Supplementary Online Content


Trial protocol
A randomised, double-blind, multi-centre placebo controlled trial of dexmedetomidine for patients with agitation and delirium in the intensive care unit

Dexmedetomidine to Lessen ICU Agitation: The DahLIA trial

Clinical Trial Protocol
Version 5 – 24 AUG 11
General Information

1.1 Title
1.2 Chief investigator
1.3 Coordinating and data management centre
   1.3.1 Austin Hospital staff
   1.3.2 Responsibilities
1.4 Management Committee (provisional working group)
   1.4.1 Members
   1.4.2 Responsibilities
1.5 Data Monitoring Committee
   1.5.1 Members
   1.5.2 Responsibilities
1.6 Participating centres
   1.6.1 Sites
   1.6.2 Responsibilities

2 Background Information
2.1 Background
2.2 Trial rationale
   2.2.1 Trial objectives
   2.2.2 Trial feasibility
      2.2.2.1 Ethical imperative and clinical equipoise
      2.2.2.2 Investigator track record
2.3 Trial compliance

3 Trial Aim & Hypothesis
3.1 Trial aim
3.2 Hypothesis

4 Trial Design
4.1 Type/design of trial
4.2 Measures taken to minimise/avoid bias
   4.2.1 Randomisation and allocation concealment of study treatment
   4.2.2 Blinding

5 Assessment Of Efficacy
5.1 Specification of efficacy parameters
   5.1.1 Primary
   5.1.2 Secondary
5.2 Methods and timing for assessing, recording, and analysing of efficacy parameters

6 Statistics
6.1 Sample size and justification
   6.1.1 Sample size
   6.1.2 Justification
6.2 Statistical methods
6.3 Interim analyses
6.4 Criteria for the termination of the trial

7 Selection And Withdrawal Of Subjects
7.1 Subject inclusion criteria
7.2 Subject exclusion criteria
7.3 Subject withdrawal criteria
   7.3.1 Unblinding
   7.3.2 Data management of withdrawn patients

8 Treatment Of Subjects
8.1 Study treatment, description, dosage and usage regimen
8.2 Duration of expected participation
8.3 Medication(s)/treatment(s) permitted and not permitted before and/or after the trial
8.4 Accountability procedures
   8.4.1 Study treatment inspection
   8.4.2 Disposal of used and unused blinding material and study treatment
8.5 Maintenance of study treatment randomisation codes
8.6 Data to be collected in trial CRF

9 Assessment Of Safety
9.1 Adverse event and serious adverse event reporting
   9.1.1 Definitions
      9.1.1.1 Adverse Events
      9.1.1.2 Serious Adverse Events
   9.1.2 Reporting
   9.1.3 Timing of reporting and responsibilities

10 Direct Access To Data And Documents

11 Quality Control And Quality Assurance Monitoring
11.1 Study initiation
11.2 During the study
11.3 At the completion of the study
11.4 Monitoring

12 Ethical Considerations
12.1 Hospital Ethics Committee Approvals
12.2 Consent

13 Data Handling And Record Keeping

14 Financing and Insurance

15 Publication Policy

16 Project Timeline

17 Appendices

18 References
GENERAL INFORMATION

This protocol has been developed to comply with the guidelines contained in the Australian Clinical Trial Handbook,¹ published by the Australian Government.

1.1 Title

A randomised, double-blind, multi-centre placebo-controlled trial of dexmedetomidine for patients with agitation and delirium in the intensive care unit

Short title: Dexmedetomidine to Lessen ICU Agitation (DahLIA)

1.2 Chief investigator

Name: Associate Professor Michael Reade
Title: Consultant Intensivist, Austin & Northern Hospitals and the University of Melbourne
Address: Austin Hospital Intensive Care Unit, Level 2 Austin Tower, 145 Studley Road, Heidelberg VIC 3084, Australia
Telephone: (03) 9496 4838
Email: michael.reade@austin.org.au

1.3 Coordinating and data management centre

Name: Dept. of Intensive Care Medicine, The Austin Hospital
Address: Level 2
145 Studley Road
Heidelberg VIC 3084
1.3.1 Austin Hospital Staff:

<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mr Glenn Eastwood</td>
<td>Study coordinator</td>
</tr>
<tr>
<td>Ms Leah Peck</td>
<td>Assistant Study coordinator</td>
</tr>
<tr>
<td>Professor Rinaldo Bellomo</td>
<td>Director of Research</td>
</tr>
<tr>
<td>A/Prof Michael Reade</td>
<td>Deputy Director of Research</td>
</tr>
</tbody>
</table>

1.3.2 Responsibilities:

Overall management of the study including:
- Study initiation
- Contractual obligations with funders, sponsors, participating centres
- Legal accountability and indemnity authorisation
- Development of funding with NHMRC and governments
- Budgetary oversight
- Oversight of all aspects of project management and data analysis.

1.4 Management Committee (Provisional Working Group)

1.4.1 Members:

<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Michael Reade</td>
<td>Chief Investigator</td>
<td>Austin &amp; Northern Hospitals, Melbourne</td>
</tr>
<tr>
<td>Rinaldo Bellomo</td>
<td>Principal Investigator</td>
<td>Austin Hospital, Melbourne</td>
</tr>
<tr>
<td>John Mulder</td>
<td>Principal Investigator</td>
<td>Western Hospital, Melbourne</td>
</tr>
<tr>
<td>Ben Cheung</td>
<td>Principal Investigator</td>
<td>Toowoomba Base Hospital</td>
</tr>
<tr>
<td>Anthony Delaney</td>
<td>Principal Investigator</td>
<td>Royal North Shore Hospital, Sydney</td>
</tr>
<tr>
<td>Andrew Davies</td>
<td>Principal Investigator</td>
<td>The Alfred Hospital, Melbourne</td>
</tr>
<tr>
<td>Steven Webb</td>
<td>Principal Investigator</td>
<td>Royal Perth Hospital</td>
</tr>
<tr>
<td>Michael Bailey</td>
<td>Statistician &amp; data manager</td>
<td>ANZIC-RC, Melbourne</td>
</tr>
<tr>
<td>Glenn Eastwood</td>
<td>Senior Project Manager</td>
<td>Austin Hospital, Melbourne</td>
</tr>
</tbody>
</table>

1.4.2 Responsibilities:

Overseeing all aspects of the study development including:
- Design, production and approval of final protocol and case report form
- Design, production and approval of generic patient information and consent form
- Database design and management
• Study website design and maintenance
• Management of study budget and liaison with funding bodies
• Preparation and arrangement of Investigator contracts
• Management of regulatory affairs (TGA, CTN, etc, plus compliance, as far as this is possible, with the requirements of the US Food and Drug Administration and other foreign regulatory bodies)
• Co-ordination and assistance with HREC applications
• Study set up, monitoring and close out site visits
• Protocol training of Research Coordinators and Principal Investigators
• Co-ordination with pharmaceutical manufacturers
• Organisation of investigator meetings
• Data collection and data entry/transfer
• Monitoring and assessment of adverse events
• Liaison with Data and Safety Monitoring committee
• Oversight of data analysis
• Approval of writing committee and approval of presentations and publications.
• Media liaison

1.5 Data Monitoring Committee

1.5.1 Members:

<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prof Paul Myles</td>
<td>Chair</td>
<td>Alfred Hospital / Monash University</td>
</tr>
<tr>
<td>Dr Enjarn Lin</td>
<td>Anaesthetist</td>
<td>Alfred Hospital / Monash University</td>
</tr>
<tr>
<td>Dr David Daly</td>
<td>Anaesthetist</td>
<td>Alfred Hospital / Monash University</td>
</tr>
</tbody>
</table>

1.5.2 Responsibilities:

• Determination of study stopping rules
• Review of summary data of adverse events
• Liaison with study Management Committee

1.6 Participating centres:

1.6.1 Sites:

<table>
<thead>
<tr>
<th>Site Name</th>
<th>Description</th>
<th>Principal Investigator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austin Hospital, Melbourne</td>
<td>400 acute-bed tertiary referral hospital</td>
<td>Prof Rinaldo Bellomo</td>
</tr>
<tr>
<td>Northern Hospital, Melbourne</td>
<td>321 acute and sub-acute bed metropolitan hospital</td>
<td>A/Prof Michael Reade</td>
</tr>
<tr>
<td>Western Hospital, Melbourne</td>
<td>300 acute and sub-acute bed metropolitan hospital</td>
<td>Dr John Mulder</td>
</tr>
</tbody>
</table>
1.6.2 Responsibilities:

- Overall management of study at own site in line with the study protocol
- Study nurse recruitment and orientation
- Patient recruitment
- Protocol education of colleagues and attending clinicians
- Data collection and transfer from own ICU
- Data query resolutions
- Adherence to local HREC guidelines and reporting guidelines
- Adverse event reporting to HREC and the Coordinating Centre in line with study protocol.

1 BACKGROUND INFORMATION

2.1 Background

Up to 71% of critically ill patients in intensive care have delirium or psychomotor agitation at some point in their ICU stay. Delirium is unpleasant for the patient, and can contribute to long-term psychiatric disorders in ICU survivors. Agitation in intensive care is problematic, causing self-extubation, removal of catheters, increased oxygen consumption, and failure to cooperate with treatment.

In the early stages of a critically ill patient’s intensive care stay, delirium and agitation are usually masked by infusions of analgesics and sedatives. However, after the underlying pathophysiological problem has resolved, patients often remain delirious and agitated, requiring ongoing sedation, which in turn necessitates continued mechanical ventilation, which can worsen the delirium. Prolonged mechanical ventilation increases the risk of death.

There are few alternatives to heavy sedation in the treatment of ICU-associated delirium and agitation. The drug most commonly used to treat delirium is haloperidol, a centrally acting dopamine antagonist also used in the treatment of major psychoses in outpatients. Haloperidol reduces hallucinations and unstructured thought patterns, but also reduces the interaction with the
environment, producing a flat affect. There is a sedative effect, but no analgesia. Haloperidol is well-established in the outpatient management of psychosis, but has never been subjected to a placebo-controlled trial in patients with ICU-associated agitation and delirium. Evidence for efficacy is largely anecdotal. One observational series of 989 patients found haloperidol use associated with lower mortality (after adjustment for severity of illness), but the authors recognised their limited ability to control for confounding and did not recommend any change in practice. Haloperidol has a number of significant side effects, including extrapyramidal reactions (in 1-10% of patients), neuroleptic malignant syndrome (for which it is the cause in 50% of cases), prolonged QT syndrome (which can precipitate fatal arrhythmias) and urinary retention. The only other commonly used alternative medication is olanzapine. Olanzapine may cause less extrapyramidal reactions and has no cardiac toxicity, but is also a recognised cause of neuroleptic malignant syndrome. It is more expensive, its use is limited by the lack of an intravenous preparation, and it is no more effective than haloperidol.

Dexmedetomidine is a novel selective α2 agonist which relieves psychomotor agitation without causing excessive sedation, has little interaction with other drugs, and can be easily titrated to effect and ceased with a rapid offset. Its analgesic effect allows less opioid use, which might also lessen delirium. With an entirely different mechanism of action, dexmedetomidine shares no common adverse reactions with haloperidol. Transient hypertension during the administration of the loading dose, followed by hypotension and bradycardia, are the only adverse reactions reported at a higher frequency than those with placebo.

The Australian TGA approval for dexmedetomidine was supported by two large (n=353 and 401) placebo controlled trials that evaluated dexmedetomidine as a sedative, rather than as a treatment of ICU-associated delirium and agitation. In each trial, dexmedetomidine substantially reduced the need for ‘rescue’ sedative (either propofol or midazolam), and also reduced to approximately half the amount of morphine used for analgesia. These clinical trials have been limited to the 24 hour postoperative period. There is no reason to suspect that a longer infusion would be detrimental to a patient, and indeed two case series have found this approach associated with no unexpected complications.

Many sedatives cause delirium, and substituting dexmedetomidine may prevent this complication. Two recent trials have tested this hypothesis. One trial compared dexmedetomidine to lorazepam in 106 patients. Dexmedetomidine resulted in more days alive without delirium or coma and more time at the targeted level of sedation than did lorazepam. However, concerns were subsequently raised about the equivalence of dosing, cost-effectiveness, and the validity of the outcome measure studied. A second trial comparing dexmedetomidine to midazolam as a sedative in 375 mechanically ventilated patients found dexmedetomidine associated with significantly less delirium (54% vs. 76.6%) and a reduction in median time to extubation of 1.9 days. Delirium in ICU patients has many causes (such as pain, physiological disturbance, and organ dysfunction) in addition to the adverse effects of sedative medications, suggesting a sedative-sparing effect of dexmedetomidine in these trials may not have been the only mechanism of action. Moreover, even if cost-effective in preventing delirium in other health-care systems, widespread application of dexmedetomidine as a sedative is prohibitively expensive in our...
current context. We therefore wondered whether dexmedetomidine might be effective in the treatment of established delirium, reasoning that, if this were so, its use in this smaller number of patients would be sufficiently cost-effective.

We recently completed the only published study of dexmedetomidine used to control established ICU-associated delirium and agitation.\textsuperscript{18} In this pilot trial, dexmedetomidine (in comparison to haloperidol) significantly shortened median time to extubation from 48.8 (IQR 30.5-117.8) to 19.9 (IQR 7.3-24) hours ($p=0.004$) and significantly decreased ICU length of stay after study drug commencement, from 6.5 (IQR 4-9) to 1.5 (IQR 1-3) days ($p=0.004$). Three patients receiving haloperidol could not be successfully extubated and underwent tracheostomy. One patient prematurely discontinued haloperidol due to QTc interval prolongation.

2.2 Trial rationale

Despite the impressive magnitude of its results, our pilot study had significant limitations. The principal concern is the lack of blinding. If our consultants and bedside nurses had more confidence in dexmedetomidine than haloperidol, they may have been more inclined to attempt earlier extubation in dexmedetomidine patients, or proceed to tracheostomy in patients receiving haloperidol. Before recommending widespread use, we wish to test dexmedetomidine in a broader context, in a blinded placebo-controlled trial involving intubated ICU patients with delirious agitation. We presented various trial design options to the 2009 ANZICS Clinical Trials Group meeting, including replicating the pilot trial design of using both dexmedetomidine and haloperidol by continuous infusion, using both dexmedetomidine/placebo infusions and haloperidol/placebo bolus dosing, and adding dexmedetomidine or placebo to standard care, which as noted above most frequently consists of either haloperidol or olanzapine. The methodology described below (i.e. the last of these three options) is the consensus view of the optimal trial design as expressed by the peak body representing clinical research in intensive care medicine in Australia and New Zealand.

2.2.1 Trial objectives

To determine the effectiveness and safety of dexmedetomidine compared to placebo, when added to standard care, for the treatment of ICU-associated delirium and agitation in patients currently undergoing sedation and mechanical ventilation solely because a. in the opinion of their treating intensivist their agitation is so severe as to make lessening their sedation unsafe AND b. they have required either mechanical restraint and/or anti-delirium or sedative medication in the 4 hours prior to seeking consent AND c. their Confusion Assessment Method for the ICU (CAM-ICU) test \textsuperscript{19} is positive for delirium in the 4 hours prior to seeking consent AND d. their Motor Activity Assessment Scale (MAAS) score\textsuperscript{20} is 5 or more, confirming psychomotor agitation.

The primary measure of effectiveness will be number of ventilator-free hours in the 7 days following commencement of the trial medication. Principal secondary measures will be:

- time to ICU discharge,
Achieving these objectives will provide clinicians with unequivocal data about the efficacy and safety of dexmedetomidine that will be widely generalisable and applicable.

2.2.2 Trial feasibility

2.2.2.1 Ethical imperative and clinical equipoise

Dexmedetomidine is currently licensed in Australia for use in initially intubated patients in the first 24 hours following an operative procedure. Although it is currently used off-label for intubated non-surgical patients, for durations longer than 24 hours, and at higher doses than those approved, such use is not widespread and is supported by minimal evidence.

Most trials seeking to test broader application of dexmedetomidine centre on its potential as an alternative to sedatives such as propofol or benzodiazepines. While such trials show promise, dexmedetomidine is currently much more expensive than these widely used agents. This is likely to preclude the use of dexmedetomidine even if it is shown to be superior. In contrast, relatively few patients develop such problematic agitation and delirium that they remain intubated solely for this reason. Unlike propofol and benzodiazepines, which are safe and effective, the established treatments for ICU-associated agitation and delirium are of unproven efficacy and have common, serious adverse effects. If dexmedetomidine is convincingly found to be effective in such patients, it is likely it would be immediately introduced into practice as its cost would be more than offset by savings in ICU resources.

Dexmedetomidine is not currently in widespread use in Australian hospitals (anecdotal data). In those hospitals where it is approved for use, cost
considerations generally mandate that it is used only after treatment with haloperidol or olanzapine has failed. Given its convincingly superior safety profile compared to haloperidol, and the results of our pilot trial, we anticipate clinicians will be willing to enrol patients in this trial when the only alternative is embarking on conventional treatment with haloperidol.

Some clinicians may feel dexmedetomidine is superior to conventional treatment. If a trial patient has failed to respond to trial medication within 48 hours, we anticipate that such clinicians may wish to substitute open-label dexmedetomidine or haloperidol. This will be allowed. In such cases, the trial medication will be discontinued, but patient data will continue to be collected. The treatment of such data is described in detail below.

If each of the seven hospitals listed is able to recruit 10 patients per year, a yearly total of 70 patients will be recruited. According to the power calculations presented below, the trial could therefore be completed within 17 months.

2.2.2.2 Investigator track record

The investigators have an established record of excellence in the conduct of large-scale randomised-controlled trials in intensive care in Australia. Drs Reade and Bellomo have successfully conducted the pilot trial of 20 patients at the Austin Hospital over a period of two years.

2.3 Trial compliance

The management committee take responsibility for this trial and will ensure that it will be conducted in accordance with the protocol and international standards of Good Clinical Practice in the Australian context.

3 TRIAL AIM & HYPOTHESIS

3.1 Trial Aim

The primary aim of the DahLIA (Dexmedetomidine to Lessen ICU Agitation) trial is to determine, in patients with ICU-associated delirium and agitation who are otherwise pathophysiologically stable (as defined), the number of ventilator-free hours in the incident ICU admission in the 7 days following commencement of trial medication, in patients randomised to receive dexmedetomidine or placebo while receiving all other aspects of standard care.

3.2 Hypothesis

The null hypothesis assumes no difference in the median number of ventilator-free hours in this ICU admission in the following 7 days, between patients receiving dexmedetomidine and placebo for ICU-associated agitation and delirium.
4 TRIAL DESIGN

4.1 Type/design of the trial

DaHLIA will be a multicentre, prospective, randomised, placebo-controlled, double blinded trial comparing dexmedetomidine and placebo for the management of ICU-associated delirium and agitation.

4.2 Measures taken to minimise/avoid bias:

4.2.1 Randomisation and allocation concealment of study treatment:

Randomisation will be achieved using a minimisation algorithm via a password-protected secure study website.

Randomisation will be stratified according to participating institution and patient age (<=55 years; >55 years).

4.2.2 Blinding:

Both dexmedetomidine and normal saline placebo will be given by continuous infusion. Dexmedetomidine has a short distribution half-life (6 minutes),1 mandating such an infusion.

To preserve blinding of the patient, clinical staff and investigators, infusion bags will be prepared away from the bedside by a staff member not involved in assessment of patient outcome or the direct care of the patient. Such bags will be marked with a number corresponding to the study registry, with access restricted to a site research coordinator who is not responsible for ascertainment of patient outcome.

5 ASSESSMENT OF EFFICACY AND SAFETY

5.1 Specification of the efficacy parameters.

5.1.1 Primary:

The primary outcome measure for the study will be the number of ventilator-free hours in the incident ICU admission in the 7 days following commencement of trial medication, in patients randomised to receive dexmedetomidine or normal saline placebo while receiving all other aspects of standard care.

5.1.2 Secondary:

Efficacy:
- time to ICU discharge
- overall ICU length of stay
- time to extubation
• time taken to achieve a satisfactory sedation score (RASS -2 to +1 and RIKER 3 or 4)
• % ICU time spent with a satisfactory sedation score (RASS -2 to +1 and RIKER 3 or 4) in the 7 days following commencement of trial medication.
• time taken to achieve a satisfactory delirium score (CAM-ICU negative)
• % ICU time spent with a satisfactory delirium score (CAM-ICU negative) in the 7 days following commencement of trial medication.
• time taken to achieve a satisfactory agitation score (MAAS 2-4)
• % ICU time spent with a satisfactory agitation score (MAAS 2-4) in the 7 days following commencement of trial medication.
• need for supplementary sedative medication (quantified as total infusion time and mean hourly dose of propofol, morphine and midazolam)
• need for mechanical restraint (quantified as time to first not requiring restraint and % ICU time spent without mechanical restraint in the 7 days following commencement of trial medication.
• need for supplementary antipsychotic medication (quantified as number of doses and total mg delivered of haloperidol, olanzapine, quetiapine)
• need for tracheostomy
• acute hospital length of stay
• discharge destination (home, skilled nursing facility, rehabilitation, etc.)

Safety:
• Daily SOFA score
• ICU mortality
• hospital mortality
• duration and rate of vasopressor / inotropic support (quantified as total infusion time, and mean hourly dose of noradrenaline and any other inotrope)
• need for insertion of a new central venous catheter to facilitate vasopressor / inotropic support
• requirement for re-intubation

5.2 Methods and timing for assessing, recording, and analysing of efficacy parameters.

• Sedation score (RASS and RIKER scores) – representative value in every 4-hour period
• Delirium assessment (CAM-ICU) and agitation assessment (MAAS) - representative value in every 8-hour period
• Sedative medication – representative value in every 4-hour period
• Mechanical restraint – representative value in every 4-hour period
• Vasopressor rate – representative value in every 4-hour period
• SOFA score - worst value in 24 hour period
• Timing of extubation – time at which the bedside nurse considered the patient suitable for extubation, in addition to the actual time of extubation.
Data will be collected every 4 hours for the entire ICU admission following randomisation, to allow calculation of % ICU time spent at satisfactory levels of sedation, agitation, and delirium.

6 STATISTICS

6.1 Sample size and justification

6.1.1 Sample size:

The planned sample size is 96 patients.

6.1.2 Justification:

Some patients may not respond as quickly as their treating clinician may hope. Some clinicians may feel that dexmedetomidine is superior to conventional management for this indication. Seeing no response to the trial drug, they may wish to commence open-label dexmedetomidine. After 48 hours this will be allowed. In the survival analysis such patients will be treated as right censored data. Some patients who are initially intubated will undergo tracheostomy rather than being extubated. In the primary analysis, these patients will be treated as if they had been extubated at the time of liberation from mechanical ventilation for a period that subsequently lasts longer than 12 hours, although most if not all will retain their tracheostomy at this time. In a secondary analysis, they will be analysed as right censored data at the time of tracheostomy. The reason for tracheostomy will be recorded. Patients undergoing tracheostomy for an indication other than failure to liberate from mechanical ventilation due to delirium will be further analysed as a separate group.

In the pilot study, dexmedetomidine shortened mean time to extubation (compared to haloperidol, which represents the commonest form of ‘standard treatment’ likely to be given to patients in DahLIA) from 60 (SD 46) to 20 (SD 15) hours, or 108 vs. 148 ventilator-free hours in the following 7 days. A conservative extrapolation of these results into a multi-centre context would be to halve the size of the expected effect. i.e. 108 vs.128 hours. Forty-eight patients in each group would be required to have 80% chance of demonstrating a difference of this magnitude with a certainty of 95%. (total 96 initially intubated patients).

Almost all data collection, with the exception of hospital mortality, will be completed while patients are in the ICU. We therefore anticipate minimal withdrawal and loss to follow-up, and have not accounted for these factors in the sample size calculations.

A detailed statistical analysis plan will be developed before completion of recruitment. All analyses will be conducted on an intention-to-treat basis. The relatively small number of patients required to achieve sufficient power may result in imbalances in various baseline characteristics. The following baseline characteristics will be recorded: age; sex; premorbid history of abnormal mental status; diagnosis; APACHE II score in the 24 hours immediately prior to
enrolment; physical restraint prior to enrolment; midazolam, propofol, haloperidol, morphine, or other sedative or anti-psychotic use prior to enrolment; time intubated prior to randomization; and RASS \(^{22}\), RIKER\(^{23}\) and CAM-ICU \(^{24}\) scores at enrolment. Although the primary analyses will be conducted without adjustment, the effect of any baseline differences will be explored using Cox proportional hazard and logistic regression modeling.

6.2 Statistical methods:

A detailed statistical analysis plan will be developed before completion of recruitment:

- All analyses will be conducted on an intention-to-treat basis.
- Ventilator-free hours over 7 days will be compared using unpaired t-tests or Mann-Whitney U tests, as appropriate.
- Times to extubation and to intubation will be compared by means of the log-rank test and presented as Kaplan–Meier curves without adjustment for baseline covariates.
- Proportions will be compared by means of the chi-square test or Fisher’s exact test, and continuous variables will be compared by means of unpaired t-tests.
- The relatively small number of patients required to achieve sufficient power may result in imbalances in various baseline characteristics. The following baseline characteristics will be recorded: age; sex; premorbid history of dementia or other abnormal mental status; diagnosis; APACHE II score in the 24 hours immediately prior to enrolment; physical restraint prior to enrolment; midazolam, propofol, haloperidol, morphine, or other sedative or anti-psychotic use prior to enrolment; time intubated prior to randomization; and RASS \(^{25}\), RIKER\(^{23}\) and CAM-ICU \(^{26}\) scores at enrolment. Although the primary analyses will be conducted without adjustment, the effect of any baseline differences will be explored using Cox proportional hazard and linear regression modeling.

6.3 Interim analysis

No interim efficacy analysis is planned. A blinded interim safety analysis may be performed by the Data Monitoring and Safety Committee at their request but this will not affect the Type I error rate of the study.

6.4 Criteria for the termination of the trial

The Data Monitoring and Safety Committee will terminate the trial if there are substantiated reports of attributable serious adverse effects associated with either treatment arm that suggest enrolment in the trial is associated with harm, or if there is a significant increase in adverse safety outcomes at the time of any interim analysis.

7 SELECTION AND WITHDRAWAL OF SUBJECTS

7.1 Subject inclusion criteria.
Patients will be eligible for the study if, in the opinion of the treating clinician, they continue to require mechanical ventilation only because their degree of agitation requires such a high dose of sedative medication (midazolam or propofol, the only commonly used specific sedatives in our unit) that extubation is not possible, AND in the opinion of their treating intensivist their agitation is so severe as to make lessening their sedation unsafe. These criteria will be objectively quantified as follows:

a. they have required either mechanical restraint and/or anti-delirium or sedative medication in the 4 hours prior to seeking consent AND
b. their Confusion Assessment Method for the ICU (CAM-ICU) test \(^2\) is positive for delirium in the 4 hours prior to seeking consent AND
c. their Motor Activity Assessment Scale (MAAS) score\(^2\) is 5 or more in the 4 hours prior to seeking consent, confirming psychomotor agitation.

7.2 Subject exclusion criteria

- Age less than 18 years.
- Pregnancy or breastfeeding.
- Advanced dementia (in the premorbid state requiring professional nursing care)
- Open or closed head injury
- Death is deemed imminent and inevitable.
- The patient has previously been enrolled in the DahLIA study during this or an earlier ICU admission
- The patient has previously been enrolled in a clinical trial of a sedative, antipsychotic or anti-delirium medication during this ICU admission.
- Patients who could not be extubated within the following 48 hours even if delirium or agitation were corrected. This will include:
  - Patients receiving high dose opioid for analgesia (not sedation) (>40 mg/morphine/day)
  - Patients shortly to return to the operating theatre
  - Patients undergoing repeated invasive procedures, in whom it is desirable to maintain deep sedation.
  - Patients likely to require ongoing airway protection or control, or ventilatory support (for example, spinal patients with an inadequate vital capacity)
- Known allergy to haloperidol or \(\alpha\)2 agonists
- Patients who are already receiving dexmedetomidine, or clonidine if the primary indication is its sedative effect.

7.3 Subject withdrawal criteria

- If at any time during the infusion of study drug the patient develops a medical condition that would preclude their extubation or require their intubation. The study drug infusion will be stopped, but the patient will be retained in the intention to treat analysis.
- If at any time after 48 hours of study drug infusion the treating clinician believes open-label dexmedetomidine is required. The study drug infusion will be stopped, but the patient will be retained in the intention to treat analysis. (NB. prior to this
48-hour point, the study drug infusion will only be discontinued if it is thought responsible for an adverse event, NOT if it is thought to be ineffective).

- After 7 days (i.e. 7 x 24 hours) of infusion of study drug. This will be considered ‘treatment failure’, and the study drug will be stopped. Open label dexmedetomidine may be used after this time if required.

NB. Open label dexmedetomidine must be dispensed by the hospital pharmacy, and not draw from the supply of medication provided for the trial.

7.3.1 Unblinding:

Patients whose study drug infusion is discontinued will not be unblinded unless knowledge of the randomised treatment allocation would influence future patient care in a significant fashion. The physician responsible for the clinical care of the patient will have sole authority to unblind the patient, after discussion with the Study Manager or member of the Management Committee (including the site Principal Investigator).

The reason for unblinding will be provided, together with details of the name of the clinician making the decision, the date and time the decision was made and any documentation that supports the decision.

In any case of unblinding, the follow-up schedule of data collection will be maintained to enable full analysis of all patient data on an intention-to-treat basis.

7.3.2 Data management of withdrawn patients

In patients in whom the study drug infusion has been discontinued, the follow-up schedule will continue unless the patient or their representative has specifically withdrawn consent to follow up.

Patients in whom the study drug infusion has been discontinued will be included in the final analysis on an intention to treat basis.

8 TREATMENT OF SUBJECTS

8.1 Study treatment description, dosage and usage regimen

Dexmedetomidine will be administered intravenously as a maintenance infusion of 0 to 1.5 μg/kg/hour, commencing at 0.5 μg/kg/hour and titrated according to effect, for as long as deemed necessary by the treating physician. Specifically, the study medication may be (as recommended by the manufacturer) continued after extubation, and if discontinued may be restarted at any time up until ICU discharge. The clinician will have the option of using a loading dose of 1.0 μg/kg IV over 20 minutes, as recommended by the manufacturer.

Bedside nursing staff will adjust drug infusion rates as necessary, in consultation with the treating physician, aiming to achieve a Riker Sedation-Agitation Scale score of 4 or a Richmond Agitation-Sedation Scale (RASS) of 0 unless another goal is prescribed.
The study drug (dexmedetomidine or normal saline placebo) will be supplied to the bedside nurse in identical 50mL infusion syringes or 100ml or 250 ml infusion bags containing drug diluted from the original vials by an unblinded research assistant or clinical nurse not involved in the trial in each site. The drug must be prepared in the ICU (not a pharmacy location remote from the ICU) to facilitate sufficiently rapid treatment of an acutely delirious patient. The choice of syringe or infusion bags will be left to the site investigators, taking into account usual practice and the expected rate and duration of study drug infusion.

8.2 Duration of expected participation

Participation in the trial will be up until the time of discharge from acute hospital care.

8.3 Medication(s)/treatment(s) permitted and not permitted before and/or during the trial

Whilst receiving the study treatment, any other element of standard care may be administered. Specifically, haloperidol, olanzapine or other antipsychotic medications (eg. quetiapine) may be administered according to the preference of the treating clinicians. Sedatives (eg. propofol or benzodiazepines) and analgesics (eg. morphine or fentanyl) may be continued as determined by the treating clinician. The only prohibited medication will be clonidine, as clonidine (another α2 agonist) will interact with dexmedetomidine. Patient management will be otherwise unaffected and the treating clinicians will be free to provide whatever other medical care is deemed necessary for the patient.

8.4 Accountability procedures

8.4.1 Study treatment inspection:

The unblinded Research Coordinator at each hospital will be responsible for receiving, inspecting, and documenting the study medications prior to placement in the ICU store.

Each unblinded Research Coordinator will make local arrangements for carrying out the inspection procedure of the study medication. Documentation of study medication distribution, receipt, use and disposal will be kept to enable comprehensive tracking and reconciliation of all study treatments, used or unused.

8.4.2 Disposal of used and unused blinding material and study treatment:

All used, partially used and unused study medication vials should be returned to the unblinded Research Co-ordinator in each site.

The vials must then be stored until the unblinded Study Manager conducts a monitoring visit to the ICU. At this monitoring visit, the medication vials used will be checked against the record of medication administration.
At the end of the monitoring visit, the unblinded Research Coordinator will transfer all the checked vials to the agreed area where the bags will be disposed of according to local guidelines.

8.5 Maintenance of study treatment randomisation codes

Randomisation codes for patients are maintained in a data table on the firewall protected server in a password protected location at the ANZIC-RC. The server is backed up offsite and therefore there is the potential to retrieve randomisation information if the need arises.

All staff apart from the nominated statistician and the research staff member responsible for preparation of the infusion syringes in each site will be blinded as to the treatment allocation.

8.6 Data to be collected in the trial CRF

<table>
<thead>
<tr>
<th>Form No.</th>
<th>Period of study</th>
<th>Data collection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Randomisation</td>
<td>Patient identifiers, eligibility criteria, admission diagnosis</td>
</tr>
<tr>
<td>1</td>
<td>Baseline Information</td>
<td>Source and date of admission to ICU, place of residence prior to hospitalisation (home / skilled nursing facility / low level care / rehabilitation hospital / other acute care hospital) ICU admission diagnosis, APACHE II score, SOFA scores for each organ system, cardiovascular measurements, duration of mechanical ventilation (if applicable), duration of ICU admission, use of sedatives and mechanical restraint prior to randomisation,..</td>
</tr>
<tr>
<td>2</td>
<td>Every 4 hours following commencement of study medication</td>
<td>Study drug rate (max/min) &amp; total amount, use of other sedatives &amp; analgesics (max/min) &amp; total amount, use of mechanical restraint, use of vasopressors (max/min rate &amp; duration), hourly blood products, study fluid and other fluid input and output, RIKER and RASS scores</td>
</tr>
<tr>
<td></td>
<td>Every 8 hours following commencement of study medication</td>
<td>MAAS and CAM-ICU scores.</td>
</tr>
<tr>
<td>2</td>
<td>At any time during infusion of study medication</td>
<td>Need for insertion of a new central venous catheter solely to facilitate new vasopressor or inotrope support of blood pressure</td>
</tr>
<tr>
<td>2</td>
<td>At the time of extubation / tracheostomy / intubation / use of open-label dexmedetomidine</td>
<td>Duration of mechanical ventilation (if applicable), total time study drug infused, duration of continuation of study medication (if applicable)</td>
</tr>
</tbody>
</table>
9 ASSESSMENT OF SAFETY

9.1 Adverse Event and Serious Adverse Event Reporting

9.1.1 Definitions:

9.1.1.1 Adverse events

Adverse events (AEs) are defined as any untoward medical occurrence in a patient or clinical investigation subject administered an investigational intervention and which does not necessarily have to have a causal relationship with this treatment.\(^{31}\)

It is recognised that the patient population in the ICU will experience a number of common aberrations in laboratory values, signs and symptoms due to the severity of the underlying disease and the impact of standard therapies. These will not necessarily constitute an adverse event unless they require significant intervention or are considered to be of concern in the investigator’s clinical judgement.

In all cases, the condition or disease underlying the symptom, sign or laboratory value should be reported.

9.1.1.2 Serious adverse events (SAE)

SAEs are defined as any untoward medical occurrence that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event which may require intervention to prevent one of the previously listed outcomes

With particular reference to the study medications, the following are defined as serious adverse events that will require discontinuation of the study medication:
- Severe hypotension thought to be due to study treatment and requiring high dose (as defined by the treating clinician) inotropic or vasopressor support.
- Unanticipated and confirmed sustained ventricular arrhythmia

In this study all SAEs will be reported regardless of suspected causality.

9.1.2 Reporting:

SAEs which occur from the time of commencement of study medication to 72 hours post discontinuation will be reported to the Coordinating Centre by faxing the supplied SAE form. SAEs will be reported to the co-ordinating within 24 hours of study staff becoming aware of the event. Minimum information to report will include:

- Patient initials and study number
- Nature of the event
- Commencement and cessation of the event
- An investigator’s opinion of the relationship between study involvement and the event (unrelated, possibly, probably or definitely related).
- Whether treatment was required for the event and what treatment was administered.

SAEs must be reported on the fax form but may also be discussed with the Co-ordinating Centre staff or chief investigator if necessary.

Staff at the Coordinating Centre will be responsible for following-up SAEs to ensure all details are available. It is the responsibility of each site to inform their HREC of all SAEs which occur at their site, in accordance with local requirements.

Serious adverse events (SAEs) which are unexpected and thought to be related to the study treatment are subject to expedited reporting to the Therapeutic Goods Administration in Australia.

For the DahLIA study, the Coordinating Centre will report to the TGA and other investigators (for onward reporting to the HREC according to local HREC guidelines).

SAEs that are expected (because the event is recognised to be associated with the study treatment and is reported in the Product Information in Appendix #1) will also be reported but these events are not usually subject to expedited reporting to the regulatory authorities.
SAEs which are not thought to be related to the study treatment are not subject to expedited reporting. All deaths that occur during the study period will be recorded as a study outcome.

The other types of adverse event or drug reaction that are commonly reported in pre-marketing trials are listed below together with the definition of each.\textsuperscript{32}

- **Adverse Event or Adverse Experiences (AE)** – Any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. An adverse event can therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

- **Adverse Drug Reaction** – marketed medicinal products: a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease or for modification of physiological function.

- **Unexpected Adverse Drug Reaction** – An adverse reaction, the nature and severity of which is not consistent with the applicable product information (e.g. Investigator’s Brochure for an unapproved investigational medicinal product or Product Information / package insert / summary of product characteristics for an approved product).

Details of non-serious adverse events (AE), adverse drug reactions and unexpected adverse drug reactions (ADR) (as defined above) will be captured in the data collection requirements for the Study. These data will be monitored throughout the study and analysed for evidence of any possible increase in trend in AEs or ADRs (e.g. increased frequency), which may then need to be reported to the applicable regulatory authorities if any safety issues emerge during this process.

Each Principal Investigator will be responsible for deciding if any AEs or ADRs (as defined above) occur in any patient during the course of the study that are not considered to have been captured in the current data collection requirements. These AEs or ADRs will be recorded on Form 3, which includes:

- Patient Study ID
- Volume and duration of study treatment
- Nature of the reaction
- Underlying condition being treated
- Potentially confounding factors
- Outcome of event or reaction

Investigators are also advised to refer to the Investigator’s Brochure for information on adverse events and adverse reactions associated with the two study treatments.

9.1.3 Timing of reporting & responsibilities:
The Principal Investigator in each site must ensure that Serious Adverse Events which are both unexpected and thought to be related to the study treatment and are “fatal” or “life threatening” are reported to the Senior Project Manager or an assigned deputy immediately after becoming aware of the event occurring.

This can be done by telephone or fax but telephone is preferred as it assures both parties that the message has been received and will be acted on. The verbal report will be followed by a written report using the data form provided (Form 7).

The written report will be made within 7 calendar days to the Therapeutic Goods Administration (Australia), even if there is still data to come at a later stage (such as a post mortem report or laboratory result). If an SAE is both unexpected and thought to be related to the study treatment, but not fatal or life threatening, a written report will be made to the Therapeutics Goods Administration, within 15 calendar days of the event.

Further information related to the SAE may also be required and this will include information about concomitant medications, batch number of study fluid, height and weight of patient and the contact details of the reporter. The Principal Investigator should therefore be prepared to provide all additional required information.

The Senior Project Manager will be responsible for alerting the regulatory authorities of any SAEs requiring expedited notification. The report is for fatal and life threatening events is required within 7 calendar days of the initial notification of the event and should be followed by a complete report in an additional 8 calendar days. The site Principal Investigator will be responsible for providing any reports so that these deadlines and requirements can be adhered to.

The Senior Project Manager is also responsible for alerting other participating centres of the report of an SAE which has required expedited reporting.

A Serious Adverse Event which is unexpected and thought due to study treatment but which is not fatal or life threatening will also be reported to the Senior Project manager as soon as possible after the event has been recognised. The reporting timeframe to the TGA will also be as soon as possible but no later than 15 days after the first knowledge of the event.

It is the responsibility of each Principal Investigator to follow the local Hospital Research Ethics Committee procedures for expedited reporting of SAEs. Copies of any reporting and correspondence to and from the HRECs should also be sent to the Coordinating Centre.

If an unexpected SAE occurs and is thought to be study treatment related, the Investigator or treating clinician must make a decision about the need to unblind the study fluid for that patient. Wherever possible, it is preferable to maintain the blind. However, if knowledge of the study treatment type is required to treat the adverse event quickly and correctly, then unblinding may be required. The Therapeutic Goods Administration advises that retention of blinding is considered “understandable when the fatal or serious outcome is identical or
closely resembles the primary efficacy endpoint of the study. These outcomes would be considered to be ‘disease related’ and exempted from expedited reporting”.

10. DIRECT ACCESS TO DATA & DOCUMENTS

The study may be audited by government regulatory authorities or local Hospital Research Ethics Committees.

Therefore access to medical records, other source documents such as ICU charts and other study related files must be made available at all study sites for monitoring and audit purposes during the course of the study and after its completion.

11. QUALITY CONTROL AND QUALITY ASSURANCE MONITORING

11.1 Study Initiation

Prior to initiation of the study at each hospital, the Chief Investigator and Research Coordinator will conduct a one day training session at each hospital site.

The training will cover all aspects of the study protocol and procedures and will include practical training in the use of the website and the study materials. All study materials will be provided at or before the training sessions.

11.2 During the study

During the study, the Study Manager will visit all study centres on at least 2 occasions in the recruitment period.

The purpose of these visits will be to ensure that the study is conducted according to the protocol, good clinical practice guidelines and relevant regional regulatory requirements and to review study records and source documents for the specific verification of participant details, data quality and the completeness of follow-up. The Study Manager will remain blinded to the study intervention that was allocated to each patient at each site during the monitoring visit.

A report of each visit will be prepared by the Study Manager and reviewed by the Study Management Committee. A copy will be sent to the Research Coordinator and Principal Investigator so that requested actions can be highlighted and the document filed.

The specific aims and tasks of the monitoring visit are to:

- Check accuracy of data submitted to the database by conducting a source documentation check of a random sample of 10% of patients who have completed the study follow up period. A review of key data items submitted to the study database will be checked against source documentation and the overall accuracy will be recorded.

- Check for and report back to the Investigator any protocol violations that are detected.
- Reconcile retained study fluid volume and code numbers against database records to check for accuracy of data on all randomised patients.

- Review the source documentation for the primary and secondary study outcomes for every patient (death, discharge dates, renal and respiratory organ SOFA scores to check for accuracy and completeness.)

- Confirm that there is a record of consent / assent to study procedures consistent with the requirements of the relevant research ethics committee.

- Check study drug storage for correct conditions (such as temperature), adequacy of space and ease of retrieval.

- Check recruitment rate against ICU admission figures and address any shortfalls in recruitment expectations with ICU staff.

- Check data security and access.

- Check for any unreported SAEs and follow up on reported SAEs to ensure all data has been recorded and the local HREC notified.

11.3 At the completion of the study

At completion of study recruitment a final monitoring and close out visit will be conducted by the Study Manager. This will encompass the tasks outlined in general monitoring visits but will also include the collection of any remaining fluid administration sets and shoeboxes for final disposal. Secure facilities for the storage of study data for 15 years will also be re-checked at this visit.

11.4 Monitoring

Monitoring will be conducted as per the monitoring plan.

12 ETHICAL CONSIDERATIONS

12.1 Hospital ethics committee approvals

An application requesting approval to conduct this study will be submitted to the Hospital Research Ethics Committee (HREC) at each of the participating hospitals. Each application will be submitted according to the requirements of each hospital committee, all of which are formed and are conducted in accordance with the guidelines laid down by the National and Medical Research Council of Australia.31

The content and format of the patient and next of kin or legal surrogate Information Statements and Consent Forms will be approved by each ethics committee and produced in line with their own guidelines and requirements. Each participating hospital will therefore use their own consent documents as approved by their local HREC.

Each Principal Investigator will be responsible for producing regular status reports, serious adverse event reports, and any other required documentation to the local HREC in accordance with their guidelines. Any amendments or additions to the study
protocol and material must be notified to the HREC by the Principal Investigator and approved by the HREC.

It is the responsibility of the Principal Investigator at each participating hospital to keep an up to date record of all correspondence and applicable documentation with the local HREC and the regulatory authorities. A clean copy of the consent forms and Information Statements that are to be used at each hospital, together with a copy of all signed consent forms and any other consent related correspondence must also be kept in a separate file for this study, in case of any future requirement for audit purposes. As with all study records, documents must be kept for a minimum of 15 years from the end of the study.

12.2 Consent

The NHMRC National Statement on the Ethical Conduct of Research in Humans (March 2007) acknowledges in Chapter 4.4 that research involving patients who are heavily dependent on medical care, such as the patients in this study, is necessary to assess and improve the efficacy and safety of interventions used in their treatment.

A number of approaches to obtaining consent in this study have been developed from the guidelines in Chapter 4.4 of the National Statement and also from the ANZICS Clinical Trials Group Ethics Handbook for Researchers (2005). Patients eligible for this study will be too unwell or sedated as part of their treatment to be considered competent to give informed consent to participate in this study. As the study will begin when the patient requires treatment for delirium and agitation, it will not be possible for the patient’s consent and study involvement to be delayed until they are capable of giving their own consent. The National Statement provides guidance for such patients in sections 4.4.9 through to 4.4.14.

Consent will be sought from the participant’s guardian, or person or organisation authorised by law (4.4.10) (the ‘person responsible’ in Victorian law). When the person responsible cannot attend the hospital to sign a consent form within the time constraints of the study, consent for patient participation in the study may be obtained over the telephone. Telephone consent requires two people, one of whom must be a member of the research staff, to witness the consent statement from the person responsible. The telephone conversation must be documented in the patient’s medical record and signed by both of the witnesses to the conversation. As soon as the person responsible is able to attend the hospital they will be asked to sign a consent form and note that telephone consent was already provided.

In cases where the person responsible cannot be determined or contacted, the patient may be enrolled without prior consent, in accordance with the local HREC approval and legislation (as per 4.4.13). The patient will be enrolled with Procedural Authorisation and consent obtained from the person responsible as soon as possible.

The person responsible will be able to withdraw their consent for the patient to continue to participate in the study at any time, and if they choose to withdraw the patient, permission will be asked to use the data collected up to that time (as per 4.4.14).
Patients who recover sufficiently to understand the explanation of the study will be asked to consent to continue in the study procedures or be offered the chance to withdraw (as per 4.4.14). If the patient chooses to withdraw from the study procedures, they will be asked for permission to use their study-related data and for permission to collect and use outcome data.

All interaction between research staff and potential or actual participants and their relatives will take into consideration the stress or emotional factors associated with critical illness and ensure that the dependency of potential participants and their relatives on medical personnel providing treatment does not compromise the freedom of decision making to participate (as per 4.4.11).

**13 DATA HANDLING AND RECORD KEEPING**

Folders will be provided for the Research Coordinator to file any paper documents used for any form of data collection for each patient and to store the signed and dated consent form(s). A comprehensive guide to the data collection with definitions and rationale will be provided together with a paper version of the data collection forms.

A guide to accessing the data entry forms on the Website and entering all follow-up data is also provided in the Website Users Guide. All of these documents are also available in PDF format for printing from the study Website as required.

Data management will be provided by the Coordinating Centre. The principal means of data collection and data processing will be electronic via a password protected Website. All computerised forms will be electronically signed by the authorised study staff and all changes made following the electronic signing will have an electronic audit trail with a signature and date.

Comprehensive guidelines have been produced to assist in the high-quality data collection and data entry that is required to achieve the goals of the complete study analysis plan.

**14 FINANCING AND INSURANCE**

The study is an investigator-initiated study. Funding is provided through an unrestricted grant from Hospira Pty Ltd.

As an investigator- initiated study performed in public hospitals, indemnity insurance will be provided by the public hospital.

**15 PUBLICATION POLICY**

The study will be conducted in the name of the DaHLIA study investigators. Where individuals’ names are required for publication, those of the management committee will be used, with the chief investigator listed first and subsequent authors listed alphabetically. The central project coordination and data management will be provided by the Coordinating Centre, Melbourne. The principal publication from the study will give full credit to all collaborating investigators, research coordinators and institutions.
## PROJECT TIMELINE

<table>
<thead>
<tr>
<th>Date</th>
<th>Project Milestone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mar 2009</td>
<td>Presentation of protocol to ANZICS CTG meeting, Noosa</td>
</tr>
<tr>
<td>Dec 2009</td>
<td>Funding agreement confirmed</td>
</tr>
<tr>
<td>Feb 2010</td>
<td>Protocol finalised</td>
</tr>
<tr>
<td>Feb 2010</td>
<td>ANZICS CTG endorsement obtained</td>
</tr>
<tr>
<td>Mar 2010</td>
<td>Case Report Form (CRF) draft finalised</td>
</tr>
<tr>
<td>Jun 2010</td>
<td>Site initiation and induction</td>
</tr>
<tr>
<td>Jul 2010</td>
<td>Commencement of recruitment</td>
</tr>
<tr>
<td>Jul 2012</td>
<td>Database lock, data analysis and initial results</td>
</tr>
<tr>
<td>Oct 2012</td>
<td>Publication #1</td>
</tr>
</tbody>
</table>
17. LIST OF APPENDICES

A. Dexmedetomidine Product Information sheet

B. Memorandum of Understanding between Hospira Pty Ltd and the Chief Investigator

C. Participant consent forms:
   a. Person responsible
   b. Person responsible consent to continue participation
   c. Participant consent to continue participation

D. Case report forms
Appendix A.
Dexmedetomidine Product Information sheet

Precedex

Company Hospira

Primary Section: Central Nervous System - Sedatives, hypnotics

MIMS revision date: 01 Nov 2009

Active: Dexmedetomidine (as hydrochloride).
Inactive: Sodium chloride 9 mg in water.

Description
Chemical name: (+)-4-(S)-[1-(2,3-dimethylphenyl)ethyl]-1H-imidazole monohydrochloride. Molecular formula: C_{13}H_{16}N_{2}HCl. MW: 236.7. CAS: 145108-58-3. Dexmedetomidine hydrochloride is a white or almost white powder, freely soluble in water and its pKa is 7.1. Dexmedetomidine is supplied as a clear, colourless, isotonic solution with a pH of 4.5 to 7.0. Its partition coefficient in octanol: water at pH 7.84 is 2.89. Each 1 mL of Precedex contains dexmedetomidine HCl 118 microgram (equiv. dexmedetomidine base 100 microgram). The solution is preservative free and contains no additives or chemical stabilisers.

Actions
Pharmacology.
Pharmacodynamics. Dexmedetomidine is a relatively selective alpha2- adrenoreceptor agonist with a broad range of pharmacological properties. The sedative actions of dexmedetomidine are believed to be mediated primarily by postsynaptic alpha2-adrenoreceptors, which in turn act on inhibitory pertussis toxin sensitive G protein, thereby increasing conductance through potassium channels. The site of the sedative effects of dexmedetomidine has been attributed to the locus coeruleus. The analgesic actions are believed to be mediated by a similar mechanism of action at the brain and spinal cord level. alpha2-Selectivity was observed in animals following slow intravenous (IV) infusion of low and medium doses (10 to 300 microgram/kg). Both alpha1 and alpha2 activity was observed following slow IV infusion of high doses (greater than or equal to 1,000 microgram/kg) or with rapid IV administration. Dexmedetomidine has a low affinity for beta-adrenergic, muscarinic, dopaminergic and serotonin receptors.

Clinical trials.
ICU sedation. Two randomised, double blind, parallel group, placebo controlled multicentre clinical trials in a surgical intensive care unit (ICU) 754 patients being treated. All patients were initially intubated and received mechanical ventilation. Two of these trials evaluated the sedative properties of Precedex by comparing the amount of rescue medication (midazolam in one trial and propofol in the second) required to achieve a specified level of sedation (using the standardised Ramsay sedation scale) between Precedex and placebo from onset of treatment to extubation or to a total treatment duration of 24 hours. The Ramsay Level of Sedation Scale is displayed in Table 1.
In the first study, 175 patients were randomised to receive placebo and 178 to receive Precedex by intravenous infusion at a dose of 0.4 microgram/kg/hr (with allowed adjustment between 0.2 and 0.7 microgram/kg/hr) following an initial loading infusion of 1 (one) microgram/kg IV over 10 minutes. The study drug infusion rate was adjusted to maintain a Ramsay sedation score of greater than or equal to 3. Patients were allowed to receive rescue midazolam as needed to augment the study drug infusion. In addition, morphine sulfate was administered for pain as needed. The primary outcome measure for this study was the total amount of rescue medication (midazolam) needed to maintain sedation as specified while intubated. Patients randomised to placebo received significantly more midazolam than patients randomised to Precedex (see Table 2). A second prospective primary analysis assessed the sedative effects of Precedex by comparing the percentage of patients who achieved a Ramsay sedation score of greater than or equal to 3 during intubation without the use of additional rescue medication. A significantly greater percentage of patients in the Precedex group maintained a Ramsay sedation score of greater than or equal to 3 without receiving any midazolam rescue compared to the placebo group (see Table 2).

A prospective secondary analysis assessed the dose of morphine sulfate administered to patients in the Precedex and placebo groups. On average, Precedex treated patients received less morphine sulfate for pain than placebo treated patients (0.47 versus 0.83 mg/h). In addition, 44% (79 of 178 patients) of Precedex patients received no morphine sulfate for pain versus 19% (33 of 175 patients) in the placebo group. In the second study, 198 patients were randomised to receive placebo and 203 to receive Precedex by intravenous infusion at a dose of 0.4 microgram/kg/hr (with allowed adjustment between 0.2 and 0.7 microgram/kg/hr) following an initial loading infusion of 1 (one) microgram/kg IV over 10 minutes. The study drug infusion was adjusted to maintain a Ramsay sedation score of greater than or equal to 3. Patients were allowed to receive rescue propofol as needed to augment the study drug infusion. In addition, morphine sulfate was administered as needed for pain. The primary outcome measure for this study was the total amount of rescue medication (propofol).
needed to maintain sedation as specified while intubated. Patients randomised to placebo received significantly more propofol than patients randomised to Precedex (see Table 3). A significantly greater percentage of patients in the Precedex group compared to the placebo group maintained a Ramsay sedation score of greater than or equal to 3 without receiving any propofol rescue (see Table 3).

**Precedex**

<table>
<thead>
<tr>
<th>Study Two</th>
<th>Placebo N=198</th>
<th>Precedex N=203</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean total dose (mg) of propofol</td>
<td>513 mg</td>
<td>72 mg</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>782 mg</td>
<td>249 mg</td>
<td></td>
</tr>
<tr>
<td>Categorised propofol use</td>
<td></td>
<td></td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>0 mg</td>
<td>47 (24%)</td>
<td>122 (60%)</td>
<td></td>
</tr>
<tr>
<td>0-50 mg</td>
<td>30 (15%)</td>
<td>43 (21%)</td>
<td></td>
</tr>
<tr>
<td>&gt;50 mg</td>
<td>121 (61%)</td>
<td>38 (19%)</td>
<td></td>
</tr>
</tbody>
</table>

*ANOVA model with treatment centre. **Chi-square.

A prospective secondary analysis assessed the dose of morphine sulfate administered to patients in the Precedex and placebo groups. On average, Precedex treated patients received less morphine sulfate for pain than placebo treated patients (0.43 versus 0.89 mg/h). In addition, 41% (83 of 203 patients) of Precedex patients received no morphine sulfate for pain versus 15% (30 of 198 patients) in the placebo group.

**Procedural sedation.** The safety and efficacy of Precedex for sedation of nonintubated patients prior to and/or during surgical and other procedures was evaluated in two randomised, double blind, placebo controlled multicentre clinical trials. Study 1 evaluated the sedative properties of Precedex in patients having a variety of elective surgeries/ procedures performed under monitored anaesthesia care. Study 2 evaluated Precedex in patients undergoing awake fibreoptic intubation prior to a surgical or diagnostic procedure.

In study 1, the sedative properties of Precedex were evaluated by comparing the percent of patients not requiring rescue midazolam to achieve a specified level of sedation using the standardised Observer's Assessment of Alertness/Sedation Scale between Precedex and placebo.
Patients were randomised to receive a Precedex loading infusion of either Precedex 1 microgram/kg or Precedex 0.5 microgram/kg, or placebo (normal saline) given over 10 minutes and followed by a maintenance infusion started at 0.6 microgram/kg/hr. The maintenance infusion of study drug could be titrated from 0.2 microgram/kg/hr to 1 microgram/kg/hr to achieve the targeted sedation score (OAA/S less than or equal to 4). Patients were allowed to receive rescue midazolam as needed to achieve and/or maintain an OAA/S < 4. After achieving the desired level of sedation, a local or regional anaesthetic block was performed. Demographic characteristics were similar between the Precedex and placebo groups. Efficacy results showed that Precedex was significantly more effective than placebo when used to sedate nonintubated patients requiring monitored anaesthesia care during surgical and other procedures (Table 5).

In study 2, the sedative properties of Precedex were evaluated by comparing the percent of patients requiring rescue midazolam to achieve or maintain a specified level of sedation using the Ramsay Sedation Scale score > 2 (Table 1). Patients were randomised to receive a Precedex loading infusion of 1 microgram/kg or placebo (normal saline) given over 10 minutes followed by a fixed maintenance infusion of 0.7 microgram/kg/hr. After achieving the desired level of sedation, topicalisation of the airway occurred. Patients were allowed to receive rescue midazolam as needed to achieve and/or maintain an RSS > 2. Demographic characteristics were similar between the Precedex and placebo groups.

### Pharmacokinetics.

Following IV administration of Precedex, dexmedetomidine exhibits the following pharmacokinetic characteristics: rapid distribution phase with a distribution half-life ($t_{1/2a}$) of about six minutes; terminal elimination half-life ($t_{1/2}$) approximately two hours; steady-state volume of distribution ($V_{ss}$)
approximately 118 L. Clearance (CL) has an estimated value of about 39 L/hour. The mean bodyweight associated with this clearance estimate was 72 kg. Dexmedetomidine exhibits linear kinetics in the dosage range of 0.2 to 0.7 microgram/kg/hour when administered by IV infusion for up to 24 hours. Table 6 shows the main pharmacokinetic parameters when Precedex was infused (after appropriate loading doses) at maintenance infusion rates of 0.17 microgram/kg/hour (target concentration of 0.3 nanogram/mL) for 12 and 24 hours, 0.33 microgram/kg/hour (target concentration of 0.6 nanogram/mL) for 24 hours, and 0.70 microgram/kg/hour (target concentration of 1.25 nanogram/mL) for 24 hours.

<table>
<thead>
<tr>
<th>Loading Infusion (min)/Total infusion duration (hrs)</th>
<th>10 min/12 hrs</th>
<th>10 min/24 hrs</th>
<th>10 min/24 hrs</th>
<th>35 min/24 hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dexmedetomidine target concentration (ng/mL) and dose (microgram/kg/hr)</strong></td>
<td>0.3/0.17</td>
<td>0.3/0.17</td>
<td>0.6/0.33</td>
<td>1.26/0.70</td>
</tr>
<tr>
<td>t(1/2), hour</td>
<td>1.78 ± 0.30</td>
<td>2.22 ± 0.59</td>
<td>2.23 ± 0.21</td>
<td>2.50 ± 0.61</td>
</tr>
<tr>
<td>CL, litre/hour</td>
<td>46.3 ± 8.3</td>
<td>43.1 ± 6.5</td>
<td>36.3 ± 6.8</td>
<td>36.5 ± 7.6</td>
</tr>
<tr>
<td>Vss, litre</td>
<td>86.7 ± 22.9</td>
<td>102.4 ± 20.3</td>
<td>93.6 ± 17.0</td>
<td>99.6 ± 17.8</td>
</tr>
<tr>
<td>AvgCss* ng/mL</td>
<td>0.27 ± 0.05</td>
<td>0.27 ± 0.05</td>
<td>0.67 ± 0.10</td>
<td>1.37 ± 0.20</td>
</tr>
</tbody>
</table>

* Present as harmonic mean and pseudo standard deviation. † Avg Css = Average steady-state concentration of dexmedetomidine. (2.5 - 9 hour samples for 12 hour infusion and 2.5 - 18 hour samples for 24 hour infusions).

**Distribution.** The steady-state volume of distribution (Vss) of dexmedetomidine is approximately 118 L. Dexmedetomidine protein binding was assessed in the plasma of normal healthy male and female volunteers. The average protein binding was 94% and was constant across the different concentrations tested. Protein binding was similar in males and females. The fraction of dexmedetomidine that was bound to plasma proteins was statistically significantly decreased in subjects with hepatic impairment compared to healthy subjects. The potential for protein binding displacement of dexmedetomidine by fentanyl, ketorolac, theophylline, digoxin and lignocaine was explored in vitro and negligible changes in the plasma protein binding of dexmedetomidine were observed. The potential for protein binding displacement of phenytoin, warfarin, ibuprofen, propranolol, theophylline and digoxin by dexmedetomidine was explored in vitro and none of these compounds appeared to be significantly displaced by dexmedetomidine.

**Metabolism.** Dexmedetomidine undergoes almost complete biotransformation with very little unchanged dexmedetomidine excreted in urine and faeces. Biotransformation involves both direct glucuronidation as well as cytochrome P450 mediated metabolism. The major metabolic pathways of dexmedetomidine are direct N-glucuronidation to inactive metabolites; aliphatic hydroxylation (mediated primarily by CYP2A6) of dexmedetomidine to generate 3-hydroxy dexmedetomidine, the glucuronide of 3-hydroxy dexmedetomidine, and 3-carboxy dexmedetomidine; and N-methylation of dexmedetomidine to generate 3-hydroxy N-methyl dexmedetomidine, 3-carboxy N-methyl dexmedetomidine and N-methyl O-glucuronide dexmedetomidine.

**Excretion.** The terminal elimination half-life (t\(1/2\)) of dexmedetomidine is approximately two hours and clearance is estimated to be approximately 39 L/hour. A mass balance study demonstrated that after nine days an average of 95% of the radioactivity, following IV administration of radiolabelled dexmedetomidine, was recovered in the urine and 4% in the faeces. No unchanged dexmedetomidine was detected in the urine. Approximately 85% of the radioactivity recovered in the urine was excreted within 24 hours after the infusion. Fractionation of the radioactivity excreted in urine demonstrated that products of N-glucuronidation accounted for approximately 34% of the cumulative urinary excretion. In addition, aliphatic hydroxylation of parent drug to form 3-hydroxy dexmedetomidine, the glucuronide of 3-hydroxy dexmedetomidine, and 3-carboxylic acid dexmedetomidine together represented approximately 14% of the dose in urine. N-methylation of dexmedetomidine to form 3-hydroxy N-methyl dexmedetomidine, 3-carboxy N-methyl dexmedetomidine, and N-methyl O-glucuronide dexmedetomidine accounted for approximately 18% of the dose in urine. The N-methyl metabolite itself was a minor circulating component and was undetected in urine. Approximately 28% of the urinary metabolites have not been identified.
**Hepatic impairment.** In subjects with varying degrees of hepatic impairment (Child-Pugh class A, B or C), clearance values were lower than in healthy subjects. The mean clearance values for subjects with mild, moderate and severe hepatic impairment were 74, 64 and 53% of those observed in the normal healthy subjects, respectively. Mean clearances for free drug were 59, 51 and 32% of those observed in the normal healthy subjects, respectively. Although dexmedetomidine hydrochloride is dosed to effect, it may be necessary to consider dose reduction depending on the degree of hepatic impairment (see Dosage and Administration).

**Renal impairment.** Dexmedetomidine hydrochloride pharmacokinetics (Cmax, Tmax, AUC, t, CL, and Vss) were not different in subjects with severe renal impairment (creatinine clearance < 30 mL/minute) compared to healthy subjects.

In view of the limited toxicological data and the potential for higher plasma metabolite concentrations in patients with severe renal impairment, caution is advised with prolonged dosing in such patients (see Dosage and Administration).

**Gender.** No difference in dexmedetomidine hydrochloride pharmacokinetics due to gender was observed.

**Elderly.** The pharmacokinetic profile of dexmedetomidine hydrochloride was not altered by age. However, as with many drugs, the elderly may be more sensitive to the effects of dexmedetomidine. In clinical trials, there was a higher incidence of bradycardia and hypotension in elderly patients.

**Children.** The pharmacokinetic profile of dexmedetomidine hydrochloride has not been studied in children.

**Indications**

**ICU sedation.** For sedation of initially intubated patients during treatment in an intensive care setting. The use of Precedex by continuous infusion in these patients should not exceed 24 hours.

**Procedural sedation.** For sedation of nonintubated patients prior to and/or during surgical and other procedures.

**Contraindications**

Known hypersensitivity to dexmedetomidine.

**Precautions**

Drug administration. Precedex should be administered only by persons skilled in the management of patients in the intensive care or operating room setting. Continuous electrocardiogram (ECG), blood pressure, and oxygen saturation monitoring are recommended during infusion of Precedex. Dexmedetomidine may cause reduced lacrimation. Lubrication of the patient’s eyes should be considered when administering dexmedetomidine to avoid corneal dryness.

Precedex is only to be used for procedural sedation with the provision of appropriate monitoring and under the constant supervision of an appropriately trained medical practitioner. Although Precedex has sedative effects it has not been shown to be amnestic. Should amnesia be desired during procedural sedation then a drug with amnestic properties (such as a benzodiazepine) should be coadministered.

Hypotension, bradycardia and sinus arrest. Clinical events of bradycardia and sinus arrest have been associated with Precedex administration in young, healthy volunteers with high vagal tone or with different routes of administration including rapid intravenous or bolus administration of Precedex.

Decreased blood pressure and/or heart rate may occur with the administration of Precedex. Dexmedetomidine decreases sympathetic nervous activity and therefore, these effects may be expected to be most pronounced in patients with desensitised autonomic nervous system control (i.e. ageing, diabetes, chronic hypertension, severe cardiac disease). Reports of hypotension and bradycardia have been associated with Precedex infusion. If medical intervention is required, treatment may include decreasing or stopping the infusion of Precedex, increasing the rate of IV fluid administration, elevation of the lower extremities, and use of pressor agents. Because Precedex has the potential to augment bradycardia induced by vagal stimuli, clinicians should be prepared to intervene. The intravenous administration of anticholinergic agents (e.g., glycopyrrolate, atropine) should be considered to modify vagal tone. In clinical trials, glycopyrrolate or atropine were effective in the treatment of most episodes of Precedex induced bradycardia. However, in some patients with significant cardiovascular dysfunction, more advanced resuscitative measures were required.

Caution should be exercised when administering Precedex to patients with advanced heart block.
and/or severe ventricular dysfunction. Because Precedex decreases sympathetic nervous system activity, hypotension and/or bradycardia may be expected to be more pronounced in hypovolaemic patients and in those with diabetes mellitus or chronic hypertension and in elderly patients. In situations where other vasodilators or negative chronotrophic agents are administered, coadministration of Precedex could have an additive pharmacodynamic effect and should be administered with caution. Clinical events of bradycardia or hypotension may be potentiated when Precedex is used concurrently with propofol or midazolam. Therefore, consider a reduction in the dose of midazolam or propofol.

Elderly patients over 65 years of age, or diabetic patients, are more prone to hypotension with the administration of Precedex. All episodes either spontaneously reversed or were treated with standard therapy.

Transient hypertension. Transient hypertension has been observed primarily during the loading infusion, associated with initial peripheral vasoconstrictive effects of dexmedetomidine and relatively higher plasma concentrations achieved during the loading infusion. If intervention is necessary, reduction of the loading infusion rate may be considered. Following the loading infusion, the central effects of dexmedetomidine dominate and the blood pressure usually decreases.

Withdrawal. Although not specifically studied, if Precedex is administered chronically and stopped abruptly, withdrawal symptoms similar to those reported for another alpha2-adrenergic agent, clonidine, may result. These symptoms include nervousness, agitation and headaches, accompanied or followed by a rapid rise in blood pressure and elevated catecholamine concentrations in the plasma. Precedex should not be administered for longer than 24 hours.

Procedural sedation. Withdrawal symptoms were not seen after discontinuation of short term infusions of Precedex (< 6 hrs).

Adrenal insufficiency. Precedex had no effect on ACTH stimulated cortisol release in dogs after a single dose; however, after the subcutaneous infusion of Precedex for one week, the cortisol response to ACTH was diminished by approximately 40%.

In a clinical study, prolonged infusions of dexmedetomidine at doses up to 1.4 microgram/kg/hr were not associated with significant adrenocortical suppression.

Hepatic impairment. Since Precedex clearance decreases with increasing severity of hepatic impairment, dose reductions should be considered in patients with impaired hepatic function (see Dosage and Administration).

Use in the elderly. Precedex is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection in elderly patients, and it may be useful to monitor renal function.

ICU sedation. A total of 729 patients in the clinical studies were 65 years of age and over. A total of 200 patients were 75 years of age and over. In patients greater than 65 years of age, a higher incidence of bradycardia and hypotension was observed following administration of Precedex (see Precautions).

Consideration should be given to lower initial loading and maintenance doses in patients > 65 years and careful monitoring for the development of hypotension when up titrating the maintenance dose (see Dosage and Administration).

Procedural sedation. A total of 131 patients in the clinical studies were 65 years of age and over. A total of 47 patients were 75 years of age and over. Hypotension occurred at a higher incidence in Precedex treated patients 65 years or older (71.9%) and 75 years or older (73.5%) as compared to patients < 65 years (46.8%). The loading dose may be omitted or reduced and a reduction in the maintenance infusion should be considered for patients greater than 65 years of age (see Dosage and Administration).

Carcinogenesis, mutagenesis, impairment of fertility. Carcinogenicity. Animal carcinogenicity studies have not been performed with dexmedetomidine.

Genotoxicity. Dexmedetomidine was not mutagenic in vitro, in either the bacterial reverse mutation assay (Escherichia coli and Salmonella typhimurium) or the mammalian cell forward mutation assay (mouse lymphoma). In a mouse micronucleus study, dexmedetomidine was not cytotoxic to bone marrow and did not increase the numbers of micronucleated PCEs at any dose tested, both in animals maintained at room temperature and in those kept warm. In addition, dexmedetomidine did not induce chromosomal aberrations in cultured human peripheral blood lymphocytes in the absence or presence of an exogenous metabolic activation system comprised of a human S9 homogenate.

Effects on fertility. Dexmedetomidine did not affect reproductive capacity or fertility in male or
female rats after daily subcutaneous injections at doses up to 54 microgram/kg/day for 10 weeks
prior to mating in males and 3 weeks prior to mating and during mating in females. Systemic
exposure (AUC 0-24h) at this dose level was less that anticipated at the maximum recommended
human dose of 17.8 microgram/kg.

Use in pregnancy. (Category B1)
Radiolabelled dexmedetomidine administered subcutaneously to female rats on gestation day 18
crossed the placental barrier to fetal tissue. Teratogenic effects were not observed following
administration of dexmedetomidine at subcutaneous doses up to 200 microgram/kg/day in rats or
IV doses up to 96 microgram/kg/day in rabbits. Systemic exposure (AUC1 to 24 hours) at these dose
levels was three to five times greater than those in humans at the maximum recommended dose of
17.8 microgram/kg. In rats, fetal and pup bodyweights were reduced at subcutaneous doses
greater than or equal to 6 microgram/kg/day, postimplantation loss was increased at 200
microgram/kg/day, and perinatal mortality was increased at subcutaneous doses greater than or
equal to 18 microgram/kg/day. These findings are consistent with those of clonidine, another
alpha2-adrenoreceptor agonist. Dexmedetomidine has no effect on fetal bodyweight or embryofetal
viability at intravenous doses as high as 96 microgram/kg/day in rabbits. Dexmedetomidine also
produced delayed motor development in rat pups at a dose of 32 microgram/kg (less than the
maximum recommended human intravenous dose). No such effects were observed at a dose of 2
microgram/kg.

There are no adequate and well controlled studies in pregnant women. Dexmedetomidine
hydrochloride should be used during pregnancy only if the potential benefits justify the potential risk
to the fetus.

Labour and delivery. The safety of dexmedetomidine hydrochloride in labour and delivery has not
been studied and is, therefore, not recommended for obstetrics, including caesarean section
deliveries.

Use in lactation.
It is not known whether dexmedetomidine hydrochloride is excreted in human milk. Because many
drugs are excreted in human milk, caution should be exercised when dexmedetomidine
hydrochloride infusion is administered to a breastfeeding woman. Radiolabelled dexmedetomidine
administered subcutaneously to lactating female rats was distributed to, but did not accumulate in
milk.

Use in children.
Safety and efficacy of dexmedetomidine hydrochloride in children below 18 years of age have not
been studied.

Interactions
General. In vitro studies indicate that clinically relevant cytochrome P450 mediated drug
interactions are unlikely.
Anaesthetics/sedatives/hypnotics/opioids. Coadministration of dexmedetomidine
hydrochloride is likely to lead to an enhancement of effects with anaesthetics, sedatives, hypnotics
and opioids. Specific studies have confirmed these effects with sevoflurane, isoflurane, propofol,
alfentanil and midazolam. No pharmacokinetic interactions between dexmedetomidine and
isoflurane, propofol, alfentanil and midazolam were demonstrated. However, due to
pharmacodynamic effects, when coadministered with dexmedetomidine hydrochloride, a reduction
in dosage with these agents may be required.
Neuromuscular blockers. No clinically meaningful increases in the magnitude of neuromuscular
blockade and no pharmacokinetic interactions were observed with dexmedetomidine hydrochloride
and rocuronium administration.

Adverse Reactions ICU sedation. Adverse event information derived from the placebo controlled,
continuous infusion trials of Precedex for sedation in the surgical ICU setting in which 387 patients
received Precedex. In these studies, the mean total dose was 7.06 microgram/kg (SD = 2.86),
mean dose per hour was 0.51 microgram/kg/hr (SD = 0.39) and the mean duration of infusion of
15.6 hours (range: 0.17 to 29.08). The population was between 19 to 83 years of age, 43% > 65
years of age, 73% male and 97% Caucasian. Overall, the most frequently observed treatment
emergent adverse events included hypotension, hypertension, nausea, bradycardia, fever,
vomiting, hypoxia, tachycardia and anaemia (see Table 7).
Adverse event information derived from the midazolam controlled, continuous infusion trial of Precedex for sedation in a predominantly medical ICU setting in which 244 patients received Precedex for long-term sedation. Treatment emergent adverse events occurring at an incidence of >5% are provided in Table 8. The mean total dose was 72.5 microgram/kg (range: 0.1 to 489.9), mean dose per hour was 0.83 microgram/kg/hr (range: 0.18 to 1.54) and the mean duration of infusion of 3.4 days (range: 0.02 to 15.6). The population was between 18 to 89 years of age, 46% >65 years of age, 51% male and 79% Caucasian. The most frequent adverse events for this population were hypotension, tachycardia, bradycardia and systolic hypertension (see Precautions).
The following adverse events occurred between 2 and 5% for Precedex and midazolam, respectively: anaemia (2.9%, 4.1%), thrombocytopaenia (0.8%, 2.5%), atrial fibrillation (2.0%, 3.3%), abdominal distension (4.1%, 1.6%), abdominal pain (1.2%, 3.3%), diarrhoea (4.9%, 4.1%), nausea (4.1%, 1.6%), vomiting (2.0%, 4.9%), peripheral oedema (4.1%, 4.9%), pneumonia (1.2%, 4.9%), sepsis (2.5%, 2.5%), septic shock (1.6%, 2.5%), urinary tract infection (0, 3.3%), haemoglobin decreased (0, 2.5%), urine output decreased (2.0%, 3.3%), electrolyte imbalance (0.8%, 2.5%), fluid overload (1.6%, 4.1%), hypotension (2.5%, 1.6%), hypophosphataemia (2.5%, 1.6%), headache (2.0%, 0.8%), anxiety (2.5%, 0), oliguria (0.4%, 2.5%), renal failure acute (2.5%, 0.8%), acute respiratory distress syndrome (2.5%, 0.8%), pharyngolaryngeal pain (2.5%, 4.9%), pleural effusion (2.9%, 2.5%), respiratory failure (4.5%, 3.3%), decubitus ulcer (1.2%, 4.9%), and rash (0.8%, 2.5%).

Procedural sedation. Adverse event information is derived from the two primary phase 3 trials for procedural sedation in which 318 patients received Precedex. The mean total dose was 1.6 microgram/kg (range: 0.5 to 6.7), mean dose per hour was 1.3 microgram/kg/hr (range: 0.3 to 6.1) and the mean duration of infusion of 1.5 hours (range: 0.1 to 6.2). The population was between 18 to 93 years of age, 30% > 65 years of age, 52% male and 61% Caucasian.

Treatment emergent adverse events occurring at an incidence of > 2% are provided in Table 9. The majority of the adverse events were assessed as mild in severity. The most frequent adverse events were hypotension, bradycardia, and dry.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Dexmedetomidine (n=244)</th>
<th>Midazolam (n=122)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiac disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bradycardia</td>
<td>103 (42.2%)</td>
<td>23 (18.9%)</td>
</tr>
<tr>
<td>Bradycardia requiring intervention</td>
<td>12 (4.9%)</td>
<td>1 (0.8%)</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>62 (25.4%)</td>
<td>54 (44.3%)</td>
</tr>
<tr>
<td>Tachycardia requiring intervention</td>
<td>24 (9.8%)</td>
<td>12 (9.8%)</td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic Hypertension</td>
<td>30 (12.3%)</td>
<td>18 (14.8%)</td>
</tr>
<tr>
<td>Systolic Hypertension</td>
<td>69 (28.3%)</td>
<td>51 (41.8%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>26 (10.7%)</td>
<td>18 (14.8%)</td>
</tr>
<tr>
<td>Hypertension requiring intervention</td>
<td>46 (18.9%)</td>
<td>36 (29.5%)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>137 (56.1%)</td>
<td>68 (55.7%)</td>
</tr>
<tr>
<td>Hypotension requiring intervention</td>
<td>59 (23.8%)</td>
<td>33 (27.0%)</td>
</tr>
<tr>
<td><strong>General disorders and administrative site</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generalised oedema</td>
<td>5 (2.0%)</td>
<td>7 (5.7%)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>18 (7.4%)</td>
<td>3 (2.5%)</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycaemia</td>
<td>16 (6.6%)</td>
<td>2 (1.6%)</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>13 (5.3%)</td>
<td>7 (5.7%)</td>
</tr>
<tr>
<td>Hypokalaemia</td>
<td>23 (9.4%)</td>
<td>16 (13.1%)</td>
</tr>
<tr>
<td>Hypomagnesaemia</td>
<td>3 (1.2%)</td>
<td>8 (6.6%)</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>15 (6.1%)</td>
<td>7 (5.7%)</td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agitation</td>
<td>17 (7.0%)</td>
<td>7 (5.7%)</td>
</tr>
</tbody>
</table>

† Includes any type of hypertension. † Hypotension was defined in absolute terms as systolic blood pressure of < 80 mmHg or diastolic blood pressure of < 50 mmHg or in relative terms as ≤ 30% lower than pre-study drug infusion value.

The following adverse events occurred between 2 and 5% for Precedex and midazolam, respectively: anaemia (2.9%, 4.1%), thrombocytopaenia (0.8%, 2.5%), atrial fibrillation (2.0%, 3.3%), abdominal distension (4.1%, 1.6%), abdominal pain (1.2%, 3.3%), diarrhoea (4.9%, 4.1%), nausea (4.1%, 1.6%), vomiting (2.0%, 4.9%), peripheral oedema (4.1%, 4.9%), pneumonia (1.2%, 4.9%), sepsis (2.5%, 2.5%), septic shock (1.6%, 2.5%), urinary tract infection (0, 3.3%), haemoglobin decreased (0, 2.5%), urine output decreased (2.0%, 3.3%), electrolyte imbalance (0.8%, 2.5%), fluid overload (1.6%, 4.1%), hypotension (2.5%, 1.6%), hypophosphataemia (2.5%, 1.6%), headache (2.0%, 0.8%), anxiety (2.5%, 0), oliguria (0.4%, 2.5%), renal failure acute (2.5%, 0.8%), acute respiratory distress syndrome (2.5%, 0.8%), pharyngolaryngeal pain (2.5%, 4.9%), pleural effusion (2.9%, 2.5%), respiratory failure (4.5%, 3.3%), decubitus ulcer (1.2%, 4.9%), and rash (0.8%, 2.5%).

Procedural sedation. Adverse event information is derived from the two primary phase 3 trials for procedural sedation in which 318 patients received Precedex. The mean total dose was 1.6 microgram/kg (range: 0.5 to 6.7), mean dose per hour was 1.3 microgram/kg/hr (range: 0.3 to 6.1) and the mean duration of infusion of 1.5 hours (range: 0.1 to 6.2). The population was between 18 to 93 years of age, 30% > 65 years of age, 52% male and 61% Caucasian.

Dexmedetomidine to Lessen ICU Agitation (DahLIA) - Trial protocol ver.5
Postmarketing experience.
The adverse reactions that have been identified during post approval use of Precedex are provided below. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hypotension and bradycardia were the most common adverse reactions associated with the use of Precedex during post approval use of the drug.

**Body as a whole.** Fever, hyperpyrexia, hypovolaemia, light anaesthesia, pain, rigors.

**Cardiovascular disorders, general.** Blood pressure fluctuation, heart disorder, hypertension, hypotension, myocardial infarction.

**Central and peripheral nervous system disorders.** Dizziness, headache, neuralgia, neuritis, speech disorder, convulsion.

**Gastrointestinal system disorders.** Abdominal pain, diarrhoea, vomiting, nausea.

**Heart rate and rhythm disorders.** Arrhythmia, ventricular arrhythmia, bradycardia, hypoxia, AV block, cardiac arrest, extrasystoles, atrial fibrillation, heart block, T wave inversion, tachycardia, supraventricular tachycardia, ventricular tachycardia.

**Liver and biliary system disorders.** Increased gamma-glutamyl transpeptidase, hepatic function abnormal, hyperbilirubinaemia, increased alanine transaminase, increased aspartate aminotransferase.

**Metabolic and nutritional disorders.** Acidosis, respiratory acidosis, hyperkalaemia, increased alkaline phosphatase, thirst, hypoglycaemia.

**Psychiatric disorders.** Agitation, confusion, delirium, hallucination, illusion.

**Red blood cell disorders.** Anaemia.
**Renal disorders.** Urea increased, oliguria.

**Respiratory system disorders.** Apnoea, bronchospasm, dyspnoea, hypercapnia, hypoventilation, hypoxia, pulmonary congestion.

**Skin and appendages disorders.** Increased sweating.

**Vascular disorders.** Haemorrhage.

**Vision disorders.** Photopsia, abnormal vision.

Dependence.
The dependence potential of dexmedetomidine has not been studied in humans.

**Dosage and Administration**

**Note.** Dexmedetomidine hydrochloride should be administered only by persons skilled in anaesthetics or in the management of patients in the intensive care setting. Due to the known pharmacological effects, patients should be continuously monitored.

Clinically significant events of bradycardia and sinus arrest have been associated with dexmedetomidine hydrochloride administration in young, healthy volunteers with high vagal tone or with different routes of administration including rapid intravenous or bolus administration of dexmedetomidine hydrochloride.

**Adults.** Dexmedetomidine hydrochloride should be individualised and titrated to the desired clinical effect.

**ICU sedation.** **Initiation.** For adult patients, Precedex is generally initiated with a loading infusion of 1 (one) microgram/kg over 10 to 20 minutes, if needed. The use of Precedex by continuous infusion in these patients should not exceed 24 hours.

For patients being converted from alternate sedative therapy a loading dose may not be required.

**Maintenance of ICU sedation.** Adult patients will generally require a maintenance infusion of 0.2 to 1 microgram/kg/hr. The rate of the maintenance infusion should be adjusted to achieve the desired level of sedation. As a guide, it is recommended that 0.4 microgram/kg/hr should be the initial maintenance infusion. If after approximately 5 minutes sedation is not adequate, the rate of infusion can be increased in increments of 0.1 microgram/kg/hr or higher. Dosages as low as 0.05 microgram/kg/hr have been used in clinical studies. Patients receiving Precedex have been observed to be rousable and alert when stimulated. This is an expected component of Precedex sedation and should not be considered a lack of efficacy in the absence of other clinical signs and symptoms.

A dose reduction for both the loading and maintenance infusions should be considered in patients with impaired hepatic function and in patients over 65 years of age.

Precedex has been continuously infused in mechanically ventilated patients prior to extubation, during extubation, and postextubation. It is not necessary to discontinue Precedex prior to extubation.

Procedural sedation. Based on sedation scores, the loading infusion provides clinically effective onset of sedation 10 to 15 minutes after start of infusion.

**Initiation.** For adult patients, Precedex is generally initiated with a loading infusion of 1 (one) microgram/kg over 10 to 20 minutes for sedation of nonintubated patients undergoing surgical and other procedures, as well as, for initiation of awake fibreoptic intubation.

For patients with impaired hepatic function and in patients over 65 years of age, the loading dose may be omitted or reduced, e.g. 0.5 microgram/kg over 10 minutes may be suitable.

For patients undergoing less invasive procedures, such as ophthalmic surgery, the loading dose may be reduced, e.g. 0.5 micrograms/kg over 10 minutes may be suitable.

**Maintenance of procedural sedation.** Following the load, maintenance dosing of Precedex should generally be initiated at 0.6 microgram/kg/hr and titrated to achieve desired clinical effect with doses ranging from 0.2 to 1 microgram/kg/hr for all procedures. The rate of the maintenance infusion should be adjusted to achieve the targeted level of sedation.

Following the load in awake fibreoptic intubation, a fixed maintenance dose of 0.7 microgram/kg/hr should be used.

A dose reduction should be considered in patients with impaired hepatic function and in patients over 65 years of age.

**Children.** Safety and efficacy of dexmedetomidine hydrochloride have not been studied in children.

Administration. A controlled infusion device should be used to administer dexmedetomidine hydrochloride.

Strict aseptic technique must always be maintained during handling of dexmedetomidine hydrochloride infusion.
Preparation of infusion solutions is the same, whether for the loading dose or maintenance. To prepare the infusion, withdraw dexmedetomidine hydrochloride concentrate for solution for infusion 2 mL and add to sodium chloride 0.9% 48 mL to total 50 mL. Shake gently to mix well. Use as soon as practicable after dilution to reduce microbiological hazard. If storage is necessary, hold at 2 to 8 deg. C for not more than 24 hours. Parenteral products should be inspected visually for particulate matter and discoloration prior to administration. Vials are intended for single patient use only.

Compatibility. Dexmedetomidine hydrochloride has been shown to be compatible when administered with the following intravenous fluids: lactated Ringers, glucose in water 5%, sodium chloride in water 0.9%, mannitol in water 20%.

Dexmedetomidine has been found to be compatible with water solutions of the following drugs when administered via Y site injection: thiopentone sodium, vecuronium bromide, pancuronium bromide, glycopyrrolate bromide, phenylephrine hydrochloride.

Incompatibilities. Compatibility of dexmedetomidine hydrochloride with coadministration of blood, serum or plasma has not been established. Precedex must not be mixed with other medicinal products or diluents except those mentioned above.

Overdosage The tolerability of dexmedetomidine hydrochloride was noted in one study in which healthy subjects achieved plasma concentrations from 1.8 up to 13 times the upper boundary of the therapeutic range. The most notable effects observed in two subjects who achieved the highest plasma concentrations were first degree AV block and second degree heart block. No haemodynamic compromise was noted with the AV block and the heart block resolved spontaneously within one minute.

Of five patients reported with overdose of dexmedetomidine hydrochloride in the phase II/III ICU sedation studies, two had no symptoms reported; one patient received a 2 microgram/kg loading dose over ten minutes (twice the recommended loading dose) and one patient received a maintenance infusion of 0.8 microgram/kg/hour. Two other patients who received a 2 microgram/kg loading dose over ten minutes experienced bradycardia with or without hypotension. One patient, who received a loading bolus dose of undiluted Precedex (19.4 microgram/kg), had cardiac arrest from which he was successfully resuscitated.

In case of overdose, immediately contact the Poisons Information Centre for advice (in Australia, call 131 126).

Presentation Solution for injection (clear, colourless, isotonic, sterile, nonpyrogenic concentrated injection for dilution and intravenous infusion), 100 microgram/mL (as the base), 2 mL: 1’s (vials).

Storage
Store in the original container. No special storage conditions are needed. Store below 25 deg. C.

After dilution. To reduce microbiological hazard, use as soon as practicable after dilution. If storage is necessary, hold at 2 to 8 deg. C for not more than 24 hours.

Poisons Schedule S4.

Date of TGA approval or last amendment 26/08/2009
Appendix B. Memorandum of Understanding between Hospira Pty Ltd and the Chief Investigator

Clinical Study Supply and Funding Agreement

DahLIA (Dexmedetomidine to Lessen ICU Agitation) Study

Austin Hospital

and

Hospira Pty Ltd
ABN 13 107 058 328
It is agreed as follows.

1. Definitions and Interpretation

1.1 Definitions

In this Agreement, the following terms have the meanings set out below:

**Affiliates** means, with respect to any party, any person which, directly or indirectly, is controlled by, controls or is under common control with the party;

**Austin Hospital** means the Austin Hospital of Heidelberg, Victoria;

**Authorised Purpose** means conducting the Study;

**Business Day** means a weekday on which banks are open in Victoria, Australia;

**Commencement Date** means the date of this Agreement;

**Confidential Information** means all information of whatever description and in whatever form (whether written or oral) which may be disclosed by, or on behalf of, one party to the other party in connection with this Agreement or otherwise marketing strategies and business of the disclosing party, it being agreed that the Research Results constitutes information of both parties;
**CTN** means the clinical trial notification required by law to be submitted to the TGA in respect of the Study;

**Ethics Approval** means written notification of full approval of the clinical study in accordance with the current ICH GCP guidelines and the Declaration of Helsinki (1964) as per the regulatory requirements of the pertinent institutional human research ethics committee;

**Force Majeure Event** has the meaning specified in clause 9;

**Funding** means:

(a) in respect of the first 2 years following the date of this Agreement, the amount specified in clause 2(a); and

(b) in respect of patients recruited to the Study, the amounts specified in clause 2(b);

**Insolvency Event**, in relation to a person, means any of the following events:

(a) a liquidator or similar officer is appointed to that person or all of its assets; or

(b) a resolution is passed or an application to a court finds for the winding up or dissolution of that person;

**Intellectual Property Rights** means all rights and interests, vested or arising out of any industrial or intellectual property, whether protected at common law or under statute, which includes (without limitation) any rights and interests in inventions (both patentable and unpatentable), copyright, moral rights, designs (whether registered or unregistered), trade marks (whether registered or unregistered), trade secrets, plant varieties, samples, materials, data, know-how or results;

**Loss** means any and all loss, liability, damage, fee, cost (including legal costs), expense, suit, claim, demand, judgement and prosecution;

**Principal Investigator** means Associate Professor Michael Reade or such person nominated by Austin Hospital to carry out the operational requirements of the Study;

**Product** means Precedex (Dexmedetomidine HCl);

**Screen Failure** means a patient who, after provision of their written consent to undertake pre-study testing to evaluate eligibility for participation in the study, fails to meet the required standard to allow entry into the formal body of the study, as defined by the approved study protocol;

**Study** means the randomised placebo-controlled trial of dexmedetomidine for agitation and delirium (and the recognition of those conditions) in Intensive Care Unit patients as defined by the approved study protocol, comprising a maximum of 100 patients;

**Study protocol** means the ethically approved document which describes all operational requirements to conduct the Study.

**Term** means the period from the Commencement Date until the last publication of the research results (if any) of the Study; and
TGA means Therapeutical Goods Administration.

1.2 Interpretation

In this Agreement, unless the context otherwise requires:

(a) headings and notes in square brackets are for convenience only and do not affect the interpretation of this Agreement, except for the purpose of rectifying any erroneous cross-reference;

(b) words importing the singular include the plural and vice versa;

(c) words importing a gender include all genders;

(d) a reference to a paragraph, clause, annexure or schedule is a reference to a paragraph, clause, annexure or schedule to this Agreement;

(e) references to any document or agreement include references to such document or agreement as amended, novated, supplemented, varied or replaced from time to time;

(f) all monetary amounts referred to in this Agreement are in Australian currency; and

(g) a reference to a party to this Agreement includes that party’s legal successors (including executors and administrators) and permitted assigns.

2 Hospira’s obligations

(a) Hospira shall distribute to Austin Hospital a total of 100–300 milligrams (approximately 1-3 milligrams per patient) of the Product over 2 years from the Commencement Date, as follows:

   (i) The supply of Product and support is limited to a total of approximately 100 patients. Additional Product stock may be provided, depending on patient recruitment or dosing requirements. The amount of 1milligram per patient is based upon the expected need for infusion of the Product during the double blind treatment period to be up to 24 hours (as per 20 patient pilot study recently completed by Associate Professor Michael Reade and his colleagues). The use of any the Product as an open label agent (study drug withdrawal) will be the responsibility of the administering hospital.

   (ii) Hospira shall supply 40 packs of Product (5 x vials of 2mcg/2mL,10mg per pack) to the Austin Hospital, Heidleberg at the beginning of the Study to cover all Study sites and will supply further Product packs, in lots of 25 packs or more, as required depending on patient recruitment. Further distribution of Product to the Study sites will be the responsibility of Austin Hospital or its Study Co-ordinator.
(b) Hospira shall fund the Study to a total amount of $50,000 (including GST) over 2 years for use by Austin Hospital for the Authorised Purpose (Funding) and such Funding shall be paid as follows:

(i) $12,500 to cover start up costs, to be paid within 30 days of receipt by Hospira of an invoice from the Austin Hospital Intensive Care Unit Research Trust Fund following its receipt of the first Ethics Approval for a Study site; and

(ii) the balance of $37,500 to be paid in three 6 monthly instalments of $12,500 each subject to achieving agreed milestones and patient recruitment in accordance with the Study protocol.

(c) Payments will be made by Hospira Pty Ltd following receipt of a Tax invoice from the Austin Hospital Intensive Care Unit Research Trust Fund.

(d) Hospira will make payment of each instalment of the Funding within one (1) month of receipt of invoice from the Austin Hospital Intensive Care Unit Research Trust Fund, following the trigger for that instalment set out in clause 2(b), provided that Austin Hospital has met his obligations under clauses 3.1(c), 3.2(c) and 3.2(d).

(e) Payments of Funding instalments subsequent to the upfront payment will only be made once Austin Hospital has provided written certification that all patients enrolled to that date have been monitored and that all eligibility criteria, as per the approved Study protocol, have been met and all ICH GCP requirements for the inclusion of each patient have been adhered to.

(f) Funding to Austin Hospital will immediately cease if any of the following occurs:

(i) The completion of patient recruitment, as reasonably determined by Austin Hospital;

(ii) Recruitment of patients into the Study halts as requested by Austin Hospital;

(iii) The Study is terminated by a regulatory agency (including the TGA) or a Study site ethics committee;

(iv) Inadequate Study performance with respect to Study protocol compliance;

(v) Discontinuation of general Precedex product supply by Hospira for any reason.

(g) Funding support for the Study will only be provided following Hospira’s receipt of the ethics approval letters from the Austin Hospital and the CTN letter, as described under terms to be provided to Austin Hospital.

(h) All data produced by the Study will be owned by Austin Hospital but will be available to Hospira if Hospira seeks or applies for regulatory approval or PBS
listing based on data from the Study. In these circumstances, the data provided to Hospira shall be used for this purpose only.

(i) If Austin Hospital requires Product for the Study from Hospira which is in addition to the Product distributed to Austin Hospital in accordance with clause 2(a), that additional Product shall be purchased on commercial terms or negotiated by separate agreement with Hospira.

3 Austin Hospital’s obligations

3.1 Use of Funding

(a) Austin Hospital must use the Funding for the Authorised Purpose only. Should Austin Hospital not have used the Funding or a portion of the Funding for the Authorised Purpose prior to the date of termination or expiry of this Agreement, Austin Hospital will return such Funding (plus GST) or the portion to Hospira within one (1) month upon termination or expiry of this Agreement.

(b) Austin Hospital will be responsible for allocation of the Funding across the Study sites and making the allocated Funding available to each Study site.

(c) Austin Hospital must provide to Hospira written certification that each of the patients participating in the Study have met all eligibility criteria required under the Study’s protocol and all ICH GCP requirements.

(d) No Funding will be provided under clause 2(b)(ii) in respect of any patient who:
   is a Screen Failure;
   withdraws from the Study before its completion; or
   must be withdrawn from the Study before its completion by the Principal Investigator.

3.2 Conduct of the Study

(a) In carrying out the Study, Austin Hospital will be the study sponsor for the Study and will have full responsibility for the Study conduct across all Study sites in Australia, including:
   (i) diligently managing and conducting the Study in accordance with the approved Study protocol at all participating sites;
   conducting the Study in a safe, efficient and professional manner with all reasonable skill and care, and in compliance with applicable laws including being solely responsible for Principal Investigator; and
   keeping sufficient records in respect of the Study to comply with all regulatory requirements, including ICH GCP guidelines;
(b) Austin Hospital will co-ordinate and manage the obtaining and maintaining of Ethics Approvals for all Study sites in Australia prior to the commencement of patient recruitment at those Study sites;

(c) A copy of the final Ethics Approval letter for each Study site in Australia will be provided by Austin Hospital to Hospira promptly after their receipt by Austin Hospital and prior to commencement of patient recruitment at that Study site;

(d) Austin Hospital must ensure that:

(i) Product supplied by Hospira for the Study, is managed by a designated clinical trials pharmacist and the Product must be stored in isolation to all other non-clinical study pharmacy products. The Product will be appropriately labelled as “DEXMEDETOMIDINE TO LESSEN ICU AGITATION: the DahLIA trial - Austin Hospital Clinical Study” investigational product by the clinical trials pharmacist;

(ii) Product supplied by Hospira for the Study, is managed by a designated clinical trials pharmacist and the Product must be stored in isolation to all other non-clinical study pharmacy products. The Product will be appropriately labelled as “DEXMEDETOMIDINE TO LESSEN ICU AGITATION: the DahLIA trial - Austin Hospital Clinical Study” investigational product by the clinical trials pharmacist;

(iii) Product used in this Study supplied by Hospira is accounted for, as per standard clinical study investigational product accountability procedures, in accordance with the approved Study protocol. These Product accountability records must be made available to Hospira on request and to any/all pertinent clinical study auditors and monitors;

all Study participants or patients provide written informed consent prior to the conduct of any Study procedure in respect of such patients or participants;

each Study site is aware that random study site auditing by Hospira, relevant ethics committees or regulatory authorities may occur on an as required basis;

Hospira is acknowledged on all public presentations and publications authored by Australian investigators under the auspices of Austin Hospital and relevant to this Study;

all study documentation is fully maintained in accordance with ICH GCP guidelines;

all ethics committee requirements are strictly adhered to with respect to all safety adverse event reporting;
Hospira is notified of all serious and unexpected adverse events arising from the use of the Product in this Study within 24 hours of knowledge of the occurrence of such events;

the Study status is communicated to Hospira on a quarterly basis with respect to all patient recruitment activity, ethics approvals and any Study issues. This Study status update will be sent by e-mail to Hospira;

(e) Austin Hospital must immediately notify Hospira if:

(i) patient recruitment has been completed or halted prior to its completion;
(ii) the Study is terminated; or
(iii) the Study is terminated or withdrawn for any Study site;
(iv) a Study site is closed;
(v) there has been inadequate Study site performance in respect of protocol compliance; or
(vi) there are any Screen Failures;

(f) Austin Hospital will be responsible for recruitment of all patients to the Study;

(g) For the purposes of this clause 3, any email correspondence to be sent by Austin Hospital to Hospira must be sent to Charlie O’Sullivan, Director Scientific Affairs Australia & New Zealand, Hospira Pty Ltd at “charles.o’sullivan@hospira.com”.

3.3 Unsafe Study

Either party may terminate or suspend study involvement immediately if that party reasonably believes that the continuation of the Study is unsafe to the health of particular patients or staff.

4 Intellectual Property Rights

(a) The ownership of pre-existing Intellectual Property Rights remains with the party that introduces it to the Study. The parties may use each other’s pre-existing Intellectual Property Rights for the Authorised Purpose, but not otherwise without the agreement of the party which owns the pre-existing Intellectual Property Rights.

(b) The Intellectual Property Rights in any research results arising from the Study will be owned by Austin Hospital.
5 Representations and warranties

(a) Austin Hospital warrants to Hospira that:

Austin Hospital has full power and authority to enter into, perform and observe his obligations under this Agreement; and

Austin Hospital is able to procure the consent in writing to the infringement of the author’s moral rights in respect of all materials produced as part of the Study’s research results.

To the full extent permitted by law, Hospira and Austin Hospital will not be liable to the other for any special, indirect or consequential loss or damages arising under or pursuant to this Agreement.

6 Indemnity, insurance etc

(a) The design of the Study Protocol, as well as all other aspects of the Study conduct (including, but not limited to, securing and maintaining all appropriate Ethics Committee, legal and regulatory approvals) shall be solely Austin Hospital’s responsibility. Austin Hospital acknowledges that Hospira accepts no responsibility for and will not be liable for any losses, costs, damages, or other expenses arising out of or resulting from: (a) design, content, or implementation of the Study Protocol or use of Product and selection of Study subjects; and (b) any injury (whether or not Study related) to persons or damage to property involved in the Study.

(b) Austin Hospital assumes the risk of loss and indemnifies Hospira against loss directly arising from:

(i) any act or omission of Austin Hospital pursuant to this Agreement (including Austin Hospital’s commercialization and exploitation of the Study’s research results); or

(ii) any negligence or wilful misconduct of Austin Hospital in respect to the conduct of the Study.

(c) Hospira assumes the risk of loss and indemnifies Austin Hospital against loss arising directly from any act or omission of Hospira pursuant to this Agreement.

(d) Austin Hospital will ensure that all potential liabilities arising out of or connected with the Study will be covered by clinical trials indemnity liability insurance for public hospitals facilitated by the Victorian Managed Insurance Authority.
7  Confidentiality

(a) Each party will not, unless specifically authorised by the other party or by this Agreement:

- disclose any Confidential Information of the other party to a third party for any purpose other than for the purposes set out in this Agreement;
- make use of any Confidential Information of the other party for any purpose other than for the purposes set out in this Agreement; or
- make, or allow anyone else to make, copies of any Confidential Information of the other party unless for the purposes set out in this Agreement.

Each party may disclose any Confidential Information of the other party where it is required to do so under any laws or regulations, including the rules of any applicable stock exchange, provided that it gives the other party such notice as is reasonably practicable in the circumstance and allows the other party, at the other party’s cost, a reasonable opportunity to resist such requirement.

Nothing in this Agreement will restrict a party’s ability to use or disclose any information which it can prove:

- is in the public domain or comes into the public domain otherwise than as a result of an unauthorised disclosure by it or its representatives;
- is or becomes available to it from a third party lawfully in possession thereof and who has the lawful power to disclose such information to it;
- is rightfully known by it prior to the date of disclosure to it hereunder;
- is independently developed by its directors, officers or employees who have no knowledge of the information; or
- the party claiming confidentiality has disclosed to a third party without restriction as to disclosure or use.

Each of the parties:

- will use its best endeavours to prevent unauthorised disclosure of the Confidential Information of the other party, by its directors, officers and employees; and
- may disclose the Confidential Information of the other party to only those of its employees or employees of its Affiliates, sub-distributors or delegates who require the Confidential Information for the purposes of fulfilling that party’s obligations under this Agreement and, provided that such disclosure is under conditions of confidentiality consistent with those existing between the parties.
8 Termination

8.1 Cessation of Funding payments

(a) Hospira may cease to pay Funding to Austin Hospital if any of the following occur:

(i) the completion of patient recruitment as determined by the principal investigator;

(ii) a recruitment halt as requested by the principal investigator; or

(iii) Study termination by a regulatory agency (including the TGA).

(iv) Study site closure; or

(v) Inadequate Study site performance with respect to protocol compliance.

(b) Hospira is not obligated to pay any Funding where there has been any Screen Failures.

8.2 Termination of Agreement

(a) Either party may terminate this Agreement immediately by written notice to the other party if:

(i) the other party breaches any representation or warranty given under this Agreement;

the other party breaches any other term of this Agreement and fails to remedy that breach to the first party’s reasonable satisfaction within thirty (30) days after receipt of a written notice requesting it to do so;

the other party suffers an Insolvency Event;

the other party is subject to a Force Majeure Event for a continuous period of 3 months; or

any part of this Agreement is deemed to contravene any law or regulation or any code of conduct issued by Medicines Australia from time to time.

(b) Upon termination of the Agreement for any reason whatsoever or expiration, each party will, as soon as practicable, return to the other party all of the other party’s Confidential Information, whether in permanent or magnetic/computer disk form or any other form provided that each party may:

provide one copy of the Confidential Information to its legal advisers, to be held by them solely for the purpose of determining the scope of that party’s obligations under this clause; and

retain one copy of such of the Confidential Information that is required by the TGA, to be retained by that party;

Clauses 4, 5(d) and 6 will survive the termination or expiration of this Agreement.
The parties acknowledge that any termination of this Agreement will be without prejudice to any rights of either party which may have arisen prior to or as a result of such termination.

9  Force majeure

(c) Despite any other provision of this Agreement, neither party will be deemed to be in breach of this Agreement, or otherwise be liable to the other, for any delay in the performance, or the non-performance of any of its obligations under this Agreement (other than an obligation to pay money) to the extent that the delay or non-performance is outside the reasonable control of the parties including acts of God, non-supply of utilities, strikes, fires, floods, extreme drought, riot, war (declared or undeclared), embargoes, government actions or government restrictions (other than in the ordinary course of operations of the TGA and except where the action or restriction is due to the acts or omissions of the party) (Force Majeure Event), and the circumstances constituting the Force Majeure Event were notified to the other party as soon as possible thereafter provided that the party subject to the Force Majeure Event takes all reasonable action to resolve, and limit the impact of, the Force Majeure Event as soon as possible.

(d) Subject to each party's right of termination under clause 8.2(a)(iv), the time for performance of any obligation under this Agreement, except the obligation to make payment, will extend while a Force Majeure Event persists under clause 9(a).

10  Dispute resolution

(a) A party must not start court proceedings (except proceedings seeking interlocutory relief) in respect of a dispute arising out of this Agreement (Dispute) unless it has complied with clause 10.

(b) A party claiming that a Dispute has arisen must notify the other party in writing, giving details of the Dispute.

(c) During the 30 day period after a notice is given under clause 10(b) (or such longer period as is agreed in writing by the parties), each party must each appoint a senior representative and use their best efforts to resolve the Dispute.

(d) If in relation to a Dispute, a party breaches any provision of clause 10, the other party need not comply with clause 10 in relation to that Dispute.

11  Notices

(a) Any notice, request, consent or other communication given under this Agreement must be in writing and
left at the address of the addressee;
sent by prepaid-ordinary post (airmail if posted to or from a place outside Australia) to the address of the addressee;
sent by facsimile to the facsimile number of the addressee; or
if the addressee has given written notice of another address or facsimile number, sent to that address or facsimile number.

The address and facsimile number of each party is:

**Hospira:**
Hospira Pty Ltd  ABN 13 107 058 328
Level 3, 390 St Kilda Road
Melbourne  Victoria  3004
Attn: Company Secretary
Fax: +61 3 9868 0757

**Austin Hospital:**
Austin Hospital Intensive Care Unit
Level 2, Austin Hospital Tower, 145 Studley Road
Heidelberg, Victoria 3084
Australia
Fax +61 3 9496 3932

A notification of change of address or facsimile number will not take effect until the other party notifies the party changing its address that the notice of change of address has been received.

A letter or facsimile is taken to be received:

for a facsimile, on production of a transmission report by the machine from which the facsimile was sent which indicates that the facsimile was sent in its entirety to the facsimile number of the recipient. However, if transmission is complete after 5:00pm on a Business Day or is sent on a day that is not a Business Day, the message is taken to have been received at 8:00am on the next Business Day;

for a posted letter, on the third (seventh, if posted to or from a place outside Australia) day after posting; or

on the date on which a party has signed receipt of the notice delivered by air courier.
12 Assignment, subcontracting, delegation

(a) Austin Hospital may not assign or transfer any of its rights or obligations under this Agreement without the prior written consent of Hospira.

Hospira may assign or transfer or sub-contract its rights or obligations under this Agreement to any of its Affiliates.

13 General provisions

(a) Nothing in this Agreement is intended or will be construed as constituting a partnership, agency or joint venture relationship between the parties. The parties will perform all activities as independent contractors.

(b) This Agreement, including the Schedules, contains the entire agreement between the parties with respect to its subject matter and supersedes any prior agreement between the parties.

(c) A variation of this Agreement is of no force and effect unless it is in writing and signed by the parties.

(d) Waiver by either party of a breach of, or failure to comply with, this Agreement by the other party is of no effect unless it is in writing and signed by or on behalf of the first mentioned party.

(e) If any provision of this Agreement:

(i) can sustain two or more interpretations, one of which results in the term or provision being valid, legal or enforceable, that term or provision will be given that interpretation rather than an interpretation which would or be likely to result in the term or provision being invalid, illegal or unenforceable;

is to any extent held to be invalid, illegal or unenforceable:

the validity, legality, and enforceability of the remaining terms or provisions (and any application of the said terms or provisions) will not in any way be affected or impaired; and

the parties will negotiate in good faith and, if legally possible, will agree on an alternate term or provision having regard to the original intention of the parties.

14 Governing law

The governing law of this Agreement is the law of or applicable to Victoria, Australia and the parties submit to the non-exclusive jurisdiction of the courts of Victoria and of all courts having jurisdiction in appeal from the courts of Victoria.
15 GST and other taxes

(a) In this clause:

*GST Act* means A New Tax System (Goods and Services Tax) Act 1999 and any related or similar legislation;

*GST, Recipient, Supplier, Supply*, tax invoice and adjustment have the respective meanings ascribed to those terms in the GST Act.

(b) Neither party will be required to remit any amount of GST unless the other party provides a tax invoice or adjustment note, as the case may be, which is in an approved form for GST purposes.

(c) Either party may withhold any other Government tax, levy or charge from any payment it makes to the other party if legally required to do so.

(d) Any additional amount on account of GST is payable at the same time and in the same manner as the other amounts payable by the Recipient in relation to the particular supply are required to be paid to the Supplier.

(e) To the extent that the amounts for the supply consist of the reimbursement or indemnity for any liabilities, costs or expenses incurred by Supplier, in this Agreement the amount of those liabilities, costs or expenses are deemed to be net of any refund or input tax credit of GST to which the Supplier is entitled as a result of incurring the liability, cost or expense.
Execution

Executed as an agreement

Executed on behalf of Hospira Pty Ltd by an authorised representative in the presence of:

Witness  Authorised representative

Print Name  Print Name

Executed by Austin Hospital in the presence of:

Witness  Associate Professor Michael Austin Hospital

Print Name
Appendix C. Participant consent forms

1: Person responsible information and consent form
2: Consent to continue participation (person responsible)
3: Consent to continue participation (patient)

See attachments
Appendix D.
Case report forms

*Dexmedetomidine to Lessen ICU Agitation:  
The DahLIA trial*

---

Form 1 - Entry and Exit data.
*Completed by nurse, doctor or research co-ordinator at time of enrolment and ICU discharge*

**DATA COLLECTED AT THE START OF THE TRIAL**

Usual residence (circle):
- Home
- Nursing home
- Hostel
- Other (_______________)

Date of hospital admission: ______________________________

Diagnosis leading to hospital admission: ______________________________

Diagnosis leading to ICU admission: ______________________________

Date of ICU admission: ______________________________

Time of ICU admission: ______________________________

Duration of intubation prior to enrolment: ________________ hrs

Inclusion criteria (ALL are required):

- Patient requires mechanical ventilation only because (in the opinion of the treating clinician) their degree of agitation requires such a high dose of sedative medication that extubation is not possible  
  Y / N

- Agitation is so severe as to make lessening their sedation unsafe  
  Y / N

- Required either mechanical restraint and/or anti-delirium or sedative medication in the 4 hours prior to seeking consent  
  Y / N
• Confusion Assessment Method for the ICU (CAM-ICU) test is positive for delirium in the 4 hours prior to seeking consent Y / N

• Motor Activity Assessment Scale (MAAS) score is 5 or more in the 4 hours prior to seeking consent, confirming psychomotor agitation Y / N

**Exclusion criteria (if ONE is present, patient is excluded):**

• Age less than 18 years. Y / N

• Pregnancy or breastfeeding. Y / N

• Advanced dementia (in the premorbid state requiring professional nursing care) Y / N

• Already receiving dexmedetomidine, or regular clonidine if the primary indication is its sedative effect Y / N

• Non-English speaking Y / N

• Open or closed head injury Y / N

• Death is deemed imminent and inevitable. Y / N

• The patient has previously been enrolled in the DahLIA study Y / N

• Patients who could not be extubated within the next 48 hours even if delirium or agitation were corrected. This will include:
  • Patients receiving high dose opioid for analgesia (not sedation) (>40 mg/morphine/day) Y / N
  • Patients shortly to return to the operating theatre Y / N
  • Patients undergoing repeated invasive procedures, in whom it is desirable to maintain deep sedation. Y / N
  • Patients likely to require ongoing airway protection or control, or ventilatory support (for example, spinal patients with an inadequate vital capacity) Y / N

• Known allergy to alpha-2 agonists (eg. clonidine) Y / N

**Measures used to control delirium or agitation in the 24 hours prior to enrolment:**
Mechanical restraint? Y/N
Midazolam? Y/N
Propofol? Y/N
Morphine? Y/N
Haloperidol? Y/N
Olanzapine? Y/N
Other (specify __________)? Y/N

Patient weight: (i.e. the weight being used for calculating drug doses): __________

Date / Time patient was randomised: __________

Date / Time drug was started: __________

Was a bolus of study drug given at the start? __________

**APACHE II score in the 24 hours immediately prior to commencement of the trial:**
(i.e. do NOT use the APACHE score on admission to ICU)
Use last known values. Circle the appropriate box, then enter and sum the points

<table>
<thead>
<tr>
<th>Physiologic Variable</th>
<th>High Abnormal Range</th>
<th>Low Abnormal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+4</td>
<td>+3</td>
</tr>
<tr>
<td>Temperature - rectal (°C)</td>
<td>≥41°</td>
<td>39 to 40.9°</td>
</tr>
<tr>
<td>Mean Arterial Pressure - mm Hg</td>
<td>≥160</td>
<td>130 to 159</td>
</tr>
<tr>
<td>Heart Rate (ventricular response)</td>
<td>≥180</td>
<td>140 to 179</td>
</tr>
<tr>
<td>Respiratory Rate (non-ventilated or ventilated)</td>
<td>≥50</td>
<td>35 to 49</td>
</tr>
<tr>
<td>Oxygenation: A-aDO2 or PaO2 (mm Hg)</td>
<td>≥500</td>
<td>350 to 499</td>
</tr>
<tr>
<td>Arterial pH (preferred)</td>
<td>≥7.7</td>
<td>7.6 to 7.69</td>
</tr>
<tr>
<td>Arterial pH (venous)</td>
<td>≥7.2</td>
<td>7.6 to 7.69</td>
</tr>
<tr>
<td>Serum Sodium (mEq/l)</td>
<td>≥180</td>
<td>110 to 179</td>
</tr>
<tr>
<td>Serum Potassium (mEq/l)</td>
<td>≥7</td>
<td>6 to 6.9</td>
</tr>
<tr>
<td>Serum Creatinine (mg/dl)</td>
<td>≥2.5</td>
<td>2 to 3.4</td>
</tr>
<tr>
<td>Double point score for acute renal failure</td>
<td>≥50</td>
<td>50 to 55.9</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>≥60</td>
<td>46 to 55.9</td>
</tr>
<tr>
<td>White Blood Count (total/mm3)</td>
<td>≥40</td>
<td>20 to 35.9</td>
</tr>
<tr>
<td>Glasgow Coma Score (GCS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Score = 15 minus actual GCS</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A. Total Acute Physiology Score (sum of 12 above points)
B. Age points (years) ≤44=0; 45 to 54=2; 55 to 64=3; 65 to 74=5; ≥75=6
C. Chronic Health Points (see below)
Immediately post elective surgery? Y / N

APACHE II premorbid organ failure comorbidity:
If immediately post elective surgery, add 2 points if ANY of the following are present:
If non-operative or post emergency surgery, add 5 points if ANY of the following are present:

- Liver insufficiency Y / N
  (Biopsy proven cirrhosis, Documented portal hypertension, Episodes of past upper GI bleeding attributed to portal hypertension, Prior episodes of hepatic failure / encephalopathy / coma)
- Cardiovascular Y / N
  (New Heart Association Class IV Heart Failure)
- Respiratory Y / N
  (Chronic restrictive, obstructive or vascular disease resulting in severe exercise restriction, i.e. unable to climb stairs or perform household duties. Documented chronic hypoxia, hypercapnia, secondary polycythemia, severe pulmonary hypertension (> 40 mmHg), or respirator dependency.)
- Renal Y / N
  (Receiving chronic dialysis)
- Immunosuppression Y / N
  (The patient has received therapy that suppresses resistance to infection e.g. immunosuppression, chemotherapy, radiation, long term or recent high dose steroids, or has a disease that is sufficiently advanced to suppress resistance to infection, e.g. leukemia, lymphoma, AIDS)

Total APACHE II score: ____________________

SOFA score immediately prior to seeking consent
Use last known values. Circle the appropriate box, then sum the points.
<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SOFA Score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Respiration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaO2/FiO2 (torr)</td>
<td>&gt;400</td>
<td>≤400</td>
<td>≤800</td>
<td>≥200</td>
<td>≤100</td>
</tr>
<tr>
<td><strong>Coagulation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets (×10⁹/mm³)</td>
<td>&gt;150</td>
<td>≤150</td>
<td>≤150</td>
<td>≤50</td>
<td>≤20</td>
</tr>
<tr>
<td><strong>Liver</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>&lt;1.2</td>
<td>1.2–1.9</td>
<td>2.0–5.9</td>
<td>5.0–11.9</td>
<td>&gt;12.0</td>
</tr>
<tr>
<td>(µmol/L)</td>
<td>≤20</td>
<td>20–32</td>
<td>33–101</td>
<td>102–204</td>
<td>&gt;204</td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>No</td>
<td>MAP &lt;70 mm Hg</td>
<td>Dopamine ≥6</td>
<td>or dobutamine</td>
<td>or dobutamine</td>
</tr>
<tr>
<td><strong>Central Nervous System</strong></td>
<td>15</td>
<td>13–14</td>
<td>10–12</td>
<td>6–9</td>
<td>≤6</td>
</tr>
<tr>
<td>Glasgow Coma Score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Renal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>&lt;1.2</td>
<td>1.2–1.9</td>
<td>2.0–3.4</td>
<td>3.5–4.9</td>
<td>&gt;5.0</td>
</tr>
<tr>
<td>(µmol/L)</td>
<td>≤110</td>
<td>110–176</td>
<td>171–299</td>
<td>300–440</td>
<td>&gt;440</td>
</tr>
<tr>
<td>or urine output</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Adrenergic agents administered for at least 1 hr (doses given are in µg/kg/min).
To convert torr to kPa, multiply the value by 0.1333.

**Total SOFA score:** ____________
**DATA COLLECTED AT TIME OF ICU DISCHARGE:**

Status on discharge from ICU: Dead / Alive

Date of ICU discharge or death: __________

Time of ICU discharge or death: __________

Date of Hospital discharge: __________

Destination at time of hospital discharge: Home
Nursing home
Hostel
Rehabilitation hospital
Other acute hospital
Other (___________)

Was an adverse event recorded? (NB. This includes all adverse events, not just those defined as Serious Adverse events which are reported immediately on the relevant form) Y / N

If yes, give details:

Was the patient started on open-label dexmedetomidine at some point after 48 hours of trial drug? Y / N

If yes, give details:

Any other notes regarding unusual or unanticipated circumstances:
Appendix to Form 1: scoring systems

The RASS scale:

<table>
<thead>
<tr>
<th>Score</th>
<th>Term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>+4</td>
<td>Combative</td>
<td>Overtly combative or violent, immediate danger to staff</td>
</tr>
<tr>
<td>+3</td>
<td>Very agitated</td>
<td>Pulls on or removes tubes or catheters or has aggressive behavior toward staff</td>
</tr>
<tr>
<td>+2</td>
<td>Agitated</td>
<td>Frequent nonpurposeful movement or patient ventilator dyssynchrony</td>
</tr>
<tr>
<td>+1</td>
<td>Restless</td>
<td>Anxious or apprehensive but movements not aggressive or vigorous</td>
</tr>
<tr>
<td>0</td>
<td>Alert and calm</td>
<td>Not fully alert, but has sustained (more than 10 seconds) awakening, with eye contact/eye opening to voice</td>
</tr>
<tr>
<td>-1</td>
<td>Drowsy</td>
<td>Briefly (less than 10 seconds) awakens with eye contact to voice</td>
</tr>
<tr>
<td>-2</td>
<td>Light sedation</td>
<td>Any movement (but no eye contact) to voice</td>
</tr>
<tr>
<td>-3</td>
<td>Moderate sedation</td>
<td>No response to voice, but any movement to physical stimulation</td>
</tr>
<tr>
<td>-4</td>
<td>Deep sedation</td>
<td>No response to voice or physical stimulation</td>
</tr>
<tr>
<td>-5</td>
<td>Unarousable</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 1.** The RASS scale. Adapted from Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med 2002;166:1338–1344.

The MAAS scale

<table>
<thead>
<tr>
<th>Score</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Unresponsive Does not move with noxious stimuli</td>
</tr>
<tr>
<td>1</td>
<td>Responsive only to noxious stimuli. Opens eyes or raises eyebrows or turns head toward stimulus or moves limbs with noxious stimuli</td>
</tr>
<tr>
<td>2</td>
<td>Responsive to touch or name. Opens eyes or raises eyebrows or turns head toward stimulus or moves limbs when touched or name is loudly spoken</td>
</tr>
<tr>
<td>3</td>
<td>Calm and cooperative. No external stimulus is required to elicit movement and patient adjusts sheets or clothes purposefully and follows commands</td>
</tr>
<tr>
<td>4</td>
<td>Restless and cooperative. No external stimulus is required to elicit movement and patient picks at sheets or tubes or uncovers self and follows commands</td>
</tr>
<tr>
<td>5</td>
<td>Agitated. No external stimulus is required to elicit movement and attempts to sit up or moves limbs out of bed and does not consistently follow commands (for example, lies down when asked but soon reverts back to attempts to sit up or move limbs out of bed)</td>
</tr>
<tr>
<td>6</td>
<td>Dangerously agitated, uncooperative. No external stimulus is required to elicit movement and patient pulls at tubes or catheters or thrashes side to side or strikes at staff or tries to climb out of bed and does not calm down when asked</td>
</tr>
</tbody>
</table>

The Riker scale

<table>
<thead>
<tr>
<th>Level</th>
<th>Behaviors</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>Dangerous agitation. Pulls at endotracheal tube, tries to remove catheters, climbs over bed rail, strikes at staff, thrashes side-to-side</td>
</tr>
<tr>
<td>6</td>
<td>Very agitated. Does not calm, despite frequent verbal reminders; requires verbal reminding of limits, physical restraints; bites endotracheal tube</td>
</tr>
<tr>
<td>5</td>
<td>Agitated. Anxious or mildly agitated, attempts to sit up, calms down to verbal instructions</td>
</tr>
<tr>
<td>4</td>
<td>Calm and cooperative. Calm, awakens easily, follows commands</td>
</tr>
<tr>
<td>3</td>
<td>Sedated. Difficult to arouse, awakens to verbal stimuli or gentle shaking but drifts off again, follows simple commands</td>
</tr>
<tr>
<td>2</td>
<td>Very sedated. Aroused to physical stimuli but does not communicate or follow commands, may move spontaneously</td>
</tr>
<tr>
<td>1</td>
<td>Unarousable. Minimal or no response to noxious stimuli, does not communicate or follow commands</td>
</tr>
</tbody>
</table>

Figure 5. The Riker Sedation-Agitation Scale. Adapted from Fraser GL, Riker R. Monitoring sedation, agitation, analgesia, and delirium in critically ill adult patients. Crit Care Clin 2001;17:1–21.
### CAM-ICU Worksheet

**Feature 1: Acute Onset for Fluctuating Course**  
Positive if you answer “yes” to either 1A or 1B

<table>
<thead>
<tr>
<th><strong>1A:</strong> Is the patient different than his/her baseline mental status?</th>
<th>Positive</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>1B:</strong> Has the patient had any fluctuation in mental status in the past 24 hours as evidenced by fluctuation on a sedation scale (e.g., RASS), GCS, or previous delirium assessment?</th>
<th>Positive</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Feature 2: Inattention**  
Positive if either score for 2A or 2B is less than 8.

- Attempt the ASE letters first. If patient is able to perform this test and the score is clear, record this score and move to Feature 3. If patient is unable to perform this test or the score is unclear, then perform the ASE Pictures. If you perform both tests, use the ASE Pictures’ results to score the Feature.

<table>
<thead>
<tr>
<th><strong>2A: ASE Letters: record score</strong> (enter NT for not tested)</th>
<th>Score (out of 10):</th>
</tr>
</thead>
</table>

**Directions:** Say to the patient: “I am going to read you a series to 10 letters. Whenever you hear the letter “A,” indicate by squeezing my hand.” Read letters from the following letter list in a normal tone.

\[ S A V E A H A A R T \]

Scoring: Errors are counted when patient fails to squeeze on the letter “A” and when the patient squeezes on any letter other than “A.”

<table>
<thead>
<tr>
<th><strong>2B: ASE Pictures: record score</strong> (enter NT for not tested)</th>
<th>Score (out of 10):</th>
</tr>
</thead>
</table>

Directions: included on the picture packets.

**Feature 3: Altered Level of Consciousness**  
Positive if the actual RASS score is anything other than “0” (zero.)

**Feature 4: Disorganized Thinking**  
Positive if the combined score is less than 4

| **4A: Yes / No Questions**  
(Use either Set A or Set B, alternate on consecutive days if necessary): | Combined Score (4A + 4B): |
|---|---|

<table>
<thead>
<tr>
<th>Set A</th>
<th>Set B</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Will a stone float on water?</td>
<td>1. Will a leaf float on water?</td>
</tr>
<tr>
<td>2. Are there fish in the sea?</td>
<td>2. Are there elephants in the sea?</td>
</tr>
<tr>
<td>3. Does one pound weigh more than two pounds?</td>
<td>3. Do two pounds weigh more than one pound?</td>
</tr>
<tr>
<td>4. Can you use a hammer to pound a nail?</td>
<td>4. Can you use a hammer to cut wood?</td>
</tr>
</tbody>
</table>

Score: _______ (Patient earns 1 point for each correct answer out of 4)

| **4B. Command**  
Say to the patient: “Hold up this many fingers.” (Examiner holds two fingers in front of patient.) “Now do the same thing with the other hand.” (Not repeating the number of fingers.) *If patient is unable to move both arms, for the second part of the command ask the patient: “Add one more finger.”* | |
|---|---|

Score: _______ (Patient earns 1 point if able to successfully complete the entire command)

**Overall CAM-ICU** (Features 1 and 2, and either Feature 3 or 4):  
Positive | Negative
---|---

**Signature:** ____________________  
**Date/Time:** ____________________

---

Copyright © 2002, E. Wesley Ely, MD, MPH and Vanderbilt University, all rights reserved. Last updated 5-25-05

Dexmedetomidine to Lessen ICU Agitation (DahLIA) – Case report form ver. 3
### SOFA score at the end of this 24 hour period (i.e. as close as possible to 2400): - *can be completed by Research Co-ordinator*

Use last known values. Circle the appropriate box, then sum the points.

<table>
<thead>
<tr>
<th>SOFA Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiration</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaO2/ FiO2 (mmHg)</td>
<td>500</td>
<td>300</td>
<td>200</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Cardiac Output</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac Index (L/min/m²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Arterial Pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catecholamines Hypotension</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No hypotension</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP &lt; 70 mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dopamine &gt; 5 or dobutamine (any dose)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebral Nervous System</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glasgow Coma Scale</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10-14</td>
<td>10-12</td>
<td>6</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nutritional Status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elements, N, P, K, Mg, Ca, copper, zinc, iron, Fe,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>or urine output</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>e.g., proteinuria, norepinephrine, Na, K, Fe,</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.2</td>
<td>1.5-3.1</td>
<td>1.2-2.4</td>
<td>1.2-3.4</td>
<td>1.2-4.8</td>
<td></td>
</tr>
<tr>
<td>Total SOFA score:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Today, did the patient require the insertion of a new CVC solely to facilitate vasoaspressors / inotropes for hypotension? Y / N

---

If the patient was re-intubated today after first extubation following study entry:

**Time from extubation to re-intubation (if applicable):** 

---

If not still being administered, is there a suspicion that, if the drug had been continued, the patient would not have needed reintubation? Y / N / NA
Form 3 – Serious Adverse Event report form. To be completed by research co-ordinator if required

1. What are you reporting: SAE □ SUSAR* □ Pregnancy □
   *Note: if you are reporting a SUSAR the randomisation code for this patient will have to be unblinded.

2. Report Type: Initial Report □ Follow up Report □ Follow up Report #: __________

3. Protocol Title and Version Number:
   Dexmedetomidine to Lessen ICU Agitation: The DahLIA trial. Version 4

    Evaluation of Event

4. Event / Reaction: (keywords; e.g.: body site, symptoms, severity, treatment)

5. Site Principal Investigator

6. Site

7. Date of Onset: (dd/mmm/yy)

8. Time of Onset: (if available; hh:mm)

9. Criteria for definition as SAE:
   □ Resulted in Death
   □ Life threatening
   □ In-patient hospitalization or prolongation
   □ Persistent or significant disability
   □ Congenital anomaly/birth defect

   If there is more than one criteria, choose the more/most significant one. Seriousness is a regulatory definition and should not be confused with severity.

10. Describe Event: (A summary of signs and symptoms, diagnosis, treatment of event, concurrent treatment, other relevant medical history, including re-challenge details if applicable. Please include the point in the study at which the event occurred.)
### 11. In the Investigator’s opinion was the event related to the Investigational Medicinal Product?

- [ ] Definitely
- [ ] Likely
- [ ] Possibly
- [ ] Unlikely
- [ ] Not Related

### 12. Action Taken With Study Drug

- [ ] None
- [ ] Dose temporarily reduced
- [ ] Dose reduced
- [ ] Discontinued temporarily
- [ ] Discontinued

### 13. If related to IMP was this reaction unexpected (Suspected Unexpected Serious Adverse Reaction – SUSAR)

- [ ] Yes
- [ ] No
- [ ] Not Applicable

### 14. Did event/reaction abate after stopping drug?

- [ ] Yes
- [ ] No
- [ ] Not Applicable

### 15. Did event/reaction reappear after reintroduction of drug?

- [ ] Yes
- [ ] No
- [ ] Not Applicable

### 16. IMP & Concomitant Medication Information

<table>
<thead>
<tr>
<th>Drug Details (include daily dose(s) &amp; generic name)</th>
<th>Therapy Start Date (dd/mmm/yyyy)</th>
<th>Therapy End Date (dd/mmm/yyyy)</th>
<th>Date of dose prior to SAE onset (dd/mmm/yyyy)</th>
<th>Route(s) of administration</th>
<th>Indications for Use</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Patient study number**

17. Have Urgent Safety Measures been implemented?  
   - Yes
   - No
   - Not Applicable

<table>
<thead>
<tr>
<th>Outcome of Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>18. What is the outcome of the SAE?</td>
</tr>
<tr>
<td>19. Date event resolved: (dd/mm/yyyy)</td>
</tr>
<tr>
<td>20. Date patient died: (dd/mm/yyyy)</td>
</tr>
<tr>
<td>- Recovered</td>
</tr>
<tr>
<td>- Recovered with sequelae</td>
</tr>
<tr>
<td>- Continuing</td>
</tr>
<tr>
<td>- Resulted in Death</td>
</tr>
<tr>
<td>- Unknown</td>
</tr>
<tr>
<td>21. Cause of death obtained from (if patient died):</td>
</tr>
<tr>
<td>- Coroner's Inquest</td>
</tr>
<tr>
<td>- Death Certificate</td>
</tr>
<tr>
<td>- Working diagnosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Contact &amp; Signatures</th>
</tr>
</thead>
<tbody>
<tr>
<td>22. Person to contact:</td>
</tr>
<tr>
<td>22a. Centre (if multicentre trial):</td>
</tr>
<tr>
<td>23. Phone number:</td>
</tr>
<tr>
<td>24. Email address:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Signature (person completing report)</th>
<th>Print Name</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Principle Investigator Signature (if multicentre trial)</td>
<td>Print Name</td>
<td>Date</td>
</tr>
<tr>
<td>Chief Investigator Signature (if not completing report)</td>
<td>Print Name</td>
<td>Date</td>
</tr>
</tbody>
</table>

Please fax completed form to Austin Health Intensive Care Research office: 
Tel. 03 9496 3932, marked for the urgent attention of Mr Glenn Eastwood or Ms Leah Peck
Form 4: Protocol violation or study discontinuation

Completed by research coordinator after reconciliation of CRF and clinical notes, or on occurrence of one of the listed events.

**Dexmedetomidine to Lessen ICU Agitation: The DahLIA trial**

**Patient study number**

**Protocol deviation:**

- Randomisation of ineligible patient
  
  *(patient must stop receiving trial medication. Open label dexmedetomidine may be used if indicated)*

- Study treatment maximum dose (1.5 mcg/kg/hr) exceeded

- Clonidine used whilst on study drug

- Other (specify below)
  
  *(in all these cases, patient may continue to receive study drug if this is thought safe by the clinical team)*

- No protocol deviations identified

**Study drug premature discontinuation:**

- Not applicable – study drug continued until treating physician thought it no longer indicated
  
  - patient / person responsible consent withdrawn
  - able to use data
  - not able to use data
  
  suspected adverse event

  clinician ordered trial drug stopped
  
  *(reason: _________________________________)*

  after 48 hours clinician decided to use open-label dexmedetomidine

  study stopped by data safety monitoring board

  other (specify: _________________________________)
### Form 5. Study drug accounting

**Dexmedetomidine to Lessen ICU Agitation:**

The *DahLIA* trial

<table>
<thead>
<tr>
<th>Vial number</th>
<th>Patient study number</th>
<th>Date used</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
18. REFERENCES

Reference List

1. The Australian Clinical Trial Handbook. 1-3-2006. Canberra, ACT, Australia, Commonwealth of Australia. Ref Type: Pamphlet


Ref Type: Abstract


22. Sessler CN, Gosnell MS, Grap MJ et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med* 2002; **166**: 1338-44.


### Tracking Information

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Date/Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Received Date</td>
<td>June 18, 2010</td>
</tr>
<tr>
<td>Last Updated Date</td>
<td>January 18, 2015</td>
</tr>
<tr>
<td>Start Date</td>
<td>February 2011</td>
</tr>
<tr>
<td>Primary Completion Date</td>
<td>December 2013 (final data collection date for primary outcome measure)</td>
</tr>
<tr>
<td>Current Primary Outcome Measures</td>
<td>Ventilator-free hours [Time Frame: 7 days following randomisation] [Designated as safety issue: Yes]</td>
</tr>
<tr>
<td></td>
<td>The primary outcome measure for the study will be the number of ventilator-free hours in the incident ICU admission in the 7 days following commencement of trial medication, in patients randomised to receive dexmedetomidine or normal saline placebo while receiving all other aspects of standard care.</td>
</tr>
<tr>
<td>Original Primary Outcome Measures</td>
<td>Same as current</td>
</tr>
<tr>
<td>Change History</td>
<td>Complete list of historical versions of study NCT01151865 on ClinicalTrials.gov Archive Site</td>
</tr>
<tr>
<td>Current Secondary Outcome Measures</td>
<td>Time to ICU discharge [Time Frame: On hospital discharge, or 6 months (whichever is sooner)] [Designated as safety issue: Yes]</td>
</tr>
<tr>
<td></td>
<td>Overall ICU length of stay [Time Frame: On hospital discharge, or 6 months (whichever is sooner)] [Designated as safety issue: Yes]</td>
</tr>
<tr>
<td></td>
<td>Time to first extubation [Time Frame: On hospital discharge, or 6 months (whichever is sooner)] [Designated as safety issue: Yes]</td>
</tr>
<tr>
<td></td>
<td>Time taken to achieve a satisfactory sedation score [Time Frame: 7 days following randomisation] [Designated as safety issue: Yes]</td>
</tr>
<tr>
<td></td>
<td>Time taken to achieve RASS score -2 to +1 and RIKER score 3 or 4</td>
</tr>
<tr>
<td></td>
<td>%ICU time spent with a satisfactory sedation score [Time Frame: 7 days following randomisation] [Designated as safety issue: Yes]</td>
</tr>
<tr>
<td></td>
<td>%ICU time spent with RASS -2 to +1 and RIKER 3 or 4</td>
</tr>
<tr>
<td></td>
<td>%ICU time spent with a satisfactory delirium score [Time Frame: 7 days following randomisation] [Designated as safety issue: Yes]</td>
</tr>
<tr>
<td></td>
<td>% time spent with a negative CAM-ICU assessment</td>
</tr>
<tr>
<td></td>
<td>Time taken to achieve a satisfactory agitation score [Time Frame: 7 days following randomisation] [Designated as safety issue: Yes]</td>
</tr>
<tr>
<td></td>
<td>Time taken to achieve a MAAS score 2-4</td>
</tr>
<tr>
<td></td>
<td>%ICU time spent with a satisfactory agitation score [Time Frame: 7 days following randomisation] [Designated as safety issue: Yes]</td>
</tr>
<tr>
<td></td>
<td>%ICU time spent with a MAAS score 2-4</td>
</tr>
<tr>
<td></td>
<td>Need for supplementary sedative medication [Time Frame: 7 days following randomisation] [Designated as safety issue: Yes]</td>
</tr>
<tr>
<td></td>
<td>Need for mechanical restraint [Time Frame: 7 days following randomisation] [Designated as safety issue: Yes]</td>
</tr>
<tr>
<td></td>
<td>total infusion time, mean hourly dose and total dose of propofol, morphine and midazolam.</td>
</tr>
</tbody>
</table>
Time to first not requiring restraint and % ICU time spent without mechanical restraint in the 7 days following commencement of trial medication

- Need for supplementary antipsychotic medication [Time Frame: 7 days following randomisation] [Designated as safety issue: Yes]
  Number of doses and total mg delivered of haloperidol, olanzapine, quetiapine, or other anti-psychotic medication as prescribed by the treating physician

- Need for tracheostomy [Time Frame: On hospital discharge, or 6 months (whichever is sooner)] [Designated as safety issue: Yes]
  Tracheostomy deemed to be necessary by the treating physician, and actually performed.

- Acute hospital length of stay [Time Frame: On hospital discharge, or 6 months (whichever is sooner)] [Designated as safety issue: Yes]
  Total duration of admission to the acute hospital, prior to discharge to home or a skilled or unskilled nursing facility.

- Discharge destination [Time Frame: On hospital discharge, or 6 months (whichever is sooner)] [Designated as safety issue: Yes]
  Discharge to home, a skilled nursing facility, residential care, a physical rehabilitation facility, or death.

- Daily SOFA score [Time Frame: 7 days following randomisation] [Designated as safety issue: Yes]
  Daily SOFA score with recording of the component parts

- ICU mortality [Time Frame: On hospital discharge, or 6 months (whichever is sooner)] [Designated as safety issue: Yes]

- Hospital mortality [Time Frame: On hospital discharge, or 6 months (whichever is sooner)] [Designated as safety issue: Yes]
  Death in the acute care hospital

- Duration and rate of vasopressor support [Time Frame: 7 days following randomisation] [Designated as safety issue: Yes]
  Total infusion time, and mean hourly dose of noradrenaline and any other inotrope or vasopressor

- Need for insertion of a new central venous catheter to facilitate vasopressor / inotropic support [Time Frame: 7 days following randomisation] [Designated as safety issue: Yes]

- Requirement for reintubation [Time Frame: On hospital discharge, or 6 months (whichever is sooner)] [Designated as safety issue: Yes]
  Reintubation of the trachea to facilitate airway protection or mechanical ventilation, as indicated in the opinion of the treating physician

Original Secondary Outcome Measures (submitted: June 28, 2010)

- Time to ICU discharge [Time Frame: On hospital discharge, or 6 months (whichever is sooner)] [Designated as safety issue: Yes]

- Overall ICU length of stay [Time Frame: On hospital discharge, or 6 months (whichever is sooner)] [Designated as safety issue: Yes]

- Time to first extubation [Time Frame: On hospital discharge, or 6 months (whichever is sooner)] [Designated as safety issue: Yes]

- Time taken to achieve a satisfactory sedation score [Time Frame: 7 days following randomisation] [Designated as safety issue: Yes]
  Time taken to achieve RASS score -2 to +1 and RIKER score 3 or 4

- % ICU time spent with a satisfactory sedation score [Time Frame: 7 days following randomisation] [Designated as safety issue: Yes]
  % ICU time spent with RASS -2 to +1 and RIKER 3 or 4

- % ICU time spent with a satisfactory delirium score [Time Frame: 7 days following randomisation] [Designated as safety issue: Yes]
  % time spent with a negative CAM-ICU assessment

- Time taken to achieve a satisfactory agitation score [Time Frame: 7 days following randomisation] [Designated as safety issue: Yes]
  Time taken to achieve a MAAS score 2-4

- % ICU time spent with a satisfactory agitation score [Time Frame: 7 days following randomisation] [Designated as safety issue: Yes]
  % ICU time spent with a MAAS score 2-4

- Need for supplementary sedative medication [Time Frame: 7 days following randomisation] [Designated as safety issue: Yes]
  Total infusion time, mean hourly dose and total dose of propofol, morphine and midazolam.

- Need for mechanical restraint [Time Frame: 7 days following randomisation] [Designated as safety issue: Yes]
  Time to first not requiring restraint and % ICU time spent without mechanical restraint in the 7 days following commencement of trial medication

- Need for supplementary antipsychotic medication [Time Frame: 7 days following randomisation] [Designated as safety issue: Yes]
  Number of doses and total mg delivered of haloperidol, olanzapine, quetiapine, or other anti-psychotic medication as prescribed by the treating physician
• Need for tracheostomy [Time Frame: On hospital discharge, or 6 months (whichever is sooner)]
  [Designated as safety issue: Yes]
Tracheostomy deemed to be necessary by the treating physician, and actually performed.
• Acute hospital length of stay [Time Frame: On hospital discharge, or 6 months (whichever is sooner)]
  [Designated as safety issue: Yes]
Total duration of admission to the acute hospital, prior to discharge to home or a skilled or unskilled nursing facility.
• Discharge destination [Time Frame: On hospital discharge, or 6 months (whichever is sooner)]
  [Designated as safety issue: Yes]
Discharge to home, a skilled nursing facility, residential care, a physical rehabilitation facility, or death.
• Daily SOFA score [Time Frame: 7 days following randomisation] [Designated as safety issue: Yes]
Daily SOFA score with recording of the component parts
• ICU mortality [Time Frame: On hospital discharge, or 6 months (whichever is sooner)]
  [Designated as safety issue: Yes]
ICU mortality
• Hospital mortality [Time Frame: On hospital discharge, or 6 months (whichever is sooner)]
  [Designated as safety issue: Yes]
Death in the acute care hospital
• Duration and rate of vasopressor support [Time Frame: 7 days following randomisation]
  [Designated as safety issue: Yes]
total infusion time, and mean hourly dose of noradrenaline and any other inotrope or vasopressor
• Need for insertion of a new central venous catheter to facilitate vasopressor / inotropic support [Time Frame: 7 days
  following randomisation] [Designated as safety issue: Yes]
• Requirement for reintubation [Time Frame: On hospital discharge, or 6 months (whichever is sooner)]
  [Designated as safety issue: Yes]
Reintubation of the trachea to facilitate airway protection or mechanical ventilation, as indicated in the opinion of the
  treating physician

### Descriptive Information

**Brief Title**
Dexmedetomidine to Lessen Intensive Care Unit (ICU) Agitation

**Official Title**
A Randomised, Double-blind, Multi-centre Placebo Controlled Trial of Dexmedetomidine for Patients With Agitation and
Delirium in the Intensive Care Unit

**Brief Summary**
The primary aim of the DahLIA trial is to determine, in patients with ICU-associated delirium and agitation who are otherwise
pathophysiologically stable (as defined), the number of ventilator-free hours in the incident ICU admission in the 7 days
following commencement of trial medication, in patients randomised to receive dexmedetomidine or placebo while receiving
all other aspects of standard care.
The null hypothesis assumes no difference in the median number of ventilator-free hours in this ICU admission in the
following 7 days, between patients receiving dexmedetomidine and placebo for ICU-associated agitation and delirium.

**Detailed Description**
Not Provided

**Study Type**
Interventional

**Study Phase**
Phase 2
  Phase 3

**Study Design**
Allocation: Randomized
Endpoint Classification: Safety/Efficacy Study
Intervention Model: Parallel Assignment
Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)
Primary Purpose: Treatment

**Condition**
Delirium

**Intervention**

- Drug: Dexmedetomidine
  Dexmedetomidine will be administered intravenously as a maintenance infusion of 0.2 to 1.5 mcg/kg/hour, commencing
  at 0.5 mcg/kg/hour and titrated according to effect, for as long as deemed necessary by the treating physician.
  Specifically, the study medication may be (as recommended by the manufacturer) continued after extubation, and if
  discontinued may be restarted at any time up until ICU discharge. The clinician will have the option of using a loading
dose of 1.0 mcg/kg IV over 20 minutes, as recommended by the manufacturer. Bedside nursing staff will adjust drug
infusion rates as necessary, in consultation with the treating physician, aiming to achieve a Riker Sedation-Agitation
Scale 20 score of 4.
  Other Name: Precedex
- Drug: Saline placebo
An identical syringe containing only saline with no dexmedetomidine added will be supplied. Initial rate of infusion and subsequent adjustments will be the same as in the active comparator group.

**Study Arm(s)**

- **Active Comparator:** Dexmedetomidine
  Dexmedetomidine will be administered intravenously as a maintenance infusion of 0.2 to 1.5 mcg/kg/hour, commencing at 0.5 mcg/kg/hour and titrated according to effect, for as long as deemed necessary by the treating physician. Specifically, the study medication may be (as recommended by the manufacturer) continued after extubation, and if discontinued may be restarted at any time up until ICU discharge. The clinician will have the option of using a loading dose of 1.0 mcg/kg IV over 20 minutes, as recommended by the manufacturer. Bedside nursing staff will adjust drug infusion rates as necessary, in consultation with the treating physician, aiming to achieve a Riker Sedation-Agitation Scale 20 score of 4.
- **Intervention:** Drug: Dexmedetomidine
  - Placebo Comparator: Saline placebo
  An identical syringe to that in the intervention arm, but which does not contain dexmedetomidine, will be provided. The initial rate of infusion and subsequent adjustments will be the same as in the dexmedetomidine group.

**Publications**

* Includes publications given by the data provider as well as publications identified by ClinicalTrials.gov Identifier (NCT Number) in Medline.

**Recruitment Information**

**Recruitment Status**
- Completed

**Enrollment**
- 96

**Completion Date**
- December 2013

**Primary Completion Date**
- December 2013 (final data collection date for primary outcome measure)

**Eligibility Criteria**

**Inclusion Criteria:**
Patients will be eligible for the study if, in the opinion of the treating clinician, they continue to require mechanical ventilation only because their degree of agitation requires such a high dose of sedative medication (midazolam or propofol, the only commonly used specific sedatives in our unit) that extubation is not possible, AND in the opinion of their treating intensivist their agitation is so severe as to make lessening their sedation unsafe.

These criteria will be objectively quantified as follows:

- they have required either mechanical restraint and/or anti-delirium or sedative medication in the 4 hours prior to seeking consent AND
- their Confusion Assessment Method for the ICU (CAM-ICU) test is positive for delirium in the 4 hours prior to seeking consent AND
- their Motor Activity Assessment Scale (MAAS) score is 5 or more in the 4 hours prior to seeking consent, confirming psychomotor agitation AND
- their SOFA score is less than or equal to 5 in the 4 hours prior to seeking consent, predicting a mortality or around 5%.

**Exclusion Criteria:**

- Age less than 18 years old
- Pregnancy or breastfeeding
- Advanced dementia (in the premorbid state requiring professional nursing care)
- Open or closed head injury
- Death is deemed imminent and inevitable
- The patient has previously been enrolled in the DahLIA study
- Patients who could not be extubated, or who would be intubated within the following 48 hours, even if delirium or agitation were corrected. This will include:
  - Patients receiving high dose opioid for analgesia (not sedation) ( > 40 mg/morphine/day)
  - Patients shortly to return to the operating theatre
  - Patients undergoing repeated invasive procedures, in whom it is desirable to maintain deep sedation
  - Patients likely to require ongoing airway protection or control, or ventilatory support (for example, spinal patients with an inadequate vital capacity)
- Known allergy to haloperidol or alpha 2 agonists

**Gender**
- Both

**Ages**
- 18 Years and older

**Accepts Healthy Volunteers**
- No

**Contacts**
- Contact information is only displayed when the study is recruiting subjects

**Listed Location Countries**
- Australia
**Administrative Information**

<table>
<thead>
<tr>
<th>Data element</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT Number</td>
<td>NCT01151865</td>
</tr>
<tr>
<td>Other Study ID Numbers</td>
<td>H2010/03891</td>
</tr>
<tr>
<td>Has Data Monitoring Committee</td>
<td>Yes</td>
</tr>
<tr>
<td>Responsible Party</td>
<td>GLENN EASTWOOD, Austin Health</td>
</tr>
<tr>
<td>Study Sponsor</td>
<td>Austin Health</td>
</tr>
<tr>
<td>Collaborators</td>
<td>Hospira, Inc.</td>
</tr>
</tbody>
</table>

**Investigators**

| Study Chair: | Michael C Reade, MBBS DPhil | Austin Hospital & University of Melbourne |
| Principal Investigator: | Rinaldo Bellomo, MD | Austin Hospital and University of Melbourne |
| Principal Investigator: | John Mulder, MBChB | Western Hospital, Melbourne |
| Principal Investigator: | Ben Cheung, MBBS | Toowoomba Hospital |
| Principal Investigator: | Anthony Delaney, MBBS | Royal North Shore Hospital |
| Principal Investigator: | Andrew Davis, MBBS | The Alfred |
| Principal Investigator: | Steve Webb, MBBS | Royal Perth Hospital |
| Principal Investigator: | Michael Bailey, MSc PhD | Monash University |
| Principal Investigator: | Glenn Eastwood, BNurs RN | Austin Hospital, Melbourne Australia |

**Information Provided By** | Austin Health |

**Verification Date** | January 2015 |