

# ProMTED Study

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[Propofol for Migraine Treatment in Emergency Department]

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A pilot study, randomised controlled trial, to determine the length of stay in Emergency Department using IV Propofol versus Standard of Care Treatment for acute migraine patients

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**ABBREVIATIONS**

AE	Adverse event
CRF	Case Report Form
ED	Emergency Department
GABA	Gamma Aminobutyric Acid
GCS	Glasgow Coma Scale
HREC	Human Research Ethics Committee
IV	Intravenous
LOS	Length of stay
PICF	Patient Informed Consent Form
QoL	Quality of Life
SAE	Serious adverse event
SoC	Standard of care
SUSAR	Suspected unexpected serious adverse reaction
TGA	Therapeutic Goods Administration
VAS	Visual Analogue Scale

**Propofol for Migraine Treatment in Emergency Department Study Synopsis****Background**

Migraine is an exceedingly common, chronic and debilitating condition, affecting approximately three million Australians. Although, majority of the migraine patients successfully manage their symptoms and exacerbations at home with simple adjunct and medical management, presentations to the Emergency Department (ED) for treatment is common. The treatment of migraine in an ED setting can be challenging, as patients are usually refractory to home rescue therapy and the severity of symptoms worsen over time. The commonly used agents in an ED setting are chlorpromazine, prochlorperazine and sumatriptan, with variable success up to 70% efficacy in several studies.

A series of small studies and case reports have shown rapid relief of both chronic and acute migraine headache using Propofol, a lipid soluble short-acting intravenous anaesthetic. It has been postulated that the therapeutic effects of Propofol are due to its agonistic effects on the chloride channels of GABA receptors, in addition to its inhibition of afferent sympathetic action and cardiac baroreceptor reflexes. These case reports and studies on the off-label use of Propofol therapy for migraines in the ED shows a promising reduction in headache symptoms using a sedative dosing while reducing the ED length of stay and improving ED patient flows.

This study aims to determine whether the administration of intravenous (IV) Propofol at a procedural sedative dose (up to 1mg/kg) is associated with shorter length of stay compared to the standard therapy (IV Chlorpromazine or Prochlorperazine or Metoclopramide or SC Sumatriptan) for migraine relief, in an ED setting.

**Hypothesis**

Treatment of acute migraine requiring intravenous analgesia in an ED setting with the administration of IV Propofol results in shorter length of stay (LOS) in hospital (ED) than standard treatment.

**Primary objective**

- To test the feasibility of a multicentre trial to determine whether there is any difference in LOS in the ED following an IV Propofol regimen and a standard of care regimen, in the treatment of acute migraine headaches among adults presenting to an ED.

**Secondary objectives**

- To establish whether there is any difference in the safety and efficacy of an IV Propofol regimen and a standard of care regimen, in the treatment of acute migraine headaches in adults visiting ED.

**Study Design & Population**

This will be a single centre, unblinded, proof-of-concept randomized clinical trial. The study will enrol a total of 40 patients presenting to The Alfred Hospital with acute migraine headache:

1. Control Group: 20 patients will be treated with the Standard of Care (SoC) treatment (Phenothiazines or Triptans as per the treating clinician).
2. Test Group: 20 patients will undergo procedural sedation using IV Propofol at a dose of up to 1mg/kg.

**Inclusion & Exclusion Criteria****Inclusion criteria:**

1. Adult patients (age  $\geq$  18 to 65 years);
2. Diagnosis of Migraine by the treating clinician
3. Decision to commence intravenous therapy

**Exclusion criteria:**

1. Patients with fever, altered mental status or impairment of conscious state
2. Allergy to any of study drugs, eggs or soy products
3. Presence of abnormal neurological signs or suspicion of alternate diagnosis
4. History of head trauma
5. Failure to provide informed consent
6. Inability to mark a visual analogue pain scale (VAS)
7. Nursing home residents; and
8. Pregnancy

**Methods**

- All 40 patients will be randomised & enrolled into the study, after giving their informed consent, by the study investigators or designee after arrival to the Hospital's ED, as long as they meet all their inclusion criteria and none of the exclusion criteria.
- All enrolled patients will be requested to self-report their pain scores on a visual analogue scale (VAS) before and after treatment.
- Patient's baseline data, length of stay and adverse events will be collected from all enrolled patients.

**Primary outcome**

Mean Length of Stay in ED from start of treatment to treatment success (defined as relief of pain to the patient's satisfaction).

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# 1. Background & Rationale

## 1.1 Clinical & Biological Rationale

Migraine is an exceedingly common, chronic and debilitating condition, affecting approximately three million Australians, over 10 per cent of the total population [1]. The International Headache Society defines a migraine (without aura) as an idiopathic, recurring headache disorder manifesting in attacks lasting 4 to 72 hours. Typical characteristics are unilateral location, pulsating quality, moderate to severe intensity, aggravated by routine physical activity and association with nausea and/or photophobia and phonophobia [2]. Although, majority of the migraine patients successfully manage their symptoms and exacerbations at home with simple medical management or consult their general practitioners, a small but significant percentage of moderate-severe migraines present to the Emergency Department (ED) for treatment. Up to three per cent of emergency department visits have headache as their presenting complaint [3].

The treatment of migraine in patients presenting to the ED is more challenging than the treatment for a typical attack at home. This is because these patients are usually the non-responders to oral medications, with many of them having already tried at least one rescue medication without adequate relief [4-7]. The severity of the headache and its associated symptoms tends to increase over time, making it more difficult to treat as the condition prolongs [8, 9]. Typical duration of headaches at ED presentations is on the order of 24 to 72 hours in several migraine clinical trials [5, 10]. Furthermore, the frequent recurrent headaches can predispose patients to the misuse of pain relief medications.

### Pathophysiology of Migraine

The genesis of migraine headache and its pathophysiologic features are complex, and our understanding on the neurobiological mechanisms continues to evolve. According to Burstein et al., the network of neurons that sense pain signals from the dura changes over the course of a single migraine attack, and that the treatment is a moving target [11]. Current research suggests that the headache pain of migraine results from the activation of the trigeminovascular system [12-14]. Triggers thought to be chemicals, originating in the brain, blood vessel walls and the blood, activate the first phase of this system. These triggers stimulate the first set of neurons in the network, located in the trigeminal ganglion, causing pain and undergo molecular changes (release of vasoactive neuropeptides that act on mast cells, endothelial cells and platelets) that lead to hyperalgesia and hypersensitivity to intracranial pressure [14, 15]. This explains why migraine headache throbs and is worsened by bending over and sneezing.

If the pain is not stopped within the first two hours, the second phase of this system involves the sensitisation of second-order trigeminovascular neurons in the spinal trigeminal nucleus and the third-order neurons in the posterior thalamic nuclei, all receiving converging sensory inputs from meninges, scalp and facial skin [16]. The sensitisation of these neurons lead to the development of extracephalic allodynia, whereby the pain signals are generated independent of the sensory inputs from the first order neurons. During this phase, the patient notices brushing their hair, wearing earrings, taking a shower or touching their periorbital skin as painful, all manifestations of the central sensitisation resulting in cutaneous allodynia [11]. These points are important because a typical migraine patient presenting to the ED, is mostly likely to be in the second phase of the trigeminovascular system, having already tried their 'usual' medications with no relief.

Additionally, the complexity of the mechanisms involved in the genesis of migraine makes it likely to provide effective treatment, as the processes can be interrupted in several ways. As a result, several pharmacologic agents and their combinations have been studied as treatment for migraine relief.

### **Current Treatments for Acute Migraine in the ED Setting**

The most effective agents in an ED setting seem to be chlorpromazine, prochlorperazine and sumatriptan, each of which has achieved greater than 70% efficacy in several studies [17].

Chlorpromazine and prochlorperazine are phenothiazines, and are used mainly as antipsychotic drugs. Along with their main action as dopamine antagonist in the basal ganglia and limbic system, they have a multitude of other actions. These include antiemetic actions through their effect on the Chemoreceptor Trigger Zone (CTZ), and neuroleptic actions to alter the perception of pain. Additionally, chlorpromazine has a greater antagonistic action on  $\alpha$ -adrenergic receptors than prochlorperazine, and can lead to orthostatic hypotension. And they also have anticholinergic properties and have antagonists at both histamine and serotonin receptors [18]. The mechanism of action of these drugs in migraine is uncertain, and could well be attributed to a combination of actions: antiserotonin effect, antidopamine effect on CTZ, and the  $\alpha$ -adrenergic vascular effects [19].

During short-term use, some of the side effects of phenothiazines include dose dependent orthostatic hypotension, lowering of seizure threshold, dystonia, tremors and drowsiness. The reported success rates of chlorpromazine regimens in the treatment of migraine vary from 47% to 96% [19-23]. While, the reported success rates of prochlorperazine range from 67% to 92% [24-27]. In comparative trials, phenothiazines have been reported to be superior to sumatriptan [25, 28].

Sumatriptan is a specific and selective serotonin (5-HT)-1D subtype agonist and has no effects on other 5-HT receptor subtypes. The 1D receptors are specifically found in the cranial blood vessels and the action of triptans constricts the vessels that may be dilated during a migraine attack.

Due to the selective presence of presynaptic 5HT<sub>1D</sub> receptors on the central terminals of peripheral nociceptors in the dorsal horn, patients with cutaneous allodynia become highly resistant to triptan therapy with the progression of the attack [29, 30]. As a result, only third of patients are pain free at 2 hours after using a triptan, and a quarter of the migraineurs do not respond to triptans at all [31, 32]. Additionally, Sumatriptans are contraindicated in patients with a history of ischaemic heart disease and uncontrolled hypertension, pregnancy and in those using ergot preparations. Although, newer triptans such as rizatriptan benzoate and nasal spray version of sumatriptan have reported higher clinical success rates, their contraindications and the non-responsiveness to treatment for certain patient groups still poses a challenge in migraine relief.

Limitations of current treatment regimes result in prolonged length of stay for patients presenting with migraine in the ED. In addition, effectiveness of such treatment remains poor with up to a third of patients remaining in substantial pain on discharge.

### **Requirement for a clinical trial with IV Propofol**

A series of small studies and case reports have shown rapid relief of both chronic and acute migraine headache using Propofol, a lipid soluble short-acting intravenous anaesthetic [33-39]. It seems that the therapeutic effects of Propofol are due to its agonistic effects on the chloride

channels in the  $\beta_1$  subunit of GABA receptors, in addition to its inhibition of afferent sympathetic action and cardiac baroreceptor reflexes [35, 40, 41]. As a result, propofol's anaesthetic effects on the central nervous system may diminish the central sensitisation causing allodynia and hyperalgesia, attributing to its mechanism of pain relief in migraine patients [42].

The largest study was conducted by Krusz et al., they recruited 77 patients with refractory migraine and treated them with subanaesthetic doses of Propofol, with average reductions in patient-rated visual analogue pain scale was 95.4% after an average of 20 minutes following Propofol administration [35]. There were no adverse effects or outcomes related to Propofol use in these patients. The subanaesthetic dosage of Propofol in paediatric migraine headache has also shown low-dose Propofol as both safe and effective as an abortive treatment in the Paediatric ED [38]. Additionally, when Propofol has been safely administered at a sedative dosing, in migraine patients presenting to ED (in a case series) has shown rapid pain relief as well as a considerably reduced Length of Stay (LOS) in ED. The mean LOS at an urban academic ED for migraine patients was reported as 6.5 hours [SD 3.76 hours, 95% CI 6.16-6.84], obtained from a total of 465 migraine patients. The Propofol-administered patients reported in this series had an average LOS of 3.1 hours [SD 1.2 hours, 95% CI 1.92-4.28] and none of the patients had experienced apnoea, hypotension or other complications reported. [43]

Headaches are a common presenting complaint, but it is nevertheless a challenging task in an ED setting. Alleviating headache symptoms rapidly could have a positive effect on patient satisfaction and could improve ED patient flow. The safety profile in 1008 patients has been shown using Propofol for adult procedural sedation in a UK emergency department with no adverse outcomes [44]. Based on our literature review, there has only been one reported case of Propofol dependency in a layperson, and despite the abuse potential, no other data exists regarding this phenomenon [45].

Propofol is a short acting agent and can induce rapid swings in consciousness, unlike longer acting agents such as fentanyl and midazolam. Hence, Propofol is a suboptimal choice for minimal to moderate sedation in the ED given at subanaesthetic doses, because of the difficulties of staying within these specific ranges [46]. Therefore, this study will be using a sedative dosing of Propofol to address the greatest challenges of reducing the ED LOS while safely assessing and treating migraine patients, faced by emergency physicians today.

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## 1.2 Significance

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Based on the findings of Headache Australia and Allergan Survey from 435 migraineurs, "A Snapshot of the Impact of Migraine on Australians", 88 per cent of respondents surveyed said their headaches last over 4 hours, with 58% saying that it takes more than 24 hours to feel normal again, highlighting the impact of this common but debilitating condition. Migraine impacts the quality of life and activities of daily living in these patients, with 83 per cent having to miss going to work more than a few times a year and 21 per cent of the respondents to the survey said that migraine has prevented them from taking a full time job. As a result, migraine sufferers are twice as likely to have severe anxiety or depression, with 51 per cent of the respondents said they feel like little or nothing can help them and 39 per cent feel depressed. [47] Despite several treatment options for

migraine management, the condition contributes to a big portion of the burden of disease in Australia.

Given the limited understanding of migraine pathophysiology and the challenges with treating migraine patients in an ED setting, it is imperative that we investigate new treatments in patients refractory to their outpatient rescue therapy, with promise for rapid, safe and effective treatment. This study aims to determine whether the administration of IV Propofol at a procedural sedative dose (1mg/kg) is both safe and effective compared to the standard therapy (IV chlorpromazine or prochlorperazine or SC Sumatriptan) for migraine relief, in an ED setting. The above referenced case reports and series on the unconventional nature of the off-label use of Propofol therapy for migraines in the ED shows a promising reduction in headache symptoms using a sedative dosing while reducing the ED length of stay and improving ED patient flows. To the best of our knowledge, the ProMTED study is the first study in Australia to compare the length of stay outcome as well as the safety and effectiveness of the standard of care versus Propofol therapy in a randomised controlled trial. Finally, with adequate clinical evidence generated from this study and the experience, the treatment of refractory migraine headache with IV Propofol could potentially be adopted across Australia as a clinical guideline.

## 2. Aims & Objectives

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### 2.1 Research Question

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In patients presenting to the Emergency Department with headache presumed to be a “migraine” and requiring intravenous analgesia, is the administration of intravenous Propofol associated with shorter length of stay compared to that from standard of care treatment (Phenothiazines – Chlorpromazine or Prochlorperazine or Metoclopramide; or a Triptan)?

### 2.2 Aim

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To determine whether the administration of IV Propofol at a procedural sedative dose (up to 1 mg/kg) has a shorter length of stay as well as being safe and effective compared to the standard therapy (as per treating clinician) for migraine relief, in an ED setting.

### 2.3 Objectives

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#### Primary Objective

- To determine whether there is any difference in Length of Stay (LoS) in the ED following an IV Propofol regimen and a standard of care regimen, in the treatment of acute migraine headaches among adults presenting to an ED



## Secondary Objectives

- To establish whether there is any difference in safety and efficacy of an IV Propofol regimen and a standard of care regimen, in the treatment of acute migraine headaches in adults visiting ED

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## 2.4 Hypothesis

Treatment of acute migraine requiring intravenous analgesia in an ED setting with the administration of IV Propofol results in shorter length of stay in hospital (ED) than standard of care treatment.

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## 2.5 Primary Outcome

Mean Length of Stay in ED from start of treatment to treatment success (defined as relief of pain to the patient's satisfaction).

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# 3. Study Design & Methods

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## 3.1 Study Design

This will be a single-centre, randomised-controlled unblinded clinical trial. The study will enrol a total of 40 patients presenting to The Alfred Hospital with acute migraine headache:

1. **Control Group:** 20 patients will be treated with the Standard of Care (SoC) treatment (Phenothiazines or Triptans as per the treating clinician).
2. **Test Group:** 20 patients will undergo procedural sedation using IV Propofol at a dose of up to 1mg/kg.

All 40 patients will be enrolled into the study, after giving their informed consent, by the study investigators or designee after arrival to the Hospital's ED, as long as they meet all their inclusion criteria and none of the exclusion criteria.

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## 3.2 Inclusion & Exclusion Criteria

### ***Inclusion criteria:***

1. Adult patients (age  $\geq$  18 to 65 years);
2. Diagnosis of Migraine by the treating clinician
3. Decision to commence intravenous therapy

### ***Exclusion criteria:***

1. Patients with fever, altered mental status or impairment of conscious state
2. Allergy to any of study drugs, eggs or soy products
3. Presence of abnormal neurological signs or suspicion of alternate diagnosis
4. History of head trauma

5. Failure to provide informed consent
6. Inability to mark a visual analogue pain scale (VAS)
7. Nursing home residents; and
8. Pregnancy

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### 3.3 Co-enrolment & Competing Studies

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Co-enrolment of patients into other interventional (pharmacological agents or medical device) clinical trials is not permitted because of possible drug interactions that may confound the primary outcome of this study.

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### 3.4 Study Procedures

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#### 3.4.1 Assessment of Patient Eligibility & Enrolment

Upon arrival to the ED, the site investigator or designee will carry out the routine procedures of recording the patient's vital signs, taking a detailed history and performing a physical exam to ascertain the diagnosis of migraine. Migraine patients assessed as meeting the inclusion criteria, with no exclusion criteria, will be consented by site investigator or designee for the patient's participation in the study. Participants' competency will be assessed for providing free and voluntary consent. If deemed to be incompetent, the patient will not be qualified for the study, as a lack of competency will impede the participant's ability to accurately record their pain score on the Visual Analogue Scale (VAS). All consented patients will be required to fill out a baseline pain score on VAS prior to the administration of any treatment.

Patients may be administered with 1000ml of normal saline if the treating clinician is concerned about the patient's hydration level. All enrolled patients are randomised to receive either the test or the control treatment. Figure 1, illustrates a summary of study procedures.

#### 3.4.2 Randomisation & Drug Administration

Using a pseudo-random number generator and a 1:1 allocation ratio, all patients will be randomised to either test or control group. Study specific trial packs (ProMTED packs), containing an ampoule of Propofol or the SOC drug ampoule, will be randomised as per the computer-generated sequence. ProMTED packs will be colour coded (white packs for Propofol and green packs for SoC drug) and will be available in the ED containing the drugs, ProMTED sticker, baseline and post-treatment case report forms (CRFs) with VAS charts, and study instructions to facilitate the correct drug administration and study procedures at each of the time points. Each ProMTED pack has a unique study number imprinted on it, and will be used as the patient's unique identifier to protect patient's confidentiality. After the patient has been consented to the study, study enrolment is defined as the timepoint when the study investigator or designee opens the next consecutive ProMTED pack and completes the baseline CRF and VAS chart. Patients will be asked to indicate the level of their pain on a 10 cm non-hatched visual analogue pain scale, marked from "0" at one end to "10" at the other. Patients will be verbally instructed that "0" means "no pain" and "10" means the worst pain ever.

For patients randomised to the test group, the site investigator must follow the appropriate hospital protocols for procedural sedation and treat with up to 1mg/kg IV Propofol. Patients receiving Propofol therapy will be transferred to the resuscitation bay, placed on a cardiac monitor, provided supplemental oxygen by nasal cannula, end-tidal CO<sub>2</sub> monitor, with one:one nursing care during the sedation, as is standard practice for all procedural sedations performed in the emergency departments. **The start time for the LoS outcome for both test and control group patients, starts from the insertion of the intravenous line in the patient.** The drug will be administered as a slow infusion over 1 minute through a peripheral IV with a 10 mL syringe until the patient fell asleep without a rise in end-tidal CO<sub>2</sub> or a decrease in respiratory rate or oxygen saturation. The maximum dose of Propofol allowed is 1 mg/kg and will be stopped short if the desired effect is achieved with a smaller dose. The patients will be allowed to sleep until they wake up on his or her own. After the patient is arousable, and patient’s condition must be monitored and when stable and appropriate, the patient is requested to complete the post treatment VAS pain score.

For patients randomised to the control group, the recommended dosage in an ED setting [3] is as follows:

- Chlorpromazine: 25mg in 1000 mls normal saline IV over 30-60 mins (repeated if necessary), or
- Prochlorperazine 12.5mg IV,
- Metoclopramide 10mg IV or
- Sumitriptan 6mg SC

The post-treatment VAS pain score will be collected from control patients when the patients are stable and after half hour following the completion of drug administration. The VAS pain scores are repeated successively every half hour until treatment success, defined as relief of pain to the patient’s satisfaction. **The end time for the LoS outcome (in both test and control patients) is when the patient has achieved treatment success.** All other required data such as the triage waiting and discharge times and duration of sedation, dosage levels and any potential adverse events must be completed by the study investigator or a study-trained research coordinator in the appropriate CRFs found in the ProMTED packs. The ProMTED sticker is attached to patient’s progress notes (i.e. medical records) to indicate that the patient has been enrolled in the ProMTED study.

A master code corresponding to patient’s details including UR numbers and the study number will be stored in a password protected computer in a locked office at the hospital’s ED. At no point will any personnel external to the hospital study personnel will have access to this code or methods to identify the patients.

*Table 1: Data variables collected for the study*

Baseline	Post-treatment & Discharge
<ul style="list-style-type: none"> <li>• Initial Vital signs</li> <li>• Initial GCS score</li> <li>• Past Medical History</li> <li>• Medications History</li> <li>• Patient identifier(s)</li> <li>• Baseline demographics</li> <li>• Physical examination – photophobia/phonophobia/ neurological</li> </ul>	<ul style="list-style-type: none"> <li>• Vital signs</li> <li>• GCS score</li> <li>• Drug administration details: dosage, frequency, time of administration, route</li> <li>• Physical examination</li> <li>• VAS pain score(s)</li> <li>• Associated Symptoms</li> <li>• Adverse Events, SAEs, SUSARs</li> </ul>

<ul style="list-style-type: none"> <li>findings</li> <li>• Associated Symptoms including any prodromal symptoms</li> <li>• Migraine specific history</li> <li>• Time of ED presentation</li> <li>• Baseline VAS pain score</li> </ul>	<ul style="list-style-type: none"> <li>• Any prescriptions for outpatient use?</li> <li>• Length of Stay in ED</li> </ul>
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**3.4.5 Data Monitoring**

Prior to study commencement, a start-up meeting will be held at The Alfred Hospital ED for all participating study staff including nurses and/or research coordinators. During the study, the project manager will be source verifying the collected data on the paper CRFs with the hospital and patient charts (source data) to ensure the study is conducted in compliance to the clinical protocol, all applicable guidelines and regulations. The frequency of monitoring will be done at intervals of every ten patients enrolled.

A monitoring report will be prepared following each monitoring visit and reviewed by the management committee, which includes the site principal investigator, and filed in the site investigator file. Medical records, and other relevant source documents and the site investigator files must be made available to the monitor for these monitoring visits during the course of the study and at the completions of the study as needed.

**Aims of Monitoring Visits:**

- Check the accuracy of data collected by performing source data verification of the case report forms against the original source documents (hospital and patient charts/records)
- Check for protocol violations or deviations and report these to the chief investigator as necessary
- Confirm the consent procedures approved by the Alfred Health Human Ethics Committee have been followed and view each original signed consent form
- Check data security and access
- Review all SAEs and follow-up all reported SAEs
- Review investigator site files for completeness and accuracy
- Assist the study staff with any queries or problems they may have in relation to the study

**3.4.6 Protocol Deviations**

A protocol deviation is an unanticipated or unintentional departure from the expected conduct of an approved study that is not consistent with the current research protocol. A protocol deviation may be an omission, addition or change in any procedure described in the protocol. The possible protocol deviations to this study may be in the event when patient is unable to provide their VAS pain scores during or after treatment, and/or collection of follow-up information post discharge.

In the unlikely event that The Alfred Hospital is of the opinion that any aspect of the study protocol creates an immediate hazard to a trial patient, he or she may implement a deviation from or change to the protocol without prior approval from the Alfred Health Human Ethics Committee. The implemented deviation or change must be reported in a protocol deviation form and reported to the site principal investigator and Alfred Health Human Ethics Committee.

### 3.4.7 Statistical Considerations

#### Power Calculations & Sample Size

This study is a proof-of-concept, pilot study to test the feasibility of a multicenter randomized controlled trial. Therefore, it is not powered to detect a superiority of the IV Propofol for shortening ED LOS.

#### Analysis of Results

Within each treatment arm, data from both study sites will be grouped together for analysis, and study site will not be stratified or analysed as a covariate in statistical comparison between treatment groups.

For safety analysis, all adverse events will be summarised by each AE category. All adverse events reported during or after treatment will be summarised for both IV Propofol and SOC groups by body/organ system, and expressed as an incidence percentage.

All clinically relevant baseline variables will be tabulated. Categorical variables, including binary variables, will be reported by giving the number and percentage of patients in each category. Continuous variables will be reported by presenting the mean, standard deviation, median, minimum and maximum values for each. A comparability analysis of baseline variables between subjects in the test and control groups will be conducted. All baseline variables will be analysed as is, no imputation of missing data will be made. Nevertheless, missing data in the baseline variables are expected to be very limited.

## 4. Ethics

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### 4.1 Guiding Principles

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This study is to be performed in accordance with the ethical principles of the Declaration of Helsinki (June 1964 and amended 1975, 1983, 1989, 1996, 2000, 2008 and Note of Clarification 2002 and 2004), ICH GCP Notes for Guidance on Good Clinical Practice (CPMP/ICH/135/95) annotated with Therapeutic Goods Administration comments, NHMRC National Statement on Ethical Conduct in Research Involving Humans (March 2007)[49]; the New Zealand Interim Good Clinical Research Practice Guidelines (Volume 2 1998 and Volume 3 2000) and ICH GCP Notes for Guidance on Good Clinical Practice (CPMP/ICH/135/95).

### 4.2 Ethical Issues of the Study

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The ethical considerations in the study are:

- All enrolled patient must be fully competent to consent & understand study requirements
- Confidentiality of patient data

#### Informed Consent

As the study aims to recruit patients presenting to ED with acute migraine headache and with or without prodromal symptoms such as nausea and vomiting, it is important to ensure patients fully

understand the risks and benefits of the study along with the study requirements. The study investigators will assess whether the patients are competent and have the capacity to consent based on the patient's understanding of information and the ability to retain and communicate their decision of study participation. However, patients with severe headache pain complicated with prodromal symptoms might not be competent for consent. In these patients, the study investigators can try to alleviate the nausea and vomiting by administering normal saline and/or an antiemetic medication such as Ondansetron. These patients will be assessed for their capacity to consent for a second time after the successful treatment of their associated symptoms (prodromal), which may have precluded them from providing consent earlier.

It is important that all enrolled patients in this study are not just competent to consent to the study but also able to follow instructions when providing the study team with their pain score by accurately marking on the VAS. Therefore, the patients deemed to be incompetent would not be able to participate in this study, as this will risk the integrity of study results. The study team will not approach the patient's next of kin or legal surrogate for consent.

### **Confidentiality of patient data**

Study investigators or study-trained research coordinators will collect all patient data including during and after treatment, and follow-up information. Other than the study trained personnel at the participating hospitals, the patient detail will not be made available to anyone or anywhere, including publications and presentations.

The master code that links the patient UR numbers with study numbers will be stored in a password protected computer in a locked office at The Alfred E&TC. Once the follow-up data has been collected from all enrolled patients, the patients will be re-identified using the master code to combine the VAS pain scores with clinical data. At the end of all data collection, all patient identifiers will be destroyed and this data will be stored in a de-identifiable format for 7 years. No further use of this data is planned, and any further use of this data will require approval from the Alfred Health Human Ethics Committee. At no point will investigators external to Alfred Health have access to methods to identify patients. Any presentation or publication will involve summary data only and individual patient identification will not be possible.

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## **4.3 Ethics Committee Approval**

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This protocol along with other relevant study documentation will be submitted to only the Alfred Health Human Ethics Committee as part of the National Mutual Acceptance system for multi-centre clinical trials conducted in publicly funded health services. Approval of the protocol, plans for obtaining consent, and related documents will be obtained prior to the start of the study at The Alfred Hospital. It is the principal investigator's responsibility to ensure that all conditions for approval of the study are met and that amendments to the protocol or serious adverse events are also reported to the Alfred Health Human Ethics Committee as per their request.

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## 4.4 Confidentiality of Patient Data

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Upon enrolment to the study at the Hospital, patients will receive a study number. The Project Manager will compile a study enrolment log, which will link the study number to the patient name. All collected subsequent data will be identified by the study number. The enrolment log and study data will be kept separately. Follow up details of the patient and their family will be collected including name, address and contact telephone numbers. The contact details collected from patients enrolled at both sites will be used to perform the follow-up assessments. All data collected in the follow up assessment will be identified by the study code. The follow-up contact details and study data (paper CRFs - case report forms) will be kept separately, in a locked office at the EDs of both hospitals. The ProMTED study will not be entering any of the patient and study data into electronic database as part of data collection, instead manual paper CRFs will be used in the study for ease of use and efficiency, given the sample number of patients in the study.

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## 4.5 Informed Consent

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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. Patients with moderate to severe migraine headache with or without prodromal symptoms may not be able to provide informed consent.

The study investigators may try to use adjuvant therapies to treat the prodromal symptoms so that the patient is deemed competent to provide informed consent and undertake the study requirements. If patients are still incompetent and not able to provide consent, they will not be able to participate in this study and will receive the hospital's SOC therapy. No patient data will be collected from these patients.

## 5. Safety

The ProMTED study poses minimal risk to the study participants given the safety profile of Propofol administration in a variety of ED procedures requiring deep sedation, including fracture and dislocation reduction, incision and drainage of abscesses and cardioversion [50]. The following precautions will be taken in terms of technique and monitoring of patients administered with propofol:

- All patients in the test group must first undergo a standard pre-sedation assessment as per the hospital guidelines, including a review of absolute and relative contraindications to Propofol
- Reliable venous access should be in place for all procedural sedation
- As most complications of sedation are cardiorespiratory, doses of Propofol should be kept to the minimum required for patient comfort, particularly for those patients at increased risk
- Patients with depleted intravascular volume, such as those patients with dehydration (from vomiting), are a higher risk group for propofol-associated hypotension during sedation and should ideally have their volume optimised before the procedure.



- Monitoring of depth of sedation, typically by assessing the patient's response to verbal commands or stimulation must be routine as loss of response indicates the loss of airway reflexes, respiratory and/or cardiovascular depression are likely, and sedation should be lightened accordingly.
- All patients must be monitored continuously with pulse oximetry and this equipment must alarm when appropriate limits are transgressed. Additionally, there must be regular monitoring of pulse rate, oxygen saturation and blood pressure throughout the procedure.
- The procedure and the documentation must follow the requirements as indicated in ANZCA professional document PS18 and PSo6 – for 'Recommendations on monitoring during anaesthesia' and 'Recommendations on the recording of an episode of Anaesthesia care' respectively.
- Finally, all patients should be monitored until they have returned to their baseline mental status before discharge.

The administration of treatment to both test and control groups will be provided by experienced ED physicians and nurses. Potential adverse events associated with ED Propofol use include:

- Oversedation;
- Hypoxemia;
- Respiratory depression, including hypoventilation;
- Airway obstruction and apnoea;
- Respiratory arrest;
- Haemodynamic instability;
- Nausea; emesis;
- Pain with injection and unplanned admission as a result of adverse events encountered.

The frequency of AEs, such as hypoxemia, apnoea, airway obstruction, cardiovascular events and emesis, related to Propofol administration appear to be less than 5% of patient sedations [50]. These events have been readily addressed with brief interventions (e.g., supplemental oxygen, jaw thrust, assisted ventilation and IV fluid administration) and have not been characterised as requiring more extensive interventions or incurring serious patients sequelae.

The other study related procedure includes a phone call to the patients to ask about any recurrence of migraine headache, readmissions to ED and adverse events post discharge. In light of the minimal risks to patients versus the great potential benefits of pain relief from migraine headache with minimal length of stay in ED, the study investigators feel strongly that the ProMTED study of 40 patients does not warrant an independent Data & Safety Monitoring Committee.

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## 5.1 Adverse Events

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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 (adapted from the Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95 July 2000).



It is recognised that the patient population with migraine headaches will present with symptoms other than just headache, along with common aberrations in vital signs. These additional signs & symptoms will not necessarily constitute an adverse event unless they require significant intervention or are considered to be of concern according to the site principal investigator's clinical judgment. In all cases, the condition or disease underlying the symptom, sign or laboratory value should be reported e.g. renal failure rather than hyperkalaemia, and agitation rather than self-extubation.

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## 5.2 Serious Adverse Events

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Serious Adverse Events (SAE) is defined in accordance with the Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95) (July 2000) 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 that may require intervention to prevent one of the previously listed outcomes

A suspected unexpected serious adverse reaction (SUSAR) is an SAE that is not expected based on information that is currently available. Given that the safety profile of Propofol in ED use is well documented in literature, and all other case-series and reports of Propofol use in migraine patients reported no major safety concerns, we do not anticipate many, if any, SUSARs.

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## 5.3 Reporting

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SAEs and SUSARs should be reported within 24 hours of identification by telephone or email to the local principal investigator and the coordinating centre (The Alfred E&TC). However, consistent with the advice of Cook et al., adverse events already defined and reported as study outcomes (mortality, vascular occlusive events) will not be labeled and reported a second time as serious adverse events [51]. Any other reporting requirements mandated by the HREC, and relevant national and local authorities must also be followed. For SAEs and SUSARs, a preliminary telephone or e-mail report should be followed by a full report which includes copies of relevant hospital case records and other documents where applicable.

## 6. Study Funding

The ProMTED study is funded by the in-kind support from The Alfred Hospital's Emergency & Trauma Centre, for the purposes of drug administration, data collection, data analysis costs incurred as part of the study procedures.

## 7. Authorship & Publication

The study will be conducted in the name of “The ProMTED Study Investigators”. The Alfred Hospital’s Emergency & Trauma Centre will provide the central project coordination and data management. The principal publication from the study will be in the name of the ProMTED Investigators with full credit assigned to all collaborating investigators, research coordinators and institutions. Where an individual’s name is required for publication, it will be that of the writing committee, with the chair of the writing committee listed first and subsequent authors listed alphabetically. Funding bodies will be acknowledged in the publication.

## 8. Research Timelines

<b>Time frame indicators</b>	<b>Milestones</b>
<b>March 2016</b>	Protocol finalised Study organisation commenced The Alfred Health Human Ethics Committee submission
<b>April 2016</b>	Start up meeting
<b>May 2016</b>	Study recruitment commences at The Alfred Hospital
<b>September 2016</b>	Patient recruitment completed
<b>October 2016</b>	Query resolution and data cleaning completed Completed data analysis
<b>December 2016</b>	Submission of initial manuscript

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## APPENDIX A: Visual Analogue Scale (VAS)

OPTION 1

*Double-side print or photocopy the next two diagrams ensuring that the lines are exactly 10cm in length and superimposed*

*Laminate the VAS Bedside card for patient use*



**No pain**



**Worst pain  
ever**



10 9 8 7 6 5 4 3 2 1 0

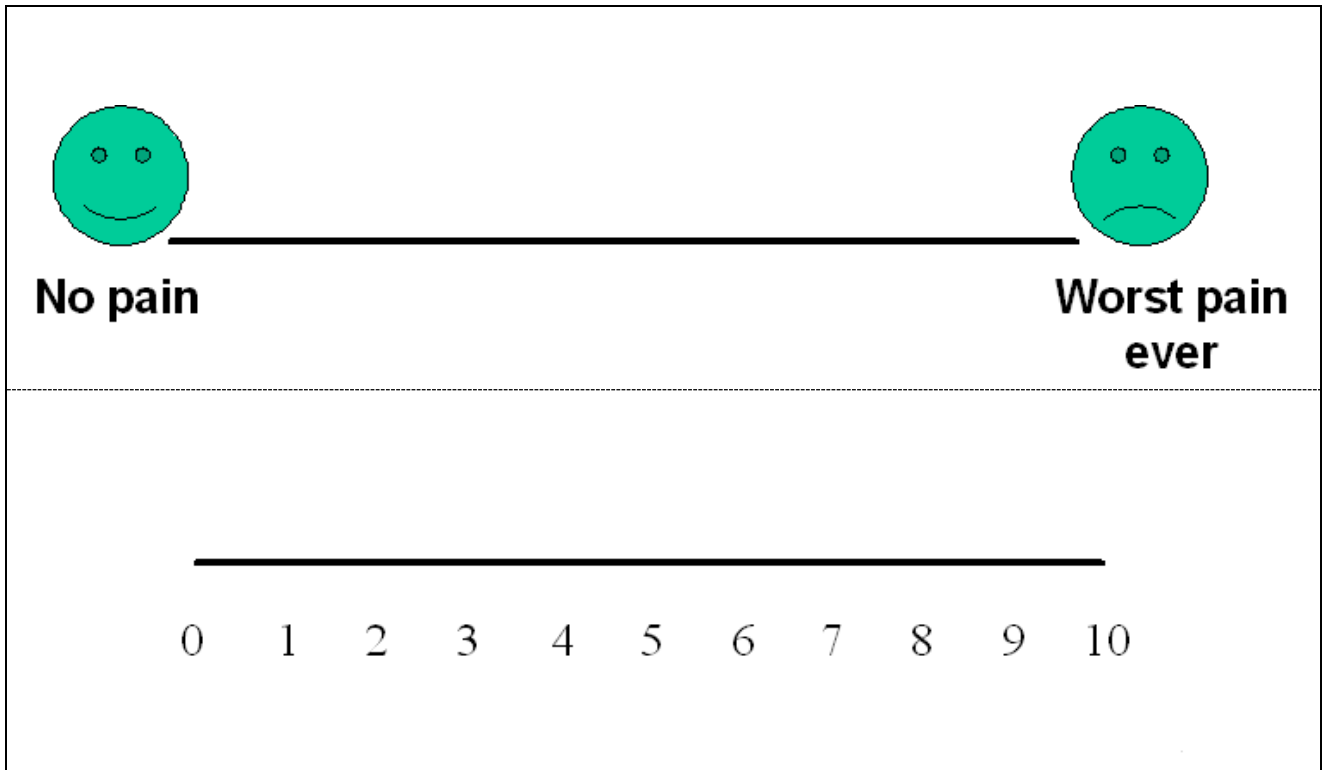
PLEASE NOTE: *For purposes of double-sided print, the numbers on this scale are reversed.*

OPTION 2

*Print or photocopy the next two diagrams on an A4 sheet ensuring that the lines are exactly 10cm in length*

*Fold at the dotted line*

*Do not show the patient the numbered scale*



## APPENDIX B: Table of Events

Study related Assessment/Procedures	ED admission	During Treatment	Post-tx or Discharge
Patient history, including presenting complaint, past medical & medications hx	X		
Vital signs, GCS, Physical exam, Associated Symptoms	X	X	X
Patient identifiers Baseline demographics	X		
Inclusion & exclusion criteria	X		
Patient Informed Consent	X		
Randomisation (1:1) to test vs. control arm	X		
Treatment administration (test or control)	X	X	
Treatment dose, frequency, duration of treatment,			
Protocol violations	X	X	X
Adverse Events, SAEs, SUSARs	X	X	X
VAS pain score – before & after treatment	X	X	X
Length of stay	X		X
Prescriptions for outpatient use			X
Assess withdrawal from study	X	X	X