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A multi-site RCT comparing regional and general anaesthesia for effects on neurodevelopmental outcome and apnoea in infants

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The GAS study

Principal Investigators
Andrew Davidson
Department of Anaesthesia, Royal Children's Hospital
Flemington Road Parkville 3052 Victoria, AUSTRALIA
Tel: +61 3 9345 5233
Mobile +61 402 271 274
Fax +61 3 9345 6003
Email andrew.davidson@rch.org.au

Mary Ellen McCann
Department of Anesthesiology,
Perioperative and Pain Medicine,
Children's Hospital Boston,
300 Longwood Avenue,
Boston, MA 02115-5737
Tel: 0011-1- 617-355-7737
Fax: 0011-1-617-730-0894
Email: Mary.McCann@childrens.harvard.edu

Chief Investigator for UK sites only
Neil S. Morton
Department of Anaesthesia
Royal Hospital for Sick Children
Glasgow G3 8SJ
Tel: 0141-201-0186
Fax: 0141-201-0186
Email: neilmorton@nhs.net

Co-sponsors for UK sites only: NHS Greater Glasgow & Clyde & University of Glasgow
Contact details: Dr Melissa McBride
R&D Directorate
NHS Greater Glasgow & Clyde
1st Floor Tennent Institute
38 Church Street
Glasgow G11 6NT
01412118548
Melissa.mcbride@ggc.scot.nhs.uk

UK Trial protocol version 1.2 date: 23 May 2009

INVESTIGATORS

(PI/chair first then alphabetical order)

Chief Investigators

Dr Andrew Davidson (PI),
A/Prof Mary Ellen McCann (PI),
Professor Charles Berde,
Dr Geoff Frawley,
Ms Pollyanna Hardy,
Dr Rod Hunt,
Dr Neil Morton,
Dr Robyn Stargatt,
Professor Andy Wolf

Associate investigators

Professor Vicki Anderson,
Professor David Bellinger,
Professor John Carlin,
Mr Tom Clarnette,
Professor Lex Doyle,
A/Prof Kate Leslie,
A/Prof Sulpicio Soriano,
Dr Suellen Walker

Site investigators- Australia
Dr Andrew Davidson- Royal Children's Hospital- Melbourne
Dr David Costi- Women's and Children's Hospital- Adelaide
Dr Mark Faigman- Department of Anaesthesia- Monash Medical Centre
Dr Philip Stephens- Mater Children's Hospital- Brisbane
Dr Thomas Mohler- Royal Hobart Hospital- Hobart
Dr Bruce Hullet- Princess Margaret Hospital- Perth

Site investigators- NZ, US and UK
Dr Niall Wilton- Starship Children's Health- Auckland
A/Prof Mary Ellen McCann- Children's Hospital Boston- Boston
Dr Neil Morton- Royal Hospital for Sick Children- Glasgow
Dr Peter Stoddart- Bristol Royal Hospital for Children- Bristol
Dr Anthony Chisakuta- Royal Belfast Hospital for Sick Children- Belfast
Dr Oliver Bagshaw- Birmingham Children's Hospital- Birmingham
Dr Annette Davis, Royal Liverpool Children's Hospital Alder Hey, Liverpool
Dr Ayman Eissa, Sheffield Children's Hospital, Sheffield
Dr Isabelle Murat- Hopital d'enfants Armand Trousseau- Paris

Project officer, Melbourne:
Ms Suzette Sheppard
Data management coordinator, Melbourne:
Ms Suzanna Vidmar

PROPOSED STUDY SITES

Australia & New Zealand

Department of Anaesthesia,
Flemington Road,
Royal Children's Hospital,
Parkville, VIC 3052 AUSTRALIA
Ph: + 61 3 9345 5233

Department of Anaesthesia,
Monash Medical Centre,
246 Clayton Road,
Clayton VIC 3168 AUSTRALIA
Ph: + 61 3 9594 3283

Royal Hobart Hospital
Liverpool Street,
Hobart TAS 7000 AUSTRALIA
Ph: + 61 3 6222 8567

Department of Paediatric Anaesthesia
Adelaide Women's and Children's Hospital
72 King William Road,
North Adelaide, SA 5006 AUSTRALIA
Ph: + 61 8 8161 7231

Department of Anaesthesia
Princess Margaret Hospital for Children
Roberts Road,
Subiaco, WA 6008 AUSTRALIA
Ph: + 61 3 8 9340 8222

Department of Paediatric Anaesthesia,
Mater Children's Hospital,
Raymond Terrace
South Brisbane, QLD 4101 AUSTRALIA
Ph: + 61 7 3840 2869

Starship Children's Health,
Private Bag 92024,
Auckland, New Zealand
Ph: +64 9 3074949

USA
Department of Anesthesiology,
Perioperative and Pain Medicine,
Children's Hospital Boston,
300 Longwood Avenue,
Boston, MA 02115-5737
Ph: +1 617 355 7737

Children's Memorial Hospital, Chicago
2300 Children's Plaza
Chicago IL 60614-3394
Ph +1 773 880 4414

Department of Anesthesia, Yale University
333 Cedar St
New Haven CT 06510-8051
Ph +1 203 785 2802

Department of Anesthesia, The George Washington University Medical Center
111 Michigan Ave
NW Washington DC 20010-2970
Ph +1 202 884 2025

Massachusetts General Hospital
55 Fruit Street,
Boston, MA 02114
Ph: +1 617 726 2000

University of Massachusetts
100 Morrissey Blvd.
Boston, MA 02125-3393
Ph: +1 617 287 5000

Tufts University School of Medicine, Boston, MA
136 Harrison Avenue,
Boston, Massachusetts 02111
Ph: +1 617 636 7000

UK & France

Bristol Royal Hospital for Children,
Upper Maudlin Street,
Bristol BS2 8BJ, UK
Ph: +44 117 342 8460

Department of Anaesthetics
Royal Belfast Hospital for Sick Children
Falls Road
Belfast BT12 6BE

Department of Anaesthesia
Royal Hospital for Sick Children
Yorkhill
Glasgow G3 8SJ
Ph: +44 138 983 0402

Department of Anaesthesia
Sheffield Children's Hospital
Western Bank
Sheffield S10 2TS

Department of Anaesthesia,
Birmingham Children's Hospital,
NHS Trust,
Steelhouse Lane B4 6NH
Ph: +44 121 333 9623

Department of Anaesthesia
Royal Liverpool Children's Hospital
Alder Hey
Eaton Road
Liverpool L12 2APS

Service d'Anesthesie-Reanimation
Hopital d'enfants Armand Trousseau
26 av du Dr Arnold Netter
75571 Paris Cedex 12
Ph: +33 144736299

Trial Steering Committee

Chair: Prof Paul Myles, Anaesthetist, Alfred Hospital, Melbourne
Prof David Bellinger, Psychologist, Boston Children's Hospital, Boston USA
Prof Charles Berde, Paediatric Anaesthetist, Boston Children's Hospital, Boston USA
Prof John Carlin, Statistician, Murdoch Children's Research Institute, Melbourne
Dr Andrew Davidson (PI), Paediatric Anaesthetist, Royal Children's Hospital, Melbourne
Dr Rod Hunt, Neonatologist, Royal Children's Hospital, Melbourne
A/Prof Kate Leslie, Anaesthetist, Royal Melbourne Hospital, Melbourne
A/Prof Mary Ellen McCann (PI), Paediatric Anaesthetist, Boston Children's Hospital, Boston USA
Prof Neil McIntosh, Neonatologist, Edinburgh, UK
Prof Andy Wolf, Paediatric Anaesthetist, Bristol, UK
Dr Neil Morton, Paediatric Anaesthetist, Glasgow, UK

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ABBREVIATIONS

GAS study – The acronym for the study

AE: Non serious adverse events
BCH: Boston Children's Hospital, Boston
BRIEF: Behavioural rating of executive function
BSID-III: Bayley scales of infant development, version III
CPAP: Continuous positive airway pressure
CRF: Case report form
CSF: Cerebrospinal fluid
DMC: Data monitoring committee
ECG: Electrocardiograph
ESPY: Experimental Delayed Alternation and Spatial Reversal Tasks
FLACC: Behavioural scale for scoring postoperative pain in young children measured in 5 areas: **f**ace, **l**egs, **a**ctivity, **c**ry, **c**onsolability
GA: General anaesthesia
GABA: Gamma amino butyric acid
HR: Heart rate
IV: Intra venous
IVH: Intra ventricular haemorrhage
NDNMB: Non-depolarizing neuromuscular blocking agent
NEPSY: Developmental neuropsychological assessment
NIBP: Non invasive blood pressure
NICU: Neonatal Intensive Care Unit or Neonatal unit
NMDA: n-methyl-d-aspartic acid
PACU: Post anaesthesia care unit – also known as the recovery ward
PI: Principal investigator
PMA: Postmenstrual age (see appendix one)
PVL: Peri ventricular leukomalacia
RA: Regional anaesthesia
RCH: Royal Children's Hospital, Melbourne
ROP: Retinopathy of prematurity
SAE: Serious adverse events
SAR: Serious adverse reaction
SUSAR: Suspected unexpected serious adverse events
TSC: Trial steering committee
UTI: Urinary tract infection
WPPSI-III: Wechsler preschool and primary scale of intelligence- Third Edition

SYNOPSIS

Title: A multi-site RCT comparing regional and general anaesthesia for effects on neurodevelopmental outcome and apnoea in infants

Chief investigators: Andrew Davidson (PI), Mary Ellen McCann(PI), Charles Berde, Geoff Frawley, Pollyanna Hardy, Rod Hunt, Neil Morton, Robyn Stargatt, Andy Wolf

Objectives: The primary objective of this trial is to determine whether different types of anaesthesia [regional versus general] given to infants undergoing inguinal hernia repair result in equivalent neurodevelopmental outcomes. Secondary objectives are to describe the frequency and characteristics of apnoea in the post-operative period after both regional and general anaesthesia for inguinal hernia repair in infants, and determine the factors associated with apnoea.

Study population: 660 infants of postmenstrual age 60 weeks age or less, scheduled for inguinal hernia repair under anaesthesia. Exclusion criteria include recognised risk factors for adverse neurodevelopmental outcome or previous exposure to general anaesthesia. Infants born at less than 26 weeks gestation will be excluded.

Design: Prospective, observer blind, multi-site, randomised, controlled, equivalence trial.

Treatment groups: The general anaesthesia group will receive sevoflurane for maintenance and induction. The airway can be maintained with a face mask, laryngeal mask or endotracheal tube, with or without neuromuscular blocking agents. Analgesia can be supplied with a caudal or ilioinguinal nerve block with bupivacaine or levobupivacaine up to a maximum dose of 2.5 mg/kg.

The regional group will have no sedative agents. The regional blockade may be with spinal block alone, spinal block with caudal block, spinal with ilioinguinal block or caudal alone. A maximum dose of 2.5 mg/kg of bupivacaine or levobupivacaine can be used.

Outcome measure: Neurodevelopmental assessments will occur at 2 and 5 years with standard neuropsychological tools. Apnoea events and interventions for apnoea will also be recorded.

Primary outcome: The primary outcome will be the WPPSI-III Full Scale IQ score at 5 years corrected age.

1. INTRODUCTION and BACKGROUND

1.1 Title: A multi-site RCT comparing regional and general anaesthesia for effects on neurodevelopmental outcome and apnoea in infants

1.1.1 Study acronym: *The GAS study*

1.2 Agents to be investigated: This trial will compare outcome in infants receiving a): general anaesthesia with the volatile general anaesthetic sevoflurane plus regional nerve blockade with the local anaesthetic bupivacaine or levobupivacaine, or b): awake regional anaesthesia using regional nerve blockade with bupivacaine or levobupivacaine alone.

1.3 Population to be studied: 660 infants of postmenstrual age 60 weeks or less scheduled for hernia repair.

1.4 Rationale

Recent animal data has provided evidence to suggest that several commonly used anaesthetic agents (including volatile anaesthetic agents) may be neurotoxic to the developing brain [1].

1.4.1 Anaesthesia in infancy

Anaesthesia in infants and neonates is becoming increasingly common. In 2002 in Western Australia 7.8% of male and 3.2% of female children aged less than 1 year had anaesthesia [2]. Of these infants 10% of the males and 20% of the females had the anaesthesia during their first 28 days of life. The use of anaesthesia in infants (and indeed in the foetus) is likely to further increase as more surgical options are available, as there is a greater appreciation of the ethical and developmental need for anaesthesia to reduce nociceptive stimuli, and as advances in anaesthesia practice reduce the short-term morbidity and mortality.

General anaesthesia in infants and neonates usually involves a volatile anaesthetic (e.g. sevoflurane, isoflurane or halothane) or an intravenous anaesthetic (e.g. barbiturate or propofol). These act via the GABA receptor. Anaesthesia may also be provided with awake regional nerve blockade using a local anaesthetic agent (for example spinal anaesthesia).

1.4.2 Apoptosis and neurodevelopment

Several studies have consistently demonstrated that neonatal rats, mice and guinea pigs exposed to GABA agonists, such as volatile anaesthetics, or to NMDA antagonists such as ketamine, have widespread neuronal apoptotic lesions and delays in achieving some developmental goals [3-7]. In rats the injury is most obvious when they are exposed to anaesthesia during the period of synaptogenesis at the age of 7 days. Recently neurotoxicity has also been demonstrated in prenatal rhesus monkeys exposed to ketamine [8].

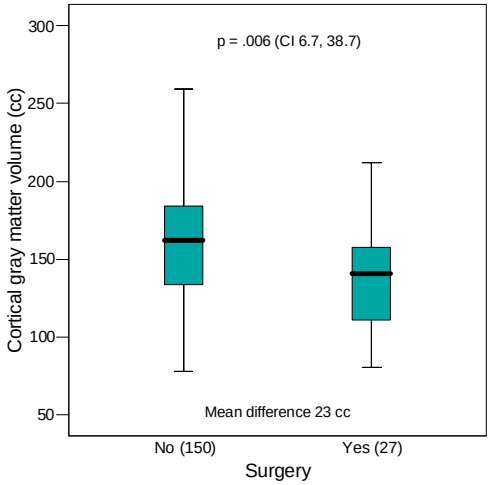
The ontogeny of NMDA and GABA receptors is consistent with the existence of a period of potential neuro-toxicity mediated by anaesthetics. The composition of neonatal NMDA receptor subunits differs compared with adults [9], and the GABA receptor is excitatory rather than inhibitory in the neonatal brain [10].

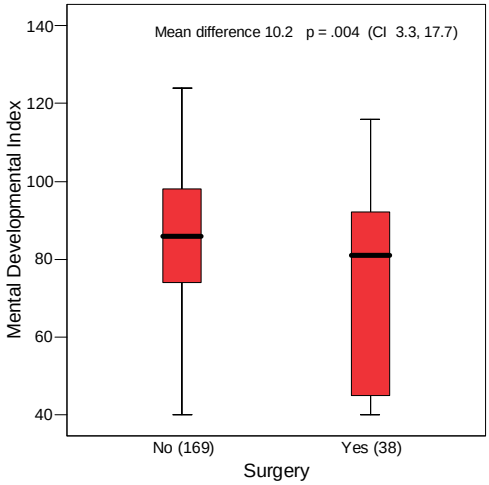
Correlation of the stages of animal neural development with that of human brain development is imprecise. In the rat the period of synaptogenesis lasts from day 4 to day 10 and peaks at day 7. In the human this equates to the period from approximately the third trimester to one year of age. Thus, in theory humans may be susceptible to anaesthesia toxicity anywhere from ante-partum to late infancy.

Interspecies variation limits the generalisation of the animal data to humans. Similarly experimental conditions for rodents may be significantly different to conditions experienced by neonates undergoing surgery and anaesthesia. Differences include, concurrent oxygen, nutrition or blood glucose management, the dose of the agents used, the different organisation and plasticity of the human brain [1, 11, 12]. Compared with the time of exposure to anaesthesia, the developmental period is considerably longer in a human compared to a rat, however from a molecular biological perspective, apoptosis could be triggered irrespective of the usual period of neurodevelopment. Due to greater plasticity it is possible that the human brain is capable of accommodating greater apoptotic injury than the rat brain without any clinically significant effect to neurological development, although the evidence for this premise is limited.

A cohort study following prematurely born human babies has suggested an association between hernia surgery in the neonatal period and sensorineural disability at 5 or more years of age [13]. This study is difficult to interpret due to multiple confounding variables. It is unclear if the injury is due to anaesthetic drug toxicity, the inflammation and stress response associated with surgery or other factors associated with surgery and anaesthesia such as transport, ventilation and pain. The difficulty of untangling associations in cohorts of this population group has been well illustrated by the confusion surrounding results from the recent large NEOPAIN studies [14, 15].

Recent data provided by Rod Hunt, one of the investigators in the Victorian Infant Brain Study Cohort have confirmed an association between surgery in the perinatal period and altered brain development at term corrected, as well as impaired neurodevelopment at two years of age. The following box plots show that those infants exposed to surgery on average have reductions in cortical grey matter volume, as well as strong evidence of lower Bailey II Mental Developmental Index at 2 years [16].





These relationships remained statistically significant after adjustment for gestation, gender and score of illness severity.

Due to the difficulties with cohort data, the best way to provide convincing evidence for the safety of volatile anaesthesia is with a prospective randomised trial. Fortuitously, in many sites, anaesthesia is provided to infants undergoing inguinal hernia repair via one of two methods – general anaesthesia (GA) or regional anaesthesia (RA). RA can be with spinal or caudal anaesthesia or a combination of both. RA can be provided without exposure to any of the agents purported to be associated with neuro-toxicity. Inguinal hernia repair is one of the most common procedures to be performed in infancy and provides a large population of infants having similar surgery. The reasons for choosing RA or GA may depend on the age of the child, the experience of the surgeon or anaesthetist, and the perceived risk of apnoea. As outlined below the risks of apnoea after modern anaesthesia are not clearly defined. The presence of equipoise in choice of anaesthesia for a single, relatively common procedure provides an ideal setting for a prospective randomised trial. The most important potentially confounding variable is the influence of prematurity on developmental outcome and choice of anaesthesia. This potentially confounding variable makes stratified randomisation and a subsequent stratified analysis essential.

1.4.3 Apnoea

Neonates, particularly those born pre-term, normally have periods of irregular breathing (periodic breathing), but in some circumstances the pauses may be longer and may be described as apnoea. Apnoea in neonates is more common in the first 12 hours after anaesthesia [17] and the risk of post-anaesthesia apnoea is greater in neonates who were born pre-term [18, 19]. The exact significance of post-anaesthesia apnoea is unknown; the probable incidence of death or permanent injury due to post-anaesthesia apnoea being very low. It is assumed that there is a spectrum of severity and consequence.

Comparing general and spinal anaesthesia, three small trials have reported a reduced risk of apnoea in high risk babies receiving spinal anaesthesia [17, 20, 21]. These studies are difficult to interpret due to small numbers, different ways of measuring

apnoea and different general anaesthesia agents used [22]. A recent Cochrane review has called for a large well designed randomised trial to address this issue [23].

New general anaesthesia volatile agents such as sevoflurane and desflurane could, in theory, lower the risk of apnoea due to their faster elimination from the body [24]. However, one recent study has demonstrated that like the older agents, the new agent sevoflurane is still associated with a higher incidence of post-operative apnoea than spinal anaesthesia [25]. Also, like earlier studies the clinical relevance of this study is uncertain without a clear understanding of what is a "significant" episode of apnoea [26].

There is clearly a need for larger trials to evaluate the efficacy of apnoea prevention strategies in neonatal anaesthesia, including the use of RA. This study will provide useful data on the frequency and clinical significance of post-operative apnoea using RA and GA with modern anaesthesia techniques.

1.4.4 Success rate and complication rate of general and regional anaesthesia

Regional anaesthesia has varying popularity. Proponents for regional anaesthesia claim that it results in a fast recovery, early feeding and low respiratory complication rate. Detractors of regional anaesthesia cite a substantial failure rate with regional anaesthesia (up to 25%) and potential for distress in the child as the block is performed. However, data supporting these comments are sparse and contradictory. This study will enable the collection of good quality data to help in answering these questions.

1.4.5 Impact

If volatile anaesthesia *is* associated with poor neurodevelopmental outcome, reducing exposure to volatile anaesthesia will have a substantial impact on the community. Although surgery in infants is often unavoidable, and withholding anaesthesia is not an option, there are alternatives to volatile anaesthesia such as purely opioid-based anaesthesia using newer agents such as remifentanil or increased use of regional local anaesthesia.

There is already considerable public and parental concern regarding the toxicity of drugs to the foetus and the newborn. Avoiding *potentially* neurotoxic drugs or environmental agents during pregnancy has become a standard of care in our society. It is not surprising that a parent's concern continues after birth.

Previously the anaesthesia community has reassured the public that anaesthesia poses no specific toxic risk to neonates, however the recent animal data suggests such a reassurance cannot now be made without qualification. Resolving this issue, or at least being better able to inform the parents with better evidence-based data, should be a priority. This study will provide convincing evidence of any risk of clinically relevant neurotoxicity after exposure to brief anaesthesia in infants.

With respect to apnoea, current guidelines are based on little evidence [22]. Neonates are often routinely kept in hospital for observation after surgery. This is costly in

terms of limited hospital resources and disruption to families. A better understanding of apnoea would have obvious and considerable cost and safety benefit.

1.4.6 References:

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1.5 Compliance

The trial will be conducted in compliance with the protocol, Good Clinical Practice (Therapeutic Goods administration, Australia) and all applicable regulatory requirements. The trial will be registered with the NH&MRC Australian Clinical Trials Registry and The National Library of Medicine (USA).
In the UK the trial will be conducted in compliance with the protocol, MRC GCP, Medicines for Human Use (Clinical Trials) Regulations 2004 as amended from time to time and the Research Governance Framework for Health and Social Care (2nd edition, April 2005)/ Community Care (2nd edition 2006), Data Protection Act, the Declaration of Helsinki and all relevant guidelines and legislation governing clinical research.

2. OBJECTIVES

2.1 Primary Aim

The primary aim of this prospective, observer blind, randomised, multi-site, controlled, clinical, equivalence trial is to determine whether different types of anaesthesia [regional vs general] given to infants undergoing inguinal hernia repair result in equivalent neurodevelopmental outcomes at 5 years of age (corrected).

2.2 Secondary Aims

2.2.1 Neurodevelopmental outcome: Compare a range of secondary neurodevelopmental measures between groups at 2 and 5 years of age (corrected).

2.2.2 Apnoea: Describe the frequency and characteristics of apnoea in the post-operative period after both regional and general anaesthesia for inguinal hernia repair in infants, and determine other factors associated with increased risk of apnoea.

2.2.3 Recovery: Collect data on the ease of performance, complication and success rate and the early recovery profile of infants in the post-operative period for both regional and general anaesthesia for inguinal hernia repair.

2.3 Hypotheses

2.3.1 Primary Hypothesis: The WPPSI-III Full Scale IQ score at 5 years corrected age in infants who are anaesthetised for hernia repair is equivalent when using general anaesthetic compared with regional anaesthetic.

2.3.2 Secondary Hypothesis: Cognitive component of the Bayley III scale of infant development measured at 2 years of age in infants who are anaesthetised for hernia repair is equivalent when using general anaesthetic compared with regional anaesthetic.

3. STUDY DESIGN

3.1 Experimental Design: Prospective, observer blind, multi-site, randomised, controlled, equivalence trial

3.2 Randomisation: Randomisation to either of the two treatment groups (GA or RA) will be by block and stratified by site and gestational age at birth. Gestational age at birth strata will be:

- 26 weeks to 29 weeks and 6 days
- 30 weeks to 36 weeks and 6 days
- 37 weeks and more

Access to randomisation numbers will be via a 24 hour web-based randomisation service set up and maintained by A/Prof Ryan at The Data Management & Analysis Centre, Department of Public Health, University of Adelaide, South Australia:
http://www.dmac.adelaide.edu.au/gasRandomisation
Entry to the website is password protected.

3.3 Blinding: The anaesthetist will be aware of the group allocation. The psychologist and paediatrician performing the 2 and 5 year neurodevelopmental assessments will be blinded to study group. Parents will not be told which group their child was in but they will be allowed to discover the group and will be told if asked. Parents will be clearly instructed that if they do discover the group then they should not inform the assessing psychologist. A record will be made of whether or not the parents or the psychologist became aware of the allocation. The apnoea assessment and recovery assessment will not be blinded.

3.4 Study duration: The duration of subject participation is five years.

- Children will be enrolled before surgery.
- Data will be collected before and during anaesthesia and in the early post-operative period.
- Formal neurodevelopmental assessment will occur at 2 and 5 years corrected age (see appendix 1 for definition of corrected age).

3.5 Source data

The following data will be collected onto the Case Report Forms (CRFs) at the corresponding times.

3.5.1 Data for eligibility

Data for potential eligibility will be collected as per the inclusion and exclusion criteria

3.5.2 Data for randomisation

For randomisation the following extra data is collected:

Mother's expected date of delivery
Birth date

3.5.3 Identifying information

The following identifiable data will be collected. Identifying data will be kept at each local site in locked filing cabinets.

Child's name
Family address and phone numbers
Child's paediatrician or family doctor
An alternate contact to find the family

3.5.4 Medical and social history

The following medical and social history data will be collected:

Language spoken at home
Family structure with details of parents including who is primary income earner, who is primary carer and details of employment status and education

Maternal age at birth of child
Presence in family of anyone with a mental or learning disorder
Gender
Method of calculating expected date of delivery
Birth weight, in kg
Apgar score at 1 and 5 minutes, mode of delivery, if the child was part of a multiple pregnancy, presence of labour, antenatal steroids, history of prolonged rupture of membranes, pre-eclampsia or chorioamnionitis
History and details of previous apnoea or respiratory support
Details of any previous neurological injury or intraventricular haemorrhage
Previous ROP or hearing defects
Previous sepsis
Days the child spent in hospital after birth and date child last discharged from hospital

3.5.5 Pre anaesthesia details. Both regional and general groups

The following data will be collected prior to anaesthesia:

Date of surgery
Current respiratory support
Current medication
Weight
Timing and details of last feed
Baseline HR, NIBP, SpO_2, temperature in a calm comforted child
Details of premedication and fluids

3.5.6 Anaesthesia details

The following data during anaesthesia will be collected

3.5.6.1 Anaesthesia details. Regional group only

Seniority of anaesthetist
Times for anaesthesia blocks and surgery
Blocks used and details of block technique including position of child, dose and concentration of bupivacaine or levobupivacaine, number of needle passes, presence of blood in needle and flow of CSF through needle
Distress of child and SpO_2 and HR during the block
Volume and type of fluid given in theatre
Blood glucose and haemoglobin
Details of any rescue therapy for low glucose, hypotension or hypoxia
Efficacy of block and activity of child during the procedure
Details of any respiratory support or apnoea during procedure
HR, NIBP, SpO_2 and activity of child every 5 minutes during surgery

3.5.6.2 Anaesthesia details. General group only

Seniority of anaesthetist
Times for anaesthesia induction and times for blocks and surgery

Blocks used and details of block technique including dose and concentration of bupivacaine or levobupivacaine, number of needle passes, presence of blood in needle and flow of CSF through needle
Details of anaesthesia induction
Details of airway management and use of any NDNMB
Volume and type of fluid given in theatre
Blood glucose and haemoglobin
Details of any rescue therapy for low glucose, hypotension or hypoxia
Efficacy of blocks
Details of awakening, airway removal and reversal of any NDNMB
Details of any respiratory complications or apnoea during awakening or after airway removed.
HR, NIBP, Inspiratory oxygen, SpO_2 and End tidal CO_2 and sevoflurane concentrations every 5 minutes during surgery

The total dose of sevoflurane will be calculated as concentration*hours dose equivalent

3.5.6.3 Details of protocol violations

Details of any protocol violation including need for opioids or nitrous oxide
Details of management for failed block

3.5.7 Surgical details

The following surgical data will be collected:

Presence of unilateral or bilateral hernia on pre-op exam
Unilateral or bilateral exploration and presence of unilateral or bilateral hernia on exploration
Seniority of surgeon

3.5.8 Post anaesthesia care unit data

In PACU (or during the first 30 minutes on the ward if PACU is bypassed) the following adapt will be collected:

Details of monitoring for apnoea
Drugs given
Number of significant apnoeas
Details of any intervention for apnoea or respiratory support needed
HR, NIBP, SpO_2 every 5 minutes during PACU stay and lowest SpO_2
FALCC scores and details of any analgesia
Presence of stridor
Time to first feed
Sunken fontanel, any persistent CSF leak

3.5.9 Post PACU details

For the 12 hours after PACU or up until routine discharge the following data will be collected.

Details of monitoring for apnoea
Drugs given
Details of any intervention for apnoea or respiratory support needed
Number of significant apnoeas
Presence of stridor
Time child discharged home

3.5.10 Follow-up day 1-5

In the period from 1-5 days post anaesthesia the following data will be collected where relevant.

Day discharged home
Details of any medical interventions initiated on day 1-5
Was the child readmitted to hospital?
Details of any evidence for infection associated with nerve blockade or presence of stridor

If child stays longer than 5 days:

Length of stay in hospital
Details of any medical intervention in the period between surgery and discharge from hospital

3.6 Details of apnoea data collection

At all sites heart rate, respiration and oxygen saturation will be continuously recorded in PACU. This data may be downloaded electronically. Details of any intervention for apnoea in PACU will be recorded. An activity sheet will be completed to identify feeding and other activity that may contribute to artefact when data is electronically collected.

After PACU all sites will monitor for apnoea using their established practices. For all patients any post-PACU intervention or change in management due to apnoea will be recorded. After PACU some children will have continuous monitoring with heart rate oxygen saturation oximetry and respiratory rate for up to 24 hours. This data may be recorded and downloaded electronically. As for PACU electronic data will be accompanied by an activity sheet.

3.7 Two year assessment data

The following data will be collected at 2 years corrected age.

3.7.1 Data for family/environmental factors at two years

Support for special needs such as audiologist, optometrist, physiotherapy, speech/language therapy, occupational therapy, orthoptist, psychologist.

Child Care arrangements, if child attends playgroup and age started at group.
Social history as per 3.5.4

3.7.2 Medical history at two years

Details of all hospital attendances and admissions to hospital after discharge following hernia repair. Exposure to any anaesthetic agents or benzodiazepines since discharge from hospital after hernia repair.

Details of any recurrence of hernia on either side since repair

3.7.3 Neurodevelopmental assessment at two years:

- Bayley Scales of Infant Development III (BSID-III): Cognitive, language and motor scales
- Paediatric assessment including neurological examination to determine presence of cerebral palsy
- Visual and hearing acuity tests
- Delayed Alternation and Spatial Reversal Tasks (Espy) [An experimental task]

It will be noted whether or not the parent or psychologists are aware of allocation.

3.8 Five years assessment data

The following data will be collected at 5 years corrected age.

3.8.1 Data for family/environmental factors at five years

Data as per 3.7.1

3.8.2 Medical history at five years

Details of all hospital attendances and admissions to hospital since 2 year assessment

Details of any recurrence of hernia on either side since repair
Details of any intervention initiated as a result of the findings at the 2 year neurodevelopmental assessment

3.8.3 Neurodevelopmental assessment at five years

- A paediatric assessment as per 2 years
- General intellectual ability, Verbal, Visuo-spatial and Processing Speed Skills from the Wechsler Preschool and Primary Scale of Intelligence - Third Edition (WPPSI-III)
- Auditory and visual attention will be assessed using the NEPSY tasks
- The behavioural features of executive dysfunction will be assessed via the behavioural Rating of Executive Function (BRIEF)

It will be noted whether or not the parent or psychologists are aware of allocation.

4. SELECTION OF SUBJECTS

4.1 Number of subjects: 660

4.2 Inclusion criteria: Any child scheduled for unilateral or bilateral inguinal hernia repair (with or without circumcision).

4.3 Exclusion criteria:

- Any child older than 60 weeks postmenstrual age
- Any child born at less than 26 weeks gestation
- Any contraindication to general *or* spinal/caudal anaesthesia (for example: neuromuscular disorder or coagulopathy)
- Pre-operative ventilation immediately prior to surgery
- Congenital heart disease that has required surgery or will require surgery or which requires ongoing pharmacotherapy
- Known chromosomal abnormality or any other known acquired or congenital abnormalities (apart from prematurity) which are likely to affect development
- Children where follow-up would be difficult for geographic or social reasons
- Families where the primary language spoken at home is *not* the language in which the WPPSI-III will be given [i.e. English for Australian sites, French for Paris site and English or Spanish for US sites]
- Known neurological injury such as cystic periventricular leukomalacia (PVL), or grade 3 or 4 intra ventricular haemorrhage (IVH) (+/- post haemorrhage ventricular dilatation)
- Previous exposure to volatile anaesthesia or benzodiazepines as a neonate or in the third trimester in utero

4.4 Enrolment

Potential participants will be identified from theatre bookings or direct contact from surgeons or anaesthetists. After identification investigators will:

- Check medical history to confirm all inclusion criteria are met and no exclusion criteria are met.
- Confirm from both surgeon and anaesthetist that participant may be suitable and seek their approval to approach the family.
- Explain the project to the child's family and obtain written consent.

4.5 Subject withdrawal criteria

4.5.1 Failed regional block with general anaesthesia

If the child is having a general anaesthetic (with sevoflurane) and the local anaesthesia block is inadequate (persistent tachycardia or hypertension), then opioids or nitrous oxide may be given at the discretion of the anaesthetist. Post-operative recovery and apnoea data will still be collected, as will neurodevelopmental data. These children will also be followed up in hospital and with a phone call 5 days post-anaesthesia as per study protocol. Subjects will not be replaced.

4.5.2 Voluntary withdrawal

Families may withdraw from the study at any stage. If they withdraw, data collected up to that point will still be used for analysis unless the family requests that it is not used. Subjects will not be replaced.

4.5.3 Cancellation of surgery

If the surgery is cancelled after randomisation and not rescheduled, or cancelled and rescheduled greater than 48 hours after randomisation, then the reason for cancellation must be noted and the case is treated as a protocol violation. The child is not replaced. If the child has a hernia repair after 48 hours, the child should receive anaesthesia at the anaesthetist's discretion. Anaesthetic, apnoea and recovery data may be collected if possible. Note that as per other violations, the child should receive two and five year developmental assessment as per protocol. If the child receives surgery for hernia repair 48 hours or more after initial randomisation then they cannot be randomised again in the trial for that later surgery.

Note surgery may be *delayed for up to 48 hours* and the child retains their position in the study with same study group and study number (provided they continue to meet inclusion criteria).

If before anaesthesia and after randomisation a decision is made by surgeon or anaesthetist that the child is no longer suitable for the study for whatever reason (apart from cancelled surgery or withdrawn consent) and the child does not receive their allocated anaesthesia protocol, then the case should be treated as a protocol violation and data collected as possible. The child should receive the same post-anaesthesia apnoea data collection and developmental follow-up as per protocol. Note that if treating staff consider that it is in the child's best interests they always have the opportunity to not follow the protocol, but only the parents can withdraw the child completely from the trial.

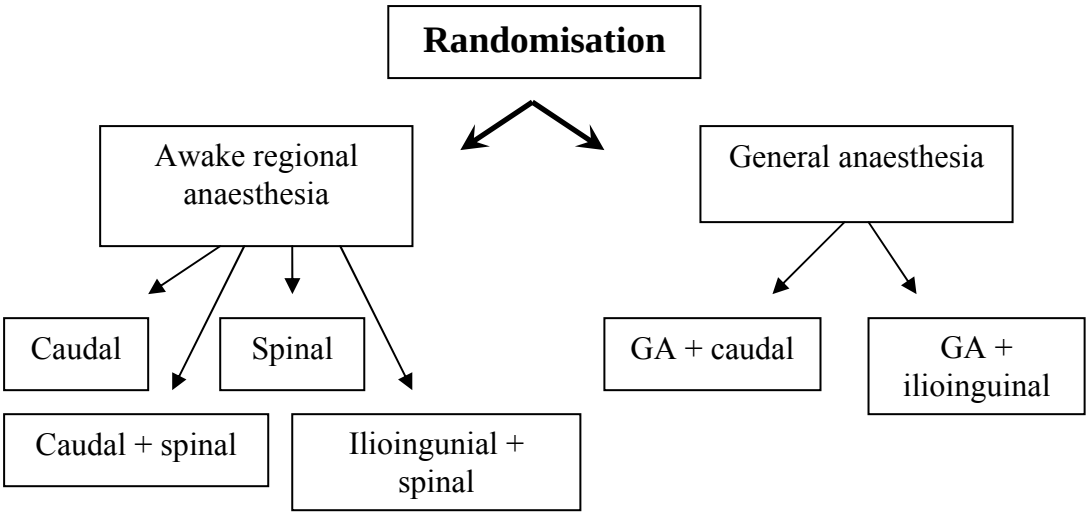
5. TREATMENT

5.1 Treatment groups: There are two groups

5.1.1 ***General anaesthesia group***: Sevoflurane for induction and maintenance of anaesthesia plus nerve blockade with caudal or ilioinguinal bupivacaine or levobupivacaine

5.1.2 ***Awake regional group***: No general anaesthetic agent and one of the following blocks:
a) Spinal block alone
b) Spinal and caudal block
c) Spinal and ilioinguinal block
d) Caudal block alone.

Note: If two blocks are used, the anaesthetist may chose to give one on completion of surgery.



5.2 Performing nerve block

5.2.1 Agent: All blocks will be with the local anaesthetic agent bupivacaine or levobupivacaine.

5.2.2 Choice of nerve block: Within each treatment group the choice of nerve block is at the discretion of the anaesthetist.

5.2.3 Experience of doctor performing nerve block
An essential component of the trial is a high success rate for regional anaesthesia. At each site awake spinal and caudal may be performed only by anaesthetists with an established high rate of success for the block (>90%). This anaesthetist may be called just to provide the block for the treating anaesthetist.

5.2.4 Asepsis: An aseptic technique is required for all blocks. This includes:

- Hands washed and sterile gloves worn
- Surgical masks to be worn
- Skin preparation with an antiseptic
- Area covered with sterile drapes

5.3 Details of General Anaesthesia group treatment protocol

5.3.1 Pre-operative management:

- Pre-operative fasting in accordance with institutional guidelines
- Premedication with oral paracetamol (acetaminophen) 20mg/kg [optional]

5.3.2 Induction:

- Sevoflurane up to 8% induction in air/oxygen mix
- No nitrous oxide
- Circuit and fresh gas flow at discretion of anaesthetist
- Oxygen concentration at discretion of anaesthetist
- IV insertion before or after induction

5.3.3 Maintenance:

- Airway maintenance: Endo-tracheal intubation, laryngeal mask or face mask only with or without an oral Guedel airway.
- A non-depolarizing neuromuscular blocking agent (NDNMB) may be used to facilitate endo-tracheal intubation.
- Analgesia with caudal local anaesthesia blockade with bupivacaine or levobupivacaine or ilioinguinal nerve local anaesthesia up to a maximum dose of 2.5mg/kg bupivacaine or levobupivacaine
- Maintenance with sevoflurane in an air/oxygen mix. Sevoflurane concentration at discretion of anaesthetist. No nitrous oxide.
- Mechanical or spontaneous ventilation to maintain end tidal CO_2 between 35 and 45 mmHg. Fresh gas flows and circuit at discretion of anaesthetist.
- Oxygen concentration at discretion of anaesthetist to maintain arterial oxygen saturation > 95%
- Reversal with neostigmine 0.05 mg/kg and atropine 0.02 mg/kg if NDNMB used.
- During anaesthesia administer Ringer's lactate solution at 4ml/kg/hr
- Warming in accordance with institutional practice

5.4 Details of Awake Regional group treatment protocol

5.4.1 Pre-operative management:

- Pre-operative fasting in accordance with institutional guidelines
- Premedication with oral paracetamol (acetaminophen) 20mg/kg [optional]

5.4.2 During anaesthesia:

- IV insertion before or after spinal/caudal, IV fluids – ringer's lactate at 4ml/kg/hr
- Oral sucrose for sedation/analgesia. No other sedation
- No volatile anaesthetic agents may be given at any stage
- Warming in accordance with institutional practice
- Oxygen by face mask or blow by at discretion of anaesthetist to maintain arterial oxygen saturation > 95%

5.4.3 Nerve blockade

5.4.3.1 Spinal anaesthesia nerve blockade:

- 25 gauge needle lumbar puncture at L2-3 or L3-4,
- Dose of bupivacaine or levobupivacaine up to 0.2 ml/kg 0.5% bupivacaine or levobupivacaine (minimum volume of 0.5ml)
- Child may be in lateral or sitting position

5.4.3.2 Caudal blockade

- Dose of bupivacaine or levobupivacaine up to 2.5 mg/kg bupivacaine or levobupivacaine, concentration at discretion of anaesthetist
- Via needle or cannula

5.5 Post-operative management for both groups:

- Paracetamol (acetaminophen) 20mg/kg oral or intravenous at discretion of anaesthetist if not given pre-operatively

- IV fluids Ringer's lactate @ 4ml/kg/hr until feeding,
- Temperature maintenance as per institutional practice
- Oxygen by face mask or blow by at discretion of anaesthetist or nurse in PACU to maintain arterial oxygen saturation > 95%

5.6 Treatments not permitted during anaesthesia

- Opioids may not be given.
- Benzodiazepines, nitrous oxide, ketamine and clonidine may not be given.
- No drugs apart from bupivacaine or levobupivacaine may be added to any nerve block

5.7 Triggers to abandon awake regional and administer general anaesthesia

If there is a failed awake regional on clinical assessment then the infant is given a general anaesthetic with sevoflurane alone and continues in the study. In this situation the airway management is at the discretion of the anaesthetist. Regional failure may be due to movement impeding surgery or a vigorous crying child that cannot be comforted.

Note: If there is total failure of a spinal then the spinal may be attempted again with another 1mg/kg bupivacaine or levobupivacaine. Total failure is defined as follows: after 5 minutes the infant continuing to vigorously spontaneously move both their legs with no evidence of motor block and withdrawing both their legs after gentle pinch to either thigh. Any suggestion of only partial failure and the child should not receive another spinal attempt. Total dose of bupivacaine or levobupivacaine for entire case may not exceed 2.5 mg/kg.

5.8 Rescue treatments

5.8.1 Blood pressure

Intra-operative and PACU; if blood pressure > 20% below baseline give IV bolus of 20 ml/kg Ringers lactate solution. Vasoactive drugs if deemed necessary by anaesthetist. Note baseline blood pressure defined as blood pressure in a comforted non-distressed child.

5.8.2 Blood glucose

Give intravenous glucose bolus 5ml/kg 10% dextrose for hypoglycaemia (Blood sugar level <3.0 mmol/L)

5.8.3 Hypoxia

Hypoxia to be managed with oxygen via mask and/or intubation in regional group and increasing FiO_2 in GA group as deemed necessary by anaesthetist.

5.9 Follow-up

For success this trial requires a high rate of retention for the 2 and 5 year assessment. Therefore a family will be excluded if geographic or extreme social circumstances make follow up difficult. Families will receive a phone call one week after the hernia repair and then cards on the child's birthdays and regular newsletters. This will be co-ordinated from Melbourne in terms of study number only and date of surgery by a prompt alerting each local site to send out a card.

6. OUTCOME

6.1 Primary outcome

The primary outcome will be the WPPSI-III Full Scale IQ score at 5 years corrected age.

6. 2 Secondary outcomes

Secondary outcomes fall into four areas:
1) Other measures of neurodevelopmental outcome
2) Incidence of apnoea
3) Other outcomes relating to anaesthesia group
4) Incidental outcomes not related to choice of anaesthesia

6.2.1 Other measures of neurodevelopmental outcome

6.2.1.1 Neurodevelopmental secondary outcomes at 2 years:

- Cognitive, motor and language scales of the Bayley Scales of Infant Development III [Bayley 2005].
- A paediatric assessment including a neurological examination to determine the presence of cerebral palsy will be conducted by a paediatrician blinded to the type of anaesthetic used.
- Data regarding visual and hearing acuity will be collected, or where not previously conducted, visual and audiology assessments will be arranged.
- Some sites will perform the experimental Delayed Alternation and Spatial Reversal tasks (Espy)

6.2.1.2 School age developmental outcome at 5 years:

- A paediatric assessment as per 2 years.
- General intellectual ability, verbal, visuo-spatial and processing speed skills are incorporated into the Wechsler Preschool and Primary Scale of Intelligence - Third Edition (WPPSI-III) The primary outcome is the full scale, while subscales will be computed as secondary outcomes.
- Auditory and visual attention will be assessed using the NEPSY tasks.
- The behaviour features of executive dysfunction will be assessed via the Behavioural Rating of Executive Function (BRIEF).

6.2.2 Apnoea

Apnoea will be defined in terms of changes in recorded vital signs and need for intervention. The timing of the apnoea will also be early or late.

6.2.2.1 Significant apnoea by vital signs

A significant apnoea will be defined as a pause in breathing of greater than 15 seconds or a pause greater than 10 seconds if associated with oxygen saturation <80% or bradycardia (20% fall in heart rate).

6.2.2.2 Significant apnoea by intervention

Any intervention for apnoea will be recorded as frequency, time and nature of intervention. Types of intervention recorded will include need for stimulation, assisted ventilation, CPAP, endo-tracheal intubation administration of a methylxanthine stimulant, delay in discharge home due to apnoea or discharge from hospital with a home apnoea monitor.

6.2.2.3 Early apnoea

Any significant apnoea in the PACU or the first 30 minutes of the NICU if PACU is bypassed or in the operating room after completion of surgery, discontinuation of general anaesthesia and removal of laryngeal mask or endo-tracheal tube.

6.2.2.4 Late apnoea

Any documented significant apnoea occurring in NICU or other hospital ward within 24 hours of completion of surgery, excluding early apnoeas.

6.2.3 Other outcomes relating to anaesthesia group:

- Success rate of nerve block
- Time taken for nerve block
- Behaviour of child during nerve block, during surgery and in PACU
- Time to first feeding

6.2.4. Incidental outcomes not related to choice of anaesthesia:

- Incidence of hernia recurrence at 2 years will be recorded. If the repair was unilateral the incidence of contralateral occurrence will be noted.

7. SAFETY

7.1 Monitoring during anaesthesia and in PACU

During all nerve blockade there will be ECG, NIBP and pulse oximetry monitoring. During anaesthesia for both groups there will be ECG, NIBP, temperature and pulse oximetry. In the general anaesthesia group there will also be agent analysis and expired CO_2. Blood glucose and haemoglobin will be measured during anaesthesia. In PACU there will be monitoring of oxygen saturation, NIBP, temperature, respiratory rate and heart rate.

7.2 Data monitoring committee

An independent data monitoring committee has been established.
The members are as follows.

- Chair: Dr Jonathan De Lima, Anaesthetist Sydney
- Dr Phil Beeby, Neonatologist Sydney
- Prof Val Gebski Statistician Sydney
- Prof Greg Hammer Paediatric Anaesthesiologist, Stanford California, USA
- Prof Dick Tibboel Paediatrician, Sophia Children's Hospital, Rotterdam, Holland

The data monitoring committee will receive interim reports every 6 months. Serious adverse events will be reported to the DMC immediately. Non-serious adverse events will be recorded and reported to the DMC be reported every 6 months. The DMC will report to the Trial Steering Committee.

The DMC will consider the rate of failed awake regional anaesthesia requiring conversion to general anaesthesia and the rate of apnoea in each group. The DMC will also consider all relevant publications and findings from other studies that are relevant to the conduct of this trial.

Codes will only be broken for reports to the Data Monitoring Committee or if requested by the TSC or DMC.

7.3 Adverse events

7.3.1 Adverse events: `An adverse event is any untoward medical occurrence or experience in a patient that occurs following the administration of the trial medication regardless of the dose or causual relationship. The Summaries of Product Characteristics for sevoflurane and bupivacaine or levobupivacaine (appended) list the possible adverse effects of these agents and their expected frequency.

Adverse events are as follows

- Apnoea requiring readmission to hospital within 48 hours of anaesthesia
- Delay in discharge due to apnoea.
- Failure of regional anaesthesia requiring sedation or analgesia (excluding oral glucose)
- Failure of regional anaesthesia requiring conversion to general anaesthesia (from either technical failure of insufficient blockade for length or scale of surgery)
- High neuraxial blockade requiring intubation
- Post-anaesthesia apnoea requiring endo-tracheal intubation
- Delay in extubation for greater than 1 hour after surgery
- Hypoxia during anaesthesia with $SpO_2 < 80$ for 5 minutes
- The administration of vasoactive drugs to support circulation
- Increase in post operative oxygen requirement or increased respiratory support for greater than 1 hour post anaesthesia
- Any other event not mentioned above that results in the child needing medical attention whether or not it is related to the allocated anaesthetic technique or measurement interventions.

Adverse events will be recorded and frequency of AEs will be reported to DMC every 6 months.

7.3.2 Serious Adverse Event: defined as the following regardless of its relationship to trial treatment

- Results in death
- Is life threatening
- Requires hospitalisation or prolongation of existing in-patient hospitalisation
- Results in persistent or significant disability/incapacity
- Is medically important or requires interventionto prevent one of the outcomes listed

Serious adverse events are the following

- Death due entirely or in part to anaesthesia
- Any death within 48 hours of anaesthesia
- Readmission to hospital due to anaesthesia complications apart from apnoea.
- Delay in discharge from hospital due to any complications apart from apnoea.
- Inability to satisfactorily complete surgery, or surgery abandoned due to inadequate anaesthesia (not including surgery successfully completed after conversion of regional to general anaesthesia)
- Evidence of local anaesthesia toxicity such as seizures or arrhythmia
- Any persisting neurological deficit from neuraxial blockade
- Meningitis or epidural abscess within 5 days of anaesthesia
- Evidence for bowel puncture with ilio-inguinal or caudal nerve blockade defined as aspiration of bowel contents
- Barotrauma during general anesthesia resulting in pneumothorax
- Cardiac arrest or bradyarythmia requiring chest compression
- Any other event not mentioned above that is life threatening event or jeopardises the patient or requires medical or surgical intervention to prevent a serious adverse event

SAEs will also be reported to the DMC and all ethics committees involved with the trial.

7.3.3 Suspected Unexpected Serious Adverse Reaction (SUSAR):
Where a serious adverse event is related to study drug and is not noted in the protocol or SmPC of bupivacaine or levobupivacaine and sevoflurane as an expected adverse reaction will be deemed a SUSAR. The Chief Investigator is responsible on behalf of the sponsor to report all SUSAR's directly to the Competent Authority (MHRA) within 7 days of being notified of the event. The Chief Investigator will ensure all SUSAR's are reported to the sponsor, ethics committees and to the co-ordinating centre in Melbourne as soon as possible thereafter.

The Robertson Centre for Biostatistics, University of Glasgow has both web-based and paper reporting systems for SUSARs and this will be used by the UK Chief Investigator to rapidly inform the MHRA, sponsor, ethics committees and co-odinating centre in Melbourne.

7.4 Report to family

The family will receive a report of the neurodevelopmental assessment at 2 and 5 years. If any significant problems are identified the family will be notified and the child's paediatrician or family doctor. The child's paediatrician or family doctor may offer relevant referral to appropriate medical or allied health professionals.

8. STATISTICAL CONSIDERATIONS

8.1 Analysis of primary outcome

Since this an equivalence study, the primary outcome will be analysed on a per-protocol analysis basis to ensure a conservative estimate in the direction of non-equivalence. The means will be adjusted for gestational age at birth. The adjusted mean difference in Full Scale IQ Score between arms will be presented with a 2-sided 95% confidence interval. Equivalence will be accepted if the confidence interval of the difference in means lies within -5 and +5 points.

8.2 Analyses of Secondary outcomes

8.2.1 Other measures of neurodevelopmental outcome

A per-protocol analysis of the mean difference of the Cognitive component of the Bayley III scale between arms adjusted for gestational age will be presented with a 2-sided 95% confidence interval. Equivalence will be accepted if the confidence interval of the difference in means lies within -5 and +5 points.

For other continuous data, groups will be compared as for the primary outcome with the gestation-adjusted mean difference in scores presented with a 2-sided 95% confidence interval. For frequency data difference in frequency between groups will be presented with a 2-sided 95% confidence interval.

8.2.2 Apnoea:

There will be four Apnoea outcomes.

- Early significant apnoea on vital signs
- Late significant apnoea on vital signs
- Intervention for early apnoea
- Intervention for late apnoea

For each apnoea outcome an adjusted regression analysis will be performed to assess associations between risk factors and apnoea.

8.2.3 Other outcomes related to anaesthesia group

All other outcomes related to anaesthesia group will be reported for each group with 2-sided 95% confidence interval.

8.2.4 Outcomes not related to anaesthesia group

These outcomes will be reported using descriptive statistics only.

8.3 Justification of numbers

The WPPSI-III full scale IQ score is a standardised score with a mean of 100 and standard deviation of 15. Cohort studies of ex-preterm babies at 5 years of age commonly show a mean of 95 and standard deviation of 15, while term babies have a mean of approximately 105 and a standard deviation of 15. A difference of 5 points (1/3 of a standard deviation) will be taken as the largest difference that would be acceptable to demonstrate equivalence.

The sample size is calculated using the two one-sided equivalence tests method (ref: Schuirmann, D.J.) with a one-sided alpha of 0.025, applied to the null hypothesis that the two methods of anaesthesia are not equivalent, and power of 90% under the alternative hypothesis that the true mean difference is one standardised score point. Restated, we require 90% probability that the 95% confidence interval for the difference in means, adjusted for gestational age at birth, will exclude a difference of 5 or more (i.e. the 95% CI will lie within the range -5 to +5), if the true difference is no more than one point. The trial then needs 598 infants in total. Enrolling 660 will allow for an average of 10% loss to follow-up.

Adjusting the analysis for gestational age at birth, according to the three categories used in the stratified randomization, will ensure that the common standard deviation assumption is protected from the differences in WPPSI-III full scale IQ mean scores between the gestational age groups. Simulations have been performed to confirm these calculations.

Reference

Schuirmann, D.J. A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability.
Journal of Pharmacokinetics and Biopharmaceutics 15(1987) pp. 657-680

9. DATA MANAGEMENT

The Clinical Epidemiology and Biostatistics Unit (CEBU) at the Royal Children's Hospital in Melbourne will be the Data Coordinating Centre for the study, and will be receiving original CRFs from central locations in the USA and the UK and entering these CRFS into a database. Boston will receive a blank duplicate of the database used in CEBU and will double enter the data using photocopied CRFs. At regular intervals the databases will be compared to identify entry errors. The following process will ensure that CEBU receives all originals and Boston receives all photocopies of CRFs.

CRFs from Australian sites will be photocopied and the originals sent to Melbourne;
CRFs from European sites will be photocopied and the originals sent to Glasgow;
CRFs from USA sites will photocopied and the originals sent to Boston.
From Glasgow the original deidentified CRFs will be sent to Melbourne and a photocopy sent to Boston. From Boston the original deidentified CRFs will be sent to

Melbourne and a copy kept in Boston. From Melbourne a deidentified photocopy of the CRFs will be sent to Boston and the original kept in Melbourne.

Melbourne, Boston and Glasgow will be responsible for identifying and chasing missing data in their region. Melbourne, Boston and Glasgow will keep all identifying data and be responsible for arranging follow-up within their region.

All chief investigators will have access to all data, but blinded to allocation.

10. QUALITY CONTROL

The WPPSI-III is an individually administered assessment. It takes 60-90 minutes to administer. Examiners will be trained and have prior experience administering and interpreting standardised assessments with infants. Typically examiners will have psychological training at the masters or doctoral level. At regular intervals the assessor will be video recorded during an assessment and the recording sent to Dr Stargatt in Melbourne to compare assessment quality across sites.

11. ETHICS

There is a strong argument to believe equipoise exists in this trial. Awake regional and general anaesthesia are both accepted standards of care for inguinal hernia repair in children. Regional anaesthesia may be more technically demanding and preferences for one or the other may vary depending on the experience of the paediatric anaesthetist. In younger patients regional anaesthesia may be associated with less apnoea than general anaesthesia but this may be less apparent with the newer general anaesthesia agents. Similarly although there is animal data for toxicity, the evidence for risk of general anaesthesia is sufficiently weak to accept general anaesthesia as an arm in the study.

When recruiting patients the researcher approaching the patient must first ensure that both treating surgeon and anaesthetist are comfortable with randomisation.

All sites will obtain approval from their local Human Research Ethics Committees. In all cases written informed consent will be obtained from parents or guardians.

An independent Data Monitoring Committee and a Trial Steering Committee have been established to oversee the trial. Both committees have independent chairs and consist of statisticians, neonatologists, a psychologist and anaesthetists experienced in trial governance drawn from Australia, USA and Europe.

12. FINANCE AND INSURANCE

See attached budget in appendix II. Insurance will be provided by institutions where the study is being performed. For UK sites only Glasgow University will provide insurance to cover non negligent harm.

13. PUBLICATION POLICY

It is expected that the neurodevelopmental outcome at 2 and 5 years will be published in a high impact journal such as Lancet or New England Journal of Medicine. A number of other publications will result from secondary outcome analysis. All publication submissions will need TSC approval.

Appendix I

DEFINITIONS OF AGE

Calculating age is an imprecise science and there are various definitions in use. The dates cannot be exact but to avoid confusion the following definitions will be used:

Expected Date of Delivery (EDD): Date mother expected the child to be born – calculated *either* by 40 weeks after first day of last menstrual period, *or* from an early ultrasound scan, *or* 2 weeks plus date of conception if assisted reproduction

Gestational Age (GA):
Calculated as: GA (in days) = 280 days - (Expected Date of Delivery – date of birth)

Chronological Age: Time elapsed since birth.
Chronological age (in days) = date of randomisation – date of birth

Postmenstrual Age (PMA): PMA = Gestational Age + Chronological Age,
Calculated as: PMA (in days) = date of randomisation – EDD + 280 days

Corrected Age: Chronological Age from Expected Date of Delivery

Inclusion criteria are:

- Gestational Age, 26 weeks or more (GA $\geq$ 182 days)
- Postmenstrual Age, up to 60 weeks (PMA $\leq$ 426 days)

By entering EED and date of birth, the randomisation program will automatically calculate Gestational Age and assign the child to the appropriate strata. If the calculated Gestational Age is less than 182 days or the Postmenstrual Age is greater than 426 days then an error message will appear and the child cannot be randomised.

Do not use the terms “Conceptual Age” or “Post Conceptual Age” and try to avoid using the term “Prematurity”. When recording EDD, note on the CRF which method is used to calculate EDD (menstrual period, assisted reproduction or scan).

Note: the date of randomisation used in the program will be the current date Australian Eastern Standard Time.

Reference:
American Academy of Pediatrics Policy Statement. Age terminology during the Perinatal Period. *Pediatrics.* 2004;114:1362-1364.

Appendix II

We expect a little over half the children that are enrolled to be from Australia/NZ sites. We plan to use Australian grants to cover the costs of establishing the study and costs for recruitment and assessment within Australia/NZ. UK grants will cover costs in UK and US grants to cover costs in the UK.

The RA, psychologist and paediatrician labour costs will be reimbursed to each site as payment per child enrolled.

Grants

The Murdoch Childrens Research Institute has provided $40,000 seed funding for this study. This will be spent meeting the costs for 2006 and part of 2007. Dr Davidson has been awarded an MCRI research fellowship to coordinate this study running for 3 years at 0.25 EFT salary support. We have also received $48,000 from ANZCA.

We will apply for $550,000 NH&MRC funding to cover direct costs of recruitment and assessment, and also to cover the salary at 0.25 EFT for A Davidson and P Hardy and 0.5 EFT for the project officer Suzette Sheppard for the duration of the study.

Boston Children's Hospital has already allocated funding to cover establishing the study in the US and recruiting in the Boston area. The US based investigators will also seek further specific US funding (FAER, SPA). In the UK, Dr Morton is seeking funding in the UK from the HTA.

Similar to the Australian strategy with NHMRC funding, the US will apply for NIH and the UK for MRC funding. The likelihood of successfully receiving funds from NIH. MRC and NHMRC are expected to substantially increase once we have established recruiting and have preliminary data on apnoea.

Appendix III

TARGETS FOR STUDY

Period ending	Sites running	Patients recruited per period	Total recruited
1/12/2006	2	12	12
1/04/2007	9	70	82
1/10/2007	13	159	241
1/04/2008	15	177	418
1/10/2008	15	132	550
1/04/2009	15	110	660