PROTOCOL

Sedation for Acute Agitation in Emergency Department Patients: Targeting Adverse Events (SIESTA)

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Statement of Compliance

This document is a protocol for a research project. This study will be conducted in compliance with all stipulation of this protocol, the conditions of the ethics committee approval, the NHMRC National Statement on ethical Conduct in Human Research (2007) and the Note for Guidance on Good Clinical Practice (CPMP/ICH-135/95).
# TABLE OF CONTENTS

## CONTENTS

Table of Contents............................................................................................................................................................................... 2

1. **Glossary of Abbreviations & Terms**..................................................................................................................................... 5

2. **Study Sites**........................................................................................................................................................................... 5
   a. Study Location/s .............................................................................................................................................................. 5

3. **Introduction/Background Information**......................................................................................................................... 6
   a. Lay Summary................................................................................................................................................................ .... 6
   b. Introduction................................................................................................................................................................ ......... 7
   c. Background information............................................................................................................................................... 7

4. **Study Objectives**................................................................................................................................................................ 9
   a. Hypothesis................................................................................................................................................................ .......... 9
   b. Study Aims................................................................................................................................................................ ......... 9
   c. Outcome Measures........................................................................................................................................................ 9
   a. Study Type & Design.................................................................................................................................................. 10

6. **Study Population**............................................................................................................................................................ 11
   a. Recruitment Procedure............................................................................................................................................. 11
   b. Inclusion Criteria........................................................................................................................................................... 11
   c. Exclusion Criteria........................................................................................................................................................... 11
   d. Consent............................................................................................................................................................................. 11

7. **Participant Safety and Withdrawal**.............................................................................................................................. 12
   a. Risk Management and Safety........................................................................................................................................... 12

8. **Statistical Methods**............................................................................................................................................................. 13
a. Sample Size Estimation & Justification

b. Statistical Methods To Be Undertaken

9. Data Security & Handling

a. Details of where records will be kept & How long will they be stored

b. Confidentiality and Security

10. References
# STUDY SYNOPSIS

<table>
<thead>
<tr>
<th>Title:</th>
<th>Sedation for Acute Agitation in Emergency Department Patients: Targeting Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short Title:</td>
<td>SIESTA</td>
</tr>
<tr>
<td>Design:</td>
<td>Prospective observational study</td>
</tr>
<tr>
<td>Study Centres:</td>
<td>Austin Hospital – leading site in VIC</td>
</tr>
<tr>
<td>Hospital:</td>
<td>Austin, Casey, Monash Medical Centre, Dandenong, Frankston, Gold Coast, Mater (Brisbane), Nambour, Townsville, Liverpool, Auckland City</td>
</tr>
<tr>
<td>Study Question:</td>
<td>What adverse events (AEs) are commonly associated with the sedative medications administered parenterally to acutely agitated patients and what are the risk factors related to these events?</td>
</tr>
<tr>
<td>Study Objectives:</td>
<td>To determine the nature, incidence and associated risk factors of AEs related with sedative medications administered parenterally to acutely agitated patients presenting to the emergency department (ED).</td>
</tr>
<tr>
<td>Primary Objectives:</td>
<td>To determine the nature and incidence of AEs related with sedative medications administered parenterally to acutely agitated patients presenting to the ED.</td>
</tr>
<tr>
<td>Secondary Objectives</td>
<td>To determine the risk factors for the AEs related with sedative medications administered parenterally to acutely agitated patients presenting to the ED.</td>
</tr>
<tr>
<td>Inclusion Criteria:</td>
<td>All ED patients aged 18 years or more, who require the administration of parenteral sedative medications for management of acute agitation in the ED.</td>
</tr>
<tr>
<td>Exclusion Criteria:</td>
<td>There will be no exclusion criteria.</td>
</tr>
<tr>
<td>Number of Planned Subjects:</td>
<td>2000</td>
</tr>
<tr>
<td>Investigational product:</td>
<td>Not applicable.</td>
</tr>
<tr>
<td>Safety considerations:</td>
<td>There is no risk to the patients. All patients will receive standard care for post-medication monitoring for vital signs, airway patency, and occurrence of AEs. All AEs will be managed as per routine clinical practice. This project is observational only and will not interfere with patient management/treatment.</td>
</tr>
<tr>
<td>Statistical Methods:</td>
<td>AEs will be analysed descriptively and will be tabulated by the sedative medications prescribed and will include the nature and incidence of each type of AEs and the management involved. Demographic and baseline characteristic variables will be tested for significant association with the development of AEs using univariate analysis.</td>
</tr>
</tbody>
</table>
Factors which are statistically significant (p≤0.1) will be entered into a regression model to isolate those which independently predict AEs.

1. **Glossary of Abbreviations & Terms**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description (using lay language)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>Adverse event</td>
</tr>
<tr>
<td>ED</td>
<td>Emergency department</td>
</tr>
<tr>
<td>EPSE</td>
<td>Extrapyramidal side effect</td>
</tr>
<tr>
<td>CRF</td>
<td>Case report form</td>
</tr>
</tbody>
</table>

2. **Study Sites**

   a. **Study Location/S**

<table>
<thead>
<tr>
<th>Site</th>
<th>Address</th>
<th>Contact Person</th>
<th>Phone</th>
<th>Email</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austin Hospital</td>
<td>Emergency Department, Austin Hospital, PO Box 5555, Heidelberg VIC 3084</td>
<td>Prof David Taylor</td>
<td>03 9496 4711</td>
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<tr>
<td>Monash Health (Monash Medical Centre, Casey Hospital and Dandenong Hospital)</td>
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</tr>
</tbody>
</table>
3. INTRODUCTION/BACKGROUND INFORMATION

a. LAY SUMMARY

Acutely agitated patients are commonly seen in the emergency department (ED). As these patients may cause harm to themselves or others, a large proportion will need to be managed with injectable forms of sedative medications (intramuscular or intravenous) such as benzodiazepines (e.g. midazolam) and antipsychotics (e.g. droperidol). However, these medications may also precipitate life threatening events (e.g. hypoventilation). Safety data related to the use of these medications for the

<table>
<thead>
<tr>
<th>Gold Coast University Hospital</th>
<th>Emergency Department,1 Hospital Boulevard Southport QLD 4215</th>
<th>A/Prof Gerben Keijzers Dr Sanjeewa Kulawickrama</th>
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</thead>
<tbody>
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<td><a href="mailto:anna.holdgate@swsahs.nsw.gov.au">anna.holdgate@swsahs.nsw.gov.au</a> <a href="mailto:Daniel.Finucci@swsahs.nsw.gov.au">Daniel.Finucci@swsahs.nsw.gov.au</a></td>
</tr>
</tbody>
</table>

This study protocol will be reviewed by Austin Health HREC for VIC sites, Gold Coast Health Service District HREC for QLD sites and South Western Sydney Local Health District HREC for NSW site.
management of acute agitation in the ED setting are scant. Acute agitation seen in the ED is usually caused by mental health issues and/or substance abuse. However, little is known which sedative medication is best suited for different groups of acutely agitated patients. The aim of this study is to determine the nature and incidence of adverse events associated with parenteral sedative medication administered to acutely agitated patients in the ED, and to determine risk factors for these adverse events.

All ED patients presenting with acute agitation, aged 18 year-old or more, who require the sedative medications given by injection for acute agitation, will be eligible. All patients will receive management based on the usual clinical practice of the ED. The choice of sedative medications is completely at the discretion of the treating doctor. Adverse events will be recorded by nursing staff using a standardised form. There will be no additional contact with the patient for the purpose of this study. The findings of this study will improve the quality of evidence in the acute agitation management in ED. This information will also facilitate optimal prescribing of sedative medications in specific groups of patients.

b. INTRODUCTION
Acute agitation is a common condition seen by ED clinical staff. It is challenging to manage because rapid decisions have to be made, often with limited patient data. Immediate risk assessment and effective intervention can reduce harm to patients and staff and allow treatment of the underlying condition. Parenteral sedative medication is often required to quickly calm severely agitated patients. The goal of treatment is to decrease dangerous behaviour and to ensure the safety of the patient and the healthcare staff. However, most clinical trials in the ED setting to date have not been designed to adequately explore adverse events (AE) associated with the study interventions. Data from observational studies is also lacking. Hence, data on the frequency and severity of the AE associated with various sedative medications are urgently needed.

Acute agitated patients in the ED setting commonly present with co-morbid medical and substance abuse issues. Few studies in small samples of patients reported that co-morbidities or concurrent substance use (e.g. alcohol ingestion) may increase the risk of patients from AEs from certain sedative medications. Validity of the findings from these retrospective studies should be further evaluated with a well-designed multi-centre prospective study.

This study aims to fill these knowledge gaps by determining the nature and incidence of AEs associated with parenteral sedative medications used for management of acute agitation in Australasian EDs. We also attempt to identify risk factors for AEs associated with the sedative medications.

c. BACKGROUND INFORMATION
Patients exhibiting acute agitation frequently present to EDs [1] and utilise significant time and resources. As these patients may cause harm to themselves or others, ED medical staff must make rapid decisions to contain the situation. Ideally, attempts should be made to calm the patient through verbal de-escalation techniques and show of force [2, 3]. However, in some circumstances, sedative medication is needed. Despite the availability of therapeutic guidelines in the management of acute agitation, marked variability is observed in current practice [4].
Anecdotally, a large proportion of acutely agitated patients in EDs will need to be managed with parenteral medications. Whilst parenteral benzodiazepines (e.g. midazolam) and antipsychotics (e.g. olanzapine, droperidol) are usually employed [5, 6]; these drugs can induce potentially life-threatening AEs. To date, there are only a handful of randomised controlled trials [7, 8, 9] in the ED setting that have explored the effectiveness and safety of some of these parenteral medications. However, these studies were not designed to adequately explore AEs associated with the studied medications. As such, there is also limited safety data relating to these parenteral medications when used for the management of acute agitation in the ED setting.

Little is known about which sedative medication is best suited for specific groups of patients. This is despite Wilson et al [10] suggesting that there may be ‘specific groups’ of patients who will experience more AEs with certain medications. Selecting the appropriate sedative medication is important to reduce the risk of harm to the patient and staff. Consequently, in current clinical practice, some ED patients with acute agitation are receiving sedative medications that may not be best suited to them and, may experience AEs as a consequence. Data which will facilitate optimal prescribing of sedative medications in specific group of patients with acute agitation in EDs are needed. The findings of this study will facilitate optimal prescribing of sedative medications in the management of acute agitation in EDs and improve the quality of care for this group of patients.
4. **Study Objectives**

   **a. Hypothesis**
   - AEs are commonly experienced by patients who receive the parenteral sedative medications in the ED during the episode of acute agitation.
   - Specific groups of patients may experience more AEs with certain sedative medications.

   **b. Study Aims**
   - To determine the nature and incidence of AEs associated with parenteral sedative medications administered to acutely agitated patients presenting to the ED.
   - To determine risk factors for AEs associated with parenteral sedative medications administered to acutely agitated patients presenting to the ED.

   **c. Outcome Measures**

   The primary outcomes of the study are the nature and incidence of AEs

   The secondary outcomes will include
   - risk factors associated with the occurrence of AEs
   - types of parenteral sedative medications currently used in the management of acute agitation in the ED
   - the proportion of patients who receive monotherapy versus combination therapy as initial drug regimens
   - ED length of stay
5. Study Design

a. STUDY TYPE & DESIGN
This will be a multi-centre prospective observational study undertaken in the EDs of ten Australasian hospitals over a period of approximately 2 years. Patients who present with acute agitation will receive management based on the usual (standard) clinical practice of their ED medical staff and local hospital policies. The choice of sedative medications is completely at the discretion of the treating doctor. Data will be collected using standardized case report forms (CRFs) (as per attachment) and will encompass the list given below.

Demographic and Baseline Characteristics
Demographic and baseline characteristics data will be collected by site investigators from the medical records. The site investigators will not collect any additional data other than those that are routinely collected as part of standard care. Specific data to be collected from the medical records include:

- demographics (age, gender)
- past medical history (medical and mental health)
- medication history (current medications and medications given by the paramedics)
- sedative medications prescribed in the ED
- other medications prescribed in the ED (other than the sedative medications)
- other interventions (e.g. physical restraint) whilst in the ED
- reasons for involuntary treatment where applicable
- history of illicit drugs and alcohol use (breath alcohol level [BAL])
- final diagnosis in ED
- disposition (date, time and place of disposition)

AEs and Management
The occurrence of AEs will be recorded as soon as they occur. This will be any time between the administration of parenteral sedative medications and discharge from the ED. Nursing staff will document, on the study CRF, the occurrence of an AE and the required management, once the event has been managed. AEs that will be recorded include:

- respiratory events: hypoventilation (<10 breaths/min), oxygen desaturation (<90% mmHg), airway obstruction (partial/complete)
- hypotension (systolic BP < 90mmHg)
- cardiac dysrhythmia
- QTc prolongation on the ECG
- extrapyramidal side effects (EPSE) [e.g. acute dystonic reaction will be assessed based on abnormal movement assessment]
- vomiting
- aspiration of stomach contents
- injuries to staff or patient
6. **STUDY POPULATION**

   a. **RECRUITMENT PROCEDURE**
   All potential participants will be ED patients who have presented for medical care. Those who require parenteral sedative medication will be identified for this study by the treating ED staff. All participants will experience usual care which includes close monitoring of vital signs and for the occurrence of AEs after sedation. No additional patient contact will be required for this study.

   b. **INCLUSION CRITERIA**
   All ED patients who:
   
   - present with, or who develop, acute agitation
   - are aged 18 years or more
   - who require the administration of parenteral sedative medications for acute agitation

   c. **EXCLUSION CRITERIA**
   There will be no exclusion criteria for this study.

   d. **CONSENT**
   Patient consent will not be sought as this is an observational study and will not interfere with usual clinical practice. We request therefore a waiver of consent. The data collected will be those which should normally be recorded in the patients' medical notes as part of routine care. Often, however, the occurrence of AEs is poorly recorded in the medical records. This is the reason we cannot undertake retrospective medical record review to collect all data. Given this, our Nurse Data Collection Form will remind staff to record all AEs and will improve the documentation of AEs.

   In regard to the waiver of consent we refer to the items in 2.3.6 of the National Statement:

   a) The research carries no more than low risk:
   
   The study is purely observational with no change in clinical practice and with no approach to or collection of data from the patients. There is no risk to the patients.

   b) The benefits justify the risks:
   
   For the first time, sedation practices and outcomes will be determined. This will guide clinical guideline development. There are, therefore, considerable benefits with no added risk.

   c) Is it impractical to obtain consent?
   
   Patients in this study will, by definition, be acutely agitated and will be in no state to give informed consent. While delayed consent may be possible in a proportion of cases, once the effects of substance abuse has worn off, it would be logistically impractical to obtain delayed consent since we will not have research assistants to obtain this consent.
d) There is no reason to think patients would not consent:

The study is purely observational, has no change to clinical practice or patient management and does not involve any data collection from the patient. There is no reason to believe that patients would not consent to this.

e) There is protection of privacy

Standard research techniques that ensure privacy will be undertaken (see elsewhere). No patient details will be divulged at any stage.

f) There is a plan to protect the confidentiality of the data

Standard research techniques that ensure confidentiality of the data will be undertaken. Data will only leave participating sites in coded (re-identifiable) format. Each site will hold the code to the data and this will not leave the site.

g) Will results have significance for the patients?

Sedation of acutely agitated patients is usually a ‘one off’ event. The results will be of no significance to the patients.

h) Will there be the possibility of commercial exploitation?

This is not a possibility at all.

i) Is the waiver prohibited by law?

No. This is an observational study undertaken as part of usual practice.

7. PARTICIPANT SAFETY AND WITHDRAWAL

    a. RISK MANAGEMENT AND SAFETY

This project does not interfere with patient management in any way. It is purely observational. As such, there are no additional clinical risks. Any risk associated with confidentiality issues will be adequately addressed (see below).
8. **Statistical Methods**

   a. **Sample Size Estimation & Justification**
   Two clinical trials on acute sedation of the agitated patients reported that AEs occurred in 11.6% [8] and 13.7% [7] of patients. In our study, to be 95% certain that the proportion of patients with AEs will lay between 11% and 14%, we will need to enrol at least 1944 patients (level of significance 0.05). Therefore, we plan to include approximately 2000 patient presentations in total from the 11 participating EDs.

   b. **Statistical Methods To Be Undertaken**
   Patient demographics and prescribing patterns will be analysed descriptively and will be reported as frequencies and percentages with 95% CI fitted around point estimates. AEs will be tabulated by the sedative medications prescribed and will include the nature and incidence of each type of AEs and the management involved. Categorical variables will be compared using the chi-square test or Fisher exact test, as appropriate. Demographic and clinical (drug, dose etc.) variables will be examined for their association with the development of AEs using univariate analysis. Factors which are statistically significant (p≤0.1) will be entered into a regression model to isolate those which independently predict AEs. All analyses will be performed using IBM SPSS Statistics Version 20 (Armonk. NY: IBM Corp.).

9. **Data Security & Handling**

   a. **Details of Where Records Will Be Kept & How Long Will They Be Stored**
   The original copy of the CRFs will remain with the site investigators at the completion of the study and will be stored according to local institutional ethics committee's requirements i.e. locked cabinets in locked rooms when unattended. The CRFs will be stored for the required seven year period after which they will be shredded. All e-data and the study database will be erased after 7 years as well.

   b. **Confidentiality and Security**
   The nurse CRF will initially be identifiable (patient’s name attached). This is necessary in order to allow access to the correct medical record and completion of the medical record CRF. Once all data has been collected on an individual patient, a study ID number will be assigned to the patient and recorded on each page of both CRFs. The front page to the nurse CRF will then be removed and stored separately and securely. At this stage, both CRFs will be rendered re-identifiable. The CRFs will then be scanned and emailed to the lead investigators for uploading of the data into the study database. The lead investigators will not know the identities of any patient as only a study number will be attached to the CRFs and they will not have access to the front page of the nurse CRF.
Once the study database has been locked down, all hardcopy CRFs will be rendered non-identifiable by destruction of the nurse CRFs – the link between the study ID numbers and the patients’ identifies. All published data, reports and conference presentations will contain summary non-identifiable patient data only.

The electronic database and files will be password protected and accessible only to the investigators.

10. REFERENCES