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Synopsis

Melatonin versus midazolam in the premedication of anxious children attending for elective surgery under general anaesthesia: the MAGIC non-inferiority RCT

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Abstract

Background: Anxiety in children prior to general anaesthesia is common, with up to half displaying distress. Anxiety and distress may lead to unsuccessful anaesthesia, together with greater postoperative pain, agitation and behavioural changes after surgery including sleep disturbances. Midazolam is the current standard premedication; however, it has adverse effects such as the potential for respiratory suppression and unpredictable effects which may result in agitation rather than anxiolysis. Melatonin is an alternative preoperative anxiolytic; however, previous trials have delivered conflicting results. The aim of this non-inferiority trial was to evaluate the effectiveness of melatonin compared to midazolam in reducing anxiety in children undergoing general anaesthesia.

Methods: We undertook a randomised-controlled, parallel-group, double-blind, non-inferiority trial in 20 United Kingdom National Health Service trusts, with an embedded qualitative study and health economic evaluation. Anxious children having day case elective surgery under general anaesthesia were randomly assigned to either control (standard of care) group: midazolam; or intervention group: melatonin. The primary outcome was preoperative distress (non-inferiority hypothesis) as assessed by modified Yale Preoperative Anxiety Scale Short Form. Secondary outcomes included safety and efficacy objectives. Analyses were by intention to treat, with an additional per-protocol analysis. The sample size of the trial was 624 children.

This synopsis should be referenced as follows:
Deery C, Bolt R, Papaioannou D, Wilson M, Hyslop M, Herbert E, *et al*. Melatonin versus midazolam in the premedication of anxious children attending for elective surgery under general anaesthesia: the MAGIC non-inferiority RCT. *Health Technol Assess* 2025;**29**(29). https://doi.org/10.3310/CWKF1987

Results: The trial was stopped early due to recruitment futility. Between 30 July 2019 and 9 November 2022, 110 children were recruited; 55 allocated to midazolam and 55 allocated to melatonin. Pre-planned analyses showed an adjusted mean difference of 13.1 (95% confidence interval 3.7 to 22.4) for the intention-to-treat population and 12.9 (95% confidence interval 3.1 to 22.6) for the per-protocol population, in favour of midazolam. In both analyses, the upper limit of the 95% confidence interval exceeds the predefined margin of 4.3; therefore, melatonin is not non-inferior to midazolam. The lower limit of the 95% confidence intervals excludes zero and thus melatonin is inferior to midazolam; the difference found is considered to be clinically meaningful. Adverse events in the midazolam arm (26%) were slightly higher than melatonin (18%); there were no serious adverse events in either arm. Challenges to recruitment included study-related factors (eligibility criteria and trial design), participant factors (caregiver stress on the day of treatment) and practitioner factors (valuing predictability). In terms of acceptability, preferences of the anaesthetist, patient and caregiver factors and medication side effects profile were influential and suggest the choice of preoperative anxiolytic is more complex than previously described.
On average, costs over the 14 days post surgery were lower for those who received melatonin (−£46.20, 95% confidence interval −£166.14 to £66.74) with a mean incremental difference in procedure success of −0.02 (95% confidence interval −0.08 to 0.004), although there was uncertainty around the results.
Conclusion: In children with preoperative anxiety, midazolam is more effective than melatonin at reducing preoperative anxiety prior to general anaesthesia, although the early termination of the trial increases the likelihood of bias.
Limitations: The trial was prematurely terminated due to recruitment futility. Despite this, a clinically meaningful and statistically significant finding was observed about the primary outcome.
Future work: There remains a need to develop or repurpose another drug with a more favourable side effects profile to midazolam.
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A plain language summary of this synopsis is available on the NIHR Journals Library Website https://doi.org/10.3310/CWKF1987.

Introduction

This report details the work undertaken to establish the comparative effectiveness and side effects profile of melatonin versus midazolam for high levels of preoperative distress in children. It arose from a call commissioned by the National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) programme, based on a Cochrane review in adults, and other systematic reviews that involved children, which suggested that melatonin may be equally as effective as standard premedication treatment with midazolam in reducing preoperative distress and anxiety as well as emergence agitation.

Rationale for research and background

There are around half a million new episodes of hospital care per year for children aged 3–14 years in the NHS requiring general anaesthesia.[3] In 2016, over a third of hospital attendances related to day case procedures.[4] Anxiety ahead of general anaesthesia is common, with up to half of children displaying distress behaviour at the point of undergoing general anaesthetic (GA).[5] Anxiety and distress in a child may lead to overall non-compliance and thus rescheduling of elective surgery; it may furthermore lead to greater postoperative pain, agitation and behavioural changes after surgery including sleep disturbances.[6–10]

Midazolam, the current standard premedication given to an anxious child ahead of surgery, has been shown to be effective,[11] 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 postoperative recovery;[12,13] 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[14] and also unpredictable effects on children which may result in agitation rather than anxiolysis – particularly in children with additional needs.[15] However, the degree of risk presented with midazolam is accepted due to an over-riding need for co-operation in the anaesthetic room. There is therefore a clear need to

evaluate whether there is an alternative anxiolytic to midazolam which is an effective and acceptable premedication for the management of the anxious child ahead of anaesthesia.

Melatonin has been proposed as an alternative premedication, with evidence that the drug may be as effective as midazolam at reducing preoperative anxiety in adults[16–22] and having an excellent safety profile.[23,24] However, studies in children have delivered conflicting results with regard to effectiveness. We presented this uncertainty in a systematic review which was unable to confirm whether melatonin was comparable in effectiveness to standard premedications, including midazolam.[25] Several limitations of the included studies were reported. Furthermore, whereas other trials had evaluated melatonin use in a general paediatric preoperative population, we proposed undertaking a trial in the specifically anxious population of children, which reflects standard practice of premedication use in the UK healthcare setting. The rationale was to evaluate if melatonin was non-inferior to midazolam, that is as effective as the standard-of-care premedication and with a better safety profile.

Objectives

The objectives from the trial are described below; some text in this section has been reproduced from the Melatonin for Anxiety prior to General anaesthesia In Children (MAGIC) Protocol.[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 (AEs) reporting and Post Hospitalisation Behaviour Questionnaire for Ambulatory Surgery (PHBQ-AS)[26] follow-up]
- allocation concealment and blinding.

Clinical objectives (safety and efficacy)

To evaluate if melatonin, in relation to midazolam, is:

- non-inferior in dealing with preoperative anxiety evaluated by Modified Yale Preoperative Anxiety Scale-Short Form (mYPAS-SF)[27,28] score over the following three standard preoperative time points recommended for the scale:
  - 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, Paediatric Anaesthesia Emergence Delirium (PAED) scale,[29] Vancouver Sedation Recovery Scale (VSRS),[30] Revised Faces Pain Scale (FPS-R) (observer and participant reported),[31] analgesia requirements, PHBQ-AS, AEs, orientation and cognitive/psychomotor function]
- non-inferior in dealing with secondary efficacy outcomes (anaesthetic failure rate)
- to describe serious adverse events (SAEs) data (summarised both at patient level and event level) and report listings between the different arms.

Integrated qualitative substudy

- To inform strategies to improve recruitment, explore clinician and patient's responses to an intervention and to explain the findings of the randomised controlled trial (RCT).
- To explore stakeholder perspectives on the patient refusal of GA, acceptance of the drugs, distress reduction, impacts on recovery such as postoperative sedation and adverse effects.
- To explore patient experiences of recruitment and the acceptability of the two drugs including taste, reduction of distress, the child's postoperative recovery and any longer-term implications.

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 1 year using both a cost-per-successful procedure and cost-per-quality-adjusted life-year (QALY) approach.

Methods for data collection and analysis

The MAGIC trial was a parallel-group, double-blind, multicentre, RCT to assess the non-inferiority of melatonin compared to midazolam in the treatment of anxiety in children (aged 3–14 years) undergoing scheduled, elective dental, ophthalmology, ear, nose and throat (ENT), gastroenterology, radiology, plastic, orthopaedic, urology or general surgery under GA. The trial was run across 20 UK hospital Trusts, including large Teaching Hospitals and smaller District General Hospitals. The primary outcome of the trial was the mYPAS-SF score[28]

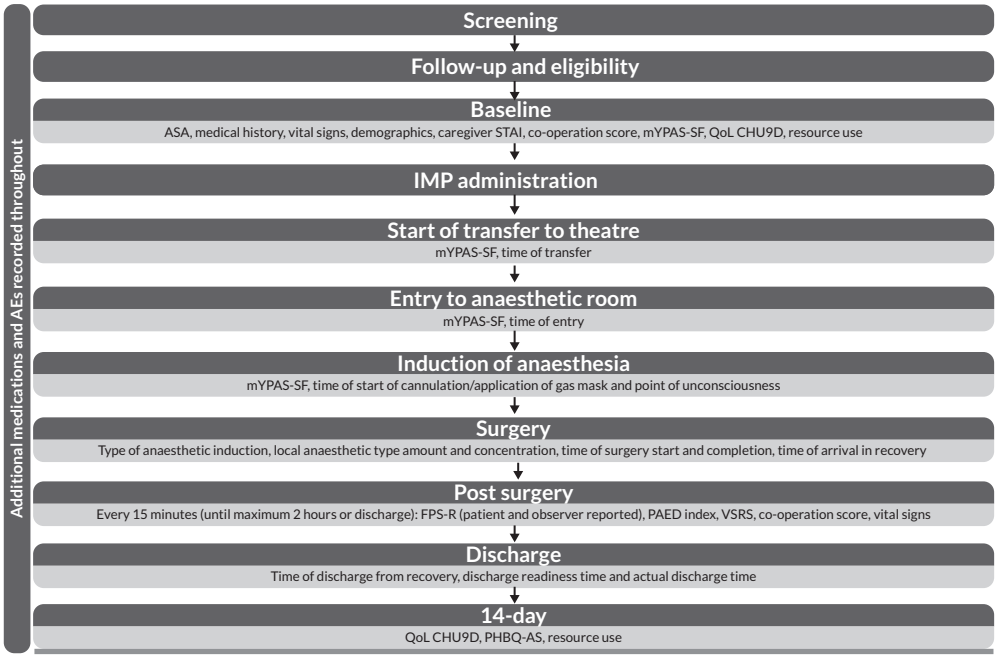

FIGURE 1 Melatonin for Anxiety prior to General anaesthesia In Children participant pathway. ASA, American Society of Anesthesiologists; IMP, investigational medicinal product; STAI, State–Trait Anxiety Inventory questionnaire;[33] QoL CHU9D, Quality of Life Child Health Utility 9D questionnaire.[34] Note: Reproduced with permission from Bolt *et al.*[2] This is an Open Access article distributed under the terms of the Creative Commons Attribution Licence, which permits unrestricted use, distribution and reproduction in any medium, provided the original author and source are credited. This figure includes minor additions and formatting changes to the original text.

measured preoperatively at three time points: start of transfer to theatre, entry to the anaesthetic room and induction of anaesthesia; adjusted for baseline score and other pre-planned covariates.[32] The pre-defined non-inferiority margin was a 4.3-point difference between the two groups, with non-inferiority being declared if the upper bound of the 95% confidence interval (CI) did not exceed this value. The intention-to-treat (ITT) and per-protocol (PP) analysis populations were coprimary for the primary outcome.

The trial was closed early due to recruitment futility; therefore, the original sample size target of 624 participants was not reached. Instead, between 30 July 2019 and 9 November 2022, 110 children and 113 caregivers were consented and randomised into the trial; 55 children were randomised to receive melatonin and 55 to receive midazolam.

Full details of the MAGIC trial have been published as a protocol here (https://doi.org/10.15131/shef.data.22220884). *Figure 1* shows the patient pathway and data collection through the trial.

Results summary

BOX 1 Research papers synthesised in the synopsis

- **Main Protocol Paper:** Deery C, Bolt R, Papaioannou D, Totton N, Herbert E, Hyslop M *et al. 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*. The University of Sheffield. Workflow; 2023. https://doi.org/10.15131/shef.data.22220884.v1
- **Statistical Analysis Plan Paper:** Herbert E, Totton N, Deery C, Bolt R, Hyslop M, Bradburn, M, *et al. MAGIC Trial – Statistical Analysis Plan*. The University of Sheffield. Workflow; 2023. https://doi.org/10.15131/shef.data.23180222
- **Main Results paper:** Bolt R, Hyslop MC, Herbert E, Papaioannou D, Totton N, Wilson M, *et al.* The MAGIC trial – a multicentre, parallel, non-inferiority, randomised controlled trial of melatonin versus midazolam in the premedication of anxious children attending for elective surgery under general anaesthesia. *Br J Anaesth* 2024;**132**:76–85. https://doi.org/10.1016/j.bja.2023.10.011. Epub November 10 2023. PMID: 37953202; PMCID: PMC10797512.
- **Internal Pilot Qualitative Paper:** Kettle J, Deery C, Bolt R, Papaioannou D, Marshman Z. Stakeholder perspectives on barriers and enablers to recruiting anxious children undergoing day surgery under general anaesthetic: a qualitative internal pilot study of the MAGIC randomised controlled trial. *Trials* 2021;**22**:458. https://doi.org/10.1186/s13063-021-05425-z. PMID: 34271982; PMCID: PMC8285773.

- **Lessons Learned Paper:** Hyslop MC, Papaioannou D, Bolt R, Wilson M, Bradburn M, Clarkson J, *et al.* Barriers and enablers to recruiting participants within perioperative and anaesthetic settings: lessons learned from the MAGIC trial. *BJA Online* 2025;**13**:100375.
- **Main Qualitative Paper**: Kettle J, Bolt R, Deery C, Papaioannou D, Rodd H, Hyslop MC, *et al*. Acceptability of midazolam and melatonin as premedications for anxious children undergoing general anaesthetic: a qualitative interview study with children, caregivers and health professionals participating in the MAGIC randomised controlled trial. *Trials* 2024;**25**:813. https://doi.org/10.1186/s13063-024-08611-x
- **Health Economics Paper:** Young T, Papaioannou D, Bolt R, Herbert E, Totton N, Hyslop MC, *et al.* The MAGIC trial (Melatonin for Anxiety prior to General anaesthesia In Children) – Health Economics Report. ***In progress of submission.***
- **Study within a trial Paper:** Herbert E, Papaioannou D, Loban A, Totton N, Hyslop M, Bolt R, Deery C. Personalised versus standard text message prompts for increasing trial participant response to telephone follow-up: an embedded randomised controlled retention trial. *Trials* 2024;**25**:108. https://doi.org/10.1186/s13063-024-07916-1

Recruitment futility

In November 2022, it was agreed with the Trial Steering Committee (TSC) and the NIHR (trial funder) that the MAGIC trial would be terminated prematurely on account of recruitment futility. *Figure 2* outlines the timeline of the MAGIC trial from opening to closure (2019–22). The trial recruited 110 participants out of the target 624, with 568 participants screened. The trial opened to recruitment in July 2019, experiencing slower than expected recruitment during its pilot phase with summer holidays affecting staff capacity and availability. Although recruitment steadily increased up to December 2020, several recruitment barriers were identified, which included:

- reduced number of children requiring premedication prior to surgery
- eligibility restrictions such as limited surgical specialties
- 24-hour ward admission protocols at some sites and younger children (3- to 4-year-olds) who were previously ineligible
- very anxious children requiring more than one premedication, for example patients with high anxiety and autism
- anaesthetist equipoise regarding melatonin use and increasing use of other premedications instead of midazolam (e.g. dexmedetomidine)
- delays on theatre lists and waiting times due to potential delays in dispensing investigational medicinal product (IMP)
- research pharmacy opening times preventing anxious children at the beginning of theatre lists from being recruited
- language barriers
- patients with high anxiety unable to provide assent or declining involvement in the trial
- research staff availability and capacity.

Barriers were discussed and changes made to the trial protocol to try and alleviate these issues (see *Appendix 1*, *Table 2* – Protocol changes) and included: expansion of inclusion criteria to allow 3- and 4-year-old children to be recruited and include more surgical specialties: gastroenterology, radiology, plastic, orthopaedic, urology or other general surgery; change to clarify assent requirement from children, with children who neither provide assent nor decline the trial (due to high anxiety) able to be enrolled based on caregiver consent and principal investigator (PI) decision (children who verbally decline to participate not be included); change to allow local care teams to send out study information to potential participants prior to their day of surgery; and change to allow children the option of reviewing the information sheet or the video and not a requirement to undertake both.

In early 2020, the coronavirus pandemic led to numerous pressures and impacted the NHS as well as research. The MAGIC trial was particularly vulnerable: routine elective surgeries were halted during the pandemic; PIs were primarily anaesthetists essential in the pandemic response for the care of severely ill COVID-19 patients on mechanical ventilators. Midazolam became subject to nationally controlled use as the drug was favoured as first-line sedation for patients requiring mechanical ventilation and our manufacturer could not source the product for trial supplies. Brexit further impacted the trial due to European Union (EU) medicinal drug imports being subject to new legislation and causing large delays to the manufacture of trial drug supplies.

The pandemic and Brexit had profound effects on trial recruitment, and recruitment was suspended on 27 March 2020. Although recruitment to the MAGIC trial recommenced on 9 October 2020, the pandemic further hampered the trial's progress with site capabilities to recruit and treat participants affected by cancellation of elective surgeries, isolation of surgical anaesthetic teams with COVID-19, and redeployment of research nurses and clinical staff to COVID-19 studies. Recruitment to the trial was stop/start between October 2020 and November 2022 due to these issues. Despite major efforts from site research teams, protocol amendments to address recruitment barriers, and genuine PI and research staff enthusiasm for the trial, there was not sufficient evidence that site participation was translating to recruits for the team to make a cogent case to continue. The changes made to the Protocol, as part of substantial amendment 5, were also insufficient to improve recruitment significantly;

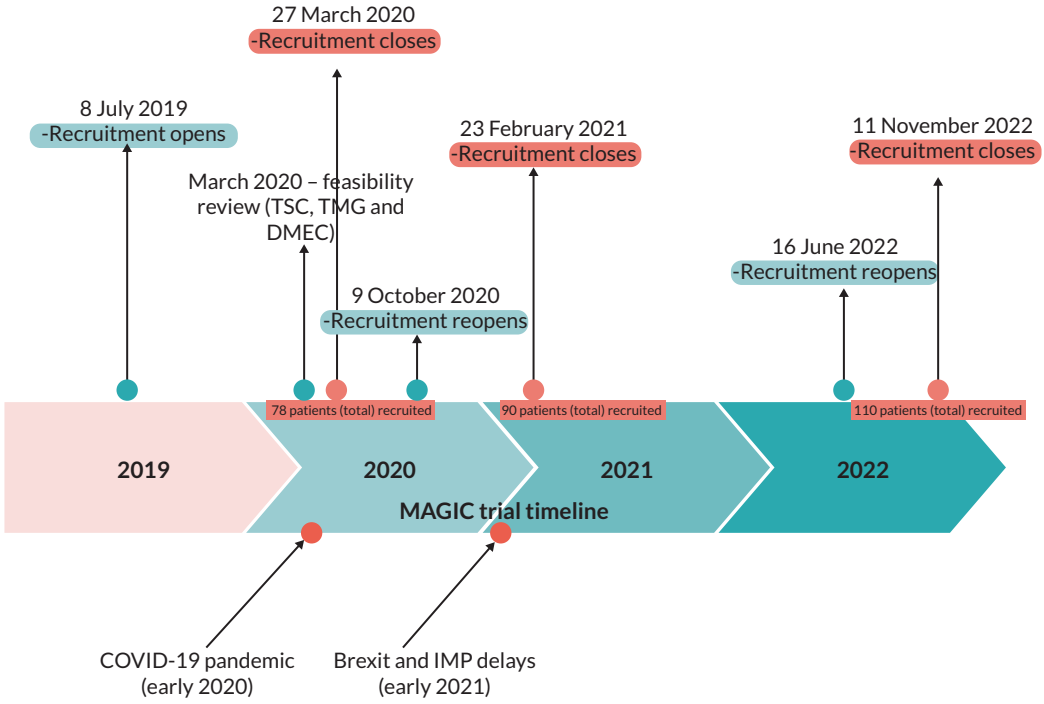

FIGURE 2 Melatonin for Anxiety prior to General anaesthesia In Children trial timeline. DMEC, Data Monitoring and Ethics Committee; TMG, Trial Management Group.

for example expansion of surgical specialties to gastroenterology, radiology, plastic, orthopaedic, urology or other general surgery only yielded four patients from those new specialties included. The last trial participant was recruited and followed up by 23 November 2022.

Primary and secondary outcomes in the Melatonin for Anxiety prior to General anaesthesia In Children trial

Results of the MAGIC trial are reported in Bolt *et al.*[2] A detailed full version of the MAGIC statistical analysis plan is also available (https://doi.org/10.15131/shef.data.23180222).[34] *Box 1* highlights the relevant research outputs generated from the MAGIC trial.

Primary outcome – modified yale preoperative anxiety scale-short form

Despite the early termination of the trial, the planned analyses as defined in the statistical analysis plan were completed as appropriate to sufficient data being available. Due to not achieving the original sample size target, *p*-values have not been reported and, instead, the presentation has focused on CIs.

The primary outcome, mYPAS-SF, represents preoperative anxiety with higher values representing increased anxiety. In the ITT analysis population, the adjusted mYPAS-SF score in the melatonin group was higher than in the midazolam group (adjusted mean difference 13.09, 95% CI 3.74 to 22.44; *n* = 92). Similar results were observed in the PP population (adjusted mean difference 12.9, 95% CI 3.1 to 22.6; *n* = 87). Melatonin was shown to be inferior to midazolam reducing preoperative anxiety in both analysis populations.

Secondary outcomes

Secondary outcomes showed small numbers of anaesthetic failure in the trial (two in the melatonin group and one in the midazolam group). Anaesthetic turnaround and recovery times were similar in the two groups [adjusted ratios of means 1.01 (95% CI 0.78 to 1.3) and 0.88 (95% CI 0.74 to 1.04), respectively]. Analgesia requirements were also similar between the groups [adjusted odds ratio (OR) 1.22, 95% CI 0.37 to 4.25]. Longitudinal analyses of repeated recovery scores (VSRS, co-operation score, FPS-R and PAED) also showed no differences between the groups[2] (see *Appendix 2*, *Table 3*).

Fourteen-day follow-up

At 14 days post surgery, the primary caregiver was contacted to complete a PHBQ-AS form to assess postoperative behavioural changes. The results of these questionnaires showed no difference between the groups (adjusted mean difference −0.03, 95% CI −0.21 to 0.14; *n* = 74). There were 11 AEs in the melatonin group among 9 of the 49 patients (18.4%, 95% CI 9.2% to 32.5%), and 23 AEs in the midazolam group among 13 of the 50 patients (26.0%, 95% CI 15.1% to 40.6%). No SAEs were reported during the trial. Using these trial results, we concluded that melatonin is inferior to midazolam at

reducing preoperative anxiety in children who require premedication and there appeared to be no impact on the success of the procedure or recovery outcomes.

Qualitative summary

An integrated qualitative substudy was undertaken to: (1) explore health professional, and patient (child) and caregiver experiences of recruitment during an internal pilot to inform recruitment strategies; (2) explore healthcare professional and patient experiences on the acceptability of the two drugs; and (3) explain the findings of the RCT.

During the internal pilot, a qualitative interview study was undertaken[35] to identify research staff perspectives on barriers and enablers to recruitment. Sixteen stakeholders including research nurses, PIs and other investigators from six trial sites participated in semistructured interviews; data were analysed in framework analysis. Barriers and facilitators related to various aspects of MAGIC, including the study itself, the potential participants and their caregivers, practitioners (and those with whom they are collaborating outside of the study, such as other clinicians and nurses) and wider setting and contextual factors. A key study-related barrier was the eligibility criteria, which was broadened during the course of the study. Barriers related to patients and caregivers included lower than expected numbers of eligible patients, and the impact of the child's anxiety on the caregivers' willingness to consider MAGIC and focus on recruitment materials. Anaesthetists and research nurses involved in MAGIC were not always available when potentially eligible patients were scheduled for treatment, while anaesthetists outside of MAGIC did not always give permission for their patients to be recruited, for example if they had preferences for other premedications. The high-pressure, fast-paced nature of the surgical day unit setting could also be a barrier, as could the hospital context, for instance there were frequent problems obtaining the trial drugs from the hospital pharmacy in time for patients at the start of the theatre list.

The acceptability of midazolam and melatonin as premedications was explored in the qualitative interview study with children, caregivers and healthcare professionals. Thirty-seven participants (23 health professionals, 10 caregivers and 4 children) were interviewed. Factors around the acceptability of melatonin and midazolam were identified. These included: effectiveness as premedication prior to a GA; administration of premedication; experience of recovery from GA; prior experiences of premedication; and associations and evidence of the range of available options for managing anxiety. Factors around the acceptability of premedications more generally were also identified and it was noted that decisions about premedications appear to be made based on several more complex factors than merely anxiolytic properties.

Health economic summary

An economic evaluation was undertaken alongside the MAGIC trial.[36] The aim of the health economic analysis was to evaluate the within-trial cost-effectiveness of melatonin for anxiety in children compared to usual care (midazolam) prior to general anaesthesia in children from an NHS and Personal Social Services perspective. Resource use was collected from case-report forms from randomisation to 14 days post surgery. The main outcome was the incremental cost-per-successful procedure with a secondary outcome of incremental cost per QALYs with QALYs measured using the Child Health Utility-9D (CHU9D). QALYs were not selected as the primary analysis due to the short (14 day) time frame of the study and the lack of evidence that QALYs would change over this time frame and due to not having a validated measure of QALYs in children across the age range of the study.

Of the 110 participants recruited, a total of 100 children had the intervention drugs prescribed, 50 in the melatonin arm and 50 in the midazolam arm. Of these, one child in the melatonin arm refused to take the drug. These 100 children were the focus of the health economic analysis. On average, costs over 14 days were lower for those who received melatonin (−£46.20, 95% CI −£166.14 to £66.74) with a mean incremental difference in procedure success of −0.02 (95% CI −0.08 to 0.004), although there was uncertainty around the results. When the incremental cost-effectiveness ratios cover more than one quadrant of the cost-effectiveness plane, it is recommended that 95% CIs are not reported owing to issues being able to distinguish between situations when the new treatment is favoured and when it is not.[37]

The study closed early owing to issues with recruitment and this has limited the economic analysis; subgroup analysis was limited to those who underwent head and neck procedures owing to small numbers by subgroup for other procedure types and age groups. For head and neck procedures (melatonin $n = 46$; midazolam $n = 47$), the results were similar to the primary cost-effectiveness analysis, on average melatonin was cheaper (mean £45.20, 95% CI −£170.39 to £76.37) with a mean incremental difference in procedure success of −0.022 (95% CI −0.09

to 0.04). The cost–utility analysis for the full sample used CHU9D to estimate utilities and was carried out after imputing missing CHU9D (43% missing data) and also produced uncertain results. The mean difference in costs remained the same as for the cost-effectiveness analysis (−£46.20, 95% CI −£166.14 to £66.74) with a mean incremental QALY 0.0 (95% CI −0.0008 to 0.0008).

Discussion and interpretation

The MAGIC trial is the first multicentred RCT comparing the effectiveness of midazolam compared to melatonin in anxious children, as a premedication prior to general anaesthesia. Despite not recruiting to the sample size target, the primary outcome in both the ITT and PP analyses showed that midazolam was more effective as a premedication than melatonin on preoperative anxiety. This was the case due to a larger effect size than expected being identified between the two treatments. This result differs from the findings of previous studies.[38,39] This may be because the previous studies had smaller sample sizes and used a sample of all available patients rather than targeting anxious patients. Therefore, previous studies are likely to be underpowered, and, as a result of including non-anxious individuals, diluted in the observation of any differences in effectiveness between the two drugs.

Regarding the secondary outcomes, no differences between the two drugs were seen. Only three patients (n = 2 in the melatonin arm and n = 1 in the midazolam arm) did not have their planned procedure due to failure to be anaesthetised. This suggests, as would be expected, that both drugs were having an anxiolytic effect. Analgesia requirements were also similar between the groups. Longitudinal analyses of repeated recovery scores (VSRS, co-operation score, FPS-R and PAED) also showed no evidence of difference between the groups. Due to the sedative effects of midazolam, it was predicted that readiness for discharge time would be less in the melatonin arm, although this was not observed.[40] It may be that any differences in secondary outcomes were not detected due to lack of power. At the 14-day follow-up, no differences were found between the two arms (PHBQ-AS). There were no SAEs in either arm. There were slightly more participants with at least one AE in the midazolam arm (13) compared to the melatonin arm (11). However, only one of these in the midazolam arm was thought to be potentially related to the premedication. Both drugs demonstrated excellent safety profiles.

A qualitative semistructured interview study was undertaken to identify facilitators and barriers to recruitment. The sample included research nurses, PIs and other investigators from six trial sites. The finding that there were fewer eligible patients than expected is frequently reported from other trials.[41,42] For the MAGIC trial, all potential sites conducted an audit prior to the trial to confirm an adequate throughput of eligible patients; however, despite this, the numbers of eligible patients fell below what was predicted.

One barrier to recruitment was the large amount of information caregivers had to digest at the time of the child's surgery, particularly when they may have been wishing to focus solely on their anxious child. Also, the caregiver may understandably be anxious themselves on the day of surgery. The decision when designing the trial to have recruitment on the day was to mirror current practice where the final decision about the need for a premedication is made by the anaesthetist responsible for the patient on the day. In response to this feedback, MAGIC did look to address this by recruiting patients at pre-assessment clinics; however, this protocol amendment was never instigated due to the early closure of the trial. Interestingly, one of the enablers to recruitment was a desire expressed by caregivers to 'give back to the NHS' by participating in research. As with other trials, eligibility criteria such as patient age (so that validated measures can be used) were a barrier to recruitment.[43] As is often the case, time constraints on key members of staff, in what is a pressured and time-sensitive environment, was a further barrier to recruitment.[43]

On average, melatonin was £14.20 less per patient over the 14-day follow-up period, although there was uncertainty in the results and the difference in effectiveness between the two drugs questions the value of this saving. This is the first study to report on the cost-effectiveness of melatonin compared with midazolam in children, young people and adults. Studies that have looked at the cost-effectiveness of midazolam have not been conclusive.[44–47]

A strength of the current study is that it is the most relevant study to inform practice in the UK NHS. It is also very strong methodologically. Patients, their caregivers and all staff delivering care, including the anaesthetists, were blind to the intervention given. The chosen outcome measure is well validated and recognised; furthermore, mYPAS-SF is applicable both in the preoperative area as well as during induction. However, a major weakness is that the target sample size was not achieved, and although a clear statistical and clinically meaningful difference in favour of midazolam was found, as stated there may not have been an adequate sample size to identify differences in the secondary outcomes. Additionally, results from

under-recruited RCTs can require caution due to large variation or bias in the sample achieved. Although the use of mYPAS-SF is a strength, other common outcome measures, such as mask acceptance or level of restraint, were not used.[48,49]

Many trials were affected by the COVID-19 pandemic.[50] MAGIC was particularly vulnerable to the impact as all routine elective surgeries halted during the pandemic; PIs were mainly anaesthetists essential in the pandemic response for the clinical care of critically ill COVID-19 patients; midazolam was favoured as first-line sedation for patients requiring mechanical ventilation. Brexit further impacted the trial due to EU medicinal drug imports being subject to new legislation which caused large delays to the manufacture of trial drug supplies.[51] A number of other challenges for recruitment included trial staff resources and availability, particularly research nurse availability, and research pharmacy opening times which meant the IMP was not available prior to the beginning of morning theatre lists as for clinical reasons, anxious children are usually placed first on a list if possible. There were also issues around anaesthetist and other staff's equipoise, resulting in an unwillingness to recruit anxious children or children with special needs.

Increased use of dexmedetomidine as a premedication in children, among UK anaesthetists, which gathered pace over the chronology of the MAGIC trial, was a further barrier to recruitment at some sites. Anecdotally, the drug is seen as better tolerated and potentially more effective as a preoperative anxiolytic, it is administered intranasally as opposed to orally, eliminating the risk of the patient spitting out the medication, and it has a superior side effects profile to midazolam.[52] However, to date, none of the studies directly comparing the drugs have confirmed dexmedetomidine's superiority as a premedication in children over midazolam.

Stakeholders were engaged through a number of patient and public involvement (PPI) groups run during the trial design process. Advice was provided from child and parent groups with respect to the wording of patient information leaflets, as well as the design and wording of an age-specific trial video. Oral and dental PPI groups provided further advice on trial design so as to ensure the patient care pathway was not adversely affected by the trial. Anaesthetist expert groups were engaged at the beginning to establish an agreed minimal clinically important difference, which informed the sample size calculations used in the trial.

All research teams were trained in mYPAS analysis using an online resource accessed through a collaboration with researchers running the 'Little Journey' trial (www.littlejourney.health/). An online mYPAS training resource shared by the Little Journey team allowed interexaminer reliability to be maintained at a κ of 0.7. This activity strengthened the available pool of research nurses available to undertake trial observations throughout recruitment, thereby improving the overall capacity for the trial.

Challenges exist in conducting perioperative trials, including operational difficulties such as research pharmacy opening times and wide variation in anaesthetist practice. In practice, decisions about premedications are taken based on the balance of several complex issues. Other relevant measures of sedation that were not used in this trial, such as mask acceptance or level of restraint, may have provided further insight into the overall effects of each of the trial medications. Wide CIs of secondary outcome measures limit their interpretation including factors not based purely on their anxiolytic properties.

Patient and public involvement

Aim

The aim of PPI in all aspects of the study was to ensure that the views of children, their caregivers and their wider families were dispersed through the research, such that the trial was acceptable, and the results would be of direct benefit to them.

Methods

We worked with PPI representatives from grant preparation through to dissemination. The study arose from a commissioned call, and we worked with child and parent representatives to further support the design and provision of information. During the design of the trial, children who had a recent GA attended a study-specific PPI meeting along with their parents.

Involvement from the PPI group was provided during the development and iteration of participant information resources – including a participant video. PPI representatives were involved in research management and troubleshooting as members of the Trial Management Group (TMG) and TSC. PPI input was sought for the interpretation of the quantitative and qualitative data, writing and dissemination of the findings to the trial participants and their caregivers.

Results of patient and public involvement input

During grant preparation, the PPI group considered the importance of the study and felt that the potential side

effects of midazolam were a strong reason to look for an alternative drug. There was unanimous agreement that measuring the ability of each drug to 'calm the child' was the most important aspect to assess, followed by the safety profile of each drug. The mYPAS-SF was discussed, and parents felt reassured to have an extra nurse in the anaesthetic room measuring this, rather than relying on the recovery nurse. Parents also felt an objective measure assessed by a researcher was more appropriate than asking the child. All children described how they would feel the same about having a GA, regardless of the surgical procedure, for example dental extractions or tonsillectomy. The PPI group suggested follow-up should be done at 2 weeks postoperatively by a single contact, as children who undergo tonsillectomy remain housebound for 2 weeks. Telephone contact was preferred for follow-up, the group discounted e-mail and advised a text message reminder.

During the trial, the PPI provided advice to improve the lay summary and assisted in the design of the interview schedules for the qualitative research. They participated in the design of the parent and child information leaflets and children's information videos to ensure the information was age-appropriate. Examples of how PPI shaped the research included consideration of how to promote recruitment when it was slower than anticipated (e.g. through relevant networks). PPI members sat on the TSC and TMG for the trial. This ensured the research was monitored in an equitable manner, particularly with respect to trial progression criteria. This also allowed PPI views on the proposed amendments to the trial procedures to improve recruitment.

Patient and public involvement members made suggestions to improve materials, which reported the trial results to ensure the needs of the service user audience were met, in particular, that the materials were age-appropriate.

Discussion of patient and public involvement input

Patient and public involvement input was key for the design of MAGIC, tailoring it to the relevant audiences and leading discussions around what would and would not work. It also helped shape the appropriate dissemination to relevant audiences.

Reflections and critical perspective

The study had the involvement of representatives with lived experience, but we noted that further input may have been helpful from those from minority ethnic groups, or those with autism, especially to address issues around language and other barriers to joining the trial as seen during the pilot phase and qualitative review.[35]

Equality, diversity and inclusion

The MAGIC trial enrolled 110 anxious paediatric patients (aged 3–14 years) undergoing GA prior to surgery, and their primary caregivers, from 20 UK hospitals sites. The mean age of participants was 7.9 years [standard deviation (SD) 2.6], with 48% male sex and 52% female sex. A total of 81% participants were American Society of Anesthesiologists (ASA) Classification System I status and 18% were ASA II status. ASA III–V was not included due to the comorbidities increasing the risk of GA. The study did include patients with neurodiversity and learning difficulties; however, there is not a breakdown of the proportions of this.

A total of 93% of the trial participants were White English, Welsh, Scottish, Northern Irish, British; 1% Indian; 1% Pakistani; 1% white and Black Caribbean; 1% white and Asian; 1% any other white background and 1% African – or 94% white ethnic background and 5% were from a non-white ethnic background. The other 1% is missing data. In Office for National Statistics data on live births in 2020 (the most recent year of recruitment into the MAGIC trial with data available), 70% of children were from a white ethnic group, and 26% of children were from a non-white ethnic group (and 4% not stated), suggesting that children within MAGIC were not fully representative of the wider population. The majority of the trial participants (66%) were undergoing dental surgery. A review by Levine[53] on childhood caries and hospital admissions in 5-year-old children showed a higher prevalence of caries in 'other ethnic group' (44.3%) and Asian/Asian British ethnic groups (36.9%) than that found in other ethnic groups and other minority ethnic children and compared to those classed as 'white'. This highlights some discrepancies with our ethnicity proportions within MAGIC participants.

The Official Statistics Hospital tooth extractions (0- to 19-year-olds) 2021 stated a clear gradient in the most deprived areas having the highest rates of caries-related tooth extractions. A wide range of hospitals from diverse geographical areas were included within the trial; this included District General Hospitals as well as specialist Children's Units, across the UK, in an attempt to broaden recruitment possibilities. The trial also included hospitals centred within more deprived areas such as Doncaster, Barnsley, Middlesbrough, Sunderland, Bolton, Glasgow, Fife, Kilmarnock and others.

As part of the PPI input into the MAGIC trial, children and parents from representative demographics were included in the design of the trial to ensure reflective and inclusive views were incorporated, including children who had recently undergone ENT and dental surgeries under general anaesthesia. A video was suggested (and devised) to support provision of trial information in a more easily understandable and manageable format. On completion, the video was presented to PPI groups and received positive feedback. However, it was noted as part of the pilot and qualitative review that language barriers remained an issue for inclusion, and future trials within this research area need to consider understanding and access to trials for children whose first language is not English.

Impact and learning

The trial results demonstrated that midazolam, the current standard of care, is the most effective treatment available; therefore, there is no immediate requirement for a change in clinical practice. Midazolam remains a safe, effective drug in the management of preoperative anxiety in children. However, we anticipate that in the longer term, further research will be required to identify an alternative premedication with an improved side effects profile. While there are other candidate anxiolytic drugs which could be evaluated, the trial findings remove melatonin from consideration as a care standard.

Lessons learnt

The MAGIC trial experienced numerous delays and challenges during its run from 2019 to 2022 as discussed in the *Recruitment futility* section. Many of the challenges to recruitment were those often experienced by RCTs; however, some issues encountered were specific to the anaesthesia and perioperative medicine setting. The 'Barriers and enablers to recruiting participants within perioperative and anaesthetic settings: Lessons learnt from the MAGIC trial'[54] paper gives an overall account of the individual challenges experienced during the trial, and potential solutions proposed to mitigate said issues, *Table 1*, taken from the article, highlight and summarise these accordingly.

TABLE 1 Melatonin for Anxiety prior to General anaesthesia In Children lessons learnt summary table

Issue encountered	Strategies to overcome	Challenge remains
Trial staff resources and availability		
Research pharmacy opening times		
• Opening times of research pharmacy were 1–2 hours later than when the surgical list commenced. Anxious patients were often placed at the beginning of surgical lists	• Whenever possible, allow consent and eligibility to be completed at pre-assessment clinics prior to surgery (eligibility may need to be reconfirmed on the day or surgery) • Consider randomisation prior to day of surgery • Consider if IMPs can be held and dispensed outside of research pharmacy (would need a risk assessment with regard to IMP accountability) • Consider if research pharmacy can be costed and staffed outside of normal hours (would need costing into trial grant applications)	• Staffing out of hours • Local staff capacity to process trial prescriptions in real time for 'on the day' randomisation and dispensation • Risk of more post-randomisation withdrawal when randomising before the day itself
Anaesthetist trainee network		
• Trainee networks uncontactable or lack of engagement	• Consider barriers and enablers for using trainee networks in the perioperative setting. An alternative model for Anaesthetic Trainee Networks required for effective engagement • Consider individual trainees, with commitment to academic experience, assigned to involvement with trial for an extended period, to champion colleague engagement	• Organisation and commitment of each network continue to vary
Associate PI scheme		
• Trainee rotations are 3–6 monthly and preclude involvement in the associate PI scheme	• Consider timelines of the associate PI scheme (currently minimum 6 months) and how this fits in with trainee rotations (3 months)	• Six-month minimum requirement for participation still required

continued

TABLE 1 Melatonin for Anxiety prior to General anaesthesia In Children lessons learnt summary table (*continued*)

Issue encountered	Strategies to overcome	Challenge remains
Recruitment projections		
• Limited staff availability • Overoptimistic recruitment projections	• Consider higher scrutiny of feasibility forms and keeping recruitment projections realistic • Contact local Clinical Research Networks to query whether support staff are available (for NIHR portfolio trials)	• Staff support and availability continue to be an issue across clinical trials
Anaesthetist equipoise		
Multifactorial choice of premedication		
The decision on the choice of premedication in children is multifactorial and not limited purely to its anxiolytic properties. Can involve: • Pharmacological effects of the drug • Clinical features and comorbidities of child • Palatability • Child acceptance of drug route	• Discrete choice experiments may be required in the planning stages of future premedication trials to determine the attributes of premedications important to healthcare professionals, patients and their caregivers	• Consider complexities of trials that are multidisciplinary in nature, that is those that require input from various clinical disciplines, and involve multifactorial decision-making when deciding a treatment pathway
Anaesthetist equipoise and variation in clinical practice		
• Local policies on prescribing practice (e.g. two premedications) • Large variation in prescribing practice among anaesthetists (e.g. use of dexmedetomidine) • Disrupted equipoise among anaesthetists regarding interventions	• Consider undertaking a survey to understand the clinical practice of anaesthetists across a large number and types of sites (i.e. Teaching Hospitals, District General Hospitals, etc.) • Site assessment templates designed to capture and ensure consistent prescribing practices for anaesthetists across sites and within sites (i.e. survey more than one anaesthetist per site)	• Variation in the degree of anaesthetist equipoise remains an ongoing issue within anaesthesia and perioperative trials
New treatments becoming available		
• For example, dexmedetomidine	• Consider the potential for the treatment landscape to vary over the lifecycle of a trial • Again, consider undertaking a survey to understand clinical practice among anaesthetists and whether newer 'off-label' drugs are/will be used	• Treatment landscapes will continue to evolve during the lifetime of a clinical trial
Dual premedication use for some subgroups		
• Several hospitals give two premedications to children as standard for preoperative anxiety. Particularly children with additional needs	• Identify local practices during feasibility or widening inclusion criteria where possible	• Site-level clinical variations may continue to be an issue within clinical trials. Exploring these at the earliest opportunity at the trial design stage is vital
Equality, diversion and inclusivity		
• Willingness to randomise some individuals, for example neurodiverse children or those with learning difficulties (experimental treatment)	• Consider greater staff education on inclusion. Children with special needs form a large part of those requiring premedications, particularly those within the dental setting. Research staff need to be aware that inclusion of these children is vital, as they represent a significant part of the population and thus deserve representation also	• Inclusivity in trials is a key research priority. Key challenges which remain are ensuring: • A more diverse research workforce and recruiters within trials • More inclusive PPI representation within trials
Recruitment setting		
Day of surgery		
• Time pressure to consent and randomise patients all on the day of surgery, in order to commence surgical lists on time, in the midst of other time pressures • Time pressure for pharmacy to blind and dispense IMP prior to surgery	• Allow flexibility to randomise before the day of surgery wherever possible, while being mindful for the potential of post-randomisation drop-outs • Consider using a range of staff to recruit patients, for example research nurses, where possible	• There will be occasions within the perioperative setting where randomisation will have to be on the day, or even at the time of surgery, which requires facilitation

TABLE 1 Melatonin for Anxiety prior to General anaesthesia In Children lessons learnt summary table (*continued*)

Issue encountered	Strategies to overcome	Challenge remains
Paediatric assent		
• Requirement for assent even in children aged 5–7 years old • Made more challenging with the requirement to assent an already anxious population	• Consider the practicalities of assenting younger and/or anxious children, and whether it may be reasonable to seek parental consent only in certain situations • PPI is crucial for input on the acceptability of including assent	• Assent continues to be recommended when recruiting children to clinical trials. This needs to be considered against the practicalities on a trial-by-trial basis

Note
Reproduced with permission from Hyslop *et al.*[54] This is an Open Access article distributed under the terms of the Creative Commons Attribution Licence, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited. This table includes minor additions and formatting changes to the original text.

Study within a trial: Melatonin for Anxiety prior to General anaesthesia In Children

Given the prevalence of the use of RCT, there is an ongoing need to develop and evaluate strategies for improving retention to increase efficiency. An assessment of optimum strategies can be completed by embedding a smaller RCT to evaluate these strategies within a real-life host trial, known as a study within a trial (SWAT).[55] In MAGIC, a SWAT was undertaken to evaluate the effectiveness of a personalised text message, including the recipient's first name, versus a standard text message, for prompting response in caregivers to answer and complete the 14-day telephone follow-up questionnaires within the trial.[56] The SWAT showed some evidence that personalised text messages can be effective at increasing response rates when data are collected via telephone. The intervention is low cost and practical to implement, suggesting further use and investigation within trials when scheduled telephone follow-ups are being used.

Dissemination plans

The findings from the MAGIC trial have been reported in several academic publications. Please see the *Publications* section for a list of outputs from the trial. The main trial results will be disseminated at Anaesthesia Research 2023 (Royal College of Anaesthetists) conference scheduled in York for 28 November 2023. The results of the trial were provided to child participants and their caregivers via postal leaflets sent out in September 2023. Our TSC/TMG PPI representatives assisted in developing a lay summary of the study results as well as reviewing the patient dissemination documents.

Links to conference presentations, publications and lay summaries will be posted on the Sheffield Clinical Trials Research Unit Twitter account and the MAGIC website.

Implications for decision-makers

This study adds to the body of literature on melatonin use by providing a definitive answer in an area where uncertainty remained. Although the study was terminated early for recruitment futility, the result was clinically meaningful and statistically significant (evidenced by the exclusion of zero in the 95% CI). The results show that melatonin is inferior to midazolam, and midazolam should remain the standard of care for premedication of anxious children ahead of surgery. However further research is needed into sourcing an alternative premedication with an improved side effects profile.

Research recommendations

We identified the following questions for future research and have indicated the area of research to which they relate.

Further interventions

- What other interventions may be effective in reducing preoperative anxiety in children?
- Is dexmedetomidine (or alternatives) a viable substitute premedication to midazolam?

Stakeholder views on important attributes of premedication

- What do stakeholders, patients and caregivers consider to be the most important in the attributes of a premedication?

Non-pharmacological interventions

- What is the clinical effectiveness and cost-effectiveness of using non-pharmacological interventions, on their own, and in conjunction with pharmacological interventions in the reduction of preoperative anxiety?

Conclusions

The trial did not reach the required sample size and therefore is prone to bias. In children with preoperative anxiety, midazolam is more effective than melatonin at reducing preoperative anxiety prior to general anaesthesia. Challenges exist in conducting perioperative trials including operational difficulties, such as research pharmacy opening times and wide variation in anaesthetist practice. There remains a clinical need to develop or repurpose another premedication with a more favourable side effects profile. In practice, decisions about premedications are taken based on the balance of several complex factors and not based purely on premedication anxiolytic properties. Future studies evaluating premedications in children may need to consider the use of discrete choice experiments to understand the preferences of children caregivers and healthcare professionals on the attributes of premedications.

Additional information

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Patient data statement

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it is important that there are safeguards to make sure that they are stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

Ethics statement

The trial was approved by North West – Liverpool Central Research Ethics Committee (18/NW/0758) on 16 January 2019.

Information governance statement

The NIHR is committed to handling all personal information in line with the UK Data Protection Act (2018) and the General Data Protection Regulation (EU GDPR) 2016/679. Under Data Protection legislation, the University of Sheffield is the Data Processor; Sheffield Teaching Hospitals NHS Foundation Trust is the Data Controller, and we process personal data in accordance with their instructions. You can find out more about how we handle personal data, including how to exercise your individual rights and the contact details for University of Sheffield's Data Protection Officer (www.sheffieldclinicalresearch.org/).

Disclosure of interests

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This synopsis was published based on current knowledge at the time and date of publication. NIHR is committed to being inclusive and will continually monitor best practice and guidance in relation to terminology and language to ensure that we remain relevant to our stakeholders.

Trial registration

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Award publications

This synopsis provided an overview of the research award 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. Other articles published as part of this thread are:

Bolt R, Hyslop MC, Herbert E, Papaioannou DE, Totton N, Wilson MJ, *et al*. The MAGIC trial: a pragmatic, multicentre, parallel, noninferiority, randomised trial of melatonin versus midazolam in the premedication of anxious children attending for elective surgery under general anaesthesia, *Br J Anaesth* 2024;**132**:76–85. https://doi.org/10.1016/j.bja.2023.10.011

Kettle J, Bolt R, Deery C, Papaioannou D, Rodd H, Hyslop MC, *et al*. Acceptability of midazolam and melatonin as premedications for anxious children undergoing general anaesthetic: a qualitative interview study with children, caregivers and health professionals participating in the MAGIC randomised controlled trial. *Trials* 2024;**25**:813. https://doi.org/10.1186/s13063-024-08611-x

Kettle J, Deery C, Bolt R, Papaioannou D, Marshman Z. Stakeholder perspectives on barriers and enablers to recruiting anxious children undergoing day surgery under general anaesthetic: a qualitative internal pilot study of the MAGIC randomised controlled trial. *Trials* 2021;**22**:458. https://doi.org/10.1186/s13063-021-05425-z

Hyslop MC, Papaioannou D, Bolt R, Wilson M, Bradburn M, Clarkson J, *et al*. Barriers and enablers to recruiting participants within perioperative and anaesthetic settings: lessons learned from the MAGIC trial. *BJA Online* 2025;**13**:100375. https://doi.org/10.1016/j.bjao.2024.100375

For more information about this research please view the award page (https://fundingawards.nihr.ac.uk/award/16/80/08).

Additional outputs

Mellor K, Papaioannou D, Thomason A, Bolt R, Evans C, Wilson M, Deery C. Melatonin for pre-medication in children: a systematic review. *BMC Pediatr* 2022;**22**:107. https://doi.org/10.1186/s12887-022-03149-w

Deery C, Bolt R, Papaioannou D, Totton N, Herbert E, Hyslop M, *et al*. *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*. The University of Sheffield. Workflow; 2023. https://doi.org/10.15131/shef.data.22220884.v1

Herbert E, Totton N, Deery C, Bolt R, Hyslop M, Bradburn M, *et al*. MAGIC *Trial – Statistical Analysis Plan*. The University of Sheffield. Workflow; 2023. https://doi.org/10.15131/shef.data.23180222

Herbert E, Papaioannou D, Loban A, Totton N, Hyslop M, Bolt R, Deery C. Personalised versus standard text message prompts for increasing trial participant response to telephone follow up: an embedded randomised controlled retention trial. *Trials* 2024;**25**:108. https://doi.org/10.1186/s13063-024-07916-1

About this synopsis

The contractual start date for this research was in December 2017. This article began editorial review in November 2023 and was accepted for publication in October 2024. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The Health Technology Assessment editors and publisher have tried to ensure the accuracy of the authors' article and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this article.

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List of abbreviations

AE	adverse event
ENT	ear, nose and throat
EU	European Union
FPS-R	Revised Faces Pain Scale (observer and participant reported)
GA	general anaesthetic
HTA	Health Technology Assessment programme
IMP	investigational medicinal product
ITT	intention to treat
MAGIC	Melatonin for Anxiety prior to General anaesthesia In Children
MYPAS-SF	Modified Yale Preoperative Anxiety Scale Short Form
NIHR	National Institute for Health and Care Research
PAED	Paediatric Anaesthesia Emergence Delirium scale index
PHBQ-AS	Post Hospitalisation Behaviour Questionnaire for Ambulatory Surgery
PI	principal investigator
PP	per-protocol
PPI	patient and public involvement
QALY	quality-adjusted life-year
RCT	randomised controlled trial
SAE	serious adverse event
SWAT	study within a trial
TMG	Trial Management Group
TSC	Trial Steering Committee
VSRS	Vancouver Sedation Recovery Scale

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Appendix 1

TABLE 2 Summary of changes to the MAGIC trial protocol

Changes to protocol	Date	Approved by
Protocol version 2.0 (not implemented): Updated in response to REC request to remove the £10 vouchers for qualitative study interviewees	19 December 2018	N/A
Protocol version 3.0 (approved version on trial opening): Updates included 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 postoperative assessments to every 15 minutes from every 10 minutes; removal of out of hours unblinding system; replacement of 'until stage 2 recovery completion'	27 March 2019	North West – Liverpool Central Research Ethics Committee Health Research Authority MHRA
Protocol version 4.0: Updates included 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 specialties: 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 caregiver consent and PI decision. Children who verbally decline to participate must not be included; change for those sites who do not have dedicated preoperative 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 participant 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 and addition of CHU9D proxy questionnaire for children aged 3–4	7 May 2020	North West – Liverpool Central Research Ethics Committee Health Research Authority MHRA
Protocol version 4.1: Updates included change to clarify assent from highly anxious children not mandatory and can be based on caregiver 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 substudy in light of the 2020 COVID-19 pandemic	28 September 2020	Non-substantial – no approvals required

MHRA, Medicines and Healthcare products Regulatory Agency.

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Appendix 2

TABLE 3 Melatonin for Anxiety prior to General anaesthesia In Children post-surgery secondary outcomes

Score	Analysis population	Time point	Midazolam		Melatonin		Adjusted mean difference (95% CI)
			n	Mean (SD)	*n*	Mean (SD)	
VSRS	ITT	15	15	12.73 (5.19)	20	14.35 (4.79)	0.122 (−1.567 to 1.811)
		30	32	14.28 (4.89)	26	17.27 (5.77)	0.122 (−1.567 to 1.811)
		45	32	17.28 (4.10)	31	18.35 (5.08)	0.122 (−1.567 to 1.811)
		60	29	18.90 (4.39)	28	19.04 (4.86)	0.122 (−1.567 to 1.811)
		75	25	20.80 (2.87)	25	19.72 (4.27)	0.122 (−1.567 to 1.811)
		90	22	20.68 (3.86)	21	19.33 (3.97)	0.122 (−1.567 to 1.811)
		105	19	20.42 (3.99)	18	18.94 (4.12)	0.122 (−1.567 to 1.811)
		120	14	21.14 (2.41)	13	19.69 (4.15)	0.122 (−1.567 to 1.811)
	PP	15	15	12.73 (5.19)	18	14.50 (5.03)	0.413 (−1.331 to 2.156)
		30	31	14.29 (4.97)	22	18.09 (5.58)	0.413 (−1.331 to 2.156)
		45	31	17.13 (4.07)	27	18.89 (4.70)	0.413 (−1.331 to 2.156)
		60	28	18.79 (4.43)	23	19.91 (4.18)	0.413 (−1.331 to 2.156)
		75	24	20.75 (2.92)	21	19.95 (4.52)	0.413 (−1.331 to 2.156)
		90	21	20.62 (3.94)	18	19.67 (4.03)	0.413 (−1.331 to 2.156)
		105	19	20.42 (3.99)	15	18.93 (4.43)	0.413 (−1.331 to 2.156)
		120	14	21.14 (2.41)	10	19.00 (4.55)	0.413 (−1.331 to 2.156)
Co-operation Score	ITT	15	38	0.92 (2.02)	38	1.39 (2.57)	−0.064 (−0.843 to 0.716)
		30	43	3.02 (2.81)	35	3.26 (3.25)	−0.064 (−0.843 to 0.716)
		45	37	4.16 (2.69)	36	4.64 (2.95)	−0.064 (−0.843 to 0.716)
		60	30	5.37 (2.40)	34	5.06 (2.80)	−0.064 (−0.843 to 0.716)
		75	31	5.90 (1.99)	31	5.32 (2.76)	−0.064 (−0.843 to 0.716)
		90	25	6.16 (1.60)	24	6.00 (2.13)	−0.064 (−0.843 to 0.716)
		105	20	6.40 (1.39)	21	6.24 (2.12)	−0.064 (−0.843 to 0.716)

TABLE 3 Melatonin for Anxiety prior to General anaesthesia In Children post-surgery secondary outcomes (*continued*)

Score	Analysis population	Time point	Midazolam		Melatonin		Adjusted mean difference (95% CI)
			n	Mean (SD)	*n*	Mean (SD)	
		120	15	6.27 (1.44)	17	6.53 (1.70)	−0.064 (−0.843 to 0.716)
	PP	15	37	0.95 (2.04)	32	1.25 (2.44)	0.047 (−0.764 to 0.858)
		30	42	2.98 (2.82)	32	3.44 (3.29)	0.047 (−0.764 to 0.858)
		45	36	4.19 (2.72)	32	4.69 (3.05)	0.047 (−0.764 to 0.858)
		60	29	5.31 (2.42)	29	5.24 (2.82)	0.047 (−0.764 to 0.858)
		75	30	5.87 (2.01)	26	5.88 (2.41)	0.047 (−0.764 to 0.858)
		90	24	6.12 (1.62)	20	6.50 (1.61)	0.047 (−0.764 to 0.858)
		105	20	6.40 (1.39)	18	6.22 (2.26)	0.047 (−0.764 to 0.858)
		120	15	6.27 (1.44)	14	6.50 (1.87)	0.047 (−0.764 to 0.858)
FPS-R (child reported)	ITT	15	4	5.00 (4.76)	5	3.40 (3.97)	0.170 (−0.388 to 0.729)
		30	16	2.31 (3.46)	14	2.43 (3.25)	0.170 (−0.388 to 0.729)
		45	21	2.86 (3.44)	22	1.64 (2.11)	0.170 (−0.388 to 0.729)
		60	22	3.23 (3.54)	24	2.54 (3.53)	0.170 (−0.388 to 0.729)
		75	23	2.22 (2.59)	22	2.23 (3.12)	0.170 (−0.388 to 0.729)
		90	19	1.53 (2.32)	20	2.30 (3.13)	0.170 (−0.388 to 0.729)
		105	18	2.44 (3.11)	17	2.00 (2.45)	0.170 (−0.388 to 0.729)
		120	12	0.67 (1.30)	14	1.71 (2.20)	0.170 (−0.388 to 0.729)
	PP	15	4	5.00 (4.76)	4	1.75 (1.71)	0.126 (−0.419 to 0.671)
		30	15	2.47 (3.52)	14	2.43 (3.25)	0.126 (−0.419 to 0.671)
		45	20	3.00 (3.46)	21	1.71 (2.12)	0.126 (−0.419 to 0.671)
		60	21	3.29 (3.62)	22	2.77 (3.60)	0.126 (−0.419 to 0.671)
		75	22	2.23 (2.65)	21	2.33 (3.15)	0.126 (−0.419 to 0.671)
		90	18	1.50 (2.38)	17	2.71 (3.24)	0.126 (−0.419 to 0.671)

continued

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TABLE 3 Melatonin for Anxiety prior to General anaesthesia In Children post-surgery secondary outcomes (*continued*)

Score	Analysis population	Time point	Midazolam		Melatonin		Adjusted mean difference (95% CI)
			n	Mean (SD)	*n*	Mean (SD)	
		105	18	2.44 (3.11)	15	2.27 (2.49)	0.126 (−0.419 to 0.671)
		120	12	0.67 (1.30)	11	2.00 (2.37)	0.126 (−0.419 to 0.671)
FPS-R (observer reported)	ITT	15	27	2.44 (3.20)	29	1.14 (1.73)	−0.046 (−0.585 to 0.493)
		30	37	2.38 (2.75)	30	1.83 (2.49)	−0.046 (−0.585 to 0.493)
		45	34	2.38 (2.93)	36	2.28 (2.87)	−0.046 (−0.585 to 0.493)
		60	31	2.32 (2.37)	32	1.91 (3.03)	−0.046 (−0.585 to 0.493)
		75	31	1.61 (2.09)	31	1.65 (2.80)	−0.046 (−0.585 to 0.493)
		90	26	1.73 (2.25)	25	1.00 (1.91)	−0.046 (−0.585 to 0.493)
		105	20	0.85 (1.35)	21	1.33 (2.24)	−0.046 (−0.585 to 0.493)
		120	15	1.13 (1.81)	16	0.94 (1.77)	−0.046 (−0.585 to 0.493)
	PP	15	27	2.44 (3.20)	24	1.12 (1.75)	0.013 (−0.610 to 0.636)
		30	36	2.44 (2.76)	26	2.04 (2.60)	0.013 (−0.610 to 0.636)
		45	33	2.45 (2.95)	31	2.58 (2.98)	0.013 (−0.610 to 0.636)
		60	30	2.33 (2.41)	27	2.26 (3.18)	0.013 (−0.610 to 0.636)
		75	30	1.60 (2.13)	26	1.96 (2.96)	0.013 (−0.610 to 0.636)
		90	25	1.72 (2.30)	21	1.19 (2.04)	0.013 (−0.610 to 0.636)
		105	20	0.85 (1.35)	18	1.56 (2.36)	0.013 (−0.610 to 0.636)
		120	15	1.13 (1.81)	13	1.15 (1.91)	0.013 (−0.610 to 0.636)
PAED	ITT	15	40	11.97 (2.36)	39	11.31 (3.74)	−0.699 (−2.039 to 0.641)
		30	43	10.05 (4.38)	38	8.32 (5.39)	−0.699 (−2.039 to 0.641)
		45	38	8.08 (4.24)	38	6.45 (5.05)	−0.699 (−2.039 to 0.641)
		60	30	5.53 (3.95)	34	5.12 (5.08)	−0.699 (−2.039 to 0.641)
		75	31	4.29 (4.04)	32	4.41 (4.74)	−0.699 (−2.039 to 0.641)
		90	25	2.96 (3.86)	25	3.16 (4.22)	−0.699 (−2.039 to 0.641)
		105	20	1.60 (2.52)	20	3.45 (3.94)	−0.699 (−2.039 to 0.641)

TABLE 3 Melatonin for Anxiety prior to General anaesthesia In Children post-surgery secondary outcomes (*continued*)

Score	Analysis population	Time point	Midazolam		Melatonin		Adjusted mean difference (95% CI)
			n	Mean (SD)	*n*	Mean (SD)	
		120	15	1.40 (3.09)	17	2.94 (3.38)	−0.699 (−2.039 to 0.641)
	PP	15	39	11.97 (2.39)	33	11.39 (3.77)	−0.856 (−2.167 to 0.456)
		30	42	10.05 (4.43)	33	7.97 (5.46)	−0.856 (−2.167 to 0.456)
		45	37	8.03 (4.28)	33	6.18 (5.20)	−0.856 (−2.167 to 0.456)
		60	29	5.59 (4.01)	29	4.83 (5.20)	−0.856 (−2.167 to 0.456)
		75	30	4.30 (4.11)	27	3.93 (4.71)	−0.856 (−2.167 to 0.456)
		90	24	3.00 (3.93)	21	2.57 (3.78)	−0.856 (−2.167 to 0.456)
		105	20	1.60 (2.52)	17	3.41 (4.21)	−0.856 (−2.167 to 0.456)
		120	15	1.40 (3.09)	14	3.00 (3.55)	−0.856 (−2.167 to 0.456)