The University Of Sheffield. Clinical Trials Research Unit. Sheffield Teaching Hospitals NHS NHS Foundation Trust MAGIC

MAGIC

The MAGIC trial (Melatonin for Anxiety prior to General anaesthesia In Children): A Multicentre, Parallel Randomised Controlled Trial of Melatonin Versus Midazolam in the Premedication of Anxious Children Attending for Elective Surgery Under General Anaesthesia

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Sheffield Clinical Trials Research Unit (CTRU)

The MAGIC trial (Melatonin for Anxiety prior to General anaesthesia In Children): A Multicentre, Parallel Randomised Controlled Trial of Melatonin Versus Midazolam in the Premedication of Anxious Children Attending for Elective Surgery Under General Anaesthesia

This document describes a clinical trial, and provides information about procedures for entering participants. The protocol is not intended for use as a guide to the treatment of other patients. Amendments may be necessary; these will be circulated to known participants in the trial.

Contents

Abbreviations - Definition of terms

AE	Adverse event
AR	Adverse reaction
ASA	American Society of Anesthesiologists
BNF	British National Formulary
CI	Chief Investigator
CRF	Case Report Form
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTRU	Clinical Trials Research Office
DMEC	Data Monitoring and Ethics Committee
DMP	Data Monitoring Plan
ENT	Ear, Nose and Throat
FPS-R	Faces Pain Scale – Revised
GA	General anaesthetic
GABA	gamma-Aminobutyric acid
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
IB	Investigator Brochure
ICH	International Conference on Harmonisation
ITT	Intention to treat
IMP	Investigational Medicinal Product
MHRA	Medicines and Healthcare Products Regulatory Agency
mYPAS-SF	Modified Yale Preoperative Anxiety Scale (Short Form)
NIHR HTA	National Institute for Health Research Health Technology Assessment
PACU	Post-Anaesthesia Care Unit
PAED	Paediatric Index of Mortality
PHBQ-AS	Post Hospitalisation Behaviour Questionnaire for Ambulatory Surgery
PI	Principal Investigator
PIBA	Press in Bottle Adaptor
PPI	Patient and Public Involvement
QA	Quality Assurance
QALY	Quality-adjusted life-year
QRI	QuinteT Recruitment Intervention
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SD	Standard deviation
SOP	Standard Operating Procedure
STAI	State-Trait Anxiety Inventory
STH	Sheffield Teaching Hospitals NHS Foundation Trust

SUSAR	Suspected Unexpected Serious Adverse Reaction
TAU	Theatre Admission Unit
TMF	Trial Master File
TMG	Trial Management Group
TMP	Trial Monitoring Plan
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction
VSRS	Vancouver Sedation Recovery Scale

Agreement Page

The clinical study as detailed within this research protocol (Version 4.1, dated 21 Sep 2020), or any subsequent amendments, involves the use of an investigational medicinal product and will be conducted in accordance with the UK Policy Framework for Health & Social Care (2017), the World Medical Association Declaration of Helsinki (1996), Principles of ICH-GCP, and the current regulatory requirements, as detailed in the Medicines for Human Use (Clinical Trials) Regulations 2004 (UK S.I. 2004/1031) and any subsequent amendments of the clinical trial regulations.

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Protocol amendments

Version	Reason for amendment
1.0	N/A – first version
2.0	Updated in response to REC request to remove the £10 vouchers for qualitative study interviewees
3.0	Updates include: - Change from PHBQ to PHBQ-AS - Removal of post box test - Update to non-permitted medication - Change to allow verbal assent for all children - Change to allow for nurse prescribers - Change to allow for postal return CHU9D questionnaires at follow up - Change of timing for post-operative assessments to every 15 mins from every 10 mins - Removal of out of hours unblinding system - Replacement of 'until stage 2 recovery completion' definition with 'up to 2 hours post arrival to PACU'
4.0	Updates include: - Change to expand inclusion criteria to allow 3 and 4 year old children to be recruited - Change to expand inclusion criteria to include more surgical specialities: gastroenterology, radiology, plastic, orthopaedic, urology or other general surgery - Change to clarify assent requirement from children. Children who neither provide assent nor decline the trial (due to high anxiety) can be enrolled based on parental consent and PI decision. Children who verbally decline to participate must not be included. - Change for those sites who do not have dedicated pre-operative clinics, to allow the team to send study information prior to the day of surgery. This will be based on PI decision of the suitability of the patient to receive this information. - Change to randomisation system from stratification to minimisation. - Change to allow children the option of reviewing the information sheet or the video and not a requirement to undertake both. - Clarification of secondary safety and efficacy objectives and outcomes. - Addition of CHU-9D proxy questionnaire for children aged 3-4.
4.1	Updates include:

	- Change to clarify assent from highly anxious children not mandatory and can be based on parental and PI (or delegated individual) decision alone - Change to clarify baseline assessments can be undertaken after randomisation - Change to allow remote consent and interviews for the qualitative sub-study in light of the 2020 COVID-19 pandemic.

Trial summary

Study Title:	The MAGIC trial (Melatonin for Anxiety prior to General anaesthesia In Children)
EudraCT no:	2018-000991-13
Sponsor:	Sheffield Teaching Hospitals NHS Foundation Trust
Funder:	NIHR HTA (project number 16/80/08)
ISRCTN no:	18296119
Project start date:	1st March 2018
Project end date:	28th February 2021
Study Design:	A double blinded, multicentre, parallel randomised controlled non-inferiority trial
Participants:	624 anxious children undergoing elective dental, ophthalmologic, ENT, gastroenterology, radiology, plastic, orthopaedic, urology or other general surgery (and 624-1248 parents will also be included).
Setting:	Participants requiring day-case elective ENT, ophthalmologic, dental, gastroenterology, radiology, plastic, orthopaedic, urology or other general surgery under general anaesthesia (GA) in secondary/tertiary care will be recruited
Inclusion criteria (see section 5.3):	1. Children aged 3-14 years 2. Children undergoing day-case elective dental, ophthalmologic, ENT, gastroenterology, radiology, plastic, orthopaedic, urology or other general surgery under general anaesthesia. 3. Pragmatically assessed by healthcare professionals as requiring premedication as per local standard care for high/expected high levels of preoperative distress prior to elective surgery under general anaesthetic, including known negative experiences, failed anaesthesia, parents displaying high levels of distress, additional/special needs or judged as unable to tolerate GA without premedication 4. ASA grades I & II 5. Parent or person with parental responsibility able to give written, informed consent
Exclusion criteria (see section 5.4):	1. Not undergoing elective, day-case dental, ophthalmologic, ENT, gastroenterology, radiology, plastic, orthopaedic, urology or other general surgery under general anaesthesia 2. Not displaying level of anxiety that would usually warrant premedication under the standard NHS care pathway 3. Reason for premedication other than anxiety 4. Current prescription of melatonin, midazolam or other non-permitted drug (please see section 7.11.2) 5. Obstructive sleep apnoea 6. ASA grades III, IV & V 7. Severe learning disability rendering child unable to communicate even with specialised support 8. Parent declines for their child to participate in trial
Intervention Treatment Summary:	0.5 mg/kg melatonin (max 20 mg) 30 mins prior to transfer to theatre
Usual Care:	0.5 mg/kg midazolam (max 20 mg) 30 mins prior transfer to theatre

Randomisation:	Participants will be randomised to either the intervention arm or control arm in the ratio of 1:1
Anticipated recruitment period:	18 months
Duration of follow-up:	Participants will be followed up for 14 days from day 0 (day of surgery)
Hypothesis:	Melatonin is not inferior to midazolam in reducing anxiety in children pre-GA with fewer side effects
Feasibility Objectives:	<u>Feasibility objectives:</u> To undertake an internal pilot trial to determine the feasibility of a full-scale trial, in terms of: 1. Recruitment 2. Retention (adverse events reporting and PHBQ- AS follow-up) 3. Allocation concealment and blinding
Primary Objective:	To assess whether melatonin is non inferior in dealing with pre-operative anxiety evaluated using the mYPAS-SF score over the three following standard preoperative time points recommended for the scale: 1. Start of transfer to TAU 2. Entry to TAU 3. Administration of anaesthesia
Secondary Objectives:	<u>Safety and Efficacy objectives:</u> 1. To evaluate if melatonin, in relation to midazolam is superior in dealing with secondary efficacy and safety outcomes (anaesthetic turnaround time, recovery time, PAED, VSRS, FPS-R, analgesia requirements, PHBQ-AS, adverse events, orientation and cognitive/psychomotor function) 2. To evaluate if melatonin, in relation to midazolam is Non inferior in dealing with secondary efficacy outcomes (anaesthetic failure rate) 3. To describe Serious Adverse Events data (summarised both at patient level and event level) and report listings between the different arms. <u>Qualitative objectives:</u> 4. An integrated qualitative study is proposed to explore experiences of recruitment and the acceptability of the two drugs. <u>Economic objectives:</u> 5. Fully-integrated health economic analysis to estimate the cost-effectiveness of introducing melatonin, compared to midazolam, over the study period. A decision tree model will be developed to estimate cost-effectiveness and cost per QALY over a 1 year period
Definition of end of trial:	The end of the trial is defined as the date of the last recruited participant's day 14 follow up visit. Sites will be closed once data cleaning is completed and the regulatory authority and ethics committee will be informed

Lay summary

The hospital anaesthetic room is a worrying place for a child, and reducing their distress leads to a better overall experience, and also improves recovery from the anaesthetic, reduces pain after surgery and avoids unnecessary reappointments and delays to operations. Currently, those children with high levels of distress are recommended a “premedication”; that is, a medicine to reduce anxiety ahead of surgery. Midazolam – the current premedication for an anxious child needing an anaesthetic – is effective, although it has many side-effects including loss of coordination and risks to breathing. Midazolam can also have unpredictable effects on anxiety, with some children becoming overexcited rather than being calmed. Melatonin, which also has anxiolytic properties, offers an alternative calming medicine, has shown promise as it avoids midazolam’s side-effects.

We will compare melatonin with midazolam in anxious children undergoing general anaesthetic for dental, ophthalmologic, ear-nose-throat (ENT), gastroenterology, radiology, plastic, orthopaedic, urology or other general surgeries. These types of treatment are the most common reasons for children to have an anaesthetic in the UK. We shall carry out the research in a number of large hospitals across England including specialist children’s centres.

We will look at children’s anxiety from the time of entering hospital until being given the anaesthetic to see if there is a difference between how good the two medicines are at calming children. We will also look at the side-effects of each medicine and assess the cost of each medicine to the NHS. After the operation, a research nurse will continue to look for side effects for 2 hours post-operatively or until each child leaves hospital, whichever is sooner. The nurse will also assess for other beneficial effects thought to occur with using melatonin, such as reducing the confusion and distress that can come after an operation as a child wakes up. Parents will be contacted by phone 2 weeks after the operation to check no problems have occurred after leaving hospital and also to complete a final questionnaire.

The views of those people who the treatment is aimed at are very important to us, and we have designed the study having taken advice from children who have already experienced a general anaesthetic for dental, ophthalmologic and ENT treatments. They have helped us identify the most important things for the trial to assess and have also provided advice on how the trial should be done. In order to get more information about what the children receiving melatonin felt about their treatment, we will invite some of the children to return after the main study to discuss how the trial went. We will ask more in-depth questions about their experience, whether they felt the medicine worked well and how acceptable it was to them.

Our work will help determine whether melatonin is a better premedication than midazolam, and we will aim to change NHS policy on pre-medications in children, should melatonin be found to be a better treatment. We will submit reports of our work to healthcare policy makers so that this change can be brought about. The conclusions of the trial will be made available to front line NHS staff at participating hospitals across all care disciplines. The study team will make sure that information also reaches the most important stakeholders of all; patients themselves.

2. Introduction

2.1 Background

There are approximately 600,000 new episodes of care per year for children aged 3-14 in the NHS, with 36% of attendances relating to day case procedures[1]. Day case and inpatient surgery therefore represent a significant proportion of NHS activity delivered to children, the majority of which is provided under general anaesthesia. Anxiety ahead of general anaesthesia is common, with up to 50% of children displaying manifestations of distress-behaviour at the point of anaesthetic induction[2]. Anxiety and distress in a child may lead to non-compliance and result in rescheduling of elective surgery; it may furthermore lead to greater post-operative pain, agitation and behavioural changes after surgery including sleep disturbance[3–7].

Midazolam, the current standard premedication given to an anxious child ahead of surgery has been shown to be effective[8], although there are numerous adverse effects which make the medication less than ideal. One major consequence of benzodiazepine drugs such as midazolam is a sedative effect, which necessitates theatre transfer of the pre-medicated child on a trolley, and also significantly delays post-operative recovery[9,10]; the current method of premedication therefore adds a significant burden on both resources and throughput. Further concerns relating to midazolam include the potential for respiratory suppression[11], and also unpredictable effects on children, which may result in agitation rather than anxiolysis – particularly in those children with additional needs[12].

The increased incidence of learning disabilities with repeated anaesthetic exposure has been documented in a landmark study by Wilder *et al*[13], which highlighted the potential long-term risks of using sedative agents such as benzodiazepines in anaesthesia of young children.

There is therefore a clear need to replace midazolam with an alternative anxiolytic in order to avoid short-, medium- and long-term consequences associated with the drug, although the overriding requirement to have available an effective premedication for the management of the anxious child ahead of anaesthesia must be met.

Melatonin is a functionally diverse hormone involved in the entrainment of circadian rhythm, exerting its effects on the two melatonin receptor subtypes, MT1 and MT2, distributed throughout the central nervous system[14]. MT1 receptors are most concentrated in the pituitary gland and hypothalamus, reflecting the circadian role of the hormone, whereas MT2 receptors are more concentrated in the retina and are considered to be related to light-dependent function[15]. Melatonin's anxiolytic properties have been confirmed in the adult population[16], and are considered to be a consequence of a facilitatory role in GABA transmission[17].

Unlike data confirming the success of melatonin as an anxiolytic in adults[18–24], trials assessing the effects of melatonin in children have produced heterogenous results[25–31]. The variability of findings may relate to differing doses of melatonin, as well as varied outcome measures and inter-examiner reliability. Moreover, previous trials have often investigated a general paediatric population rather than identifying specifically anxious children, thereby markedly diluting observable effects as an anxiolytic compared to either active or placebo control.

Melatonin offers many potential benefits over midazolam. These benefits may include greater paediatric acceptance of taste, walking rather than bed transfer from holding to theatre, improved postoperative analgesia, reduced postoperative sedation,

reduced postoperative sleep disturbance, improved recovery times and avoidance of respiratory suppression. Indeed, a report on reducing the risk of overdoses of midazolam injections in adults, named the NPSA 2008 RRR011 rapid response document, highlighted the risks of bolus dosing midazolam in adults[32], and identifying a safer alternative drug which bears comparable anxiolytic effect in children is an important healthcare priority.

2.2 Rationale

Previous trials analysing the success of melatonin as a pre-medication in children have demonstrated conflicting results; the target population in such trials has been inclusive of non-anxious children, and therefore the true effect of melatonin on the anxious child versus any comparator is likely to have been diluted. We therefore propose to include only those cases that would normally receive pre-medication as per local practice at sites for anxiety as part of the standard care pathway.

Dental extractions and tonsillectomies compose the two most common operations for children undergoing general anaesthesia in the UK, accounting for 60,000 and 34,000 operations per year, respectively[33,34]. Site of surgery, operative time and postoperative pain are comparable in these groups. Dental and ENT surgery therefore constitute the most significant patient base for undertaking research into anaesthetic premedication. Although having a smaller number of operations per year (18,00 procedures) ophthalmology provides a further group of potential patients[1]. The anaesthetic care pathway of dental, ophthalmology and ENT patients is identical to other specialties, maintaining external validity of preoperative anxiety measures to that of the general preoperative population. A comparable postoperative patient group also carries the advantage of allowing robust assessment of complications such as pain and recovery time; such measures would otherwise demonstrate high variability if assessed using a more heterogeneous surgical cohort. Children undergoing elective dental, ophthalmologic or ENT operations are usually medically fit and well, which enhances the validity of using existing safety data for melatonin as reference safety information.

After the pilot phase of the trial, in reference to the lower recruitment numbers than anticipated from only enlisting from dental, ophthalmology and ENT patient pools, the TSC agreed the study should expand to include other surgical specialities. These specialities include gastroenterology, radiology, plastic, orthopaedic, urology or other general surgery paediatric patients. The main part of the MAGIC trial will involve recruitment of all these patients using randomisation by minimisation. The primary end point mYPAS-SF assessment is validated to children as young as two years old[35]. Further details regarding this change is provided in section 6.

Systematic review of the literature has identified seven studies which have assessed the efficacy of melatonin in children prior to surgery. In three studies melatonin was demonstrated to be as effective as midazolam, with two studies showing comparable reductions in anxiety[27,29], and a further study demonstrating a comparable reduction in propofol requirements. In two further studies where midazolam was not the direct comparator, melatonin was again found to be as effective as the active control[28,36]; due to sample size considerations, one of the papers highlighted a need for further studies to be done[31]. A final study identified through systematic review, utilised melatonin at doses lower than those applied to the other 6 studies, with melatonin found to be less effective than midazolam in reducing anxiety, although demonstrated some efficacy including a direct dose-dependent effect on emergence delirium[25].

Evidence suggests that Melatonin's anxiolytic effect is concentration-dependent, with those studies demonstrating equivalence to active controls having used higher dosing

regimens[26–28,31] compared to studies with more limited effect[25]. The dosing schedule of 0.5mg/kg is a standard high dosing protocol[26,27,29–31] due to a maximum solute concentration of 1mg/ml being achievable for immediate release melatonin suspension, along with fluid volume restrictions related to consumption of premedication in a preoperatively starved child. Recently, Impellizzeri et al also chose this same dosing schedule in children aged 8-14 years[31], based on knowledge of melatonin's dose dependent analgesic and sedative effects[37]. The results of this study demonstrated comparable anxiety levels between children who received melatonin versus midazolam, although the authors again highlighted the need for a further, larger scale study. Despite a capped dose, melatonin has been used in much higher concentrations in the management of neonates[38]. Phase 1 studies in neonates have included: giving 5 daily enteral doses of melatonin 10 mg/kg (no capped dose specified) alongside hypothermia in children with a gestational age of >6 hours with hypoxic ischaemic encephalopathy (HIE); and a single dose of 20 mg melatonin in premature neonates with sepsis.

Several studies have demonstrated administration of melatonin in large doses is associated with low toxicity or side effects in adults[39–42], reflecting the safety of the drug. Most studies involving melatonin have reported no adverse events, and very few adverse events have been reported where melatonin has been used as a pre-medication, all of which have been minor. Only two studies have reported adverse events[28,36]. In both, the events were reported across all arms of the studies, including a placebo arm in one trial. As placebo and melatonin groups reported comparable adverse events, both in type and frequency, the research indicates that the adverse events were likely due to the anaesthetic process rather than a result of melatonin consumption. Adverse events included post-operative nausea and vomiting, cough and hiccough.

Less success has been noted in trials utilising melatonin in concentrations below 0.5mg/kg[25,28]. The scheduling of melatonin 30 minutes prior to theatre transfer is consistent with a recent systematic review of melatonin's clinical pharmacokinetics in fasted children exposed to immediate release formulations[44], and is furthermore consistent with a pragmatic trial design comparing against usual care (midazolam, 30 minutes prior to transfer)[44].

Previously, the only licensed formulation of melatonin in the UK was Circadin (2mg tablets), although this is commonly used off-license in children with sleep disorders and attention deficit hyperactivity disorder (ADHD). Modified release melatonin such as Circadin is used to assist sleep maintenancy, whereas immediate release melatonin is used to help induction of sleep in children with sleep disorders and ADHD. In June 2019, Colonis Pharma received marketing authorisation for Melatonin 1mg/ml Oral Solution, indicated for short-term treatment of jet-lag in adults. The formulation does not currently have approval for use in paediatric populations (0-18). Unlicensed melatonin liquid is also used in patients with feeding tubes, as the tablets can block the tube. An unfeasible number of Circadin tablets would be required for use as premedication, and a crushed suspension would require an excessive volume of liquid due to starvation requirements pre-GA. The Children's BNF does however provide guidance for accessing unlicensed immediate release formulations of melatonin[46]. All immediate release preparations are unlicensed, such as the liquid formulations of KidMel, KidNaps, & NeoMel. The melatonin liquid used for MAGIC will be manufactured as closely to KidMel as possible.

Melatonin has limited solubility in water, restricting the maximum concentration that can be achieved in solution to 1 mg/ml. Prior to GA, the maximum volume of liquid permitted by anaesthetists is generally 20 ml, and therefore a maximum dose of 20 mg melatonin can be given. As midazolam is also routinely capped at a dose of 20 mg

prior to GA, capping melatonin at 20 mg would also be necessary for blinding purposes.

In summary, the available data suggest a 0.5 mg/kg dose, with capped dose of 20 mg, is safe for use in this population and setting. Several studies have indicated that this dosing regimen is efficacious[26,27,29,31]. Furthermore, the water solubility of melatonin, along with pre-GA starvation requirements, limit the maximum dose as described above. Therefore, a definitive trial is needed to test whether this premedication is effective in the anxious (rather than general) pre-surgical population.

2.3 Justification for why this research is needed now

Midazolam, the current standard premedication in anxious children undergoing general anaesthesia, is recognised as having an unfavourable side-effects profile and presents a degree of risk which is accepted due to an overriding need for compliance in the anaesthetic room. At present, a suitable alternative drug is not available. There is compelling evidence that melatonin is a suitable anxiolytic premedication in adults[16,18–24], although as yet there is insufficient evidence to adopt melatonin as a routine premedication in children awaiting general anaesthetic. If the evidence observed in the adult population is transferrable to a paediatric context, it might imply not only safer practice, but also increased patient throughput, improved postoperative recovery, simplified drug storage requirements (as midazolam is a schedule C drug) and reduced side-effects. A pragmatic RCT assessing the effectiveness of melatonin compared to the current standard is therefore warranted.

3. Aims and objectives

The main aim of this study is to evaluate the clinical non-inferiority and cost effectiveness of melatonin, and to assess melatonin's side-effects profile compared to midazolam in the premedication of anxious children prior to general anaesthesia for elective ENT, ophthalmological, dental, gastroenterology, radiology, plastic, orthopaedic, urology or other general surgeries, .

3.1 Objectives

3.1.1 Feasibility objectives:

To undertake an internal pilot trial to determine the feasibility of a full-scale trial, in terms of:

- Recruitment
- Retention (adverse events reporting and PHBQ-AS follow-up)
- Allocation concealment and blinding

3.1.2 Clinical objectives

<u>Safety and Efficacy</u>

To evaluate if melatonin, in relation to midazolam is:

- Non inferior in dealing with pre-operative anxiety evaluated by mYPAS-SF score over the following three standard preoperative time points recommended for the scale[35, 47]:
    - Start of transfer
    - On entry into anaesthetic room
    - On induction of anaesthesia

- Superior in dealing with secondary safety and efficacy outcomes (anaesthetic turnaround time, recovery time, PAED, VSRS, FPS-R, analgesia requirements, PHBQ-AS, adverse events, orientation and cognitive/psychomotor function)
- Non inferior in dealing with secondary efficacy outcomes (anaesthetic failure rate)

To describe Serious Adverse Events data (summarised both at patient level and event level) and report listings between the different arms.

3.1.3 Integrated qualitative study

An integrated qualitative study will explore experiences of recruitment and the acceptability of the two drugs. Qualitative studies have helped inform strategies to improve recruitment to previous trials, explore clinician and patient's responses to an intervention and to explain the findings of the RCT[47]. The qualitative study will take place during the internal pilot and the main trial.

The qualitative component of the internal pilot will contribute to understanding the recruitment process and retention as recommended by the QuinteT Recruitment Intervention (QRI)[48]. Semi-structured interviews will be conducted by an experienced research associate with a purposive sample of children, parents and other stakeholders (those recruiting and clinical team members) to ensure a wide range of views are captured. Diversity will be sought in terms of: trial participation status (patient consented or withdrawn), type of surgery, patient demographics and trial site. Interviews will ideally be conducted face-to-face, however interviews may be conducted via telephone if this is not convenient. Sampling, data collection and analysis will occur concurrently until data saturation has been reached. A topic guide has been devised to explore accounts of: the trial recruitment process, verbal and written information, influences on decision making and trial procedures. Obstacles and challenges to recruitment will be identified for discussion with the CI, TMG and CTU to inform the design of the main trial and recommendations made of ways to support those involved in recruitment.

The qualitative component of the main trial will explore the experiences of:

- Children and parents of the acceptability of the pre-medications, including taste, reduction of distress, the child's post-operative recovery and any longer term implications. Based on our PPI work these were highlighted as areas of concern.
- The clinical team members (research nurses, nursing staff, anaesthetists, operating department practitioners) of children having the two pre-medications, including their perspectives on patient refusal of GA, acceptance of the drugs, distress reduction, impacts on recovery such as postoperative sedation and any adverse effects.

3.1.4 Economic objectives

Fully-integrated health economic analysis to estimate the:

- Cost-effectiveness of introducing melatonin, compared to usual care, over the study period and modelled to 1yr using both a cost per successful procedure and cost-per QALY approach

4. Trial design

This study is a parallel group (allocation 1:1), double blind (anaesthetist, surgeon, IMP administrator and observer nurse will be fully blinded, with patient allocation concealment), individual participant-randomised, stratified, multicentre, trial to evaluate the non-inferiority of melatonin against midazolam in dealing with pre-operative anxiety (mYPAS-SF score) in children undergoing surgery. The study will be conducted in twenty to twenty five large NHS trusts. Qualitative interviews will be conducted in 5-6 sites during the internal pilot to identify any problems encountered with recruitment and inform the trial procedures during the main trial. Further qualitative interviews in the main trial will provide insight into stakeholder and patient acceptability of both drugs.

Trusts will be running the study across a number of surgical specialities, so anaesthetic trainee research networks will be involved in recruitment, co-ordinated by a research nurse. This method has previously demonstrated rapid recruitment in other high-profile NIHR-funded trials[50, 51]. Eligibility may be assessed at a pre-surgery appointment if applicable, but eligibility will only be confirmed at the point of clinical assessment on the day of surgery by the site PI, consultant surgeon, consultant anaesthetist, or surgical trainees in order to identify those children usually assessed as requiring a premedication for preoperative anxiety. After opportunity to further consider the study information, option to view a child-friendly information video and ask questions, candidates shall be approached for consent by the site PI, consultant surgeon, consultant anaesthetist, anaesthetic or surgical trainees, or research nurse. On the day of surgery, participants shall be randomised to receive midazolam or melatonin 0.5mg/kg pre-medication 30 minutes prior to theatre transfer (capped dose of 20 mg). Patients shall be observed by a blinded research nurse or medical trainee throughout the preoperative period until anaesthetic induction, and then monitored post-operatively upon arrival in PACU until the point of discharge. Patients shall be followed up 14 days after discharge by research nurses or anaesthetic or surgical trainees via telephone to assess post-discharge outcome measures and to ensure safety follow-up. The trial is powered to show, in the primary analysis, whether melatonin is equivalent to midazolam in the reduction of children's anxiety prior to general anaesthesia, quantified by mYPAS-SF scale.

Pre-medication usage shall be audited at each site prior to trial commencement, during pilot and at 12 months in order to confirm that comparable proportions of patients are receiving pre-medication over the course of the trial, compare to the usual practice preceding trial commencement. Pragmatic assessment of suitability for pre-medication shall be consistent with Tan and Meakin's review article[52], which provides guidance on patient selection for pre-medication in the conjunction with alternative interventions including play therapy and other psychological interventions.

The selected age range covers the peak incidence of children attending dental, ophthalmological and ENT surgery as confirmed by local audit and the literature[53, 54].

4.1 Feasibility pilot

There will be an initial phase of the trial that will be an internal pilot. The internal pilot trial will be set up in a minimum of 10 sites. The progression criteria will be applied to data collected during the first 6 months of recruitment. To allow time for collation of 14-day follow-up data, the progression criteria will be assessed by the TSC at the end of the following month. The progression criteria will be based on achieving the objective criteria detailed above in Section 3.1.1. Clinical and patient-reported outcome data

from the internal pilot will be included in the final analysis. Recruitment will be ongoing during the time of analysing the pilot data.

Sheffield CTRU will aggregate study data to assess the feasibility of the research and intervention protocol. Eldridge *et al* discuss viewing progression criteria in pilot trials as guidelines rather than strict criteria by which to determine progression to the main trial[55]. The emphasis is placed on independent discussion of the feasibility of changes to the trial protocol to allow progression. We have employed the approach recommended by Eldridge *et al*[55] of a traffic light system to judge feasibility and the following feasibility criteria will be reviewed by the Trial Steering Committee:

Recruitment:

A) Red: trial is not feasible- accrual of fewer than 78 participants (40% of the target for the pilot and 12.5% of the target for the full trial), in the first six months of recruitment.

B) Amber: trial may be feasible if appropriate changes made- recruitment of between 79 and 155 participants in the first six months of recruitment would trigger discussion with the Trial Steering Committee regarding the changes possible to the trial protocol and procedures that could improve the recruitment to the trial. The qualitative interviews conducted during the internal pilot (see sections 4.3 & 12.3) will also inform possible procedural changes that are necessary.

C) Green: trial is feasible - accrual of 156 or more participants (80% of the target for the pilot and 25% of the target for the full trial), in the first six months of recruitment.

Retention:

A) Red: trial is not feasible- retention of fewer than 64 participants randomised between in the first six months of recruitment (approx. 40% of those expected to have completed their 2-week follow-up), all of whom should have received safety follow-up and post-discharge telephone follow-up.

B) Amber: trial may be feasible if appropriate changes made- retention of between 65 and 127 participants (41-79% of those expected to have completed their 2-week follow-up) randomised in the first six months of recruitment would trigger discussion with the Trial Steering Committee regarding the changes possible to the trial protocol and procedures that could improve the retention in the trial. The qualitative interviews conducted during the internal pilot (see sections 4.3 & 12.3) will also inform possible procedural changes that are necessary.

C) Green: trial is feasible – retention of 128 or more participants randomised in the first six months of recruitment (approx. 80% of those expected to have completed their 2-week follow-up), all of whom should have received safety follow-up and post-discharge telephone follow-up.

Preservation of blinding:

There is potential (although minimised as far as possible) for the anaesthetist and research nurse observer in the trial to become unblinded; both from the child's taste reaction and also the differing effects of trial medications on the child (melatonin provides anxiolysis without sedation). Midazolam's flavour is associated with rejection of the drug in 14% of cases[56]. To remove the possibility of unblinding of the anaesthetist and observer research nurse as a result of the child's taste reaction, a separate IMP administrator (either another research nurse or ward nurse) will

administer the trial IMPs. The IMPs will be packaged as blinded medications; so the potential for unblinding is only as a result of any possible child taste reaction. Both IMPs will have the same flavourant to mask the taste of the IMP as much as possible.

Any instances of suspected unblinding will be recorded, including the reasons for and time point of unblinding. The overall rate of unblinding and preservation of data integrity shall allow the trial steering committee to make an informed decision on trial feasibility and also allow discussion of future steps to improve blinding where necessary.

The observer research nurse and anaesthetist will be asked to complete a short data collection form which will record if

a) either personnel believe they have been unblinded
b) the reason for unblinding, for example, how the participant behaves
c) at what stage in the process of data collection unblinding occurred
d) the perceived group which the apparently unblinded child was allocated

This data will be presented as a standing agenda item on the 6-monthly TSC meeting and will be presented along with a summary of the frequency of reported unblinding, as agreed with the TSC at the first meeting.

Alternative trial designs were considered before concluding that the chosen approach to blinding was most appropriate to this study. These alternatives included 1) a double dummy design whereby both IMPs and matching placebos were used and 2) having both IMPs matched exactly for taste. These options were presented to a PPI group, who endorsed the chosen option over the double dummy design or taste-matching, due to the additional burden on the child to consume two trial medications as opposed to one, or be unnecessarily exposed to an unpleasant bitter taste that could dissuade them from fully consuming the active drug.

Double dummy design: In this design four IMPs would have been required. Children would have been asked to take two drugs, 1 being active drug, the other a placebo of the other drug. This would mean that any reaction to taste could be for the placebo of the active drug and therefore not unblind the IMP administrator. However, due to the differences between midazolam and melatonin it would become apparent which active drug the child had taken as midazolam is a strong sedative. Excess liquids are also prohibited prior to general anaesthetic and with the dosing proposed for the study this would have exceeded the limit. In addition, there were concerns of the child not taking the second IMP if the first one had a bitter taste meaning that they may not take the active drug. These factors, along with the additional cost of such a design, lead to the design being discarded.

Taste matched IMPs: In this design both IMPs would be taste matched so that the IMP administrator would be not be unblinded as a result of taste reactions. However, as this is to be a pragmatic trial, altering the IMPs in this way did not seem acceptable as it is not a reflection of the products within standard care. In addition to this, as acceptability of the IMPs is part of this trial, it was decided that this was not an appropriate trial design.

Whilst there is a difference in the effects of midazolam and melatonin, it was agreed that the double-blind trial design that has been adopted is the most pragmatic. The sedatory effects of midazolam are addressed in section 2.1 and the taste difference above and steps taken to avoid possible unblinding by these factors.

4.2 Primary endpoint

Preoperative distress by modified Yale Preoperative Anxiety Scale (mYPAS-SF)[35, 47] (on theatre transfer, on entry into anaesthetic room, on induction).

4.3 Secondary endpoints

4.3.1 Clinical endpoints

Efficacy:

- Emergence agitation (PAED index[57])
- Postoperative sedation (Vancouver Sedation Recovery Scale[58], recovery time)
- Postoperative pain (Revised Faces Pain Scale, FPS-R[59]; postoperative analgesia requirements, intraoperative local anaesthetic amount) – FPS-R to be both patient and nurse-reported
- Failed anaesthesia
- Orientation and cognitive/psychomotor function (Cooperation score[60])

PAED, VSRS and FPS-R indices to be recorded every 15 minutes in the post-anaesthesia care unit (PACU) for 2 hours after entry to PACU unless the child is discharged earlier than this.

Parent-reported:

- STAI (State-Trait Anxiety Inventory[61]) – parental anxiety; self-reported, measured at baseline
- Post-discharge behaviour, eating, anxiety, aggression, apathy and sleep disturbance (Post-Hospital Behaviour Questionnaire; PHBQ-AS[62]); by research nurse - telephone interview at 14 days

Harms/Adverse Events: all AEs/harms will be recorded. Known AEs are respiratory depression, nausea and vomiting, which will be monitored as part of adverse event collection. Post-operative vital signs and antiemetic use will also be recorded. Please see section 9 for further information on AE collection.

4.3.2 Qualitative endpoints

- As recommended by the QuinteT Recruitment Intervention (QRI) semi-structured interviews will be conducted with children, parents, those recruiting to the trial and clinical team members during the internal pilot. The findings of these interviews will identify improvements to the conduct and design of the main trial to aid recruitment and retention in the main trial.
- The qualitative component of the main trial will explore the experiences of the clinical team of children having the pre-medications and the acceptability of the drugs to children and parents.

4.3.3 Economic endpoints

- Cost-effectiveness analysis; resource use, health-related quality of life; CHU9D[63], costs and incremental cost-effectiveness (cost per QALY and cost per successful procedure).

4.4 Blinding

This will be a double-blinded study (as described in section 4.1) whereby the patient, treating physicians, surgeons, anaesthetists and assessor (RN, trainee or other trained person) will be blinded. The first research nurse (or ward staff member or other trained person) administering the IMP may become unblinded as a result of the child's taste reaction. The trial pharmacists will be unblinded.

4.5 mYPAS-SF training

All sites will be provided with mYPAS-SF training in order to ensure consistency of assessment across sites and staff[35, 47]. This will be detailed in a separate mYPAS-SF training document.

5. Selection and withdrawal of participants

5.1 Screening

The study will recruit children (aged 3-14 years) scheduled for elective dental, ophthalmological, ENT, gastroenterology, radiology, plastic, orthopaedic, urology or other general surgeries. Wherever possible, potential participants (i.e. those perceived as requiring a pre-med) will be identified at the time of pre-op assessment before the day of surgery (i.e. where this exists in the pre-operative pathway at an individual site) and will be approached with an information sheet. In those sites who do not have dedicated pre-operative clinics, based on individual PI decision, potentially anxious patients may also be sent study information prior to the day of surgery. Where this is not possible it will be done on the day of surgery. **Eligibility can only be confirmed on the day of surgery**. On the day of surgery, potential participants will be approached to enrol with the option of viewing an information video shown on a tablet computer and/or an age appropriate patient information sheet. Parents will also be provided with a written information sheet for the trial. .

As the study is a Clinical Trial of an Investigational Medicinal Product (CTIMP) a medically- or dentally-qualified individual (site P.I. or other with delegated responsibility) will confirm eligibility and provide clinical oversight.

Screening and enrolment logs will be maintained at site and requested by CTRU on a regular basis.

5.1.1 Patient referral pathway

Given the multi-disciplinary nature of the trial, each site should have a named lead surgeon in the relevant areas they are recruiting from and a lead anaesthetist.

As Trusts will be running this trial across multiple surgical specialties, often across more than one hospital site, we will involve anaesthetic and surgical trainee research networks in the work of recruitment, co-ordinated by a research nurse. It will ensure that when there are simultaneous clinics at different locations or the research nurse is unavailable/sites unable to provide other individuals to deputise, recruitment can proceed as normal. A research nurse, trial surgeon, anaesthetist, anaesthetic or surgical trainee will have an initial face-to-face discussion with each potential participant on arrival at pre-operative assessment where possible, or on the day of surgery. During this discussion the need for a pre-med will be determined and, if eligible, trial information will be given to the patient. Eligibility can only be confirmed by a delegated individual, as above.

5.2 Informed consent

If the individual is eligible for the study, then the anaesthetist, trial surgeon, research nurse or trainee will take consent. Parental consent is a requirement for child participation and the relevant forms must be signed. Written assent should also be sought from the child if possible, but it is not a mandatory requirement. In cases where a child is unable to give written assent, verbal assent can be taken and documented in the patient notes instead. In cases where the child is extremely anxious and neither assent nor declining participation can be determined, where parental consent has been obtained, it will be the decision of the PI (or delegated researcher able to take consent for the trial) as to whether they include the patient in the trial. The decision process around inclusion of these patients must be documented thoroughly in the patient notes. Consent must only be undertaken on the day of surgery. For morning-of-surgery consenting[64], consent shall take place in a side room to ensure no undue pressure is placed on the participants, with clinicians receiving trial-specific training as well as GCP training to safeguard a fair and equitable consent process. Child-centred resources will also be used, including a short video[65]. Local sites will tailor the consent and drug administration procedures to ensure that surgical consent for the operative procedure is obtained in advance of trial drug administration.

5.3 Inclusion criteria

1. Children aged 3-14 years
2. Children undergoing elective dental, ophthalmological, ENT, gastroenterology, radiology, plastic, orthopaedic, urology or other general surgeries under general anaesthesia.
3. Pragmatically assessed by healthcare professionals as requiring pre-medication as per local standard care for high/expected high levels of preoperative distress prior to elective surgery under general anaesthetic, including known negative experiences, failed anaesthesia, parents displaying high levels of distress, additional/special needs or judged as unable to tolerate general anaesthetic without premedication
4. ASA grades I & II
5. Parent or person with parental responsibility able to give written, informed consent.

5.4 Exclusion criteria

1. Not undergoing elective, day-case dental, ophthalmological, ENT, gastroenterology, radiology, plastic, orthopaedic, urology or other general surgeries under general anaesthesia
2. Not displaying level of anxiety that would usually warrant pre-medication under the standard NHS care pathway
3. Reason for pre-medication other than anxiety
4. Current prescription of melatonin, midazolam or other non-permitted drug (please see section 7.11.2)
5. Obstructive sleep apnoea
6. ASA grades III, IV & V
7. Severe learning disability rendering child unable to communicate even with specialised support
8. Parent declines for their child to participate in the trial

6. Randomisation and enrolment

Once eligibility has been confirmed and consent acquired, the participant will be randomly allocated, on a 1:1 basis, to either the control or treatment arm of the trial. The delegated person performing the randomisation will access a web-based randomisation system provided by epiGenesys through the Sheffield CTRU. Patient details (ID, date of birth and stratification variables) will be entered into the Sheffield CTRU web-based randomisation system and the treatment allocation and randomisation number will be returned. An email confirming randomisation will be sent to the PI, research nurses and trial pharmacist. Randomisation will be completed using minimisation on centre, surgical speciality and gender (male/female). Participants will be allocated a treatment pack by pharmacy that relates to the relevant IMP. Pharmacy will blind-label the pack before dispensing.

7. Trial treatment

In this trial both midazolam and melatonin will be an investigational medicinal products (IMPs). A flavourant will be added to both IMPs. Hospital stock midazolam and melatonin should not be used.

The IMPs are being manufactured by Huddersfield Pharmacy Specials and will be manufactured in accordance with GMP.

7.1 Dose

0.5mg/kg 1mg/ml midazolam or 1mg/ml melatonin will be used at a maximum dose of 20mg in 20ml. The IMP will be given as a single-dose on the day of surgery, 30 minutes prior to transfer to theatre.

7.2 Packaging

The IMPs will be supplied in a 25ml (to allow for overage) amber glass bottle with Press-in Bottle Adaptor (PIBA) insert, which will contain an oral/enteral syringe that is compatible with the press-in bottle adaptor. Blinded bottles will be individually packaged in a carton with a tear off label for pharmacy use.

7.3 Storage

IMPs should be stored in Pharmacy as per the IMP and Pharmacy manual. Temperature logs must be maintained throughout the trial and any temperature deviations must be reported to CTRU immediately upon becoming aware.

7.4 Ordering IMP

IMPs can only be delivered to recruiting sites once they have been activated which will be following MHRA and REC approval and CTRU confirmation of activation.

7.5 Dispensing

A medically qualified person, or nurse prescriber if delegated by the PI, on the delegation log, will provide a prescription to pharmacy for the trial participant. Local prescription templates may be used. Pharmacists will be responsible for dispensing the IMP in accordance with the MAGIC trial IMP and Pharmacy manual.

7.6 Administration

A trained research nurse, ward staff or trainee, as specified on the delegation log, will administer the blinded IMP orally via syringe to the patient 30 minutes prior to transfer to theatre. All administered drug should be recorded in the patient notes and on the relevant CRF. Please refer to the IMP and Pharmacy manual for further guidance on IMP administration.

7.7 Accountability

Pharmacy are required to maintain accountability logs of all received, dispensed and disposed IMP.

Please refer to the IMP and Pharmacy manual for further guidance.

7.8 Dose modifications

As this is a single-dose study, dose modifications will not be permitted.

If a child spits out their drug, then they should be observed to see if the drug has taken effect or not. If deemed fit for surgery, they shall continue with their assessments as per protocol. If the child is not fit for surgery following spitting out the drug or the anaesthetist wishes to re-dose the child with another medication, then the child will be discontinued from trial treatment and treated as a withdrawn patient (see section 8.8).

All incidents of spitting out IMP should be recorded on the relevant CRF.

7.9 IMP recall and destruction

Any unused or expired IMP shall be disposed of in line with local practice guidelines after seeking permission from the CTRU study manager first, as per the IMP and Pharmacy manual.

In cases where IMP needs to be recalled the CTRU will notify sites immediately of this and request the necessary IMP to be quarantined. The IMP must not be used unless authorised to do so by the CTRU.

7.10 Overdoses

An overdose of trial drug is considered unlikely in this study. An adverse event relating to overdose is also considered unlikely in this study, as participants will be in hospital at the time of receiving medication and under the care of a named anaesthetist. In the unlikely event of an error in the administration of the IMPs, this will be reported to the CTRU and the Sponsor as a protocol non-compliance, as soon as it is identified. This is likely to be assessed as a major non-compliance, and the Sponsor will advise on the appropriate action to be taken. The incident will also be reported through normal local Trust reporting procedures.

All medications taken by the participant will be recorded in the CRF, including dosage information, where specified, or overdose.

7.11 Concomitant mediations

7.11.1 Permitted concomitant medication

The following medications are permitted but must be recorded on the concomitant medication CRF:

- Anti-epileptics
- Stimulants
- Anti-depressants
- Antibiotics
- Other medication used as part of standard care that is not listed below

7.11.2 Non-permitted concomitant medication

The following medication is not permitted under any circumstances on the trial (other than those listed below):

- Melatonin
- Beta blockers
- Anti-coagulants
- Benzodiazepines
- Long term (defined as requiring regular prescriptions) sedative/hypnotic drugs

The following should be avoided but if the patient has taken them for more than two months and remained stable they will be permitted and should be recorded on the CRF:

- Amisulpride (Solian)
- Chlorpromazine (Largactil)
- Haloperidol (Haldol)
- Olanzapine (Zyprexa)
- Risperidone (Risperdal)
- Sertindole (Serdolect)
- Sulpiride (Sulpidil, Sulpor)
- Thioridazine (Melleril)
- Trifluoperazine (Stelazine)

Restrict/Take with caution:

- **CYP3A inhibitors**:
  - Azole antifungals
  - Macrolide antibiotics
  - HIV protease inhibitors
  - Diltiazem
  - Atorvastatin
- **CYP3A inducers:**
  - Rifampicin

7.12 Unblinding

An emergency unblinding (codebreak) procedure (described in the unblinding SOP) will be in place to enable hospital staff to reveal the allocation of treatment when it is deemed essential for their on-going clinical care to determine whether the patient received melatonin or midazolam. This will immediately provide treatment allocation to

the site and automatically alert the CTRU study team and local Principal Investigator (PI) by email that a participant has been unblinded.

Out of hours unblinding will not be available due to the unblinding system only being accessible by the research team or by telephone contact with CTRU staff.

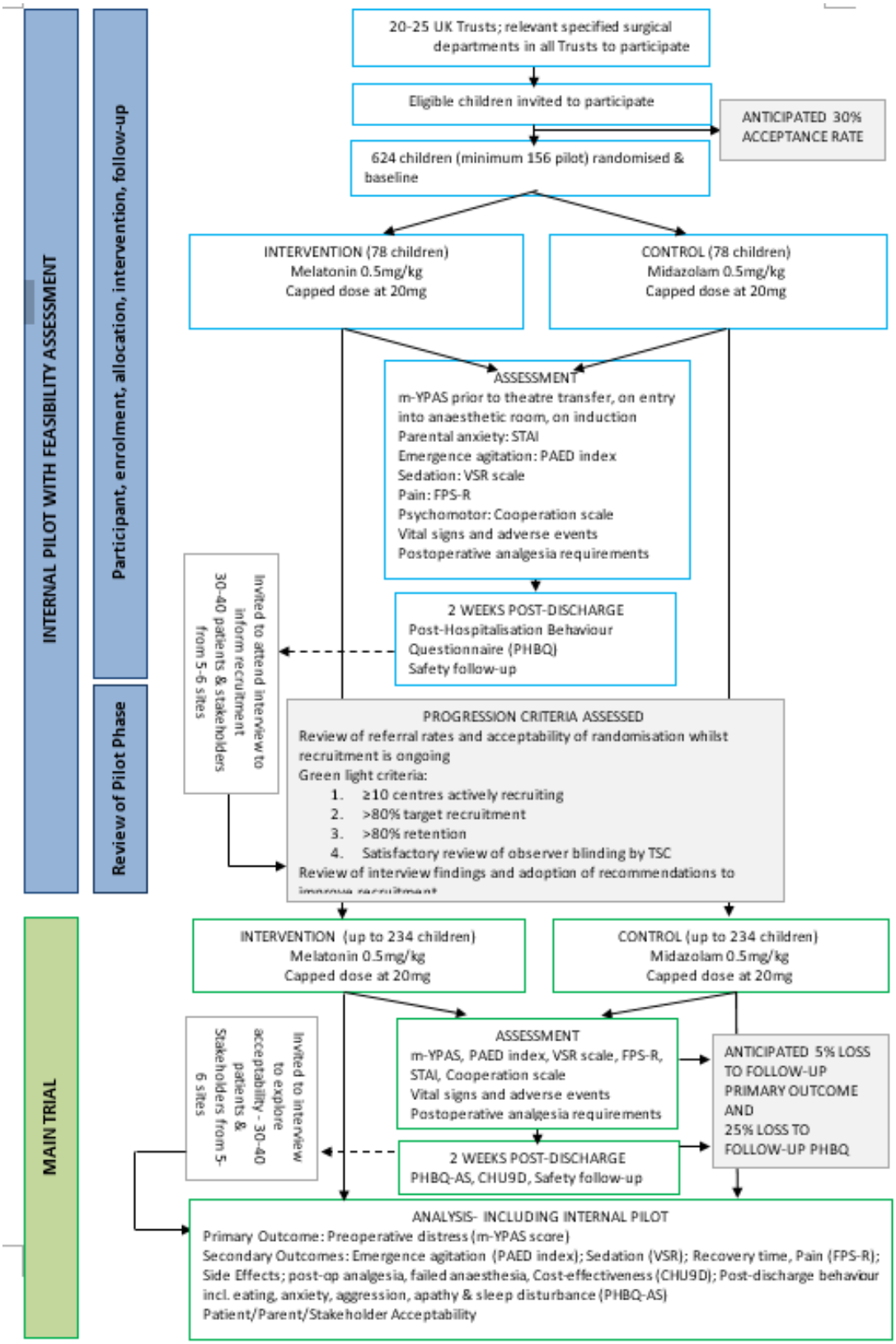
Melatonin has a half-life of 35-50 minutes[66], and therefore will be almost completely eliminated at the point of discharge to home, with most children who undergo day case dental or ENT surgery being admitted for a minimum period of around 4 half-lives of the drug. An out-of-hours unblinding service is therefore not required for melatonin, as potential adverse events are deemed only possible over the period the child is admitted for their surgery. Moreover, melatonin is an endogenous compound; basal levels of melatonin are present in a normal physiological state, and any small volumes of residual drug at the point of discharge will be of a concentration below that of the natural diurnal variation of melatonin within the plasma[67, 68].

The comparator drug (midazolam) is routinely administered to anxious children ahead of anaesthesia. One of the main effects of clinically-significant levels of midazolam is sedation; post-operative assessments over the recovery period ensure that every child is discharged after sedation from all drugs, including the general anaesthetic, has worn off before allowing discharge home. Midazolam is recognised as delaying discharge home due to its sedative effect; this delay represents a waiting period over which the remainder of midazolam is cleared, leading to loss of sedation which is required for the judgement of discharge readiness. Again, by virtue of the standard post-operative protocols in place to assess discharge readiness, a child will only be discharged home at the point where clinically insignificant levels of midazolam remain within the plasma, and therefore there is no need for unblinding after the point of discharge.

For these reasons, the assessment has been made that out of hours cover by the research teams or by CTRU is not required.

8. Assessments and procedures

8.1 Study flow chart



8.2 Trial assessments

Baseline

On the day of surgery, following consent and eligibility confirmation, the following assessments should be completed by staff delegated to do so by the PI on the delegation log:

To be completed by research team:

- American Society of Anaestheiologists physical status
- mYPAS-SF
- Cooperation score
- Vital signs
- Resource Use

To be completed by the children aged 7-14:

- QoL – CHU9D

Information on the patient's medication history, concomitant medications and demographics should be collected and recorded in the patient's notes.

To be completed by one or both parents/legal guardian:

- STAI
- QoL – CHU9D (proxy questionnaire for children aged 3-6 or 3-4, selection to be based on patient's age))

IMP administration

IMP should be administered 30 minutes prior to the patient transfer to theatre. The person administering the IMP will ensure the patient notes are updated as such. If the administrator is a ward nurse who does not have GCP training then another member of the trial team will need to update the CRF. Pharmacy are responsible for updating the accountability logs.

Transfer to Theatre

Following administration, the blinded assessor will accompany the patient on transfer to the theatre. The following information needs collecting at the start of transfer:

- mYPAS-SF (start of transfer, on entry into anaesthetic room, on induction of aneasthesia) – this must be completed by the same member of staff who undertook the baseline mYPAS-SF assessment.
- Additional medication given
- Adverse events
- Timings of:
    - Entry to theatre
    - Administration of anaesthesia

Surgery

During surgery the following information should be recorded:

- Time of completion of surgery

- Additional medication given
- Adverse events

Post-surgery

Post-surgery the following information should be recorded:

- Additional medication given including analgesia usage
- Adverse events
- Time to post-operative recovery
- Vital signs (every 15 minutes if recorded on the patient chart)
- Time to discharge readiness
- Time to actual discharge

The following assessments should be completed every 15 minutes in post-operative recovery by the research team for 2 hours after entry to post-operative recovery unless the child is discharged (or confirmed ready for discharge) earlier than this:

- Observer reported FPS-R
- Cooperation score
- PAED index
- VSRS

The following assessments should be completed every 15 minutes in post-operative recovery by the children team for 2 hours after entry to post-operative recovery unless the child is discharged (or confirmed ready for discharge) earlier than this:

- FPS-R

14 day follow up via telephone

The following information should be recorded at the Day14 visit:

- Additional medication
- Adverse events

The following assessments should be completed by a parent:

- QoL – CHU9D (proxy questionnaire for children aged 5-6 or 3-4, selection to be based on patient's age)
- PHBQ-AS
- Resource Use

The following assessments should be completed by the child:

- QoL – CHU9D (for children aged 7-14)

In the event the child will not be available at the time of the telephone call, eg. as they will be at school, please provide the parent or guardian with the age appropriate CHU9D and a pre-stamped envelope to take away with them for completion on day 14. The questionnaire should then be posted to CTRU using the pre-stamped envelope.

A study completion form should be completed for all children who complete the trial.

8.3 Schedule of assessments

Assessments	Screening	Baseline	30 minutes pre-transfer to theatre	Start of transfer to theatre	Entry to anaesthetic room	Induction of anaesthesia	During surgery	Arrival at PACU	Post-surgery	Discharge	14 days post-surgery [d]
Eligibility assessment	X										
Consent[e]		X									
Current medication		X									
Demographics		X									
ASA score		X									
STAI[c]		X									
mYPAS-SF		X		X	X	X					
QoL – CHU9D[h]		X									X
Vital signs		X							X[f]	X	
Cooperation score		X							X[f]		
Resource Use		X									X
IMP administration[a]			X								
Adverse events		X	X	X	X	X	X	X	X	X	X
Clinical outcome data[b]					X	X	X	X	X	X	

Concomitant medications[g]			X	X	X	X	X	X	X	X	X
Patient reported FPS-R[f]									X		
Observer reported FPS-R[f]									X		
PAED index[f]									X		
VSRS[f]									X		
PHBQ-AS											X

[a]*IMP to be administered 30 +/- 10 minutes prior to transfer to theatre*
[b]*Clinical outcome data:*

- *Failure to progress with anaesthesia*
- *Time of entry to anaesthetic room*
- *Time of anaesthetic induction*
- *Point of unconsciousness*
- *Use of sevoflurane*
- *Local anaesthetic type, amount and concentration*
- *Time of surgery completion*
- *Time of entry in PACU*
- *Time to discharge readiness*
- *Time to actual discharge*

[c]*To be completed by one or both parents /legal guardians*
[d]*To be completed via telephone*
[e]*Parental consent required for child participation as well as completion of study assessments.. Additional parental consent to be taken if more than one parent/legal guardian completing assessments.*
[f] *To be repeated every 15 minutes for 2 hours unless the child is discharged earlier than this*
[g] *To include all additional medication given including analgesia usage but not medications given for anaesthesia*
[h] *Proxy CHU9D form available for 3-4 and 5-6 year old children, selection to be based on patient's age*

8.4 Procedures for assessing safety

The following measures will be used to assess safety:

- PAED
- VSRS
- FPS-R
- PHBQ-AS
- Analgesia requirements

In addition to these measures adverse events will be collected and monitored.

8.5 Procedures for completing the Quality of Life CHU9D questionnaire

The CHU9D is a paediatric generic preference based measure of health related quality of life. It consists of a descriptive system and a set of preference weights, giving utility values for each health state described by the descriptive system, allowing the calculation of quality adjusted life years (QALYs) for use in cost utility analysis.

Children aged 7-14 years will use the full questionnaire and a proxy questionnaire is available for either 3-4 or 5-6-year-old children.

8.6 Procedure for completing the qualitative interviews

8.6.1 Children and parents

Participants will be asked during the initial consent process if they agree to being approached to take part in a qualitative interview. A purposive sample of those who agree to be approached will be contacted by the research associate to arrange the interview and consent. Children will be identified from MAGIC trial records using variables of trial participation status (patient consented or withdrawn), type of surgery, gender and age. Interviews will ideally be conducted face-to-face in a location convenient to participants although telephone interviews will be offered for convenience. Before the start of each interview the researcher will obtain informed consent from the parent/guardian for their child and themselves to be interviewed and assent will also obtained from the child.

Each child-parent/guardian dyad will take part in one interview together. The interviews will be audio-recorded. To facilitate communication with children at face to face interviews, participatory approaches will be available for the child to choose (e.g. drawings, playing with Play-Doh and toys)[69]. The topic guide for the pilot trial was developed from literature on recruitment and retention in trials. The topic guide for the main trial will be developed based on the findings of the pilot trial interviews, from the literature on acceptability and through discussions with the trial management group. The interviews will be transcribed by an external company and the transcripts checked.

8.6.2 Stakeholders

Stakeholders involved in MAGIC will also be invited to take part in an interview. For the pilot trial a purposive sample of those involved in taking consent and clinical team members (including research nurses, nursing staff, anaesthetists, operating department practitioners) will be recruited to explore issues of recruitment and retention. For the main trial a purposive sample of members of the clinical team will be recruited to explore their perspectives on patient refusal of general anaesthesia, acceptance of the drugs, distress reduction, impacts on recovery such as postoperative sedation and any adverse effects.

Stakeholders will be contacted via email to invite them to take part with a participant information sheet attached. If they express an interest in being interviewed a suitable time and location to hold the interview will be organised. If a face-to-face interview is not possible the interview will be conducted over the telephone and recorded. Prior to the interview informed consent will be obtained. Interviews will be audio-recorded, transcribed by an external company and the transcripts checked. Data will be anonymised.

8.7 Loss to follow up

Participants will be defined as lost to follow up if they do not attend visits or contribute data after reasonable attempts have been made to contact the patient. This is defined as three failed attempts to contact the patient or by day 21 post-surgery, whichever comes sooner. Post-surgery questionnaires will be sent in the post to the patient on these occasions as a final attempt to collect the missing data. If a participant is lost to follow up, this will be recorded in the CRF using the study completion/discontinuation form.

8.8 Patient withdrawals

Participants may withdraw their consent for the study at any time, without providing a reason for this. If this occurs, this will be documented on a study completion/discontinuation form and the patient notes, and no further data will be collected for this participant for the study. If a participant does volunteer a reason for their withdrawal of consent, this will be documented on the form. Any data collected up to the point of the participant's withdrawal will be retained, and used in the final analysis, and this is made clear to the patient at the time of consent.

Participants may also be withdrawn from the study after receiving the blinded IMP (due to a clinical decision e.g. spitting out the IMP and requiring a re-dose), These patients will not be followed up but will be included in the ITT analysis.

8.9 Trial closure

The study will end after the last follow-up visit of the last study participant. Sites will be closed once data cleaning is completed and the regulatory authority and ethics committee have been informed.

9. Safety reporting

ICH-GCP requires that both investigators and sponsors follow specific procedures when reporting adverse events/reactions in clinical studies. These procedures are described in this section.

9.1 Definitions

The definitions of the EU Directive 2001/20/EC Article 2 based on the Principles of ICH-GCP apply to this protocol. These definitions are given in Table 1 below.

Table 1: *Definitions of Adverse Events and Reactions*

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical study patient to whom a medicinal product has been administered irrespective of relationship
Adverse Reaction (AR)	Any AE that is judged, in the opinion of the PI, to be related to an investigational medicinal product or a non-investigational medicinal product.
Unexpected Adverse Reaction (UAR)	An adverse reaction, the nature or severity of which is not consistent with the information about the medicinal product in question set out in the Investigator Brochure (IB).
Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR)	Respectively any adverse event, adverse reaction or unexpected adverse reaction that: • Results in death • Is life-threatening* • Requires hospitalisation or prolongation of existing hospitalisation** • Results in persistent or significant disability or incapacity • Congenital anomaly/birth defect • Is another important medical event***

**The term life-threatening in the definition of a serious event refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event that hypothetically might cause death if it were more severe, for example, a silent myocardial infarction.*

***Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, that has not worsened or for an elective procedure do not constitute an SAE.*

****Other important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event/experience when, based upon appropriate medical judgement, they may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.*

9.2 Recording and reporting of adverse events

All AEs and ARs will be recorded on the adverse event report form, within the participant CRF, including those that fulfil the criteria for being serious (see section 9.1). Sites are asked to enter all available information onto the MAGIC trial database as soon as possible after the site becomes aware of the event.

SAEs, SARs and SUSARs will require more detailed information to be recorded. In such cases, the event must also be reported to the Sheffield CTRU within 24 hours of

the site becoming aware of the event. The CTRU will notify the Sponsor of each of these events.

9.3 Study centre/Investigator responsibilities

All AEs and ARs, whether expected or not, will be recorded in the participant's medical notes and recorded on an adverse event form within the CRF. SAEs and SARs will be notified to the CTRU within 24 hours of the investigator becoming aware of the event.

9.3.1 Assessment of relatedness

The investigator should make an assessment of relatedness prior to sending the SAE form to the CTRU where possible. Relatedness will need to be assigned to one of three categories: reasonable possibility of being related, no reasonable possibility of being related or not assessable. Events judged as reasonably possibly related or not assessable will be considered as related for the purpose of onward reporting.

9.4 SAE notification procedure

CTRU will be notified of all SAEs, within 24 hours of the investigator becoming aware of the event). Investigators must notify CTRU of all SAEs occurring for each participant from the time of consent until the participant has completed the trial (i.e. 14 day follow-up period

The SAE form must be completed by the investigator (a medically or dentally qualified person). In the absence of the investigator the form will be completed by a member of the study team and faxed/emailed as appropriate. The responsible investigator will subsequently check the SAE form, make changes as appropriate, sign and re-send the form to CTRU as soon as possible.

All SAE forms must be sent by fax to 0114 222 0870 or email to ctru-saes-group@sheffield.ac.uk. Receipt of the initial report should be confirmed within one working day. The site research team should contact the study team at CTRU if confirmation of receipt is not received within one working day. Alternative arrangements during holiday periods will be confirmed by the study manager.

Concomitant medications will not be collected on SAE forms as standard. However, for any event classified as a SAR or SUSAR CTRU may request additional information on concomitant treatments to facilitate onward reporting.

9.4.1 Follow up

Initial SAE reports must be followed by detailed reports when further information becomes available. SAEs will be followed up by CTRU for the relatedness assessment, if not initially provided, until complete and the CI has made an expectedness assessment where appropriate.

Participants must be followed up until clinical recovery is complete and laboratory results have returned to normal or baseline, or until the event has stabilised. Follow up information will be provided on an SAE report marked as such.

9.5 CTRU responsibilities

The Chief Investigator or delegate will be responsible for the assessment of expectedness. An unexpected adverse reaction is one not previously reported in the Reference Safety Information (RSI) used in the study, or one that is more frequent or more severe than reported in the RSI. If a SAR is assessed as 'unexpected', it is classified as a SUSAR.

Section 4.8 of the Melatonin 1mg/ml oral solution SmPC will be used as the RSI for all events deemed related to melatonin. Section 4.8 of the Buccolam 2.5mg oromucosal solution SmPC will be used as the RSI for all events deemed related to midazolam.

The CTRU is responsible for reporting each SAE to the Sponsor in the form of a line listing at pre-defined intervals.

The DMEC and TSC will also receive information on all AEs and SAEs, at a frequency agreed with each committee and documented in the appropriate charter/terms of reference.

9.6 SUSARs

All SAEs should be recorded on an SAE form, and faxed or emailed to the CTRU within 24 hours of discovery. The CTRU will be responsible for assessing expectedness and, when appropriate, reporting SUSARs to the Sponsor, for notification to the MHRA as per the MAGIC SAE Reporting Procedures document. Each site will be informed of SUSARs occurring across the study.

9.7 Reporting overdoses during the trial

If an overdose occurs, this will be recorded using the Overdose Report form within the CRF. The Chief Investigator and the TMG will be informed and clinical advice sought where required. A protocol non-compliance form should also be completed.

Any participant who has an overdose during the course of the study will be followed up, irrespective of any treatment withdrawal or changes.

The DMEC and TSC will be advised at each meeting, of any overdoses reported since their previous meeting

10. Statistics

10.1 Sample size

A sample size calculation has been based on the primary outcome of mYPAS-SF scores at three time points (start of transfer to TAU, entry to TAU and administration of anaesthesia), whilst adjusting for baseline scores, on a non-inferiority basis. Following a review of current literature and expert opinion, it was suggested that a minimum clinically important difference would be 12.96 on the mYPAS-SF scale. A non-inferiority margin of one-third of this will be used, giving a value of 4.3 (0.172 standardised effect size). This represents less than one-point change on any one of the domains within the mYPAS-SF outcome. A standard deviation of 25.0[70], a correlation of 0.5[71] between baseline and follow-up measures, a one-sided test with an alpha of 2.5% and power of 90% assuming no difference between the drugs, results in

a sample size requirement of 592 patients (296 per arm). Assuming 5% attrition, 624 children will need to be recruited to the trial. 1-2 parents per child will also be recruited into the trial (therefore 624-1248 parents).

For the qualitative components, previous similar studies suggest data saturation will be reached with 30-40 interviews in the pilot trial and a similar number in the main trial.

10.2 Analysis

10.2.1 Internal pilot

At the end of the internal pilot, a review of recruitment and retention will be evaluated on the current trial participants. No statistical testing will be applied at this stage and the data will be evaluated for all participants and not split between treatment group.

10.2.2 Interim Analysis

There are no planned interim analyses but the DMEC will review unblinded data and may recommend the trial is stopped due to safety concerns.

10.2.3 Analysis populations

Intention-to-treat population (ITT): comprised of all participants that are randomised regardless of drug intake, non-compliance, protocol deviations or withdrawals that occur post-randomisation. Participants will be analysed based on the treatment they were randomisation to. Patients will be included within the analysis as long as they have completed the baseline measure and at least one of the three follow-up measures. The primary analysis population will not contain any imputed data but a sensitivity analysis on the primary analysis outcome will contain data from multiple imputation.

Per-protocol population 1: comprised of all participants that are randomised, took at the whole dose of the study drug and had no major protocol deviations and therefore adhered to trial treatment. The participants will be analysed based on the treatment they received as defined by the protocol, as there cannot be any cross-over within the study between treatments, this will always be the treatment group that the participant was randomised to.

Per-protocol population 2: As with per-protocol population 1 but did not need to take the whole dose of the drug but received at least some of the drug.

Safety population: comprised of all participants who received at least one dose of the study drug. The participants will be analysed based on treatment they were receiving.

Primary analysis will be completed on both ITT and per-protocol population 1 which will both need to demonstrate statistically significant non-inferiority to declare the treatment as non-inferior (ICH E9 guidelines).

10.2.4 Statistical analysis

The primary outcome will be analysed using a multiple linear regression model with treatment, time, baseline value, stratification variables and participant (as a random effect) entered into the model. The 95% confidence intervals for the difference between treatment groups will be reported as well as the associated p-value. Non inferiority will

be declared if the upper limit of the two sided 95% confidence interval on the difference (melatonin vs midazolam) does not exceed 4.3.

As this analysis assumes that there is going to be a consistent treatment effect over time, a sensitivity analysis will be completed using the same model as outlined above but including the interaction term of time and treatment to evaluate is this assumption is valid.

Other continuous, longitudinal secondary outcomes will be analysed in the same way. A logistic regression will be undertaken to analyse longitudinal binary outcomes using a model similar to that for the continuous outcomes. Differences between treatment groups will be reported as odds ratios with associated 95% confidence intervals and p-values.

In the case of missing data, the missing data mechanism will be explored and multiple imputation may be applied as a sensitivity analysis as appropriate. Other sensitivity analyses will be performed in order to evaluate the robustness of the primary analysis[72].

The statistical analysis will be reported according to CONSORT guidelines extension for non-inferiority trials[73,74].

A full Statistical Analysis Plan (SAP) will be written and circulated to the Trial Management Group and independent committees before being signed-off.

10.2.5 Analysis of qualitative data

Framework analysis will be used for analysis of the qualitative data from the internal pilot and main trial as it provides a pragmatic approach[75] which produces results that can be easily incorporated into RCTs[76]. The analysis will involve the following stages: identifying initial themes, labelling the data, sorting the data by theme and synthesising the data. NVivo software will be used to manage the data. During analyses of data from the internal pilot constant comparison techniques will be used, as recommended in the QRI, to identify 'clear obstacles' and 'hidden challenges'[48]. The results will be discussed with the CI, TMG and CTU.

During analyses of data from the main trial regular meetings will be held with a subgroup[77] of the TMG and separately with the PPI group to discuss the emergent themes and consider the implications of these for the findings of the trial. The analyses will be conducted by an experienced research associate with support from Prof. Zoe Marshman.

10.2.6 Health-Economic analysis

Analysis will be done in conjunction with the HEAP (Health economic analysis plan).

Measures

The primary analysis will be a cost-effectiveness analysis using the resource use and the number of successful procedures undertaken over the study period; comparing immediate release oral melatonin with standard care (oral midazolam). The analysis will take a NHS and Personal Social Services (PSS) perspective, with an additional cost - utility analysis that looks at costs per quality adjusted life year using the CHU-9D questionnaires taken. A decision tree model will then be developed to estimate cost-effectiveness over a 1yr period.

Resource Use

Resource use information related to clinical time, anaesthetic time, recovery time, medication costs including premedication costs and also pain and anti-emetic medication used as in-patient and at discharge ("To Take Outs") will be collected on case record forms (CRF). The CRF will be completed by the research nurse at baseline and 14 days. Parental time off work will be collected by questionnaire at baseline and 14 days and will be used in sensitivity analysis to look at cost effectiveness of melatonin from a wider perspective. Unit costs will be derived from appropriate sources including: NHS Agenda for Change (2016), British National Formulary (2016), and the Office of National Statistics annual survey of hours and earnings (2016).

Incremental Cost Effectiveness Ratio (ICER)

Mean incremental costs and effects will be combined into an ICER, and sampling uncertainty represented by plots on the cost-effectiveness plane and associated cost-effectiveness acceptability curves (CEACs). The CHU-9D will be used to measure quality of life at baseline and 14 days. However, given that QALYs will be collected over a short time period and it is unclear whether sedation has long-term effects on quality of life, this analysis will not be used as a primary analysis but the cost per QALY will be examined in secondary analysis (National Clinical Guideline Centre, 2010). QALYs will be estimated using straight line interpolation between data points. If there are issues with missing data then this will be imputed using multiple imputations assuming data are missing at random[78].

Cost Effectiveness Analysis

A decision tree will be constructed to explore the cost-effectiveness of melatonin over a 1-year time frame. This model will follow a similar structure to that by the National Clinical Guideline Centre that looked at sedation in children and young people for diagnostic therapies (National Clinical Guideline Centre, 2010). As with the trial based analysis, results will be presented in terms of an ICER and CEACs.

11. Trial supervision

The MAGIC trial will be led by the Chief Investigator working in co-ordination with the co-applicants and Sheffield CTRU. The Sponsor will be Sheffield Teaching Hospitals NHS Foundation Trust. Sheffield CTRU will take responsibility for project management and have set up a Division of Duties for governance and safety reporting with the Sponsor. There is a dedicated trial manager who is supervised by the CI and a Sheffield CTRU Research Fellow, and will liaise with the whole study team. The CTRU Research Fellow will provide oversight for delivery of all CTRU support including trial management, data management, QA, randomisation, statistics, health economics, analysis reporting and dissemination. Health Research Authority (HRA) approval will be sought prior to commencement of the trial at participating centres.

Three committees will govern study conduct, deliver the trial, monitor study performance and ensure its safety; TSC, DMEC and Trial Management Group (TMG). The committees will function in accordance with Sheffield CTRU standard operating procedures.

11.1 Trial Steering Committee (TSC)

The TSC will consist of an independent chair, dental professionals, ENT clinician and anaesthetists and one patient representative. The role of the TSC is to provide

supervision of the protocol and statistical analysis plan, to provide advice on and monitor progress of the study, to review information from other sources and consider recommendations from the DMEC. The TSC can prematurely close the trial, should this be recommended by the DMEC. The TSC will meet at six-monthly intervals as outlined in the TSC terms of reference.

11.2 Data Monitoring and Ethics Committee (DMEC)

The DMEC will consist of an independent statistician, dentist and anaesthetist with clinical trial expertise. The DMEC will review reports provided by the CTRU to assess the progress of the study, the safety data and the critical endpoint data as required. The DMEC will assess the recruitment progress following the pilot phase to assess whether continuation to the main study is feasible. The DMEC will assess the accumulating data, and in particular any data related to the safety in accordance with the DMEC charter.

The DMEC will meet 6-monthly with meetings comprising an open session to which members of the study team may attend, followed by a closed session with independent members only and to which unblinded data will be available. The DMEC may recommend the trial is stopped or modified on the basis of the data, in writing, to the chair of the TSC.

All life threatening and fatal SAEs will be reported to the DMEC within 24 hours of the CTRU being notified.

11.3 Trial Management Group (TMG)

The Trial Management Group (TMG) consists of the CI, other site PIs, collaborators and staff from CTRU. The CI will chair monthly meetings to discuss the day-to-day running of the study, including any implementation issues. The TMG will receive reports from the TSC and DMEC to manage trial progress.

12. Data collection

12.1 Clinical, patient-reported and harm data

The timing of post-operative data collection will be anchored to the time on entry into post-operative recovery, since this is reliably documented in the clinical record, and shall also represent the point at which the patient regains contact with the observer nurse, or trainee. Safety follow-up and post-discharge data will be collected simultaneously by research nurses, anaesthetist or surgical trainees by telephone at 14 days following an initial text reminder.

12.2 Data confidentiality

Participant confidentiality will be respected at all times and the principles of the UK General Data Protection Regulation (GDPR) will be followed. The investigators will ensure that identifiable data is kept securely and protected from unauthorised parties.

Data management will be provided by the University of Sheffield Clinical Trials Research Unit (CTRU) who adhere to their own Standard Operating Procedures (SOPs) relating to all aspects of data management, including data protection and

archiving. A separate data management plan (DMP) will detail data management activities for the study in accordance with SOP (Shef/CTRU/DM009).

The investigator or delegate at each site will maintain comprehensive and accurate source documents to record all relevant study information regarding each participant. The CTRU will provide worksheets (shadow CRFs) to allow the site staff to check what is required for a visit. The worksheets do not need to be completed if alternative source documentation is provided. However, they must be completed for data points where source documentation is not collected elsewhere and where completed, worksheets must accurately reflect the database as they form part of the source data.

Participants will only be identified on the study database by their trial ID number. All CRFs will only identify the participant by their trial ID also. All participants will be assigned a unique study ID number at screening that will link all of the clinical information collected for them on the study database. It will also be used in all correspondence between CTRU and participating centres.

Study records, including source data, will be stored for 25 years after the completion of the study by participating sites, before being destroyed. Each investigator is responsible for ensuring records are retained and securely archived during the retention period and information supplied to the Chief Investigator and Sponsor. Where trial related information is documented in the medical records, those records will be retained for at least 25 years after the last patient last visit. Access will be restricted to authorised individuals.

Data held by the CTRU will be stored in accordance with the archiving Standard Operating Procedure (CTRU SOP PM012) for 25 years following completion. Archived documents will be logged on a register which will also record items retrieved, which will be done by named individuals, from the archive. Electronic data will be stored in an 'archive' area of the secure CTRU server for a minimum of 25 years to ensure that access is future-proofed against changes in technology. Electronic data may also be stored (e.g. on a compact disc or USB flash drive) with the paper files.

13. Data access and quality assurance

The study will use the CTRU's in-house data management system (Prospect) for the capture and storage of study specific participant data. Access to Prospect is controlled by usernames and encrypted passwords, and a comprehensive access management feature will be used to ensure that users have access to only the minimum amount of data required to complete tasks relevant to their study role. This feature can also be used to restrict access to personal identifiable data.

The study nurse (or relevant trained and delegated individual) at each site will enter data from source documents into the study specific Prospect database when available. After data have been entered, electronic validation rules are applied to the database on a regular basis; discrepancies are tracked and resolved through the Prospect database. All entries and corrections are logged with the person, date and time captured within the electronic audit trail.

Participant confidentiality will be respected at all times. All research data will be anonymised, and will only be identifiable by the participant's study ID number. No patient identifiable data will be transferred from the database to the statistician.

Participating investigators shall agree to allow study-related monitoring, including audits, ethics committee review and regulatory inspections by providing direct access to source data and documents as required. Participants' consent for this will be obtained as part of the consent process.

13.1 Site assessment

Throughout this protocol, the trial 'site' refers to the hospital at which trial-related activities are conducted. Participating sites must be able to comply with:

- Trial treatments, clinical care, follow up schedules and all requirements of the trial protocol
- Requirements of the UK Policy Framework and the Medicines for Human Use (clinical trials) Act (SI 2004/1031 and all amendments)
- Data collection requirements

All participating sites must have an appropriate Principal Investigator (PI) i.e. a health care professional authorised by the site, ethics committee and regulatory authority to lead and coordinate the work of the trial on behalf of the site. Other investigators at site wishing to participate in the trial must be trained and approved by the PI, and this must be documented on the site delegation log and training records. All investigators must be medical doctors or dentists and have experience in either paediatric dentistry, ENT, ophthalmology, gastroenterology, radiology, plastic, orthopaedic, urology or other general surgery or anaesthetics.

All site staff, including research staff, must be appropriately qualified by education, training and experience to perform the trial related duties allocated to them, which must be recorded on the site delegation log. CVs for all staff must be kept up to date, and copies held in the Investigator Site File (ISF), and the Trial Master File (TMF). Staff should also have completed GCP training within the last 2 years, ensure this is renewed every 3 years, and copies of the GCP certificate are held within the ISF and TMF.

Before each site is activated, capability to conduct the trial will be assessed and documented using a site assessment form. The CTRU will arrange a site initiation visit with each site, site staff will be trained in the day-to-day management of the trial and essential documentation required for the trial will be checked. Once all the required documentation is in order, and site staff have been trained, CTRU will formally activate the site to start recruitment. Sites should not open to recruitment until CTRU have provided this confirmation of activation.

13.2 Risk assessment

Risk assessment has been performed by the Sponsor and CTRU prior to the start of the study, and will be continually evaluated in accordance with Sheffield CTRU Standard Operating Procedures. The level of risk, as agreed with the Sponsor, is Type B as per MHRA guidelines. Central and on-site monitoring (including Pharmacy) will be undertaken at a level appropriate to the detailed risk assessment, and will be documented in the Trial Monitoring Plan (TMP). This will include (at a minimum):

1. Source Data Verification (SDV)
2. SAEs/SUSARs – reported to the Sponsor and followed up to resolution
3. Resolution of data queries
4. Investigator site file and pharmacy file maintenance

5. Training records for site staff (trial specific and GCP) and appropriate delegation of duties
6. Patient consent procedures and eligibility
7. Reporting of protocol non-compliances

13.3 Reporting serious breaches and non-compliances

A “serious breach” is a breach which is likely to effect to a significant degree –

- the safety or physical or mental integrity of the participants of the trial; or
- the scientific value of the trial

The sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase. The sponsor of a clinical trial will notify the licensing authority in writing of:

- any serious breach of the conditions and principles of GCP in connection with that trial;
- or the protocol relating to the trial, as amended from time to time, within 7 days of becoming aware of that breach.

All serious breaches and protocol non-compliances should be reported to CTRU within 24 hours of becoming aware.

13.4 On-site monitoring

On-site monitoring will be performed according to the MAGIC TMP and in line with the Sheffield CTRU Study Monitoring SOP.

A site initiation visit will be performed at each participating site before each site recruits their first participant. During this visit, the Monitor will review with site staff the protocol, study requirements and their responsibilities to satisfy regulatory, ethical and Sponsor requirements.

Regular site monitoring visits will occur throughout the study and additional visits will be undertaken where required. At these visits, the Monitor will review activity to verify that the:

1. Data are authentic, accurate and complete.
2. Safety and rights of the patient are being protected and
3. Study is conducted in accordance with the approved protocol and study agreements, GCP and all applicable regulatory requirements.

Accurate and reliable data collection will be assured by verification and cross-check of the eCRF against Investigator’s records by the Study Monitor (source document verification) (see section 12 for further details on data collection). Study Monitor will contact and visit sites regularly to inspect CRFs throughout the study, to verify adherence to the protocol and completeness, consistency and accuracy of the data being entered on the CRFs. Monitoring visits will also include a pharmacy visit to review processes, documentation and accountability of study drug.

A close-out visit will be performed after the last patient last visit at each site. Further close-out activities may be carried out remotely after this time, up to database freeze.

13.5 Central monitoring

CTRU staff will review entered data for possible errors and missing data points. A central review of consent forms will also be completed, and sites will be requested to post consent forms to CTRU on an ongoing basis. This will be made clear to the participant prior to their consent to the trial. CTRU will receive pharmacy dispensing logs centrally, which will be taken to on-site monitoring visits to allow full source data verification. Details will be included in the IMP and Pharmacy manual.

13.6 Regulatory information

As a CTIMP, the trial will be conducted in accordance with ICH GCP and the Clinical Trials and Medicine for Human Use (Clinical Trials) Regulations 2004. A site agreement between the Sponsor, participating sites and Sheffield CTRU outlines responsibilities of all parties and is to be signed prior to commencement of recruitment at sites. All clinicians responsible for recruiting patients to the trial will be required to complete training in International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP).

14. Publication

Results of the study will be disseminated through peer reviewed scientific journals and at clinical and academic conferences, as well as submission of a final report to the funder, which will be made available online.

Details of the study will also be made available on the Sheffield CTRU website. Summaries of the research will be updated periodically to inform readers of ongoing progress.

Information throughout the course of the study may be disseminated at conferences and other events, providing this does not relate to any endpoint, but these must be with the approval of the Chief Investigator, and the funder must be informed with sufficient notice.

The study will also be added to the EudraCT trial repository and the ISRCTN register.

The results will be published on a freely accessible database within one year of completion of the trial. Anonymised datasets will be made available after publication of the main trial results.

Full details, including guidance on authorship are documented in the MAGIC Publication and Dissemination Plan.

15. Finance

MAGIC is funded by the UK NIHR Health Technology Assessment (HTA) Programme (project number 16/80/08) and details have been drawn up in a separate agreement. Further details are included in the collaborator agreement.

16. Ethics approval

Before initiation of the study at participating sites, the protocol, informed consent forms, and information materials to be given to the participants will be submitted to an NHS Research Ethics Committee for approval. Any further amendments will be submitted and approved by the ethics committee.

In addition, the study will be submitted for HRA review and approval. Recruitment of study participants will not commence until the letter of approval has been received from the HRA.

17. Regulatory approval

The study will be conducted in accordance with the UK Clinical Trials Regulations 2004 and as such will be submitted to the Medicines and Healthcare Regulatory Agency (MHRA) for review. The study will not commence recruitment until a Clinical Trial Authorisation (CTA) has been granted by the MHRA.

18. Sponsor and site approval

Before initiation of the study at participating sites, the protocol, informed consent forms, and information materials to be given to the participants will require sponsor approval.

In addition, the study will be submitted to individual sites for review and approval. Recruitment of study participants will not commence at a site until letter of approval/confirmation of capability & capacity (CCC) has been issued.

19. Indemnity / Compensation / Insurance

The University of Sheffield has in place clinical trials insurance against liabilities for which it may be legally liable, and this cover includes any such liabilities arising out of this clinical study.

Standard NHS indemnity operates in respect of the clinical treatment which is provided.

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