Title:	**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 Dental and ENT Surgery Under General Anaesthesia
Sponsor:	**Sheffield Teaching Hospitals NHS Foundation Trust**
	RESEARCH PROTOCOL **Draft version 0.2** **8th November 2017**

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Protocol amendments
None

1. SUMMARY OF RESEARCH

DESIGN Parallel group, single blind, individual participant-randomised controlled trial.

SETTING Elective ENT and dental surgery under general anaesthesia in secondary/tertiary care.

TARGET POPULATION Anxious children undergoing elective dental or ENT surgery.

INCLUSION CRITERIA Pragmatically assessed by healthcare professionals as requiring premedication for high/expected high levels of distress prior to elective dental/ENT surgery under GA, e.g. known negative experiences, failed anaesthesia, additional needs or judged as unable to tolerate GA without premedication; ASA grade I & II; not currently prescribed melatonin/midazolam; aged 6-14.

EXCLUSION CRITERIA Severe learning disability rendering child unable to communicate even with specialised support; not satisfying inclusion criteria.

HEALTH TECHNOLOGIES ASSESSED
Control: Oral midazolam 0.5mg/kg (max 20mg) 30 mins prior to transfer to theatre.
Intervention: Immediate release oral melatonin 0.5mg/kg (max 20mg) 30 mins prior to theatre transfer.

COSTS AND OUTCOMES
Primary outcome: Preoperative distress by modified Yale Preoperative Anxiety Scale (m-YPAS)[6] (on theatre transfer, on entry into anaesthetic room, on induction)

Secondary outcomes:

Clinical:
- emergence agitation (PAED index[10])
- postoperative sedation (Vancouver Sedation Recovery Scale[11], recovery time)
- postoperative pain (Revised Faces Pain Scale, FPS-R[12]; 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[13], modified post-box test[14])

    PAED, VSR and FPS-R indices to be recorded every 10 minutes in the post-anaesthesia care unit (PACU) until stage 2 anaesthetic recovery is completed.

Patient-reported:
- STAI (State-Trait Anxiety Inventory[15]) – parental anxiety; self-reported, measured at baseline
- post-discharge behaviour, eating, anxiety, aggression, apathy & sleep disturbance (Post-Hospital Behaviour Questionnaire; PHBQ[16]); by research nurse - telephone interview at 14 days

Qualitative:
- 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 in the main trial.

- The qualitative component of the main trial will explore the experiences of the clinical team of children having the premedications and the acceptability of the drugs to children and parents.

Economic:
- Cost-effectiveness analysis; resource use, health-related quality of life; CHU9D[17], costs and incremental cost-effectiveness (cost per QALY and cost per successful procedure).

Harms/Adverse Events: respiratory depression, postoperative vital signs, nausea and vomiting, antiemetic use

SAMPLE SIZE
A sample size of 592 (296 per arm) is sufficient to declare non inferiority under the following assumptions: 1 baseline and three post-randomisation timepoints evaluated (correlation 0.5), 90% power, 1 sided alpha of 2.5%, no difference between drugs, non-inferiority margin of 4.3 points, SD of 25 points. The standardised non inferiority margin (0.172) is less than one third of the standardised placebo contrasted MCID (0.48) from Jenkins *et al*[β]. Accounting for 5% drop out, 622 subjects will be randomised.

DIFFERENCE BETWEEN CURRENT AND PLANNED CARE PATHWAYS
Exchange of midazolam (Schedule 3 controlled drug) for melatonin (not controlled drug); the care pathway otherwise remains unchanged

ANALYSIS
Data to be reported according to the CONSORT statement[18]. Primary outcome (as well as continuous secondary outcomes) to be analysed by a mixed model fitting the terms treatment, time, baseline, centre, subject (random term) as covariate. A logistic regression will be used to evaluate categorical outcomes. Sensitivity analyses will be used to evaluate robustness[19]. Qualitative data will be analysed using framework analysis[20].

PROJECT TIMETABLE
Recruitment target: n=1.2 to7.8 per centre per month at 10 centres. Three year study: 10m set-up; 18m recruitment; 1m follow-up; 1m closeout and 6m analysis & write-up. Internal pilot evaluates objective stop-go criteria based on m11-17, using traffic-light system[4]; green light criteria of (1)n=156 (80%) participants randomised; (2)expected protocol; (3)80% retention

EXPERTISE IN STUDY TEAM
Multidisciplinary team including different clinical specialities (paediatric dental, oral surgery, ENT, anaesthetics) across 10 UK centres, methodologists (trial management, statistics &health economics) and NIHR FICTION trial Chief Investigator to support successful implementation.

Figure 2. Flow chart

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                              ┌─────────────────────────────────────┐
                              │  10 UK Trusts; dental and ENT         │
                              │  departments in all Trusts to         │
                              │  participate                          │
                              └─────────────────────────────────────┘
                                              ↓
                              ┌─────────────────────────────────────┐    ┌──────────────────────┐
                              │ Eligible children (aged 6-14)         │ →  │ ANTICIPATED 30%       │
                              │ invited to participate                │    │ ACCEPTANCE RATE       │
                              └─────────────────────────────────────┘    └──────────────────────┘
                                              ↓
                              ┌─────────────────────────────────────┐
                              │ 622 children (156 pilot) randomised   │
                              │ & baseline m-YPAS                     │
                              └─────────────────────────────────────┘
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INTERNAL PILOT WITH FEASIBILITY ASSESSMENT

Participant, enrolment, allocation, intervention, follow-up

INTERVENTION (78 children) Melatonin 0.5mg/kg Capped dose at 20mg	CONTROL (78 children) Midazolam 0.5mg/kg Capped dose at 20mg

ASSESSMENT
m-YPAS prior to theatre transfer, on entry into anaesthetic room, on induction
Parental anxiety: STAI
Emergence agitation: PAED index
Sedation: VSR scale
Pain: FPS-R
Psychomotor: Cooperation scale, post-box
Vital signs and adverse events
Postoperative analgesia requirements

2 WEEKS POST-DISCHARGE
Post-Hospitalisation Behaviour Questionnaire (PHBQ)
Safety follow-up

Invited to attend interview to inform recruitment 30-40 patients & stakeholders

Review of Pilot Phase

PROGRESSION CRITERIA ASSESSED
Review of referral rates and acceptability of randomisation
Green light criteria:
1. All centres actively recruiting
2. >80% target recruitment
3. >80% retention
4. Satisfactory review of observer blinding by TSC
Review of interview findings and adoption of recommendations to improve recruitment

MAIN TRIAL

INTERVENTION (233 children) Melatonin 0.5mg/kg Capped dose at 20mg	CONTROL (233 children) Midazolam 0.5mg/kg Capped dose at 20mg

ASSESSMENT
m-YPAS, PAED index, VSR scale, FPS-R, STAI, Cooperation scale, post-box
Vital signs and adverse events
Postoperative analgesia requirements

Invited to interview to explore acceptability - 30-40 patients & stakeholders

ANTICIPATED 5% LOSS TO FOLLOW-UP PRIMARY OUTCOME AND 25% LOSS TO FOLLOW-UP PHBQ

2 WEEKS POST-DISCHARGE
PHBQ, Safety follow-up

ANALYSIS- INCLUDING INTERNAL PILOT
Primary Outcome: Preoperative distress (m-YPAS score)
Secondary Outcomes: Emergence agitation (PAED index); Sedation (VSR); Recovery time, Pain (FPS-R); Side Effects; post-op analgesia, failed anaesthesia, Cost-effectiveness (CHU9D); Post-discharge behaviour incl. eating, anxiety, aggression, apathy & sleep disturbance (PHBQ)
Patient/Parent/Stakeholder Acceptability

2. BACKGROUND

2.1 Clinical Problem

There are approximately 600,000 new episodes of care per year for children aged 5-14 in the NHS, with 36% of attendances relating daycase procedures[21]. Daycase 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[22]. 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[23-27].

Midazolam, the current standard premedication given to an anxious child ahead of surgery has been shown to be effective[28], 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 premedicated child on a trolley, and also significantly delays post-operative recovery[29, 30]; 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[31] and also unpredictable effects on children which may result in agitation rather than anxiolysis – particularly in those children with additional needs[32].

The increased incidence of learning disabilities with repeated anaesthetic exposure has been documented in a landmark study by Wilder *et al* [33], which highlighted the potential long-term risks of using sedative agents such as benzodiazepines in anaesthesia of young children. Although the authors identified that the link between repeated anaesthesia and learning difficulties may be related to a confounding factor, animal studies concur that GABA activating drugs such as midazolam can trigger apoptotic neurodegeneration in the developing brain[34].

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.

2.2 Health Technology

Melatonin is a functionally diverse hormone involved in the entrainment of circadian rhythm, exerting its effects on MT1 and MT2 receptor subtypes distributed throughout the central nervous system[35]. 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[36]. Melatonin's anxiolytic properties have been confirmed in the adult population[37], and are considered to be a consequence of a facilitatory role in GABA transmission[38].

Unlike data confirming the success of melatonin as an anxiolytic in adults, trials assessing the effects of melatonin in children have produced heterogenous results[2, 39-41]. 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.

Despite the equipoise surrounding melatonin's effectiveness compared to midazolam in children, the drug offers many potential benefits over midazolam. These benefits may include greater paediatric acceptance of oral formulations, 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, the NPSA 2008 RRR011 rapid response document highlighted the risks of bolus dosing midazolam in adults[42], and identifying a safer alternative drug which bears comparable anxiolytic effect in children is an important healthcare priority.

2.3 Rationale

To establish comparative effectiveness and side effect profile of melatonin versus midazolam as premedication in children aged 6-14 with high levels of preoperative distress prior to elective GA for dental extractions & ENT operations, and to determine whether melatonin offers sufficient benefit to warrant change in standard NHS practice.

2.4 Evidence explaining 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 sneed 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[37], although as yet there is insufficient evidence to commission melatonin as a 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 and reduced side-effects. A pragmatic RCT assessing the effectiveness of melatonin compared to the current standard is therefore warranted.

3. RESEARCH QUESTION, AIM AND OBJECTIVES

3.1 Research questions

1. Is melatonin as an effective a premedication as midazolam in the management of anxious children undergoing elective general anaesthesia?
2. Does melatonin offer a side-effects profile superior to midazolam?

3.2 Aim

To evaluate the clinical and cost effectiveness of melatonin, and to assess melatonin's side-effects profile compared to midazolam in the premedication of anxious children prior general anaesthesia for elective ENT and dental surgery.

3.3 Objectives

3.3.1 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 follow-up)
- Allocation concealment & blinding

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3.3.2 Clinical Objectives
Efficacy
To evaluate if melatonin, in relation to midazolam is:
- Non inferior in dealing with pre-operative anxiety evaluated by m-YPAS score over the 3 standard preoperative timepoints recommended for the scale[6]
- Superior in dealing with secondary efficacy outcomes (anaesthetic turnaround time, recovery time)
- Non inferior in dealing with secondary efficacy outcomes (anaesthetic failure rate)

Harms and Safety
- To evaluate if melatonin, in relation to midazolam is superior in dealing with secondary safety outcomes (PAED, VSR, FPS-R, analgesia requirements, PHBQ, nausea & vomiting, respiratory suppression, orientation and cognitive/psychomotor function)
- To describe Serious Adverse Events data (summarised both at patient level and event level) and report listings between the different arms.

3.3.3 Integrated Qualitative Study

An integrated qualitative study is proposed to 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[43]. 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 as recommended by the QuinteT Recruitment Intervention (QRI)[3]. Semi-structured interviews will be conducted by an experienced research associate with a purposive sample of children, parents, 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, declined or withdrawn), type of surgery (dental or ENT), patient demographics and trial site. Interviews will ideally be conducted face-to-face, however interviews with health professionals may be conducted via telephone if this is not convenient. Sampling, data collection and analysis will occur concurrently until data saturation has been reached. Previous similar studies suggest data saturation will be reached with 30-40 interviews. A topic guide will be 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. Participant information sheets, consent forms and the study protocol will be revised, as required, as a result of these interviews.

The qualitative component of the main trial will explore the experiences of:
- children and parents of the acceptability of the premedications, including taste, reduction of distress, the child's post-operative recovery and any longer term implications. Based on our PPI work in developing this application these were highlighted as areas of concern.
- the clinical team members (research nurses, nursing staff, anaesthetists, operating department practitioners) of children having the two premedications, 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.

Semi-structured interviews will be conducted with a purposive sample of children, parents, and clinical team members towards the end of the main trial. Interviews will ideally be conducted face-to-face. The sampling frame will include type of surgery (dental or ENT), patient demographics (age and socio-economic status) and trial site. Previous similar studies suggest data saturation will be reached with 30-40 interviews.

3.3.4 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. RESEARCH PLAN

A parallel-group RCT will be conducted in ten large NHS trusts. A mixed methods approach will be employed, whereby qualitative interview schedules shall inform us on the success of enrolment during internal pilot, identify any problems encountered and assist recruitment during the main trial. Further qualitative interviews shall provide insight into stakeholder and patient acceptability of melatonin.

All children scheduled for elective ENT or dental surgery under general anaesthesia will receive separate parental and children's information leaflets along with their postal appointment letter. Eligibility will be confirmed at the point of clinical assessment by the site PI, consultant surgeon, consultant anaesthetist or anaesthetic trainees in order to identify those children usually assessed as requiring a premedication for preoperative anxiety. After opportunity to further consider the study information, view a child-friendly information video

and ask questions, candidates shall be approached for consent by the site PI, consultant surgeon, consultant anaesthetist or anaesthetic trainees, or research nurse. On the day of surgery, participants shall be randomised to receive midazolam or melatonin 0.5mg/kg premedication 30 minutes prior to theatre transfer (capped dose of 20 mg). Patients shall be observed by a blinded research nurse or anaesthetic trainee throughout the preoperative period until anaesthetic induction, and then monitor the patient 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 trainees 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 m-YPAS scale.

5 HEALTH TECHNOLOGUES BEING ASSESSED

5.1 Standard Oral Midazolam (Control)

Standard 0.5mg/kg midazolam taken 30 minutes prior to theatre transfer (capped dose 20mg)
Although theoretical trials have often assessed oral midazolam taken 1 hour prior to surgery, scheduling of midazolam as a premedication 30 mins ahead of surgery represents standard NHS practice. Indeed, paediatric clinical data suggests peak plasma midazolam concentration is reached at 30 mins and is partially eliminated by 1hr[44].

5.2 Oral Melatonin (Intervention)

Melatonin 0.5mg/kg immediate release liquid formulation taken 30 minutes prior to theatre transfer (capped dose 20mg).
The optimal dose of melatonin for means of achieving anxiolysis in children remains uncertain. Most studies demonstrating melatonin efficacy in children have utilised a dosing schedule of 0.5mg/kg[2, 39, 41, 45], with a capped dose of 20 mg[2]. Despite this capped dose, melatonin has been used in much higher concentrations in the management of neonates[46], reflecting the safety of the drug. Less success has been noted in trials utilising melatonin in concentrations below 0.5mg/kg[40]. 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[47], and is furthermore consistent with a pragmatic trial design comparing against usual care (midazolam, 30 minutes prior to transfer).

The only licensed formulation of melatonin in the UK is Circadin (2mg tablets), and this is used off-license in children. 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 formulations of melatonin[48] and liquid melatonin formulations are frequently used in children who cannot swallow tablets and need larger doses of melatonin for overnight sedation (e.g. children with nasogastric tubes). Whilst the Sheffield Children's Hospital (and other sites) procure liquid melatonin as a 'Special'[49] and these products are manufactured under GMP, there is no requirement for a Qualified Person (QP) to be named on a Manufacturer's "Specials" Licence for release of a finished unlicensed product. MRHA advice has been sought to confirm the requirements and documentation to obtain clinical trials authorisation for a trial using liquid melatonin and they have confirmed that these products will need to be produced under MA IMP license for the trial with full QP release. This unfortunately increases the cost of procurement of both melatonin and midazolam significantly from their procurement for standard clinical use (see section 18).

6. DESIGN

Parallel group (allocation 1:1), single blind (anaesthetist, surgeon and observer nurse will be fully blinded, with patient allocation concealment), individual participant-randomised, stratified, multicentre, randomised trial to evaluate the non-inferiority of melatonin against midazolam in dealing with pre-operative anxiety (m-YPAS score) in children undergoing surgery.

7. TARGET POPULATION

7.1 Description

Children undergoing elective dental or ENT surgery, requiring premedication for management of preoperative anxiety ahead of general anaesthesia. Previous trials analysing the success of melatonin as a premedication 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 premedication 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[50, 51]. 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. The anaesthetic care pathway of dental 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 and ENT operations are usually medically fit & well, which enhances the validity of using existing safety data for melatonin as reference safety information.

7.2 Inclusion Criteria

- Children aged 6-14 undergoing elective dental or ENT surgery under general anaesthesia. Sedation.
- Pragmatically assessed by healthcare professionals as requiring premedication* for high/expected high levels of preoperative distress prior to elective dental/ENT surgery under GA, including known negative experiences, failed anaesthesia, parents displaying high levels of distress, additional/special needs or judged as unable to tolerate GA without premedication
- ASA grades I & II
- No previous exposure to melatonin or midazolam
- Parent or person with parental responsibility able to give written, informed consent

*Premedication usage shall be audited at each site prior to trial commencement, during pilot and at 12m in order to confirm that comparable proportions of patients are receiving premedication over the course of the trial, compared to the usual practice preceding trial commencement. Pragmatic assessment of suitability for premedication shall be consistent with Tan & Meakin's review article[52], which provides guidance on patient selection for premedication 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 and ENT surgery as confirmed by local audit and also the literature[53, 54], and furthermore reflects both the minimum age validated as reliably communicating self-reported measures such as Faces Pain Scale[55], and the maximum age of a "child" as defined for use of midazolam in conscious sedation[56].

7.3 Exclusion Criteria

- Not undergoing elective, day-case dental or ENT surgery under general anaesthesia
- Not displaying level of anxiety that would usually warrant premedication under the standard NHS care pathway
- Reason for premedication other than anxiety
- Current prescription of melatonin or midazolam
- Obstructive sleep apnoea
- ASA grades III, IV & V
- Severe learning disability rendering child unable to communicate even with specialised support

8. SAMPLING

8.1 Sites
We will recruit from ten NHS hospital trusts, whose R&D departments have satisfied the team that they agree to the cost-structure of the trial and have satisfactory throughput of potentially eligible patients. We currently have agreements in principle and a Principal Investigator identified at eight NHS Trusts to recruit between 21 and 180 participants per centre over an 18 month period (an eventual steady state of between 1.3-7.8 participants per centre per month). Total ENT and dental patient throughput at all centres is approximately 950 patients per month, with an estimated 10-15% of patients requiring premedication, as confirmed through audit data obtained from each trust. Using audit data projections, most centres will recruit around 5 participants per month. Given the multi-disciplinary nature of the trial, we have also ensured that each site has named a lead dental surgeon, ENT surgeon and anaesthetist. All site leads have had opportunity to comment on the key trial processes e.g. recruitment, administration of IMP.

We conducted an audit of dental procedures under GA for our target population in Sheffield over a 2-week period in September 2016; 18 patients (6-12yr) requiring midazolam for preoperative anxiety. Activity over this period was consistent with our yearly throughput of around 2,500 elective dental surgeries under day-case anaesthesia. Extrapolating this to a monthly total means 18 patients per month may be eligible. ENT procedures were similarly examined with a potential pool of 30 premedicated patients per month. Assuming a 30% eligibility/acceptance rate, this suggests recruitment of 9 ENT participants/month.

These estimates are more optimistic than the data reported from the other large centres such as Aberdeen, Leeds, Manchester and Liverpool, of which each recorded an ability to recruit 5 to 10/month from the dental and ENT population based on recruiting 30% of potential participants. We have therefore used a more conservative estimate for Sheffield of 7.8/month to remain consistent with data from other sites. In addition, the numbers recruited per month need to be balanced with the numbers treated per month given the short window between recruitment and surgery. Following discussions with Research Nurse managers at the sites, it does not appear feasible to secure Research Nurse resources for more than 10 participants per month given the intensity of the data collection periods and the scheduling of the surgical lists. Smaller sites have confirmed ability to recruit between 1.2 to 4.8 participants/month.

We feel we have been justifiably conservative in assuming a 30% acceptance rate given the target population is anxious children. It is difficult to predict how an anxious parent/child will respond to trial invitation; the qualitative work undertaken in the internal pilot will analyse this and feed back into the recruitment strategy. In anticipation of possible acceptance lower than 30%, the trial will be extended to recruiting participants undergoing ophthalmic surgery.

8.2 Sample size and effect size
The primary outcome is m-YPAS over three timepoints. The choice of non inferiority margin (4.3 points unstandardized; 0.172 standardised) has been based on the following considerations:

i) the margin is less than one third of the standardised placebo contrasted MCID (0.48) from Jenkins et al[6]
ii) it is a small fraction compared to the range of the scale (score ranges from 22.5 to 100, with higher scores indicating greater anxiety)
iii) it is consistent with consultant paediatric anaesthetist opinion on what is a clinically important difference in premedication effect
iv) Jenkins et al[6] cited a study for which one arm could be considered non inferior to midazolam (as it has been stated to be effective against placebo): on the cited study[7] (Kain et al) the arm "family-centered preoperative ADVANCE preparation program" was declared to be "effective in the reduction of preoperative anxiety and improvement in postoperative outcomes".

When compared to midazolam the difference in m-YPAS "ADVANCE group-Midazolam group" (data from table 2, row "Introduction of mask at induction") was 3 points (95% CI: -3.66 to 9.66 points). This means that an effective treatment in reducing preoperative anxiety (ADVANCE) is accepted to be up to 9.66 points worse to midazolam (upper limit of the 95% CI). Assuming the same analysis of our trial was run, (accounting for correlation hence applying a correcting factor to SD of 0.645), this would lead to a 95% CI of -1.30 to 7.30. We therefore considerer our choice of margin (4.3 point) to be justified given that we expect the

limit of the Confidence Interval in our trial (4.3 points) to be more conservative. We believe our assumption is consistent, as Kain's work involved a similar clinical setting and comparable age group to our trial.

The SD has been based from Kain *et al*[7]

Three time points have been chosen on the assumption that there is not a time by treatment interaction (i.e. the treatment effect is constant among timepoints). This has been corroborated by a search on the pharmacokinetics on both drugs[44, 47] and is consistent with figure 3 of Kain *et al*[7].

A correlation of 0.5 has been based on Frison and Pocock[8].

Hence, a sample size of 592 (296 per arm) is sufficient to declare non inferiority under the following
assumptions: one baseline and three timepoints evaluated (correlation 0.5), 90% power, 1 sided alpha of 2.5%, no difference between drugs, non inferiority margin of 4.3 points, SD of 25 points. Accounting for a 5% drop out rate in the primary outcome measure, 622 subjects will be randomised.

8.3 Recruitment
We aim to recruit children (aged 6-14yrs) scheduled for elective dental or ENT surgery. Potential study participants will be identified when booked for pre-operative assessment and sent batched invitation sheets. As per PPI recommendations separate parent and child information sheets will be sent along with the initial appointment letter. Potential participants will be identified at the time of outpatient assessment and will be approached to enrol with the aid of a children's information video shown on tablet computer.

As Trusts will be running this trial across two surgical specialties, often across more than one hospital site, we will involve anaesthetic trainee research networks in the work of recruitment, co-ordinated by a research nurse. This method has achieved rapid recruitment in other high profile NIHR-funded trials[57, 58]. 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 or anaesthetic trainee will have an initial face-to-face discussion with each potential participant on arrival at pre-operative assessment.

8.4 Consent
If the individual is eligible for the study, then the anaesthetist, trial surgeon, research nurse or trainee will take consent. A sticker attached to the front of the patient case notes shall help identify participants who have received trial information leaflets and a further sticker used when consent has been given. Consent will be undertaken during the preoperative appointment if available; if this is unachievable (e.g. high levels of anxiety manifesting on the day of surgery), consent will be undertaken on the day of surgery. For morning-of-surgery consenting, 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. This approach to morning-of-surgery consenting has been successful in previous trials[59]. We will also explore satisfaction with the consent process using the DelibeRATE tool[60]. 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. 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.

8.5 Randomisation
Once eligibility has been confirmed, consent acquired and baseline data taken, the participant will be randomly allocated to either the treatment arm (n=312; 296 + 5%) or the control arm (n=312). The doctor or nurse performing randomisation will access a web-based randomisation system provided by the Sheffield CTRU. Patient details (ID, date of birth) will be entered into the Sheffield CTRU web-based randomisation system and the treatment allocation will be returned. Randomisation will be stratified by centre, using permuted blocks of random size. Participants will be allocated to a numbered treatment pack kept in the local site pharmacy or Theatre Admission Unit. Once a participant's details are entered, randomisation will be performed via a web-based system and a unique medication pack number allocated. Participants, hospital staff and research staff will all be "blind" to allocated treatment, unless the formal "unblinding" procedure is undertaken (Section 11).

9. DATA COLLECTION

9.1 Internal pilot feasibility outcomes

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[4]. 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*[4] 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 six months between Months 11 and 16 inclusive.
B) Amber: trial may be feasible if appropriate changes made- recruitment of between 79 and 155 participants in the six months between Months 11 and 16 inclusive 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 six months between Months 11 and 16 inclusive.

Retention:
A) Red: trial is not feasible- retention of fewer than 64 participants randomised between months 11 and 16 (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 randomised between months 11 and 16 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 between months 11 and 16 (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:

We recognise 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 trail medications on the child (melatonin provides anxiolysis without sedation). We will record any instances of unblinding, including the reasons for & timepoint of unblinding. The overall rate of unblinding and preservation of data integrity shall allow the 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 believes they have been unblended

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.

9.2 Clinical, patient-reported and harm data

The timing of post-operative data collection will be anchored to the time on entry into PACU, 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. Building data collection timelines from this point will ensure consistency of recording and reduce variability which could be time-dependent. Safety follow-up and post-discharge data (Table 1) will be collected

simultaneously by research nurses or anaesthetist trainees by telephone at 14 days following an initial text reminder, as advised by the parent and child PPI group.

Table 1. Quantitative data collection

	Following consent	Baseline (Admission)	Transfer	Entry Anaesthetic room	Application of mask	Peri-op	Post-op	14 days
Baseline and other covariates								
Demographics (gender, age, height, weight, ethnicity)	✓							
American Society of Anesthesiologists physical status[24]		✓						
Specialty and scheduled procedure		✓						
Parental Anxiety (STAI)		✓						
Primary outcome								
mYPAS		✓	✓	✓	✓			
Patient-reported outcomes								
Revised Faces Pain Scale (FPS-R)							✓	
Health related quality of life, CHU9D		✓						✓
Clinical outcomes								
Failure to progress with anaesthesia			✓	✓	✓			
Time of entry into anaesthetic room				✓				
Time of application of mask/cannulation					✓			
Time of completion of intubation					✓			
Use of Sevoflurane & end-tidal volume						✓		
Local anaesthetic type, concentration and amount*							✓	
Time of surgery completion						✓		
Time of extubation						✓		
Time of arrival at PACU							✓	
Observer-rated FPS-R							✓	
Orientation/Psychomotor		✓					✓	
Analgesia usage (type, amount)							✓	
Vital signs (SaO$_2$, HR, BP)							✓	
Time to discharge readiness							✓	
Time to actual discharge							✓	
Cost data								
Medication use (for health economic analysis)							✓	
Harms and Safety								
Emergence agitation (PAED index)							✓	
Vancouver Sedation Recovery Scale (VSR)							✓	
Nausea and vomiting			✓	✓	✓		✓	
Anti-emetic use			✓	✓	✓		✓	
Serious Adverse Events			✓	✓	✓	✓	✓	✓
Post-Hospital Behaviour Questionnaire (PHBQ)								✓
Parental time off work post-discharge								✓
Unblinding								
Observer unblinding			✓	✓	✓	✓	✓	
Anaesthetist unblinding			✓	✓	✓	✓	✓	

Footnote:
a. delibeRATE scale to be used at time of consenting to explore satisfaction with consent process
b. Adopted elements of QRI to be collected over pilot phase; invitation of those patients/parents declining entry into trial to interview as well as those enrolling
c. Patient/parent to be invited back for qualitative interview after post-discharge follow-up; data collection to include:
- Parent/patient acceptability of drug, taste, distress reduction, experience of post-operative recovery, any longer term implications, patient refusal of GA
- Stakeholder perspectives on patient refusal of GA, acceptance of the drugs, distress reduction, impacts on recovery such as postoperative sedation and adverse effects

Primary outcome
1. Difference in m-YPAS scale, (measured on transfer, on entry into anaesthetic room and on application of mask) between treatments.

Patient-reported outcomes
2. Difference in Revised Faces Pain Scale (FPS-R) between treatments. A variable number of timepoints will be evaluated. The first timepoint will be 10 minutes after waking up from anaesthesia, then every 10 minutes up to readiness for discharge
3. Parental State-Trait Anxiety Inventory (STAI) at baseline.

Clinical
Non-inferiority analyses:

4. Difference in proportions of subjects experiencing failure to progress with anaesthesia between treatments: anaesthetist reporting of anaesthesia abandonment and reasoning

Superiority analyses:

5. Time from entry into anaesthetic room until application of mask/cannulation
6. Time from application of mask/cannulation until completion of intubation
7. Time from surgery completion until time of extubation; times taken from ORMIS database
8. Time from surgery completion until time of arrival at PACU
9. Difference on Observer-rated FPS-R: between treatments. A variable number of timepoints will be evaluated; the first timepoint will be on arrival at PACU, then every 10 minutes up to readiness for discharge.
10. Difference in change in Cooperation Scale/ modified post-box test between treatments every 30 minutes up to readiness for discharge or to a maximum of 120 minutes
11. For each of the following category/drugs: analgesia - ibuprofen, paracetamol, fentanyl, morphine; anti-emetics - cyclizine, dexamethasone, ondansetron. To assess difference between arms in the proportion of subjects for which the category/drug under consideration has been used. This will be taken from the case note prescription chart
12. For each of the following category/drugs: analgesia - ibuprofen, paracetamol, morphine; anti-emetics - cyclizine, dexamethasone, ondansetron; difference in total quantity of category/drug used in consideration between arms. This will be taken from the case note prescription chart. Appropriate unit of measurements for each category/drug will be used as well.
13. Vital signs (SaO$_2$, HR, BP): taken from post-operative observation chart
14. Time from arrival at PACU to discharge readiness: noted by research nurse
15. Time from arrival at PACU to actual discharge: noted by research nurse

Cost
16. Resource usage (for health economic analysis): 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"), parental time off work.

Harms and Safety
17. Difference in emergence agitation (PAED index): taken every 10 mins as itemised in (8)
18. Difference in Vancouver Sedation Recovery Scale (VSR): taken every 10 mins as in (8)
19. Difference in proportion of subjects experiencing nausea, and mean number of episodes of vomiting: nausea recorded as binary data (yes/no), vomiting recorded as number of episodes
20. Difference in anti-emetic use: taken from case note prescription chart as itemised in (9) & (10)
21. Difference on Post-Hospital Behaviour Questionnaire (PHBQ) between treatments: this will be taken by the research nurse at 2-week follow-up
22. Difference in frequency and proportion of patients reporting at least one Serious Adverse Event for each treatment. Additionally, these characteristics will be summarised (frequency and proportion): Intensity (Mild, Moderate, Severe),

relationship (Definite, Probable, Possible, Unlikely, Unrelated, Not assessable), is SUSAR, is Death.
23. Difference in frequencies of Serious Adverse Events for each treatment.
24. Difference in listing of Serious Adverse Events for each treatment.

Serious adverse events (SAEs) will be reported in accordance with the sponsor's (STH) standard operating procedure. All SAEs occurring up to 14 days after surgery (end of involvement in the trial) will be reported immediately to the sponsor on learning of their occurrence. Delegated site trial staff will be responsible for recording all adverse events and making them known to the Principal Investigator. An Investigators Brochure (IB) will be maintained by the trial team as the reference safety information for reporting SAEs.

10. SAFETY PRECAUTIONS

An emergency unblinding (codebreak) procedure 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. A 24 hour unblinding service will be available via the randomisation system, which will immediately provide treatment allocation to the site and automatically alert the study team and local Principal Investigator (PI) by email that a participant has been unblinded. In case the web and phone system are unavailable, emergency unblinding envelopes will also be prepared by the Investigational Medicinal Product (IMP) manufacturer according to the randomisation schedule and stored with the IMPs at site. Tamper stickers will be checked regularly to ensure envelopes have not been opened and are returned sealed to the central study team to ensure full accountability. If an envelope is opened it will be recorded as a participant unblinding event.

11. DATA ANALYSIS

11.1 Analysis Sets
The following analysis sets will be used in the reporting of the study:

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

Intention-to-treat population (ITT): comprised of all participants randomised regardless of drug intake. The participants will be analysed based on Treatment Pathway. Additionally, modified ITT could be declared depending, for example, on withdrawal status and outcome availability.

Per-protocol population: comprised of all participants randomised who took at least one dose of study drug and have no major protocol deviations. Analysis based on Treatment Pathway.

11.2 Statistical Analysis
The statistical analysis will be reported according to CONSORT guidelines as well as the extension for non-inferiority trials (57). Two populations will be coprimary (per protocol and intention to treat) (ICH E9 guidelines).

The primary outcome and other continuous longitudinal outcomes will be analysed using a random effects model with participant, treatment, time, baseline value and centre entered into the model. The 95% confidence intervals for the difference on treatment effect will be reported as well as the associated P value. Non inferiority will be declared if the upper limit of 95% Confidence Interval on the difference (melatonin-midazolam) does not exceed 4.3. In 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 (Thabane2013)[19]. 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. Further details will be provided in a separate statistical analysis plan.

11.3 Analysis of Qualitative Data
Qualitative interviews will be audio-recorded and transcribed verbatim. Framework analysis will be used for analysis of the qualitative data from the internal pilot and main trial as it provides a pragmatic approach[20] which produces results that can be easily incorporated into

RCTs[61]. 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'[3]. 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[62] 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 ZM.

11.4 Health-Economic Analysis

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 (Little & Rubin, 2002).

Cost Effectiveness Analysis: A decision tree will be constructed to explore the cost - effectiveness of melatonin over a 1yr 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.

12. DISSEMINATION AND PROJECTED OUTPUTS

Our strategy for making the outputs of this research have real NHS impact relies on involving key stakeholder groups with the task of dissemination and knowledge transfer (KT). KT goals are:

1. Change/confirm current policy through Royal Colleges/NICE and other individual organisations
2. Change practice amongst professionals and patients

12.1 Clinicians and the Research Community (Passive Diffusion)
The findings of our research will be made available to the clinical community by publication in high "impact", peer reviewed journals. Presentations at national and international conferences to clinicians involved in the care of surgical patients will serve as platform for further dissemination.

12.2 Health care policy makers (Active Dissemination)
We will provide specific reports on trial findings for healthcare policy makers. With the support of the Trial advisory group, we will ensure that key research evidence is made available to the Department of Health, Royal Colleges of Surgery and Anaesthesia, NHS Trusts and other stakeholders.

If funded, formal adoption of the study by the National Institute of Academic Anaesthesia Peri-operative Clinical Trials Network will be sought (http://www.niaa-hsrc.org.uk/Clinical-Trials-Network). This body promotes and fosters national research endeavour in high-quality perioperative applied health research and a study of this nature represents precisely the sort of multidisciplinary, NHS-relevant trial that it was created to support. Adoption would provide the study with a potent conduit of dissemination via the NIAA and the regular news emails from its affiliated "Health Services Research Centre" reaching all members of the Royal College of Anaesthesia, currently numbering some 10,000 clinicians. These are key physicians charged with prescribing the intervention under scrutiny and adoption of the recommendations generated by the proposed research would be vital for its success.

12.3 Patients and NHS staff
In partnership with our participating hospitals and PPI representatives, our findings will be made available to front line NHS staff, across all care disciplines. Open access publication will ensure the implications of our research findings are rapidly available, as widely as possible. Lay members of the study group will facilitate sharing information with groups representing the interests of surgical populations and their carers at a local, regional and national level.

12.4 Continued knowledge dissemination
The Healthcare Quality Improvement Partnership (HQIP) will be engaged via the NIAA Health Services Research Centre (http://www.niaa-hsrc.org.uk/HSRC_home) to promote research conclusions and make recommendations on adoption of national standards.

12.5 Impact
Evidence generated from a definitive, rigorously designed study will have immediate, generalisable relevance to thousands of NHS patients. The capacity to alter decision making practices or processes at an organisational level is far easier when there are clear goals to attain. In this sense, the primary outcome measure (m-YPAS) is manifestly important and easily understood. Elective dental and ENT surgeries are common and are undertaken throughout NHS secondary and tertiary care. Evidence driven quality improvement in this milieu could have an immediate, sustainable impact on the safety of premedication in children prior to general anaesthesia and also improve patient experience. It also has the potential to achieve this in a cost-effective manner. The simplicity of the intervention renders it ideally suited for swift adoption into national policy, such as NICE Guidance, Royal College recommendations or Specialist Society guidelines if clinical and cost effectiveness is proven.

13. PLAN OF INVESTIGATION
13.1 Timetable
We propose a 36-month study, with 10 months set-up due to the necessity of obtaining MHRA approval and manufacture of the IMPs, 18 months recruitment, one month follow-up, and seven months for close-out and analysis.

13.2 Internal pilot
The initial phase of the trial will be an internal pilot. The internal pilot trial will run at all 10 sites. The progression criteria will be applied to data collected from the beginning of Month 11 (projected Oct 2018), to the end of Month 16 (projected March 2019). 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 9. Clinical and patient-reported outcome data from the internal pilot will be included in the final analysis.

14. PROJECT MANAGEMENT

14.1 Oversight
The study will be registered with the local R&D department of each centre and Sheffield Teaching Hospitals NHS Trust will act as the sponsor. Three committees will be established to govern the conduct of this study and will function in accordance with Sheffield CTRU standard operating procedures: a Trial Steering Committee (TSC), a Data Monitoring and Ethics Committee (DMEC) and a Trial Management Group (TMG). The TSC will consist of an independent chair, other professionals with relevant clinical and academic experience and two patient representatives. The DMEC will consist of an independent statistician, and at least

two independent physicians with clinical trials expertise. There will be no interim analyses (other than for the purposes of the blinded internal pilot) or definitive stopping guidelines, but the DMEC will be able to request unblinded data and recommend study termination to the TSC/ funder on grounds of safety/ futility. The TSC and DMEC will meet every 6 months from the start of the trial and both groups will review solicited and spontaneously reported adverse events and other unintended effects of the interventions or trial conduct. The Trial Manager will be jointly supervised by the CI (CD) and Sheffield CTRU Lead (DP), meeting at weekly intervals, and will liaise with the whole study team. Central and site monitoring will be undertaken at a level appropriate to a risk assessment performed by the sponsor or their delegate. The CI will chair monthly TMG meetings, at which the day-to-day implementation of the study will be discussed.

14.2 Research governance

The trial will be conducted in accordance with ICH GCP and the Clinical Trials and Medicine for Human Use (Clinical Trials) Regulations 2004. Sheffield Teaching Hospitals (STH) NHS Foundation Trust was the trial Sponsor. The trial will be a Clinical Trial of a Medicinal Product (CTIMP) covered by the Medicines and Healthcare products Regulatory Agency (MHRA) from whom we will apply for a Clinical Trial Authorisation. A site agreement between the Sponsor, participating site, CTRU and University of Sheffield will outline responsibilities of all parties and 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).

Blinded treatment packs will be manufactured by a specialist provider. All products will be checked by a qualified person (QP) prior to release. Treatment packs will be labelled with a randomisation code in accordance with a randomisation schedule supplied by the CTRU and distribute packs to sites. The specialist provider will maintain an Investigational Medical Products Dossier (IMPD) and relevant documentation.

Blinded treatment packs will be manufactured, assembled and labelled as per ECGMP annex 13 requirements to enable the treatment to be identified and the batch source of the materials traced. An unblinded pack number list and randomisation schedule (accessed via the online randomisation system using a unique username for the specialist provider of the IMPs) will allow the IMP provider to identify which arm of the trial each pack belongs to, and label the kits with a randomisation code. IMPs will be supplied on a demand basis to the participating sites with minimal waste of materials. Treatment pack accountability logs will be maintained by all parties (production units, CTRU, sites, hospital pharmacies, Theatre admission Units), to allow full reconciliation of IMPs including assignment to patients.

14.3 Site Monitoring

On-site monitoring will be performed before (prior to recruitment commencing at site), during (after 3rd patient recruited, and then annually) and after recruitment ends at a trial site. Monitors will check the following during site visits:
- Source Data Verification (SDV) – data recorded on the CRFs against available source documents
- SAEs/SUSARs (Suspected Unexpected Serious Adverse Reactions) - reported to the sponsor and followed up to resolution
- Resolution of data queries
- Investigator site file maintenance
- Training records for site staff (trial specific and GCP) and appropriate delegation of duties
- IMP accountability and storage of IMPs in and pharmacy
- Patient consent procedures
- Reporting of protocol deviations/violations

14.4 IMP production

Monitors independent to the study team will check Qualified Person release certificates for all batches of product and verified that labelling with randomisation number have been done correctly according to the randomisation number and unblinded kit list.

15. APPROVAL BY ETHICS COMMITTEES
HRA approval will be sought before the start of the trial. Protocol amendments, once approved by the funder and the HRA, will be communicated to study personnel and R&D offices by Sheffield CTRU.

16. PATIENT AND PUBLIC INVOLVEMENT

16.1 Aims of active involvement
The aim of involving patients in the study is to make the study more attractive to eligible patients, procedures more acceptable to participants and outputs more useful to patients. In this regard, PPI is essential throughout the set-up period (to guide planning), the accrual period (to guide challenges to implementation) and the write-up period (to support development of the plain language and scientific summaries).A series of meetings have been held, involving parents and children who have recently undergone general anaesthesia for dental or ENT surgery, at both the outline and full application stages; they have made critical changes to the protocol to make it more acceptable and meaningful to patients.

16.2 Description of the patients and carers to be involved
All parent and child PPI representatives have direct experience of recent general anaesthesia for dental surgery or ENT surgery. PPI representatives have followed the usual pre-operative care pathway, and some members of the group experienced very high levels of pre-operative anxiety. All representatives reported a positive overall treatment experience, although one parent and child dyad expressed concerns over any future treatments due to a very negative experience in the anaesthetic room. The representatives have been consulted at PPI meetings held both prior to, and subsequent to outline, and therefore have a clear understanding of the trial, its aims and objectives.

16.3 Methods of involvement
Should the grant be funded we will convene a patient panel who will meet on a 4-monthly basis to instruct the trial team (represented by the study manager and C.I.), with two or more PPI representatives attending trial management group meetings in between. Patient representatives not on the trial team will also be invited to join the Trial Steering Committee. PPI representatives will be invited to contribute during the write-up period to ensure the needs of a service-user audience are met.

17. EXPERTISE
The research team has the appropriate expertise and the right blend of multidisciplinary skills, including patient representatives, multidisciplinary clinicians, statisticians, health economists, programmers and trialists with experience of running CTIMPs in accordance with Statutory Instrument 2004 No. 1031 the Medicines for Human Use (Clinical Trials) Regulations 2004.

Patient representatives
Mrs. Jamie Buckley and Mrs. Julie Child-Cavill are two PPI group members whose children have undergone recent ENT surgery for tonsillectomy.

Trial Mentorship
Professor Jan Clarkson is co-director of the Dental Health Services Research Unit, PI on three NIHR HTA trials and will be the trial mentor.

Anaesthesia and pain
Dr Ayman Eissa is a consultant anaesthetist at Sheffield Children's Hospital and will be the joint CI

Dr Matt Wilson is a consultant anaesthetist and NIHR Clinician Scientist. He will be the advisor on the trial management group. He has previous experience as the Chief Investigator of a CTIMP in acute pain research (RESPITE).

Dr. Hamish Paton is a consultant anaesthetist and PI for Barnsley District General Hospital.

Dr. Sian Rolfe is a consultant anaesthetist for Royal Manchester Children's Hospital.

Dental

Professor Chris Deery is a consultant paediatric dentist, Dean of the Sheffield School of Clinical Dentistry and Yorkshire Lead for the NIHR FiCTION trial. He is lead applicant and will be the joint CI.

Dr. Zoe Marshman is a reader/ honorary consultant in public health dentistry with experience of being a PI on two NIHR projects, whose expertise lie in child centred research. Zoe is the qualitative lead.

Professor Julian Yates is a consultant oral surgeon and PI for Manchester Hospitals.

Dr Simon Atkins is a senior clinical lecturer/ honorary consultant oral surgeon and recruitment champion for Sheffield Children's Hospital.

Dr Robert Bolt is a clinical lecturer/ specialist in oral surgery, with an interest in sedation. He is chair of the Sheffield Oral & Dental PPI panel and will be recruiter and trial PPI chair.

Professor Helen Rodd is a consultant paediatric dentist/ recruitment champion for Sheffield Hospitals. She is internationally recognised for child-centred oral health research, which embraces both qualitative and quantitative methodologies.

Dr. Fiona Gilchrist is a senior clinical lecturer and honorary consultant in paediatric dentistry, and is an expert in child anxiety management.

Dr. Sondos Albadri is a reader/honorary consultant in paediatric dentistry and site PI for Liverpool. She is the PI for the NIHR RECUR trial.

ENT
Professor Jaydip Ray is Consultant & Clinical Director for ENT at Sheffield Children's Hospital. He is currently CI & PI for several NIHR portfolio studies and is the CI in an EU multi-centre trial with the first global recruitment in Sheffield. He will be ENT recruitment champion.

Trainees
Anaesthetic trainee networks include: NWRAG; SHARC.

Specialists in design and analysis
Diana Papaioannou is a proposal developer and experienced Trial Manager of Sheffield CTRU. She will provide support for design, conduct and write-up of the trial, and line manage the study manager.

Mr Oscar Bortolami is Senior Trials Unit Statistician, Sheffield, CTRU. He will provide oversight of design and analysis.

Economist
Dr Tracey Young is a senior health economist with over 20 years' experience in the design, analysis, reporting and writing of economic evaluations including NIHR RfPB-funded research.

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