinical team sure the patient is feeling well enough to be seen, the study nurse will introduce themselves to the patient and undertake the following;
  - Explain the study.
  - Complete the eligibility screening as per the CRF-A
    - Some items will be obtained while in discussion with the participant
    - Other items will be completed by referring to the participant clinical file
    - Further items of an investigational or interventional nature will not be confirmed until after the consent of the proxy has been obtained
  - Check to confirm the proxy has signed the consent form
  - Request permission to obtain blood samples if required
15.1.7 Amendment 7

Date of amendment – 1st April 2009

Statement of intent – This amendment further clarifies the protocol following initial recruitment and review of the protocol at a study wide workshop.

List of general changes
Minor editorial and formatting changes have been made.

List of specific changes

Change # 1:
3.1 Inclusion Criteria. The use of the Nudesc in selecting participants has been clarified. The NuDesc is a five item scale, only 3 of which will be used within this study. The criteria has been clarified to reflect this.

Old Text
Score on Nursing Delirium screening scale items 2 (inappropriate behaviour), and/or item 3 (inappropriate communication), and/or item 4 (illusions/hallucinations) ≥1.

New text
Score on Nursing Delirium screening scale items 2 (inappropriate behaviour), and/or item 3 (inappropriate communication), and/or item 4 illusions/hallucinations) ≥1 (items 1 and 5 are not targeted symptoms in this study and will not be used in this assessment)

Change #2
5.2 Dosing schedule
This section has been further amended following a study site workshop where protocol uncertainties were clarified, and protocol changes made as a result. The dose adjustment description has been amended to enable changes ‘at or after’ 24 hours if the symptoms persist or recur.

The dose titration description now clarifies the use of only 3 items of the NuDesc scale.

The schedule table has been amended in order to clarify the dose adjustment requirements. As the schedule takes into account differences between age groups and the use of a loading dose further descriptions within the text of this section has been amended to better describe this.

New text
Where-ever possible the loading dose should be given at same time as first dose. If the time to first dose is long loading dose can be given initially, prior to first dose which will be given at scheduled time after discussion with investigator.

Change #3
5.3 Dosing schedule timeline
This section has been amended to reflect the changes made in section 5.2 in order to better describe the dosing for the different age groups, the use of the loading dose, and the description of the use of 3 items of the NuDesc.
Change #4

5.9 Drug supply
This section has been amended to better reflect the actual description of drug supply for this study.

Old text
The drug will be supplied in the following manner;
New text
All study drug will be manufactured by an external facility and supplied to each site pharmacy in pre-prepared and coded bottles. The drug will be supplied in the following manner;

Change #5

5.13 Dose modification
This section has been amended. The section heading has been made clearer and the contents of the table are now consistent with changes made elsewhere in the sections described above.
New section title: 5.13 Dose modification for reduction of cessation (toxicity or resolution).
The descriptive text below the table has been changed.

Old text
first dose increase is on commencement dose of 0.5 mg (or 0.25 mg if > 65 years not loading dose), Dose modification for either risperidone, haloperidol, or placebo arms.
New text
For dose increments (titration) refer to section 5.2 Dosing schedule

The table in this section has been expanded in order to clarify the clinician treatment of according to the NuDesc and the ability of the participant to swallow.

Old table.

<table>
<thead>
<tr>
<th>ABILITY TO SWALLOW ORAL SOLUTION</th>
<th>RESPONSE (NUDESC SCORE)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Can swallow</td>
<td>Complete response</td>
<td>Lack of efficacy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Continue on study</td>
<td>Further therapy decided by treating clinician</td>
<td></td>
</tr>
<tr>
<td></td>
<td>protocol</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dose reduction as per study protocol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Can’t swallow</td>
<td>Further therapy</td>
<td></td>
<td>Further therapy</td>
</tr>
<tr>
<td></td>
<td>decided by treating</td>
<td></td>
<td>decided by treating</td>
</tr>
<tr>
<td></td>
<td>clinician</td>
<td></td>
<td>clinician</td>
</tr>
</tbody>
</table>

The text below this table describing the continuing clinician choices has been deleted and replaced with text within the table as below.

New table.
### RESPONSE (NUDESC SCORE)

<table>
<thead>
<tr>
<th>Symptom resolution* or delirium resolution# (see table 5.13)</th>
<th>Lack of efficacy (no response or partial response)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ABILITY TO SWALLOW ORAL SOLUTION</strong></td>
<td></td>
</tr>
<tr>
<td>Can swallow</td>
<td>Continue on study protocol blinded using dose reduction schedule as section 5.13 or Further therapy decided by treating clinician</td>
</tr>
<tr>
<td>Can’t swallow</td>
<td>Option to remain on study protocol for five days. At end of 5 days if patient does not meet criteria for discontinuation (symptom resolution or delirium resolution) study drug should be stopped and clinician can change to alternative therapy of choice. or Further therapy decided by treating clinician</td>
</tr>
</tbody>
</table>

*Symptom resolution defined as Sum of Nudesc items 2 (inappropriate behaviour), and 3 (inappropriate communication), and 4 (illusions/hallucinations) < 1 for 48 hours

*Delirium resolution defined as MDAS score < 7 for 48 hours

When change to agent of clinician choice and ceasing study drug, the clinician remains blinded to whether patient received active antipsychotic or not and will institute new agent with re-titration as will not have information of whether active agent was received and its dose level. Rapid retitration within 24 hours is possible with appropriate access to as required doses.

In all study participants, regardless of above choices, secondary outcomes and collection of data for economic evaluation will occur unless consent has been withdrawn.
15.1.8 Amendment 8

Date of amendment – 16th October 2009

Statement of intent – This amendment further clarifies the protocol following initial recruitment and review of the protocol at a study wide workshop.

List of general changes
Minor editorial and formatting changes have been made.

List of specific changes

Change # 1:

3.1 Inclusion Criteria. The requirement for English and the primary language has been removed. If a health care interpreter is available, they can be used in order to assist the consent process for both the proxy and the participant (if delirium resolves).

- Old Text
  - English speaking
- New text
  - English speaking or access to health care interpreter

Change # 2:

3.2 Exclusion Criteria. Exclusion due to use within the previous 7 days unnecessarily excludes those people who have had incidental or occasional antipsychotics administered. This exclusion will now exclude for a 48 hour period.

- Old Text
  - Antipsychotic use within past 7 days
- New text
  - Antipsychotic use within past 48 days

Change # 3:

7.1 Metabolic factors. A recent review (Lipscombe LL, Lévesque L, Gruneir A, et al. Antipsychotic drugs and hyperglycemia in older patients with diabetes. Arch Intern Med. 2009; 169(14):1282-1289.) has shown that people with diabetes are at increased risk of hyperglycaemia when taking antipsychotics. Daily blood sugar levels will be monitored in this group.

- New text
  - Those participants who are diabetic are vulnerable to increased blood sugar levels when administered antipsychotics. In this group, daily BSL will be taken.
Change # 4:
8.3.1 Proxy consent. The change to the inclusion criteria has been included in this section.

- Old Text
  - Obtaining consent for this study will be a process of information exchange between the study staff, the potential proxy and any other person the potential proxy believes should be included in the discussion.

- New text
  - Obtaining consent for this study will be a process of information exchange between the study staff, the potential proxy and any other person the potential proxy believes should be included in the discussion (a health care interpreter can be used).

Change #5:
8.3.5 Participant consent. Participants are asked to consent to the study if capacity is regained on resolution of delirium. Non English speaking participants will not be excluded from the study, but will be offered a health care interpreter to assist with the consent process.

- Old Text
  - Participant consent will be obtained at the time of symptom resolution in order to record participant recall of distress. Where possible this consent will be obtained within the presence of the person who gave the proxy consent for the study, and will be carefully scripted and practised by study staff in order to reduce burden and potential conflict over the initial consent.

- New text
  - Participant consent will be obtained at the time of symptom resolution in order to record participant recall of distress. Where possible this consent will be obtained within the presence of the person who gave the proxy consent for the study, and will be carefully scripted and practised by study staff in order to reduce burden and potential conflict over the initial consent. A health care interpreter may be used if appropriate.

The third paragraph in this section contains an error. The current version states that the proxy will sign and date the consent form, this should read ‘participant’ not ‘proxy’. The text has been changed accordingly.

Change #6:
7.9.4 Metabolic factors. While reviewing the protocol the bilirubin level was found to be incorrect, this has now been corrected.

- Old text
  - Bilirubin levels of greater than 20 000 µmol/L (1169.6 mg/dL) (hepatic impairment).

- New text
  - Bilirubin levels of greater than 20µmol/L (1169.6 mg/dL) (hepatic impairment).
15.1.9 Amendment 9

Date of amendment – 6th May 2010

Statement of intent – This amendment further clarifies the protocol following initial recruitment and review of the protocol at a study wide workshop.

List of general changes
None

List of specific changes

Change # 1:

3.2 Exclusion Criteria. The use of anti-psychotics has been further explained. Single low dose ‘PRN’ haloperidol has been found to be excluding potential participants and hindering recruitment. The trial management committee have updated this criteria to allow single doses if the dose was at or below the study dose and greater than 24 hours prior to study commencement.

- Old Text
  o Antipsychotic use within past 48 hours.
- New text
  o Regular antipsychotic use within past 48 hours. A single ‘as required’ (PRN) dose of haloperidol, prochlorperazine or levomepromazine is allowed if
    - administered more than 24 hours previously
    - the dose was at or below the study dose for the age group
    - prescribed for a non delirium indication

Change # 2:

5.4 Dose schedule timeline. The table that explains the maximal dosing for the over 65 year age group is incorrect. Dose 3 can me a maximal dose of 1.0mg, the current diagram shows 0.75mg.

- Old Text
  o 0.75mg
- New text
  o 1.0mg

Change # 3:

8.1 Table of study measures. The Charlson Comorbidity Index time points have been reduced to once only at baseline.
15.1.10 Amendment 10

Date of amendment – 2nd December 2013

Statement of intent – This amendment further clarifies the analysis plan. There has been no change in primary outcome or sample size calculation.

Change 1#

Adding of the new study statistician to the Investigator team

Change 2#

Clarification that the primary end point is change in score at follow-up from baseline, defining specifically “baseline” and follow-up”

Old text: **Primary endpoint:** Sum of scores on Nursing Delirium screening scale items 2 (inappropriate behaviour), 3 (inappropriate communication), and 4 (illusions/hallucinations) at 72 hours.

New text: **Primary endpoint:** Change in sum of scores on Nursing Delirium screening scale (NuDesc) items 2 (inappropriate behaviour), 3 (inappropriate communication), and 4 (illusions/hallucinations) from baseline and follow-up (on day 3), where baseline is the average of the eligibility score on entry to the trial and the score obtained before the first dose is given, and follow up is the average of the last morning and evening scores on the third day.

Change 3#

The clinical response used for the power calculation has been listed specifically for clarity with addition of the following text:

**Clinical response:** A one-unit change between baseline and follow up scores.

Change 4#

The study has been powered on a comparison between risperidone and placebo arms as primary comparison. The new wording for the sample size calculation reflects the primary comparison, whereas the old wording accounted for the sample needed for secondary comparisons (i.e 55 participants in haloperidol arm as well = total 165). For clarity the wording has been changed to reflect primary comparison only and also to refer directly to the clinical response which was used to determine this sample size.

Old text: A total sample size of 165 patients (55 risperidone, 55 haloperidol, 55 control) will provide 80% power, at a 2-tailed type I error of 0.05, to detect a difference of 0.55 SD unit between any two treatment means. The sum of NuDesc scores (item 2, 3 and 4) at 72 hours will be compared by analysis of variance. The corresponding score at baseline will be used as a covariate. Intention to treat analysis will be used.

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New text: A total sample size of 110 patients (55 risperidone, 55 control) will provide 80% power to detect a difference in change of NuDesc score of 1 unit assuming a baseline Standard deviation of 1.92 units, and a correlation of at least 50% between baseline and followup scores. The change in sum of NuDesc scores (item 2, 3 and 4) between baseline and follow up will be evaluated as the group effect (coded 0/1) from the regression of the average of follow up scores on the average of baseline scores and group. Intention to treat analysis will be used.

Change 5#

The null hypothesis wording has been changed to reflect clarity in wording for primary outcome (as per change 1#)

Old text: There is no difference between oral risperidone (delivered in oral solution with dose titrated to effect – dose range of 0.5 mg/24 hours to 4mg/24 hours) and oral placebo solution in the management of targeted delirium symptoms at 72 hours from treatment commencement.

New text: There is no difference between change in sum of scores on Nursing Delirium screening scale (NuDesc) items 2 (inappropriate behaviour), 3 (inappropriate communication), and 4 (illusions/hallucinations) between baseline and follow-up in the oral risperidone (delivered in oral solution with dose titrated to effect – dose range of 0.5 mg/24 hours to 4mg/24 hours) and oral placebo solution arms.

Change 6#

The secondary null hypotheses wording has been changed to reflect clarity in wording for primary outcome (as per change 1#)

Old text: 1. There is no difference between oral haloperidol (delivered in oral solution with dose titrated to effect – dose range of 0.5 mg/24 hours to 4mg/24 hours) and oral placebo solution in the management of targeted delirium symptoms at 72 hours from treatment commencement.

2. There is no difference between oral risperidone (delivered in oral solution with dose titrated to effect – dose range of 0.5 mg/24 hours to 4mg/24 hours) and oral haloperidol solution (delivered in oral solution with dose titrated to effect – dose range of 0.5 mg/24 hours to 4mg/24 hours) in the management of targeted delirium symptoms at 72 hours from treatment commencement.

New text:

1. There is no difference between change in sum of scores on Nursing Delirium screening scale (NuDesc) items 2 (inappropriate behaviour), 3 (inappropriate communication), and 4 (illusions/hallucinations) between baseline and follow-up in the oral haloperidol (delivered in oral solution with dose titrated to effect – dose range of 0.5 mg/24 hours to 4mg/24 hours) and oral placebo solution arms.
2. There is no difference between change in sum of scores on Nursing Delirium screening scale (NuDesc) items 2 (inappropriate behaviour), 3 (inappropriate communication), and 4 (illusions/hallucinations) between baseline and follow-up in the oral risperidone (delivered in oral solution with dose titrated to effect – dose range of 0.5 mg/24 hours to 4mg/24 hours) and oral haloperidol solution (delivered in oral solution with dose titrated to effect – dose range of 0.5 mg/24 hours to 4mg/24 hours) arms.

Change 7#

Section 11 also have been updated to reflect the above changes with the new text as follows:

Old text:

11.2 Statistical analysis of primary null hypothesis:

The sum of NuDesc scores (item 2, 3 and 4) at 72 hours (morning score by researcher) will be compared by analysis of variance. A linear contrast will be constructed to compare risperidone and control groups. The corresponding score at baseline will be used as a covariate. Intention to treat analysis will be used. For patients who die during 72 hour period the last recorded NuDesc score will be used in the analysis.

New text:

11.2 Statistical analysis of primary null hypothesis:

The change in sum of NuDesc scores (item 2, 3 and 4) between baseline and follow up will be evaluated as the group effect (coded 0/1) from the regression of the average of follow up scores on the average of baseline scores and group. Intention to treat analysis will be used. For patients with missing values at any of the 4 time points that comprise the primary endpoint, NuDesc scores will be imputed using multiple imputation with 20 resamples.

Old text:

11.8 Power and sample size

A total sample size of 165 patients (55 risperidone, 55 haloperidol, 55 control) will provide 80% power, at a 2-tailed type I error of 0.05, to detect a difference of 0.55 SD unit between any two treatment means.

New Text:

11.8 Power and sample size

A total sample size of 110 patients (55 risperidone, 55 control) will provide 80% power to detect a difference in change of NuDesc score of 1 unit assuming a baseline standard deviation of 1.92 units, and a correlation of at least 50% between baseline and follow-up scores.
Prior to study close blinded checks of the standard deviations in each arm will be conducted to review the sample size required to provide 80% power.

**15.1.10 Amendment 11**

Date of amendment – 30th October 2014

Statement of intent – This amendment further clarifies the analysis plan. There has been no change in primary outcome or sample size calculation.

Change 1#

Statistical analysis plan has been included for the multivariate analyses, which will use random effects mixed models (section 11.7).

New Text:

All multivariable secondary analyses will control for the same variables used to impute in the primary analysis. Participants and time will be entered as random effects. Study site will be entered as a higher order random effect, given significant model improvement. For all continuous outcomes, time will be reparametrized by adding a time-squared term. For delirium symptom scores and MDAS, a time-squared by group interaction will be entered into the model to improve fit. Mixed models will be validated by examining the residuals visually for normality, homoscedasticity and independence using quantile normal and scatter plots.

Change 2#

Covariates amended (removal of brain metastases, Charlson comorbidity index, and clinician rated anticholinergic score, addition of life limiting illness) (section 11.7). This was to reflect recent data from an epidemiology study by this team, which demonstrated no impact of clinician rated anticholinergic score on delirium symptoms over time, to use one scale as measure of comorbidity rather than two (Charlson Comorbidity index is heavily weighted by cancer diagnosis so CIRS was deemed more representative of comorbidity in the palliative population), to adjust for impact of type of life limiting illness (cancer or non-cancer), and brain metastases is included as an possible item in CIRS and also can cause cognitive impairment. It also is clarified that the dose equivalents are oral (oral morphine equivalents and oral diazepam equivalents)

Old text:

Covariates will include baseline measurements of performance status (AKPS score), clinical rated anticholinergic score, opioid dose in morphine equivalents, benzodiazepine dosage (diazepam dose equivalents), comorbidity burden (Charlson comorbidity index and cumulative illness rating scale scores), brain metastases (present/absent), and prior cognitive impairment (yes/no).

New Text:

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Covariates will include baseline measurements of performance status (AKPS score), opioid dose in oral morphine equivalents, benzodiazepine dosage (oral diazepam equivalents), comorbidity burden (cumulative illness rating scale scores), life limiting illness type (cancer, non-cancer), and prior cognitive impairment (yes/no).

Change 4#

Statistical analysis plan for survival has been added (section 11.4)

New Text:

Survival will be modelled using a Cox regression frailty model, clustering over site, after verifying that the proportional hazards assumption is met.

Change 5#

Statistical analysis plan for multiple imputation have been added (section 11.2)

New Text:

NuDesc scores will be imputed using multiple imputation with 50 resamples, with predictive mean matching using age, gender, eligibility delirium symptoms score (NuDesc score item 2, 3, 4), AKPS, CIRS, baseline morphine and diazepam equivalents, prior cognitive impairment and life limiting illness.
15.2 Consent forms (see attached)

15.3 Proxy information sheet (see attached)

15.4 Patient Information Sheet (see attached)

15.5 Staff information sheet (see attached)

15.6 CRFs (see attached)

15.7 Other related forms

15.7.1 Memorial Delirium Assessment Scale
15.7.2 NuDESC
15.7.3 Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)
15.7.4 Extrapyramidal Symptom Rating Scale (ESRS)
15.7.5 Richmond Agitation Sedation Scale (RASS)
15.7.6 Cumulative Illness Rating Scale (CIRS)
15.7.7 Charlson comorbidity index
15.7.8 EORTC _ QLQ – 30 (version 3)
15.7.9 Facit Pal
15.7.10 Benzodiazepine conversion table
15.7.11 Opioid conversion table
15.7.12 Concurrent medications record
15.7.13 Caregiver reported distress scale
15.7.14 Nursing staff reported distress scale
15.7.15 Patient reported distress scale
15.7.16 Adverse event report form

15.8 SOP’s related to this study.

15.8.1 Adverse event reporting
15.8.2 Data management
15.8.3 Randomisation
15.8.4 Monitoring

15.9 Product information

15.9.1 Risperidone prescribing information
15.9.2 Haloperidol prescribing information