KINDER

KETAMINE INTRANASALLY DELIVERED IN THE EMERGENCY ROOM

A multicentre randomised control trial of IN versus IV/IM ketamine for paediatric sedation in the Emergency Department. Is a totally needle-free approach feasible?

Study protocol version 2.0 (24/02/2016)

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Protocol version

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None of the investigators will receive any financial benefit stemming from the outcome of this trial. In particular, none of the investigators have any affiliation with or financial interest in any manufacturers or distributors of ketamine or any of the various mucosal atomiser devices presently available.

Trial registration

The KINDER trial is undergoing the registration process with the Australian and New Zealand Clinical Trials Registry. The outcome of this registration process and the registry number shall be communicated to the HREC when registration has been successful.

Sponsorship and funding

The KINDER study has been successful in obtaining funding through a QEMRF grant for the total sum of $63,015 (ex GST). This was offered during round 24 of QEMRF grants in 2015 and the QEMRF identifier for the grant is EMSS-234R24-2015-BURMAN

We are also seeking funding through a SERTA Grant application for a further $40 000 which has been submitted to The Townsville Hospital and Health Service Research Trust Fund Advisory committee with outcomes of this application expected to be released in late March 2016.

Milestones

	Start Date	Completion Date
Literature Review	24/06/2015	25/08/2015
Drafting of Protocol	21/08/2015	5/09/2015
QEMRF Funding Application	7/09/2015	7/12/15
SERTA FundingApplication	18/01/2016	Late March2016
Ethics/Governance Approvals	02/2016	04/2016
Staff Recruitment	Following Ethics Approval	To be completed by the commencement of the project
Protocol Training	April 2015	Ongoing until completion of study
Patient/Sample Recruitment	May 2016	January/February 2017
Patient Follow-Up/Data Collection	May 2016	March 2017
Data Entry	Ongoing throughout study	March 2017
Data Monitoring	Ongoing throughout study	March 2017
Data Analysis	April 2017	April 2017
Write Up	May 2017	May 2017
Publication	September 2017	
Presentations	April 2016	Continuing after publication

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Background

Sedation of children in the Emergency Department (ED) for either urgent therapeutic procedures that may be painful or which require a still and cooperative child (such as wound closure, abscess drainage, foreign body removal, lumbar puncture or fracture reduction) or to obtain critical diagnostic information (for example via medical imaging) is an important aspect of emergency medical practice for which a considerable and evolving body of evidence has developed over several decades[1]. Sedation and analgesia for painful procedures is certainly considered a standard of care that should be offered to all children undergoing painful procedures where possible[2]. While there are some published guidelines[3, 4] there is considerable variation in practice both locally and internationally in terms of choice of sedative agent and conduct of the procedure of sedation [1, 5, 6]. Most of the literature relates to parenteral routes of administration of sedative drugs, typically intravenous (IV) or intramuscular (IM) routes, due to the ability to titrate the dose and the reliability of drug effects when administered via these routes[1].

In this study we are looking to explore whether ketamine, an agent already in common use for procedural sedation of children via the IV and IM routes, can be feasibly administered via the intranasal (IN) route, an alternative and relatively novel parenteral route, at least in the ED, to provide many theorised benefits over IV/IM administration. Potential benefits include removal of the requirement to give a child a painful needle, decreased pain and anxiety, decreased time to effective analgesia, improved time to achievement of the intended therapeutic or diagnostic measures, greater patient, parental and physician satisfaction and improved emergency department logistics and patient flow. It is hypothesized that this could occur without a loss of sedative efficacy and without increased rates of adverse effects or increased overall ED length of stay (EDLOS).

Since the early 1990s, great effort has been made to improve the experience of children in the emergency department, especially in regards to painful procedures [7, 8]. Historical accounts of “brutacaine”, an ironic description of barbaric methods of holding children down to achieve compliance for painful procedures, would now seem fanciful if such practices were not actually common place and which, evidence suggests, still occur [9]. The concept of the “Ouchless ED” has arisen and has led to a host of measures, as part of a cultural shift in paediatric emergency care, that aim to reduce the pain that children experience in the ED, both through greater attention to earlier and more effective analgesia and through elimination or minimisation of pain that occurs as a result of medical intervention[10]. Pharmacologic measures include local anaesthetic agents and aggressive multimodal analgesia, as well as procedural sedation in place of physical restraint for painful procedures [8-10]. Non-pharmacologic measures include distraction techniques, needle-free wound closure techniques, reassurance, positive psychology, parental involvement in the procedures and lowering the child’s general level of arousal and fear by creating more child-friendly treatment spaces[8-10].

Recognition has been given to the extent to which a child, already rendered into suffering from their injury or illness, should be protected from further unnecessary iatrogenic pain and discomfort and also from the anxiety and distress that is due to anticipation of painful procedures that are to follow[7]. There is evidence to support “iatrogenic needlephobia” and pre-conditioning to anxiety caused by prior exposure (e.g. from childhood vaccinations or previous medical procedures)[10] as well as more significant long-term psychological sequelae that may arise from iatrogenic pain, such as increased rates of somatisation and post-traumatic stress disorder[8, 10]. Failure to address these issues may well contribute to needlephobia throughout life[11] which may have especially

significant implications for those children with chronic conditions who present most often for medical assistance and treatment.

As doctors we are bound by the principle of "First do no harm" and as such should actively embrace this humane approach to the treatment of children. While adequate analgesia and sedation for painful procedures, now commonplace in Australian EDs, is a vast improvement on "brutacaine", elements of "brutacaine" persist when a child is held down against his/her will for the purposes of intravenous cannulation or intramuscular injection as a means of delivering a sedative or analgesic dose. A recent study has highlighted this very issue of brutalised intravenous access as an ongoing concern[12] which rises as a new (or rather redefined) frontier in the battle for an "Ouchless ED".

Common efforts currently used to reduce the pain of paediatric cannulation include local anaesthetic creams to numb IV cannulation sites. The authors have observed several problems with this technique:

1. It takes 30-40 minutes for most of these preparations to work, meaning that IV cannulation occurs often longer than 1 hour after the decision to apply the cream
2. The cream is not always effective and is often wiped off by an active or distressed child despite attempts to contain the cream at the intended site
3. It is not always possible to identify the ideal sites to apply the cream
4. If the cream is ineffective then the cannulator must decide whether to wait for a further 30 minutes for another application of cream or cannulate despite inadequate or absent local anaesthesia
5. If the cannulator is delayed then the cream is removed meaning that the intended site may not be numb when the cannulator returns to cannulate the child
6. Children are highly distressed by the presence of the needle itself, by the tightly constricting tourniquet and by being held down for the procedure of cannulation even in the absence of pain from the needle
7. To cannulate a small child, typically at least 3 staff members are required to hold the child, assist with holding still the limb being cannulated, assist with passing equipment and with securing the cannula, as well as actually inserting the cannula. Clearly this is a highly labour intensive activity in the ED.

It can be seen that cannulating children who are already distressed may prolong the time until their painful condition receives appropriate treatment. Further, the process of cannulation may not always be pain-free even when local anaesthetic cream is applied. Even when children do not feel pain from the needle they are frequently highly distressed by the process. As such paediatric cannulation should only ever be used when absolutely necessary. IN ketamine may reduce or obviate the need to cannulate (IV) or use a needle (IM) for paediatric ED sedation.

It is in this context of humane treatment of children in the emergency department that the investigators wish to explore the intranasal route of sedative administration in the emergency department as a means of establishing a totally needle-free approach to paediatric emergency sedation. The agent considered most likely by the investigators to be efficacious via the intranasal route, have a satisfactory safety profile and be readily adopted by emergency physicians when used intranasally, is ketamine.

Ketamine is an optically inactive racemic mixture of equal quantities of 2 enantiomers, with the S(+)-ketamine enantiomer being the active enantiomer and twice as potent as the racemic form[13]. Non-racemic preparations of

ketamine are not available in Australia but are available in some European countries[13, 14]. All preparations of ketamine in Australia come in 100mg/mL concentrations in 2 mL ampoules[14]. Ketalar ® is the most commonly used preparation of ketamine in Australia and is the preparation available at all the proposed research sites. In terms of procedural sedation, ketamine (Ketalar ®) has an established TGA-listed indication as the sole anaesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation[15]. To improve the external validity of this practical study, we will therefore use the preparations already available in Australian EDs.

Ketamine has highly complex mechanisms of action with its principal effects primarily attributed to its role as an antagonist of the NMDA (N-methyl-D-aspartate) glutamate receptor[13]. For example, this action is largely responsible for the anaesthetic, amnestic and analgesic actions. Ketamine also has activity at opioid (mu, delta and kappa), monoaminergic, nicotinic and muscarinic receptors, amongst other less fully understood receptor activity[13]. Ketamine's emetogenic properties are inhibited by ondansetron implying a serotonergic effect as well[13]. It has activity at L-calcium channels, sodium channels (local anaesthetic effects) and potassium channels. These complex actions likely contribute to the primary effect and also may explain the spinal analgesic effects, the attenuation of chronic pain and the various psychic effects, as well as many of ketamine's side effects[13]. In non-catecholamine deplete patients, inihibition of norepinephrine uptake (either centrally or peripherally) at least partially explains the hyperadrenergic side-effects of the drug (such as elevations in heart rate and blood pressure) and also contributes to the analgesic and anaesthetic properties[13, 16]. Ketamine's most characteristic effect is a rather unique "dissociative anaesthesia" whereby dissociation between thalamo-neocortical and limbic systems results in sensory inputs reaching cortical receiving areas but failing to activate association areas, with obtundation of the reticular activation system[13]. Under ketamine anaesthesia, a patient's eyes are typically open and demonstrate nystagmus (sometimes even at sub-dissociative doses) and there is a variable amount of hypertonus and non-purposeful and occasional apparently purposeful movements[16]. Adequacy of sedation is judged by absence of purposeful movements in response to noxious stimuli[16].

Ketamine's history now extends back over 50 years, being first developed in 1962 amid efforts to identify an anaesthetic agent with analgesic properties and without the severe psychodisleptic effects or abuse potential of other cyclohexamine derivatives [13, 17]. Ketamine was first used in humans between 1965 to 1970 as a dissociative anaesthetic[17, 18]. Since that time ketamine has found widespread usage for multiple pharmacotherapeutic purposes not limited to its anaesthetic actions, which found particular utility in developing nations without advanced anaesthetics training or infrastructure[19-21]. These applications include analgesia and sub-anaesthetic sedation and anxiolysis [19] and more recently for multiple psychiatric indications[22]. Ketamine is frequently used as an agent in ED procedural sedation[1, 6, 23] and is increasingly becoming the agent of choice in induction of anaesthesia in critically ill and injured patients[24-26] due to its favourable haemodynamic profile, maintenance of spontaneous respiratory drive (where that is desirable) and neuroprotective properties in this setting. As an analgesic, ketamine has a well-established role in the perioperative and chronic pain settings [16, 27, 28] and is rapidly acquiring a profile in the management of acute pain, including in the ED and in the prehospital environment[29-32]. Ketamine is clearly still undergoing an expansion of therapeutic use both for novel and the more established indications. As such ketamine is an agent quite familiar to most emergency physicians who could therefore be expected to adopt intranasal administration in paediatric sedation if this practice were supported by evidence.

Within the paediatric population specifically, ketamine also has a history of both established and novel use. Ketamine is a well-established agent for use in paediatric sedation within the ED, especially in Australia, where ketamine is the preferred agent in tertiary paediatric EDs and large mixed EDs [6]. Ketamine is also increasingly used in children for analgesia, via either the IV or IN routes[33, 34].

Underlying the established and expanding use of ketamine, aside from its protean pharmacodynamics, is its very well-established safety profile. Ketamine is a well-studied drug having been studied in over 10000 patients in over 105 studies [35]. The relative safety of ketamine compared with alternative agents is an almost universal theme expressed within the literature across all indications, all patient groups, all routes of administration and in diverse settings from the operating theatres to the ED, the battlefield and the prehospital environment and in both developing and developed nations[3, 20, 27, 29-32, 34, 36-40]. Aspects of its clinical effects that contribute to its safety is the maintenance of airway protective reflexes even in deep sedation; maintenance of spontaneous ventilation with minimal, very rare or clinically insignificant hypoventilation; extremely rare apnoea; low rates of hypopnoea and very infrequent hypoxia; maintenance or slight increase in cardiac index with increase in rate pressure product of often over 100% and increases in blood pressure but minimal changes to systemic vascular resistance due to direct smooth muscle relaxation; maintenance of cerebral perfusion pressure during induction of anaesthesia or deep sedation. Further, ketamine is renowned for its wide therapeutic window[13, 16]. This is highlighted by a small series of 9 paediatric patients who received iatrogenic overdose of up to 100-fold doses of IV and IM ketamine with no serious clinical sequelae or long-term problem (2 patients required brief assisted ventilation and 2 patients were intubated as a precaution only)[41].

Considerable specific evidence regarding the safety of ketamine for paediatric sedation has been gathered from both randomised control trials and case series [7, 42-44]. In general serious adverse effects of ketamine when used for paediatric sedation are very rare and life-threatening adverse events are exceedingly so[7]. The safety even in extreme overdose as mentioned above is of particular relevance in the paediatric population where weight based dose miscalculations can occur. It is also of relevance to IN ketamine administration where the pharmacokinetics appear to be more variable than via IM or IV, leading to less predictable plasma levels [13, 45, 46].

The pharmacokinetics of ketamine are of particular relevance to the proposed study as the study is investigating a possible departure from the more commonly used parenteral routes of intravenous and intramuscular administration of sedative drugs in favour of the intranasal route. Ketamine is highly lipid soluble with low protein binding leading to an extensive volume of distribution of 2.3L/kg at steady state[13]. Bioavailabilities via intravenous, intramuscular, intranasal, rectal and oral routes are 100%, 93%, 50%, 25% and 20% respectively[13]. Peak plasma levels occur within 1 min via the IV route and within 5 min via the IM route[13]. Ketamine is metabolised to both active and inactive metabolites. The most studied and predominant active metabolite is norketamine which first appears in the blood 2-3 min after IV ketamine administration and reaches a peak at 30min[13]. While ketamine elimination clearance is high (equal to liver blood flow) with a elimination half-life of 2-3 hours, norketamine persists more than 5h after ketamine administration and it's pharmacologic effects, particularly analgesia, contributes to ketamine's ongoing effects during the elimination phase with analgesia significantly outlasting anaesthesia [13, 16], this being beneficial for ketamine's use in painful procedures. Termination of anaesthetic effect is due to redistribution from the brain to other tissues rather than from metabolic elimination[16].

The efficacy of IV and IM ketamine to achieve adequate sedation for paediatric procedures is well-established with figures ranging from 90-100% [7, 13, 16, 42, 47]. This compares very favourably with all other drugs considered for this purpose. Since ketamine was first used for paediatric sedation in the emergency department, there has been a convergence in agreed dose for IV and IM administration of 0.5-2.0mg/kg and 3-5mg/kg respectively, these doses achieving similar efficacy to higher doses used in earlier studies in the 1990s[7]. Consistent with our understanding of the wide therapeutic window of ketamine, a study of 1022 patients who received IM ketamine found no significant difference in efficacy, time to sedation, time to recovery, emesis or other complication between any dose groups[7, 44]. The duration of action of ketamine by the IV route, in terms of significant sedation requiring ongoing monitoring in hospital, is typically about 25 minutes[7, 43]. Via the IM route, recovery time to discharge-ready is significantly longer at 82-100 minutes [7, 44].

The IV and IM routes are therefore well-established in paediatric emergency sedation using ketamine. This is not true of the IN route, despite widespread use of IN ketamine outside the emergency department for sedation purposes. IN ketamine has reduced bioavailability (50%) compared with IV, with more variable but typically decreased rates of rise in plasma concentrations and an increased time to peak plasma concentrations, lower peak plasma concentrations, and more prolonged elimination compared with IV/IM administration [45, 46]. The doses required for IN administration are subsequently higher than for IV or IM administration to achieve the same level of sedation [13, 45, 46]. The investigators wish to assess whether these differences in pharmacokinetics will lead to practical differences in terms of adequacy or duration of sedation. While there is sparse direct literature evaluating IN ketamine for ED sedation, there is however an established and growing body of related literature describing the established and evolving utility of the IN route in general, the IN route for analgesia (both for fentanyl and ketamine) and the IN route for ketamine sedation outside of the emergency department. This literature is now summarised to provide a basis for the proposed study.

The intranasal route of drug administration has long been utilised as a rapidly accessed pain-free alternative to the IV route with comparable time to onset of central nervous system action due to the highly vascular nasal mucosa [48, 49]. In general higher drug doses are required to offset incomplete absorption from the nasal mucosa [13, 16, 33, 48, 49]. The advent of proprietary mucosal atomisation devices (MADs, such as the LMA® MAD Nasal™) has further simplified the intranasal administration of drugs. Compared to the droplet instillation method, MADs have multiple advantages including ease of use due to its compatibility with widely available Luer™ lock syringes, safe & effective delivery of volumes up to 1ml per nostril, smaller drug particle size of 30-100microns resulting in better bioavailability and higher patient satisfaction [48, 50]. The MAD are already in common usage in Australian EDs and will be used throughout the proposed study.

In fact, the intranasal route is already well-established in emergency paediatric analgesia, especially in Australia, with significant local experience with IN fentanyl approaching a standard of care. Multiple studies demonstrate safety and efficacy of intranasal fentanyl in the management of acute pain in children [51]. One study showed that intranasal fentanyl was rapidly bioavailable resulting in therapeutic serum levels within 2minutes of administration reflecting the rich vascularity of nasal mucosa and avoidance of hepatic first-pass metabolism[49] . Most of the studies on IN fentanyl have arisen in Australian EDs indicating that Australian researchers and practitioners are leading the world in expanding the application of the intranasal route of drug administration in children[51].

In addition to the local experience with fentanyl, Australian researchers have explored IN ketamine in paediatric analgesia and a recent randomized trial has shown intranasal ketamine to be comparable to intranasal fentanyl in the management of moderate to severe pain in children with limb injuries and was also shown to be safe and well-tolerated[33]. This complements the wider literature supporting IN ketamine for analgesia in both hospital and pre-hospital settings in adults and children [40, 52]. This established efficacy, safety and patient tolerance of IN ketamine for analgesia in children is germane to the proposed study where higher doses will be utilised to achieve dissociative sedation. Moreover, the growing familiarity of IN ketamine for analgesia in Australian EDs suggests that IN ketamine for sedation is a reasonable progression.

Of even greater pertinence is the very significant literature extending as far back as the early 1980s describing the efficacy and safety of IN ketamine for sedation in the operating theatres or dental clinics[13, 16, 19]. Multiple studies in the anaesthetic and dental literature have explored the pharmacokinetics, safety and efficacy of intranasal ketamine in children [45, 46, 53-67]. These studies have found that doses of less than 5mg/kg resulted in mild anxiolysis and good pain control with little effective sedation, 5-6mg/kg resulted in light sedation and 9-10mg/kg led to deeper sedation. The study by Aldrete et al found that titrated doses of intranasal ketamine resulted in successful sedation in 98% of cases [54]. A review of some of the aforementioned studies found that intranasal ketamine had a bioavailability of 50%, time to onset of action of 3.6-9.4min, peak effect at 18-20min, a time to recovery of 30-69min and doses of 3-9mg/kg resulted in no serious adverse events[68]. This data would suggest that IN ketamine at appropriately titrated doses of up to 10mg/kg should provide adequate sedation for painful procedures in the ED with rapid onset of action al and that the time to recovery is at least comparable to the times reported for IM ketamine sedation as cited earlier.

Given the proven safety profile of ketamine as a sedative across a very wide dose range and its established efficacy via the intranasal route, there is a surprising lack of studies exploring the emergency applications of paediatric intranasal ketamine sedation. We could find only one small ED study which had to be terminated early due to a high proportion of sedation failures but did find that a dose 9mg/kg of intranasal ketamine resulted in a higher proportion of successful sedations than 3mg/kg or 6mg/kg [69]. From this study and the aforementioned anaesthetic and dental studies, doses <9mg/kg may not achieve the level of sedation required for painful procedures such as fracture reduction but may remain appropriate for sedation for non-painful or minimally painful procedures.

The researchers believe that there is a sufficient evidence base supporting the proposed investigation of IN ketamine sedation in the ED at a dose of 5mg/kg for non-painful procedures and 10mg/kg for painful procedures. The proposed trial will evaluate these doses compared with standard doses of IV ketamine (1.0-2.0mg/kg) and IM ketamine (4-5mg/kg). 5mg/kg would be administered via sequential dosing of left and right nostrils with 2.5 mg/kg. Top up to 7.5-10mg/kg could occur with repeat administration of2.5mg/kg boluses at 5 min if sedation with 5mg/kg is found to be inadequate to initiate the given procedure. A requirement for >10mg/kg to initiate the procedure would be considered a failure of sedation via this route in this study and would typically require IV cannulation rather than top up IN doses, although for longer procedures that are successfully initiated at 10mg/kg, top up doses beyond a total of 10mg/kg would be considered appropriate.

This assessment of the literature would be consistent with the findings of the recent review article into intranasal ketamine sedation in the ED which concluded that the evolving evidence supported intranasal ketamine use for paediatric sedation[68].

In this study, because of the very high safety profile of ketamine via all routes and with its wide therapeutic index, IN sedation will not be followed mandatorily with intravenous cannulation unless there is an outstanding indication for IV cannulation, including likely operative disposition or need for venous access for phlebotomy or other therapies. As such, we expect that the entire sedation and the associated procedure will be performed without needing to gain IV access in nearly all cases. Urgent parenteral access for resuscitative purposes (either IV or IO) would be available during all administrations to provide safety for the extremely rare case of serious adverse events. Given the rapidity with which intraosseous access can be obtained in paediatric resuscitation and the utility of the intraosseous route for resuscitation and even RSI, the absence of a cannula in this patient group is felt to impose no significant added risk[70, 71]. The frequency at which IV cannulation was required for management of complications of sedation in the intranasal group is indeed an important evaluable outcome of this study.

If concern arises regarding sedation of children in the absence of IV access, attention can be directed to the wide literature and routine practice of oral sedation with less safe agents such as midazolam, chloral hydrate and inhalational sedation with nitrous oxide, all of which regularly occur in Australian emergency departments, operating theatres and other paediatric settings on a daily basis, almost always without IV access.

While the authors have considered alternative agents that might provide sedation via the intranasal route, including dexmedetomidine and midazolam, it is felt that these agents all suffer significant disadvantages in comparison with ketamine affecting their likely safety or efficacy or likelihood of adoption by Australian emergency physicians. Dexmedetomidine and midazolam are two such potential alternative paediatric intranasal sedative agents that have been examined in previous studies [66, 67, 72-74]. While dexmedetomidine shows promise as an IN sedative-analgesic agent, there is limited experience with dexmedetomidine in the emergency setting, not only in Australia but also internationally [65, 75, 76]. Nevertheless, if the IN route for sedation in children is established, dexmedetomidine may be an agent that will attract further research in the future. The lack of analgesic effect of midazolam requiring significant concomitant doses of opiate analgesia along with the well-established respiratory depression caused by midazolam which can be synergistic with opiate-mediated respiratory depression are significant draw backs in terms of the suitability of IN midazolam for use in the frequently painful procedures performed in the ED. The intranasal route was chosen over other needle-free routes like the oral route given the relative paucity of studies of oral ketamine, lack of clarity regarding and likely highly variable pharmacokinetics of oral ketamine and potential problems with a higher rate of reported vomiting and refusal to swallow oral medications [48, 77-80].

In summary, the proposed study is aligned with advances in a humane approach to care of children in the emergency department and is consistent with the recent trend of Australian research advancing the role of IN drug administration in the ED. The proposed study hopes to fill a surprising gap in the literature to explore the role of IN ketamine for paediatric emergency sedation. IN ketamine has not been adequately explored for paediatric sedation in the ED, despite significant associated literature suggesting that this is a feasible option with many possible benefits.

The novel approach is supported by:

- a long history of IN drug administration recently augmented with modern mucosal atomisation devices
- significant local experience and literature supporting IN fentanyl use in children, indicating familiarity of this route in the ED
- extensive literature describing IN ketamine for sedation and anxiolysis in the operating theatres and for painful dental procedures
- growing literature and experience with IN ketamine for analgesia in children and adults
- significant familiarity with ketamine for paediatric sedation in the ED via other routes
- the overwhelming safety of the medical use of ketamine
- significant literature advocating for "Ouchless ED" concepts

The benefits that may be achieved include:

- A needle-free approach to paediatric sedation
- Reduced pain associated with IV cannulation of children
- Reduced anxiety related to IV cannulation of children
- Reduced time to effective analgesia due to earlier performance of the therapeutic procedure
- Reduced time from identification of an injury requiring a painful procedure to completion of that procedure by obviating time-consuming IV cannulation
- Reduced short- and long-term psychological distress associated with IV cannulation
- Increased parental and child satisfaction with care
- Increased physician satisfaction with care

IM ketamine sedation is associated with a longer EDLOS compared to IV ketamine sedation but most literature suggests IM ketamine is not otherwise associated with an increased rate of adverse effects or post-sedation vomiting[7]. It is likely due to the more rapid pharmacokinetics of IN compared with IM ketamine, that both the onset of action and the duration of sedation via the IN route falls in between that of IV and IM. However, it is also possible that the more prolonged recovery of IN compared with IV may be offset by the decreased time from arrival in ED to performance of the procedure due to removal of the time- and resource-consuming procedure of paediatric cannulation. It is hypothesized therefore that the net EDLOS for IN administration of ketamine for sedation will be shorter than that of IM and no longer than that for IV. It is also possible that the intranasal administration of ketamine may not be as well-tolerated as we suspect due to nasal irritation or bad taste, although it is unlikely that it would be less tolerated than a needle approach. The impact, positive or negative, of IN ketamine on EDLOS and the tolerance of this route to children and their caregivers are secondary outcome measures to be evaluated in this study as practical factors affecting uptake of this novel route.

We postulate that if intranasal ketamine does turn out to be a safe, better tolerated and equally effective alternative to IV or IM ketamine sedation, it will be a shot in the arm for emergency physicians constantly endeavouring to minimize pain and distress to children needing diagnostic and therapeutic procedures in the emergency department.

KINDER - KETAMINE INTRANASALLY DELIVERERED IN THE EMERGENCY ROOM: A multicentre randomised control trial of IN versus IV/IM ketamine for paediatric sedation in the Emergency Department. Is a totally needle-free approach feasible?

Study aims

1. Investigate the feasibility of a novel needle-free approach to paediatric sedation in the emergency department
2. Investigate the scientific merit of IN ketamine sedation of children in the emergency department
3. Investigate the practical merit of IN ketamine sedation of children in the emergency department
4. Improve emergency paediatric sedation practices consistent with humane processes of paediatric emergency care
5. Establish a greater evidence base for the intranasal route of sedative drug administration in the emergency department

Study hypotheses

1. That IN ketamine sedation will not require significant rates of IV cannulation to safely complete the procedure where an IV cannula is not already considered essential for a patient's ongoing care
2. That IN ketamine (10mg/kg) will provide non-inferior sedation compared with IV ketamine (1.0-2.0mg/kg) and IM ketamine (4-5mg/kg)
3. That IN ketamine would be associated with higher parental/caregiver satisfaction with the overall procedure and general care in the emergency department
4. That IN ketamine would be associated with greater physician satisfaction with the overall performance of the sedation and the process required to ready the patient for sedation
5. That IN ketamine sedation will lead to earlier readiness for performance of the procedure or diagnostic intervention and hence earlier procedural completion
6. That IN ketamine sedation will not be associated with an overall increase in EDLOS
7. That IN ketamine sedation will not be associated with an increased rate of emesis, unpleasant psychomimetic effects or other adverse events

Trial design and setting

The trial will be a multisite open label randomised control trial of IV, IM, IN ketamine for paediatric sedation in the emergency department.

The trial will be conducted over 4 sites:

1. The Townsville Hospital Emergency Department, The Townsville Hospital Health Service, Townsville, Queensland
2. Bundaberg Hospital Emergency Department, Wide Bay Hospital and Health Service Emergency Department, Bundaberg, Queensland
3. Hervey Bay Hospital Emergency Department, Wide Bay Hospital and Health Service Emergency Department, Hervey Bay, Queensland
4. Redcliffe Hospital Emergency Department, Metro North Hospital and Health Service, Redcliffe, Queensland

KINDER - KETAMINE INTRANASALLY DELIVERERED IN THE EMERGENCY ROOM: A multicentre randomised control trial of IN versus IV/IM ketamine for paediatric sedation in the Emergency Department. Is a totally needle-free approach feasible?

Eligibility Criteria

Inclusion Criteria

1. Child of age >12 months and <11 years
2. Weight >10kg and <40kg; corresponding to 100-400mg IN ketamine
3. Considered by appropriately qualified senior treating clinician (FACEM or SMO) to have an indication for emergency department sedation

Exclusion Criteria

1. IV cannula already in situ at time of consideration for recruitment; or required for non-sedation indications prior to initiation of the sedation
2. Any previous adverse reaction or allergy to ketamine or other components of Ketalar®
3. Past history of significant cardiac disease, especially pulmonary hypertension
4. ASA > 1
5. Predicted difficult bag-mask ventilation or laryngoscopy
6. Critical illness
7. Severe trauma
8. Procedure better managed in operating theatre
9. Communicating hydrocephalus or other pre-existing condition predisposing to raised intracranial pressure (head injury is not an exclusion criteria unless meeting definition of major trauma)
10. Disease of the nose, significant coryza or nasal discharge, nasal obstruction or other condition preventing effective administration by the IN route

Outcomes

Primary

1. Sedation efficacy/adequacy for procedure

Secondary

1. Incidence of minor and serious adverse events
2. Parental/caregiver satisfaction with procedure
    a) At time of recovery
    b) At >48h post procedure

a. Physician satisfaction with sedation process including preparing patient for sedation and the process of obtaining parenteral access

3. Requirement for IV cannulation during IN sedation not otherwise required for expected clinical course. That is, requirement for cannulation to either manage complications of IN sedation or to achieve adequate sedation with IV top up ketamine doses. This will provide evidence of the proportion of paediatric emergency sedations that can be performed entirely needle-free.
4. Time from triage to procedure complete
5. EDLOS

Interventions

Recruited patients shall be randomised to one of 2 arms, Usual Care (U) or Intranasal (N). IV and IM have been combined into a single group for purposes of practicality in terms of ease of conduct of the study and the data analysis, and also given concerns about external validity, with requirement of the study to compare a needle-free approach to the current diversity of practice using needle-based approaches.

Usual Care IV/IM (U)

In keeping with this trial being a practical study of a novel needle-free approach versus the range of current needle-based approaches, for patients randomised to the U arm clinicians will be free to choose either IV or IM routes and will also be free to choose the dose of ketamine administered by either of these routes.

For the U group, no recommendations shall be made about the timing of administering the drug in relation to performance of the procedure. No recommendations will be made regarding when or how to obtain IV access if this route is chosen.

Recommendations regarding dosing shall be made but not mandated:

Intramuscular route chosen

Recommended dose: 4-5 mg/kg IM ketamine; given as single dose into anterolateral thigh as soon as treating clinician/s ready to initiate sedation/procedure.

Child needs to be adequately restrained to ensure correct intramuscular administration.

If this single initial IM dose remains ineffective to initiate the procedure at 15 minutes post administration, or if a prolonged procedure requires top up doses, an IV cannula should be placed and titrated further 0.25-0.5mg/kg doses of IV ketamine should be given to achieve adequate sedation.

Intravenous route chosen

Recommended dose: 1.0-2.0 mg/kg IV ketamine (total initial dose); given by slow IV push of titrated doses (e.g. 0.5mg/kg) over 1-2 minutes as soon as the treating clinician/s are ready to initiate sedation/procedure

If further or top up doses are required to achieve or maintain sedation, then it is recommended that this occur via 0.25-0.5mg/kg doses of IV ketamine

Intranasal (N)

IN ketamine 10mg/kg, should be given in a staged and titrated fashion as outlined below. Doses inconsistent with this protocol will be considered protocol violations.

1. 10 minutes before ready to initiate procedure:
   2.5mg/kg (0.025mL/kg Ketalar ®) right/left nostril via MAD
   AND
   2.5mg/kg (0.025mL/kg Ketalar ®) other nostril via MAD
   Total initial dose = 5mg/kg

2. Assess level of sedation after 2 minutes from initial dose (8 minutes before procedure expected to begin)

3. If initial 5mg/kg dose of sedation is considered insufficient to initiate procedure at this point, further IN doses can be titrated up to total initial load of 10mg/kg to achieve adequate dissociation/sedation to initiate procedure. Do this by alternating further doses of 2.5mg/kg between nostrils:
   2.5mg/kg (0.025mL/kg Ketalar ®) right/left nostril via MAD
   AND/OR
   2.5mg/kg (0.025mL/kg Ketalar ®) other nostril via MAD

If 10mg/kg is reached and sedation is still insufficient to allow initiation of procedure 15 minutes after the first intranasal dose was administered, this shall be considered failed IN sedation and an IV cannula should be placed to allow titrated 0.25-0.5mg/kg doses of IV ketamine to achieve adequate sedation. The incidence with which this occurs shall impact the needle-free outcome.

For a prolonged procedure after successful initiation, repeated IN doses of 2.5mg/kg can be given to alternating nostrils 5 to 10 minutely.

It should be emphasised that while it may take longer to titrate the dose via the IN route compared with the IV route, this can be performed by the sedationist while the proceduralist finalises readiness for the procedure. It is anticipated that this longer titration period, if it occurs, shall be offset by the time saved by obviating IV.

Post-intervention care

Following the sedation, the child shall be subject to full non-invasive monitoring (see safety section) in the resuscitation room until they are considered sufficiently recovered. Recovery shall be defined by the below modification of the Aldrete Score[81] with a score ≥ 7 required for discontinuation of non-invasive monitoring. As soon as this score is achieved, the patient requires no further period of monitoring unless there are specific concerns raised by the treating clinician. An example of such a specific concern might be severe distressing emergence phenomenon.

Figure 1. Modified Aldrete Score[81] will be used for determination of recovery sufficient to discontinue monitoring and for discharge to home or ward environment.

Activity
- Normally independently walking child: able to ambulate as normal for the patient - 2 points
- Child normally unable to walk: return to pre-sedation level of mobility (e.g. crawling) – 2 points
- Unsteady ambulation or activity slightly less than usual - 1 point
- Unable to ambulate/move - 0 points

Respiration
Must not have had episode of aspiration during sedation; aspiration mandates admission for observation +/- active management
- RR within limits for age, no hypoventilation - 2 points
- Hypoventilation, RR below normal range for age, SpO2<95% - 1 point, call for Doctor review
- Apnoeic - 0 points, not for discharge, call for assistance, immediate BLS measures

Circulation
- BP within normal range for age - 2 points
- BP slightly outside normal range for age - 1 point
- BP markedly abnormal - 0 points Call for Doctor review of patient

Consciousness
Given that many paediatric sedations take place in ED in the evening and often around or after a child's usual bed-time, a child (> 6 months of age) may be discharged asleep if more than 1 hour has elapsed since last IV sedative/narcotic, or >2 hours since last IM sedative/narcotic AND if the child is rousable with gentle stimulation.
- Fully awake (normal age appropriate verbalisation or interactivity, follows commands) - 2 points
- Rousable but unable to follow commands (if usually able) - 1 point
- Unresponsive - 0 points, not for discharge until rousable.

Colour
- Pink - 2 points
- Pale, blotchy - 1 point
- Cyanotic - 0 points, Not to be discharged, check respiratory status, apply O2, call for Doctor review

Total
Total score must be > 7 to allow conclusion of full non-invasive monitoring.

Patients are suitable for discharge to home or ward environments at this point also depending on completion of other aspects of care.

Other requirements for discharge:
- operative bleeding controlled
- no current vomiting
- pain controlled adequately
- an analgesic plan for home management of pain
- must have appropriate transport home arranged
- discharge advice given

A physician can decide to observe a child longer despite a score >7 although this would be infrequently necessary

The following will NOT be considered indicators of incomplete recovery requiring admission for observation:

1. Drowsiness or confusion when the child will still rouse to voice and obey commands appropriately
2. Mild ataxia when the child can be safely cared for despite this
3. Isolated or occasional vomiting

Patients otherwise meeting indications for discharge but showing any of these 3 signs can still be discharged with careful advice to the parents, caregivers or inpatient teams.

Discharge advice to be rendered to parents/caregivers or inpatient ward staff is detailed further in the section on safety.

Concomitant care

For both arms of the trial, supplemental analgesia should be given when pain is present with choice of agents, routes of admission and doses left to the discretion of the treating clinicians. For the IN arm, clinicians shall be encouraged to consider the IN route (e.g. IN fentanyl) over inserting an IV line solely for parenteral opiates when there is no other indication to place an IV. Provision of ondansetron and other anti-emetics will be left to the discretion of the treating clinician. Antisialogogues (such as atropine) should be available at the bedside and doses pre-calculated for all paediatric patients in this trial but use shall be at the discretion of the treating clinician.

Recruitment

Patients meeting the inclusion criteria presenting to the research sites will be identified by the treating emergency department clinician and their parents/caregivers approached for possible inclusion in the trial. A FACEM or SMO will confirm that there is an appropriate indication for ED procedural sedation. Demographic information including age, gender and primary injuries will be recorded by staff at baseline.

Patients will be recruited by emergency doctors working at the research sites who will receive education and coaching regarding the trial along with frequent reminders to consider recruiting eligible patients. No financial or material incentive to encourage recruitment will be offered to patients the parents/caregivers or clinicians.

Safety issues

The safety profile of ketamine is well-established, as described in the background above. The rate of Adverse Events (AEs) and Serious Adverse Events (SAEs) have been well documented for IV and IM sedation in the emergency department. The rate of adverse events via the IN route is less clear and this study will contribute to establishing literature around the safety of IN ketamine sedation in the emergency department. Given that the pharmacokinetics of IN ketamine are intermediate between that of the IM and IV routes of administration, the investigators believe that the rate of adverse events shall also be intermediate between these two groups. However, the current literature suggests that differences in adverse events are not marked between the IV and IM groups, apart from duration of action, and hence recovery time, being longer in the IM group and perhaps a slightly higher incidence of vomiting in the IM group. Therefore it is unlikely that IN ketamine will have significantly altered rate of

adverse events compared to the more established routes of administration, although the incidence of adverse events is an important outcome being investigated in this trial.

Figure 2. List of established side-effects and adverse effects of IV/IM ketamine for paediatric sedation [7, 23, 82, 83].

Side effect/Adverse event	Significance
Very common	
Random purposeless limb movements: 6.6-67%	Undistressing to the patient, considered benign
Nystagmus: 20%	Undistressing to the patient, considered benign
Reports of double vision or other transient visual disturbance during emergence >50%	Rarely distressing to the patient, considered benign
Common	
Emergence reactions: 0.9%-20.7%	Usually very well tolerated and undistressing in children
Hypersalivation 3.3-30%	Rarely significant enough to require treatment with antisialogogues. Extremely rare requirement for airway management due to profound salivation
Lacrimation: 12-25%	Undistressing to patient, not "tears" due to pain
Delayed vomiting: 6.6-20%;	most commonly reported as approximately 1/6 patients. More common with IM route. Usually related to moving the patient (e.g. driving home). Rarely refractory or troublesome
Ataxia: 6.7-15%	Child needs to be kept calm for 24 hours and prevented from engaging in risky physical activity; similar to advice provided following any anaesthetic
Elevations in heart rate and blood pressure >50%	Benign in children, well tolerated, duration of effect closely related to duration of dissociation
Occasional	
Distressing emergence reactions <6%	Usually very transient (<5 minutes) and not remembered. If severe or prolonged can be treated effectively with midazolam
Vivid dreams: 5.8 -13.2%	Can occasionally be nightmares
Transient facial rash/flushing: 1.9-10%	No clinical significance, spontaneously settles
Persistent pronounced drowsiness <5%	May require prolonged observation prior to discharge
Rare	
Transient mild hypoxia: 1.6-7.3%	Rarely requires intervention
Allergic reaction <1%	Severe reaction extremely rare
Very rare	
Transient apnoea: 0.1-0.8% (more common with IV route)	Of no clinical significance
Transient laryngospasm not requiring intervention 0.3-1.5%	Of no clinical significance
Vomiting during the period of sedation <1:1000	Aspiration extremely rare
Extremely rare	
Persistent laryngospasm requiring intervention <1:10 000	Specific management includes physical manoeuvres to relieve the laryngospasm, brief positive pressure ventilation to overcome the obstruction and very rarely administration of paralytics and intubation
Aspiration (case reports only)	No reports of serious sequelae
Requirement for advanced airway management or intubation <1:30 000 (case reports only)	Despite infrequency, resuscitation capabilities will be in place for this purpose

From **Figure 2** it can be seen that severe or life-threatening adverse events are very infrequent via the IV and IM routes and the rates of such are likely to be similar via the IN route. Nevertheless, multiple safeguards shall be in place to ensure that there is immediate and appropriate management of these extremely unlikely adverse effects.

At all sites, all patients eligible for the study will have their sedation performed in the resuscitation bay or other suitably equipped dedicated procedural area, unless clinical requirements strongly require an alternative location (e.g. sedation for CT).

The conduct of all instances of ketamine sedation in this study will be in accordance with the highest standards of emergency department sedation. These include:

1. A FACEM (Fellow of the Australasian College for Emergency Medicine) or Emergency Senior Medical Officer (SMO) will be responsible for selection of the patient for sedation and recruitment into the trial.
2. A FACEM/SMO shall be available to provide immediate oversight of the sedation at all times
3. The sedation shall occur in either a fully equipped resuscitation bay stocked with the full complement of paediatric resuscitative equipment and drugs, or alternatively, in a dedicated procedural room with full capacity to provide paediatric resuscitation.
4. Prior to sedation, a comprehensive safety assessment shall be performed which will include:
    a. Formal assessment for predicted difficult airway: LEMON
    b. Anaesthetic history including known difficult airway
    c. Sedation history of failed sedation or severely distressing emergence phenomenon
    d. Aspiration risk
    e. Hypoventilation risk
    f. ASA grade
    g. General contraindications to emergency department procedural sedation
    h. Specific contraindications to ketamine therapy
    i. Inclusion and exclusion criteria for this study
5. A detailed and thorough process of setting up for procedural sedation should occur, including:
    a. Ensuring that the sedation can be safely performed in light of the overall workload of the department
    b. Ensure all necessary staff are available and ready
    c. Ensure that the patient is in the appropriate area as above
    d. Readying all appropriately sized equipment required for managing a paediatric airway, including to intubation and surgical/percutaneous airway
    e. Consideration given to the positioning of the patient in anticipation of possible need for airway management with patient sedated in position appropriate for intubation if pain or behavioural issues or other clinical issues do not prevent this
    f. Consideration of the appropriateness of adjunctive medications, based on individual clinician preference tailored to the age of the patient
6. Equipment for urgent IV access should be set up next to the patient in the sedation area and an assessment of the ease of IV cannulation should be made in readiness for the unlikely event that an IV cannula would be

required. An IV cannula should only be inserted if required for urgent management of the complications of sedation, unless otherwise necessary for other aspects of the patient's care.

7. Intraosseous (IO) cannulae should be sized and pre-selected and at the bedside +/- EZIO ™ or other similar familiar proprietary device, with site of insertion pre-assessed, for availability should the requirement for parenteral access be immediate.
8. Access to IV fluids with a recommendation being for 20mL/kg of 0.9% NaCl to be decanted into a burette for IV administration of medicines (e.g. in the Usual Care arm) and fluid resuscitation as necessary.
9. A dedicated appropriately trained senior emergency Registered Nurse shall be present throughout the procedure from the preparation phase until the child is considered recovered. This nurse shall record all details of monitoring, medication administration, procedural events and timing and other data collected for the study during the sedation, as well as assist with fluid and or medication delivery.
10. Full continuous non-invasive monitoring shall be used throughout the procedure, as appropriate, and will include heart rate monitoring via electrocardiographic monitoring, respiratory rate monitoring via continuous wave form nasal end tidal CO_2 monitoring and via direct measurement or impedance, saturations via pulse oximetry, 5 minutely cycled non-invasively measured blood pressures
11. The doctor providing the sedation (sedationist) shall be either a FACEM, SMO or an emergency department registrar for whom direct observation and supervision by a FACEM or SMO is available.
12. The doctor or other individual performing the procedure (proceduralist) shall not be the same person as the doctor performing the sedation

There are no reports of delayed life-threatening events following discharge after ketamine sedation. However, as with advice rendered to other patient groups who have received sedation or anaesthesia, the Patient Information and Consent Form shall include a discharge recommendation to ensure avoidance of certain activities which may place a post-sedated patient at increased risk. In the paediatric population this amounts to advice to parents to observe children closely, prevent exposure to activities such as independently climbing stairs or other elevated structures, assistance or hand-holding crossing roads, avoidance of bike riding or skateboard riding or other physical activities requiring high level cognitive or psychomotor skills.

Consent

After a patient has been identified as suitable for recruitment, the treating clinician shall approach the patient and their parent/caregiver to invite them to participate in the study. Full written consent, as per the Parent Consent and Information Form will be required from the legal guardian prior to recruitment. Consent will entail an explanation of the project, its aims, hypotheses and process of randomisation. The adverse effects of ketamine shall be explained as well as an estimate regarding their frequency and severity and the relative likelihood based on the various routes of administration.

Modifications

Withdrawal from the trial can occur at any time at which a patient's legal guardian requests withdrawal. If a patient's legal guardian requests withdrawal from the trial, permission will be sought to continue to collect follow-up data including safety and satisfaction information. If this is declined than all study records pertaining to the patient will be destroyed.

Randomisation and blinding

Responsibility for randomisation

The clinician recruiting the patient will be responsible for performing the randomisation.

Sequence generation

Randomisation will be via computerised random number generator in a 1:1 allocation ratio, stratified to painful/non-painful procedure to ensure both U and N groups will be balanced in regards to this potential confounding variable. The randomised number will be used to label an envelope containing the allocation.

Allocation concealment

Once eligibility is confirmed and informed consent obtained; clinicians will open a sequentially numbered (randomised number) opaque envelope to reveal the patients allocated treatment group. Treating clinicians will be required to enter patient details onto the envelope prior to opening and obtaining the allocation.

Blinding

It will not be possible to blind the parents/caregivers, the patient or the treating clinicians or researchers from route of administration. As such this shall be an unblinded study.

Data collection methods and process

All study information will be recorded on purpose designed Case Report Forms (CRFs). Four CRFs have been created:

1. CRF 1 will be completed by the treating clinician at the time of the procedure. There shall be 2 versions of this form with one for each arm of the trial, the forms only differing upon one page. At randomisation, clinicians will be directed to take either a Usual Care CRF 1 or a IN Ketamine CRF 1.
2. CRF 2 will be completed by a member of the research team, usually between 48hours and 14 days post the procedurebut allowing up to 90 days to complete if multiple failed attempts to contact the participants' parent/caregiver have occurred.

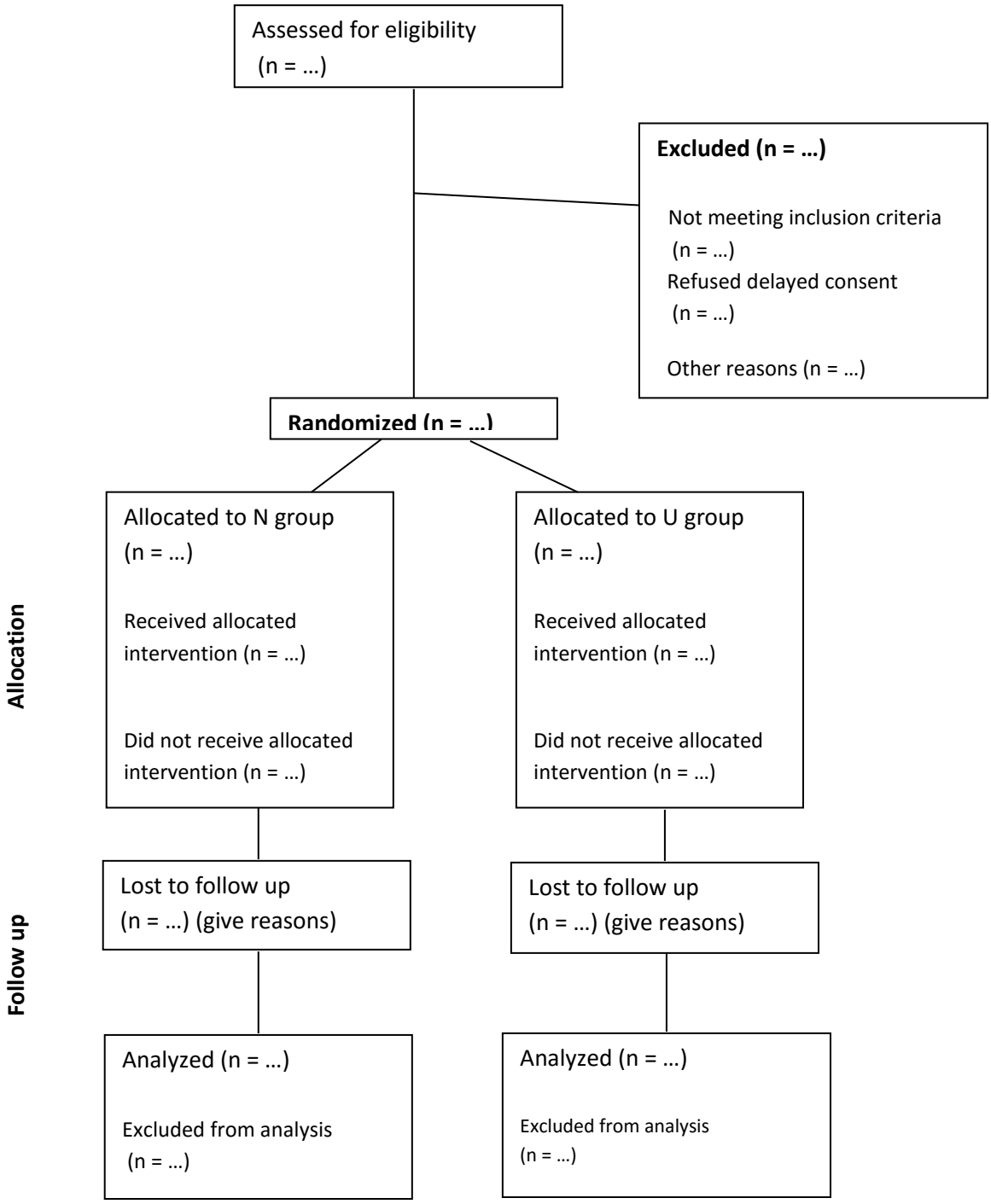
CRF 1 will be available in the ED in the study packs for completion during and immediately after the procedure. It will have a checkbox list for eligibility criteria. It will record basic demographic information such as patient age and date of birth, weight, and baseline details about the patient including American Society of Anaesthesiology classification for each study subject. It will also collect information about cannulation/needle insertion, number of attempts at insertion and reasons this was required. Patient observations, pain scores and details of the administration of ketamine and other drugs and any procedures conducted will be noted. CRF 1 will also incorporate the FLACC Scale score to capture patient comfort reflecting depth of patient sedation. It will contain the parent/guardian and clinician satisfaction surveys. Minor side effects will be recorded in this document and on a separate page serious

adverse events can be documented and detailed to provide a Serious Adverse Events and Adverse Events Case Report Form.

CRF 2 will be conducted by follow-up telephone call to the parent/care giver between 48 hours to two weeks after the procedure. One of the study team members will call the identified parent/caregiver within the specified timeframe. The nominated parent/caregiver will be asked to answer questions about the child's health since discharge (eg. delayed vomiting, bad dreams, persistent drowsiness, inability to return to school or normal activities, problems with balance). They will also be asked to provide an indication of their satisfaction with the procedure/sedation and their overall experience in the emergency department on a 5 point Likert-scale. The member of the research team completing the form shall also access the medical record to obtain and record details of triage time and Australasian Triage Score, discharge time, whether the sedation was for a painful procedure and a list of pre-hospital and inhospital medications given during the clinical episode.

A CONSORT diagram showing flow of participants through the trial is shown on the next page.

Figure 3.CONSORT diagram showing flow of participants through the SPECIAL-K trial.



Data points to be collected

In reference to the primary and secondary outcomes of the study, the points of data that shall be collected via the Case Report Forms pertaining directly to each stated study outcome are summarised below:

Primary outcome

1. Sedation efficacy/adequacy for procedure
   Efficacy of sedation will be defined as the proportion of patients for whom adequate sedation could be achieved within each arm of the study. For each subject, sedation will be considered adequate if both of the following occur:
   a) The depth of sedation was sufficient to allow the procedure to be completed
      AND
   b) The child did not display significant pain or discomfort as evidenced by FLACC score ≤ 3 throughout the procedure (see Figure 3)

   As such, both the adequacy to complete the procedure and 5 minutely FLACC scores shall be recorded throughout the sedation and procedure. The timing of painful stimuli shall also be recorded to correlate with the FLACC scores measured during the period of painful stimuli.

Figure 3 The Face, Legs, Activity, Cry, Consolability scale (FLACC scale) [84]

Behaviour	0 points	1 point	2 point
Face	No particular expression or smile; *vacant dissociated expression typical of ketamine**	Occasional grimace or frown, withdrawn, disinterested	Frequent to constant quivering chin, clenched jaw
Legs	Normal position or relaxed; *ketamine-induced myotonia**	Uneasy, restless, tense *(discern from ketamine-induced myotonia)**	Kicking or legs drawn up
Activity	Lying quietly, normal position, moves easily; *ketamine-induced myotonia**	Squirming, shifting, back and forth, tense Uneasy, restless, tense *(discern from ketamine-induced myotonia)**	Arched, rigid or jerking
Cry	No cry (awake or asleep)	Moans or whimpers; occasional complaint	Crying steadily, screams, sobs, frequent complaints
Consolability	Content, relaxed, *dissociated**	Reassured by touching, hugging or being talked to, distractible	Difficult to console or comfort

*Italicised additions to the FLACC Scale indicate expected findings specific to appropriate ketamine dissociation/sedation

The FLACC scale is an observed distress scale validated for use in children 2 months to 7 years (the target population of this study), in particular in relation to short duration or episodic pain such as that which might be required during emergency procedural sedation[84-86]. The score across each domain is totalled with maximum score being 10 and minimum being 0. The scoring is as follows:

0 No pain or discomfort
1-3 Mild pain or discomfort
4-7 Moderate pain or discomfort
8-10 Severe pain or discomfort

A score of ≤3 during the application of painful stimuli will be required for the sedation to be considered adequate.

Secondary outcomes

1. Incidence of minor and serious adverse events

A list (see below) of established side effects, minor adverse events and major adverse events shall be included in the CRF 1 and the treating physicians will be asked to check their occurrence.

Free space shall be provided to allow for recording of other unanticipated adverse events.

Side effects (BSEs) - considered benign

- Significant non-purposeful movements
- Nystagmus
- Visual disturbance
- Pleasant psychomimetic effects on emergence
- Hypersalivation not requiring significant intervention
- Vomiting during the period of sedation
- Transient laryngospasm not requiring intervention
- Minor elevations in HR
- Minor elevations in BP
- Persistent ataxia/balance effects

Minor Adverse Events (MAEs) – significant differences may impact adoption of IN route

- Unpleasant taste in mouth
- Burning in nose during IN drug administration
- Pain at cannula site or IM injection site
- Delayed vomiting after the period of sedation (not refractory or persistent or distressing)
- Delayed vomiting that is refractory or persistent or distressing
- Brief requirement for basic supportive airway manoeuvres or brief bag mask ventilation
- Severe agitation or distressing emergence requiring re-sedation or other complex management

Serious Adverse Events (SAEs) – significant differences likely to impact adoption of IN route

- Requirement for advanced airway management or intubation
- Prolonged apnoea requiring supported ventilation or advanced airway

- Other Requirement for prolonged basic supportive airway manoeuvres or prolonged bag mask ventilation
- Aspiration
- Persistent laryngospasm requiring intervention (nature of intervention specified)
- Other severe physiologic disturbance requiring resuscitative or urgent therapeutic intervention

2. Parental/caregiver satisfaction with procedure

At time of recovery

Using modified 5 point Likert scales, parents/caregivers will be asked to rate their:

- satisfaction with level of child's comfort
  - before the procedure
  - during the procedure (if present)
  - after recovery from the procedure
- Satisfaction with the level of sedation (if present for the sedation)
- Satisfaction with timeliness/expediency of the performance of the procedure
- Satisfaction with various aspects of the route of administration
  - Pain/discomfort due to the route of ketamine administration
  - Anxiety, discomfort or distress due to the route of ketamine administration
  - The child's apparent tolerance of the route of ketamine administration

At >48h post procedure

Using modified 5 point Likert scales, parents/caregivers will be asked to rate:

- Their overall satisfaction with the procedure and sedation and care provided
- The amount and severity of vomiting after discharge
- The presence of persistent drowsiness
- The presence of persistent ataxia/imbalance
- Pleasant vivid dreams
- Nightmares
- The ability of the child to return to school or normal activities after 24 hours

The occurrence of other adverse events post-discharge will also be sought from parents/caregivers.

3. Physician satisfaction with sedation process including preparing the patient for sedation and the process of obtaining parenteral access

Using modified 5 point Likert scales, physicians will be asked to rate:

- Level of sedation
- Sedation adequacy to efficiently complete procedure
- Satisfaction with route of administration (including process of obtaining IV access or administering IM or IN dose)
- Timeliness of procedure (delayed or appropriate)
- Willingness to use same route again for this indication

4. Requirement for IV cannulation during IN sedation not otherwise required for expected clinical course.

   Data points on IVC and ION will include:
   - Incidence of insertion of IVC, ION or both.
   - Indication for IVC or ION:
     - For IV route of sedative drug administration as part of randomisation to Usual Care (U)?
     - For inadequate IN sedation requiring top up IV ketamine?
     - For inadequate IM sedation requiring top up IV ketamine?
     - To manage complications following IN administration of ketamine?
       - Was this IVC/ION actually used to administer any therapy?
     - To manage complications following IM administration of ketamine?
       - Was this IVC/ION actually used to administer any therapy?
     - For indications unrelated to the sedation itself e.g. ongoing parenteral analgesia, antibiotics, IV fluid requirement?
5. Time from triage to procedure complete

   Data shall be obtained from various sources, as per the CRFs, to determine timing of procedure in relation to triage
6. EDLOS

   Overall EDLOS shall be determined from triage time to time discharged home or to an inpatient ward. Discharge to an emergency department short stay unit shall NOT be considered to terminate EDLOS for the purposes of this study as a sedation process that leads to increased occupation of short stay units would not be considered a positive outcome. It is not anticipated that many patients sedated via any route will require short stay admission if close attention is paid to evidence based criteria for discharge post-ketamine sedation, as defined above in post-intervention care.

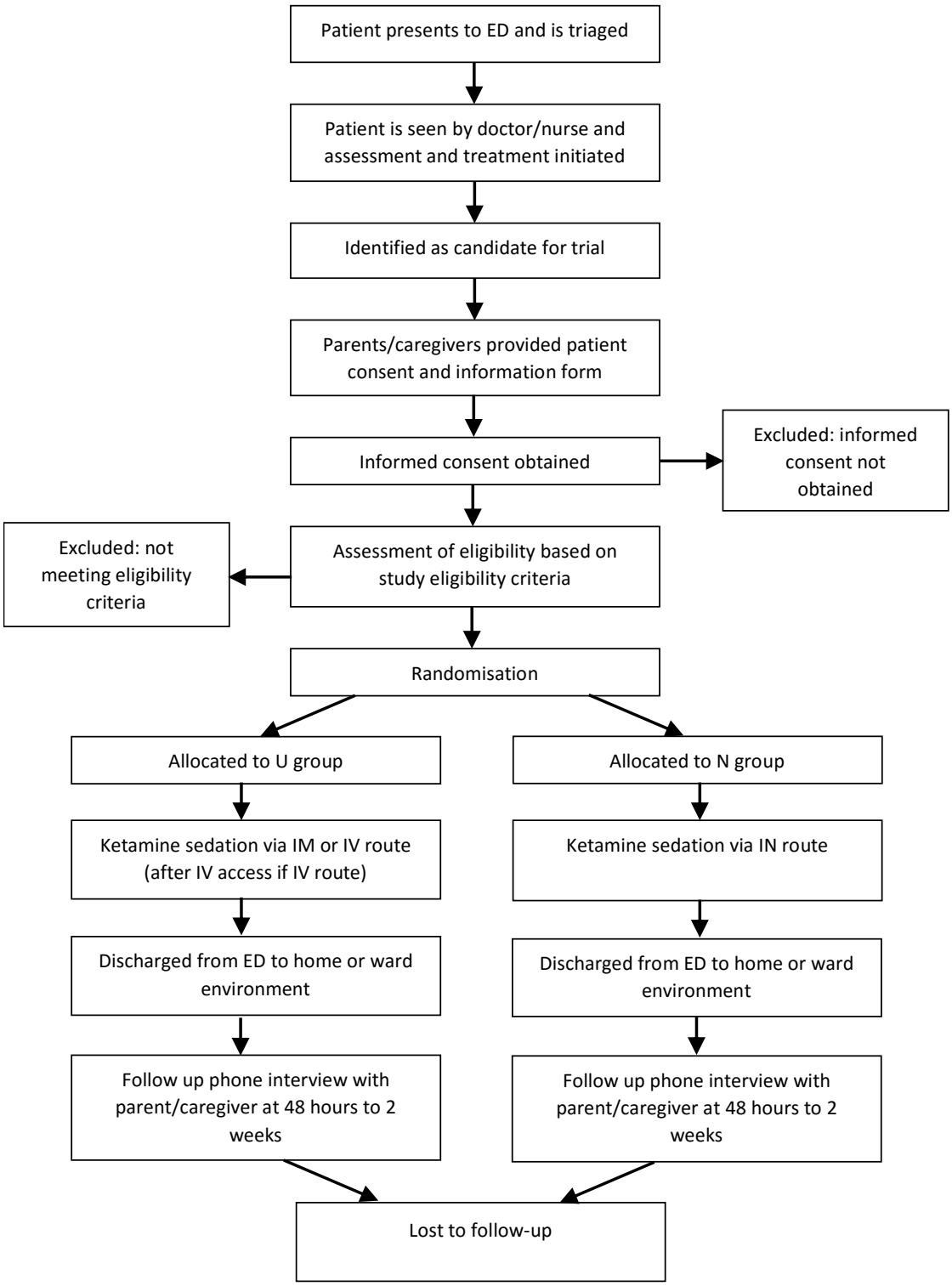
Other data points that shall be collected but which do not pertain directly to each of the stated study outcomes but which will affect analysis, including factors affecting similarity of the study groups (e.g. indication for procedure, baseline health characteristics etc), are contained in the CRFs.

Participant retention

The points of data collection occur at the time of sedation and in the immediate period thereafter and on only one further point at follow up following the sedation. As such participant retention is likely to be high.

Participant timeline

Figure 4 – Participant timeline



Data management

Data will initially be written on CRF 1 provided in the study packs. Completed study packs will be placed in a cardboard letter box designated for completed packs at each of the study sites. Research nurses at each of the study sites will be responsible for collecting these completed packs (weekly in Townsville and fortnightly at the other sites). Data from the study packs will then be entered electronically to a computer data base designed for the trial by each of the 4 study nurses. Further data not recorded in the study packs will be obtained from EDIS or ieMR electronic systems, or from phone interview of the caregivers and while this information will initially be recorded on CRF 2, it shall subsequently be entered into and stored on the secure study database. Original hard copies of materials will be stored in a secured location for a period of 5 years as required by institutional policy.

All forms of the data will be kept in a secure location. Access to this data will be restricted to the primary investigators. The electronic data will be password protected and these passwords will be changed regularly. A back up of the electronic data will be stored off-site in a secure location and retained for the post study period as required by institutional policy.

Data safety monitoring and periodic review

Data safety monitoring shall be conducted by the investigators with pre-defined periods of review at 3 and 6 months post-initiation of recruitment or at each 100 recruited subjects, whichever comes sooner. An external independent data monitoring committee is not considered necessary or practical for this project given that it is open label (meaning investigators will be able to observe developing patterns without unblinding data) and because the short duration of recruitment would mean that typical data monitoring committee processes are unlikely to lead to changes to the trial prior to completion of recruitment. [87] At each period of review, the data shall be analysed for clear evidence of inferiority of IN ketamine necessitating early termination of the trial, and performance of IN ketamine in terms of secondary outcome measures, in particular frequency of adverse effects and serious adverse effects (see section below **Reporting of AEs and SAEs**). Also assessed with each periodic review shall be frequency of protocol violations, performance of the multiple study sites and quality and safety of data capture and management.

Ethical considerations

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 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 and NHMRC National Statement on Ethical Conduct in Research involving humans (March 2007).

Potential risks and benefits to study participation

The main risk to the patients participating in this study is that this mode of delivery of ketamine has not commonly been used for ED sedation and its use is currently not supported by evidence. As such, neither the optimal dose nor the rate of adverse effects are known for ED sedation with IN ketamine. However, the evidence cited above describing the use of ketamine for sedation in dental and anaesthetic settings would indicate that IN ketamine sedation in the ED would not cause an increased rate of adverse effects. This is further supported by the pharmacokinetics of intranasal ketamine from which it would be expected that effects such as depth of sedation and

duration of anaesthesia will be intermediate between IN and IM routes and therefore unlikely to be significantly different from current usual practice. The authors feel that there is not likely to be an increased rate of adverse effects attributable to the IN route and this study will contribute to the literature supporting this. The absence of ED specific evidence with this promising route of sedative delivery underscores the rationale for this study.

Potential benefits to the participants are many. These include:

a) Possibility that no needle will be given to the patient at any time, if randomised to the IN group
b) Subsequent decreased pain and general distress caused by cannulation, if randomised to the IN group
c) More rapid readiness for a painful procedure in the IN group and subsequent reduction in time to effective analgesia achieved by earlier completion of pain-relieving procedures

Hospital Research and Ethics Committee approvals

This protocol will be submitted to a Human Research and Ethics Committee constituted as per the NHMRC National Statement on Ethical Conduct in Research involving humans (March 2007).

Given this is a multicentre trial, we have booked our trial for ethical review with the Queensland Health Central Coordinating System. This application has been allocated the HREC Reference Number: **HREC/15/QTHS/167**.

Following HREC approval, the investigators have a responsibility to ensure that:

a) all conditions for approval of the study are met
b) amendments to the protocol are approved by the HREC, and
c) serious adverse events are reported to the HREC as required by that committee.

Sample size calculations

The sample size calculation is based on the non-inferiority of IN Ketamine compared to standard treatment with regard to the binary outcome of procedural sedation adequacy, as defined above in section **Data points to be collected**. The non-inferiority design was favoured as it is thought that the delivery of procedural sedation using the IN route has significant advantages over the conventional routes to justify use if it is demonstrated to be non-inferior by the pre-specified margin. Existing literature suggests that the percentage of procedural sedation success in the Usual Care (U) arm will be within the range of 90-98%[7, 13, 16, 42, 47]. Using an estimate of 95% success in the usual care arm in our trial, a 5% margin of non-inferiority, with a one sided alpha of 5% and 90% power we would require 326 participants per group or 652 in total[88].

Calculations performed on:

https://www.sealedenvelope.com/power/binary-noninferior/ [89]

And confirmed using the formula

$$n= 2\pi(1-\pi)/\Delta^2 \times (Z_{1-\alpha} + Z_{1-\beta})^2$$

Where:

π = proportion with the outcome
Δ = smallest detriment which would still be clinically significant
n = number per group
(*Z* values using standard tables for alpha and beta)

Statistical methods for analysis of primary and secondary outcomes

Data will be entered into an Excel spreadsheet, access to which will be available only to study investigators. Data will be stored in a safe and secure location. Data will be analysed using SPSS 22.0. Continuous variables will be tested for normality. Based on the outcome of the test, parametric Student's T test or non-parametric Mann-Whitney test will be carried out to determine the differences in data. Categorical data will be analysed using the Chi-squared analysis. A p value < 0.05 will be considered statistically significant.

All data will be analysed on an intention to treat basis. Patients who withdraw or are lost to follow up will be regarded as treatment failures for data analysis purposes and analysed with imputed data.

Reporting of AEs and SAEs

The AEs and SAEs that will be recorded have been listed in the section **Data points to be collected**. Separate case report forms will be developed to record AEs and SAEs. AEs and SAEs should be reported on the source documents and CRF. SAEs should be reported to the Principal Investigator within 24 hours of the study staff becoming aware of the event. The principal investigator shall subsequently notify the HREC of all SAEs.

Authorship, dissemination and data sharing

The Principal Investigator, Dr Luke Burman, has been chiefly involved in developing this protocol, with contributions from Dr Vinay Gangathimmaiah and Dr Jeremy Furyk and detailed advice and recommendations from Dr Greg Treston and Dr Jeremy Furyk.

Following completion of data analysis and interpretation, the investigators will convene to discuss and assign authorship of the main study report. It is anticipated that application for publication to a reputable peer-reviewed journal shall be made by late 2017 for publication in early 2018.

De-identified complete data-sets will be available on direct request to the Principal Investigator from 3 years after study publication. All versions of the study protocol will be available through the Australian and New Zealand Trial Registry.

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