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Quality Improvement Study

QUALITY IMPROVEMENT STUDY

Barriers and enablers to recruiting participants within paediatric perioperative and anaesthetic settings: lessons learned from a trial of melatonin versus midazolam in the premedication of anxious children (the MAGIC trial)

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Abstract

Background: Poor recruitment is one key reason for premature closure of randomised controlled trials. The Melatonin for Anxiety prior to General Anaesthesia In Children (MAGIC) trial was a multicentre randomised controlled trial of melatonin *vs* midazolam in the premedication of anxious children, before surgery. The trial ran between 2019 and 2022, closing early because of recruitment futility. This paper describes the challenges that arose during the trial and offers recommendations for the design of future perioperative trials.

Methods: A case-based approach was used to identify barriers to recruitment. As part of a qualitative sub-study, semi-structured interviews with local site teams, participants, and caregivers also explored barriers and enablers to recruitment.

Results: Issues encountered included time sensitivity within pressured environments; feasibility of paediatric assent; research pharmacy availability; variation in anaesthetist equipoise; multifactorial decision-making issues in premedication selection; and the Associate Principal Investigator scheme being unable to support trials within anaesthetic trainee rotations. Future paediatric perioperative medicine trials could consider funding for research pharmacy outside of working hours; conducting risk assessments for study drugs to be held on theatre admission units; and a tailored design of site feasibility assessments to help address variation in practice. Challenges remain for the feasibility of including anaesthetic trainees within the Associate Principal Investigator scheme structure.

Conclusions: There are significant challenges to recruitment for paediatric clinical trials in anaesthesia and perioperative medicine. The MAGIC trial highlighted variations within anaesthetic practice at individual, local, and regional levels. Lessons learned from the MAGIC trial identifies specific barriers to paediatric trial enrolment, offer solutions and discusses ongoing challenges.

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Keywords: early termination of clinical trials; general anaesthesia; paediatric anxiety; perioperative care; poor recruitment; reasons for recruitment failure

Randomised controlled trials (RCTs) are the gold standard for assessing the therapeutic benefit of an intervention; however, one-quarter of RCTs are prematurely discontinued.[1] Poor recruitment is one of the key reasons for premature closure[1–4]; with just 56% of trials funded by the National Institute of Health Research (NIHR) successfully recruiting to their final target sample size.[4]

There are numerous challenges in recruiting participants to clinical trials, applicable across all clinical disciplines and settings. Challenges can include overestimation of eligible participants, lack of equipoise amongst recruiters on the effectiveness of the trial intervention, lack of engagement by recruiters, high burden for participants involving the demands and challenges of the trial, new emerging evidence, treatments, or both, funding issues, context-specific logistic obstacles (e.g. emergency admissions), timings and settings of intervention delivery, intrinsic barriers to include those from marginalised groups, long waiting lists, and high recruitment target numbers.[2–9]

Anxiety before surgery in the paediatric population is well recognised.[10,11] Whilst effective non-pharmacologic techniques exist to manage anxiety, pre-medicating anxious children with an anxiolytic before general anaesthesia is standard practice in the United Kingdom (UK). The Melatonin for Anxiety prior to General Anaesthesia In Children (MAGIC) trial (ISRCTN registry: ISRCTN18296119) was an RCT of melatonin *vs* midazolam (standard of care) in the premedication of anxious children attending for elective surgery under general anaesthesia (Fig. 1). The trial was delivered across 20 National Health Service hospital sites and aimed to recruit 624 anxious children aged 3–14 yr old from a range of surgical specialties.[12] Full details of the trial have been published.[12,13] An integrated qualitative sub-study was also run as part of the MAGIC trial.[14] Some of the data and information in this paper have previously been published in these source articles. The MAGIC trial was funded by The National Institute for Health Research: Health Technology Assessment (NIHR HTA) as a commissioned call, requesting a trial of melatonin as a premedication for anxious children, having identified the evidence gap and promise of melatonin.

Between July 2019 and November 2022, 568 anxious patients were screened, and 110 participants were randomised to receive either melatonin or midazolam.[12] Fig. 2 describes participant recruitment and retention within the trial. The COVID-19 pandemic had profound impact, with recruitment suspended during the early pandemic period. However, the MAGIC trial also experienced recruitment issues before this during its pilot phase (interim analysis). During the pilot phase, 78 participants were recruited, within the 'Amber' zone, falling 78 participants short of the 'Green' zone (n=156). The 'Amber' rating was defined in the MAGIC protocol (with funder agreement) as a trigger for discussion with the trial steering committee regarding the changes possible to the trial protocol and procedures that could improve recruitment to the trial. The qualitative interviews, designed and led by qualitative researchers, conducted during the internal pilot informed of possible procedural changes to address this. The pilot feasibility review was discussed with both the trial steering committee and the data monitoring and ethics committee within the first quarter of 2020, a time when the COVID-19 pandemic had already started to impact research. The study team recommended potential changes to the protocol (fed back through qualitative interviews and study management meetings) that could potentially improve trial recruitment. Both oversight groups agreed to relevant protocol changes (presented in Appendix A, Supplementary Table S1) to be made. We instigated changes to improve recruitment. NIHR reviewed the trial in summer 2020 and independently made the decision to continue with the trial. All research was impacted by the COVID-19 pandemic[15] and Brexit[16]; however, MAGIC was particularly vulnerable. Routine elective surgeries were halted during the pandemic and midazolam was subject to nationally controlled use. The drug was favoured as first-line sedation for patients requiring mechanical ventilation, therefore the trial investigational medicinal product (IMP) manufacturer could not source the product for trial supplies. Brexit further impacted the trial as a result of European Union (EU) medicinal drug imports being subject to new legislation, causing delays to manufacture of the trial drug. The pandemic resulted in significantly increased waiting times; it was reported by sites that some parents were unwilling to consent to their child's participation, in case the anxiolytic was unsuccessful and surgery therefore did not go ahead.

In November 2022, it was agreed with the trial steering committee and the NIHR (trial funder) that the MAGIC trial would be terminated prematurely because of recruitment futility.

The aim of this paper is to describe the challenges that arose from one RCT in anaesthesia and perioperative medicine, focusing on the issues specific to this setting, and those applicable to a paediatric population.

Methods

A case-based approach was used involving real-world scenarios summarised from discussions, both internally and externally (including site teams, the core study team, trial management group, trial steering committee, and data management committee). Findings were collated from the central trial implementation team, ongoing feedback from local site research teams, and the qualitative research findings,[14] to identify and describe the main barriers to recruitment for the trial.

Results

Several factors impacted recruitment. These included trial staff resources and availability (e.g. research pharmacy opening times); anaesthetist equipoise (multifactorial choice of premedication); and variation in clinical practice at a trial site level (participant inclusivity) and recruitment settings. Table 1 groups and summarises the challenges to recruitment, strategies to overcome these and ongoing challenges that

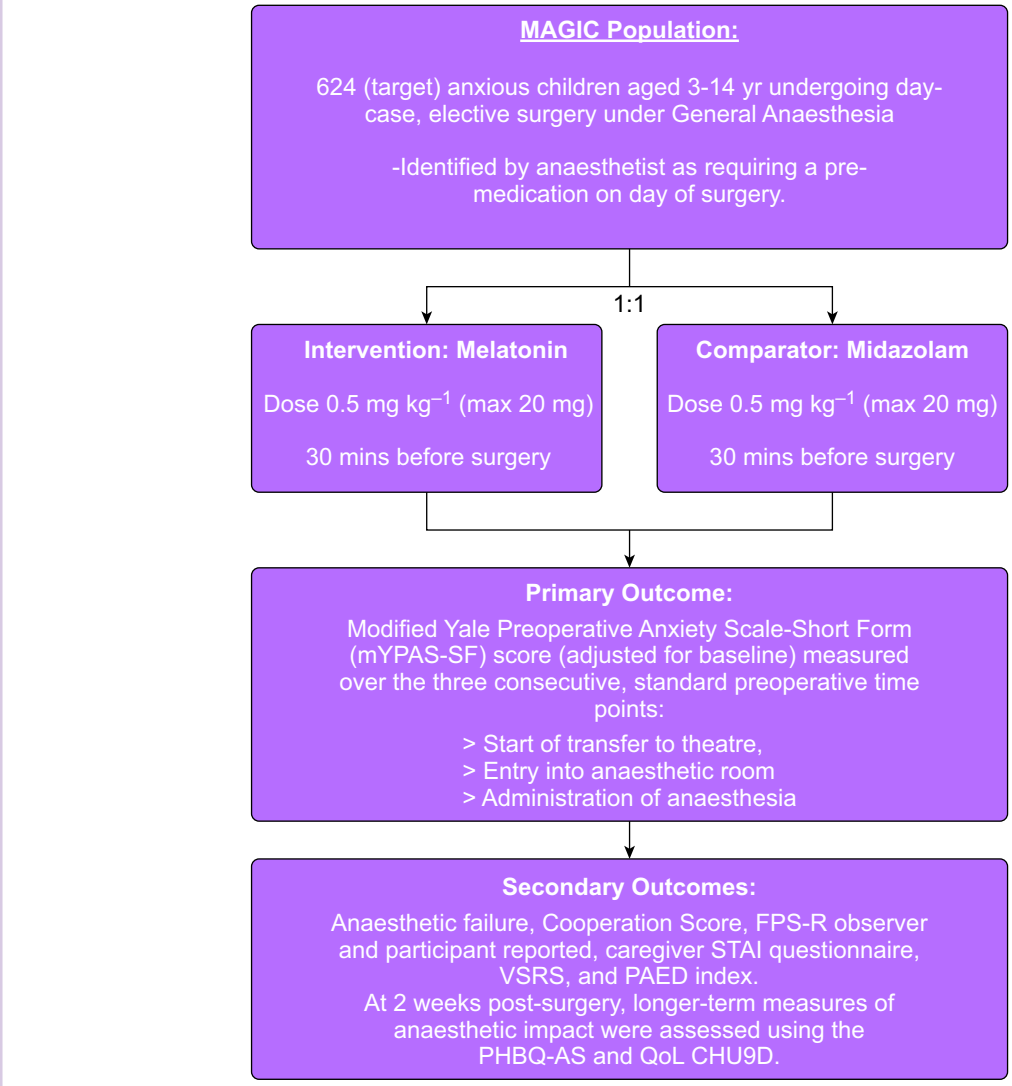

Figure 1. MAGIC trial summary overview. FPS-R, Faces Pain Scale revised; PAED index, Paediatric Anaesthesia Emergence Delirium scale; PHBQ-AS, Post Hospitalization Behavior Questionnaire for Ambulatory Surgery; QoL CHU9D, Quality of Life Child Health Utility 9D; STAI, State Trait Anxiety Inventory questionnaire; VSRS, Vancouver Sedation Recovery Scale.

remained, with each of these being explored further in the following sub-sections.

Trial staff resources and availability

Recruitment and management of the MAGIC trial involved a multidisciplinary team compiled of anaesthetists, surgeons, research nurses, and pharmacists. The issues within MAGIC relating to staff resources and availability were: research pharmacy opening times; anaesthetic trainee network and the Associate Principal Investigator scheme; and limited recruiting sites and research staff. These are expanded upon below.

Research pharmacy

As highlighted within the pilot qualitative review, many MAGIC sites reported issues with recruitment as a result of research pharmacy delays in study drug dispensing.[14] The MAGIC trial aimed to recruit those with high levels of preoperative distress in the opinion of the healthcare professional, which in most cases could only be assessed on the day of surgery. It is routine accepted practice for surgical teams to place the most anxious patients earlier on the theatre list, to reduce anxiety-provoking waits, meaning research pharmacies were either not open when these children were scheduled or there was insufficient time for consent, randomisation, and dispensation. To counteract this, some sites advised they would bring research pharmacy staff in earlier than their standard working shifts, whilst other sites preferred to move patients (who were still deemed anxious) placeing them later in the day on the list.

In standard UK practice, pre-medications are readily available on the ward for use. To relieve time pressures, we explored allowing IMP to be stored and dispensed on the ward; however, this carried additional risks to IMP accountability by

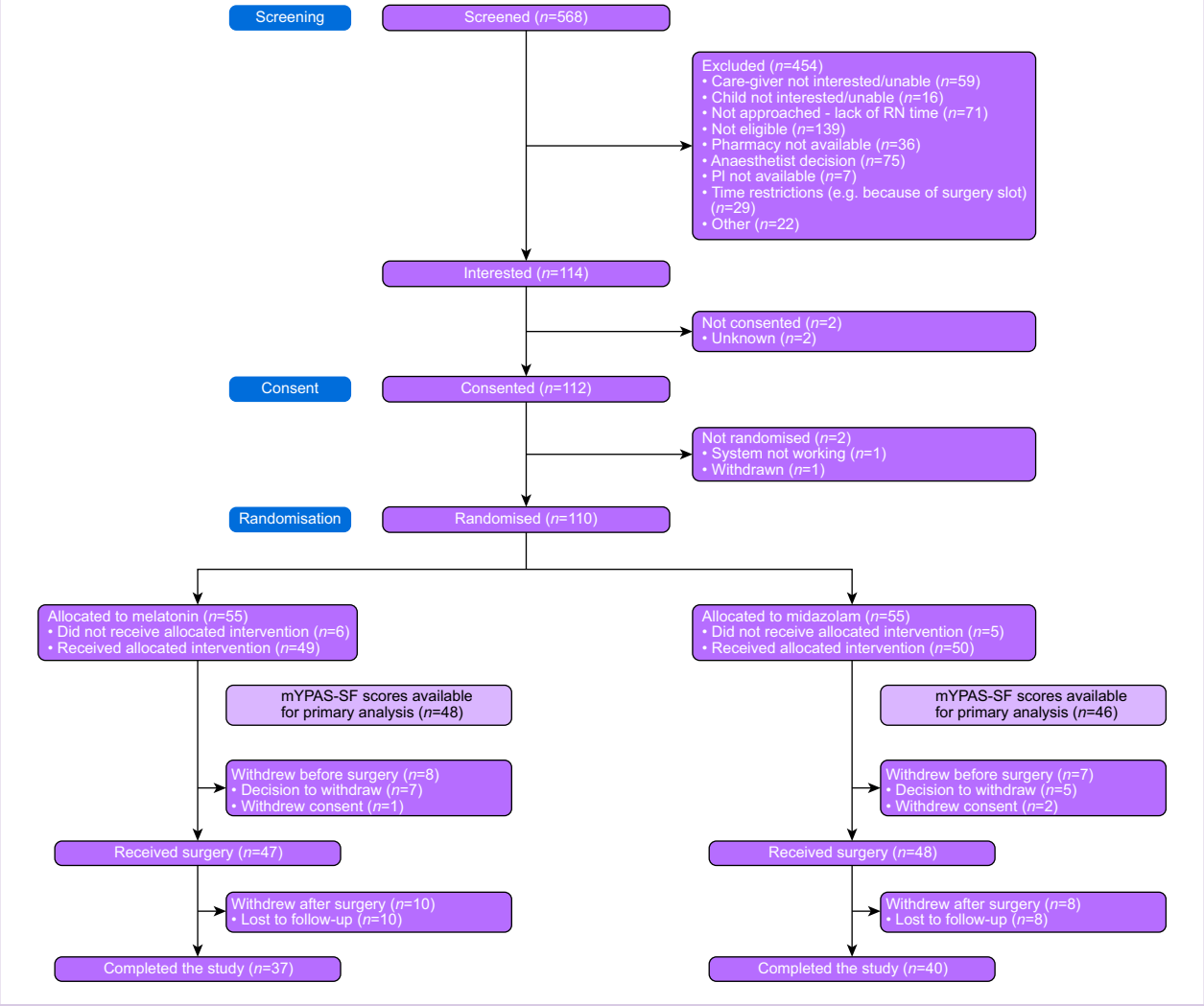

Figure 2. Consort flow of the MAGIC trial.[12] mYPAS-PS, modified Yale Preoperative Anxiety Scale-Short Form; PI, principal investigator; RN, research nurse.

removing research pharmacy oversight, increasing risk of IMP unblinding, requirements for additional non-blinded site staff, and safe storage of a controlled IMP on the ward. Subsequently we revised our consent process to allow participants to be randomised before their day of surgery to enable pharmacies to dispense IMP as soon as they opened, thus enabling recruitment of anxious children to remain first on the theatre list, with eligibility re-checked before administration of IMP. However, we did not receive regulatory approval before early closure of the study, so the effect of this change on trial recruitment is not known.

Associate Principal Investigator scheme and anaesthetic and surgical trainee networks

Resourcing demands in clinical trials are well recognised[1–3,6–8,14]; therefore the MAGIC trial attempted to pre-empt this and engaged with Anaesthetic, Dental and Surgical Research Trainee Networks. This approach had been used successfully to boost recruitment to other studies[17,18] and provide opportunities for trainees to support running clinical trials. MAGIC also planned engagement with the NIHR Associate Principal Investigator scheme, a 6 month in-work training opportunity, providing practical experience for healthcare professionals commencing their research career.

The MAGIC trial was registered as part of the NIHR Associate Principal Investigator scheme and with multiple trainee research networks. Our experience was that support from these networks for the delivery of MAGIC and recruitment was limited, particularly regarding anaesthetic trainee networks. The organisation of subspecialty training requires that anaesthetic trainees undertake clinical rotations, sometimes every 3 months. This is especially relevant regarding subspecialty rotations (e.g. paediatric anaesthesia). This frequency in personnel 'turnover' relative to the timescale of the trial produced obstacles to induction of trainee staff in trial procedures and maintaining their status on a delegation log. Furthermore, the brevity of trainee rotations automatically meant they were not eligible for the Associate Principal Investigator scheme (6-month minimum requirement). This also had a further impact on trial staff resources, making it difficult to retain staff long enough for the required training.

Table 1 Summary of clinical trial recruitment isssues and lessons learned within anaesthetic and perioperative medicine. CRN, Clinical Research Network; IMP, investigational medicinal product; NIHR, National Institute of Health Research; PI, principal investigator.

Issue encountered	Strategies to overcome	Challenge remains
I. Trial staff resources and availability		
Research pharmacy opening times: • Opening times of research pharmacy were 1–2 h later than when 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 before surgery (eligibility may need to be reconfirmed on the day of surgery). • Consider randomisation before 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. 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 continues 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).	• 6-Month minimum requirement for participation still required.
Recruitment projections • Limited staff availability. • Overoptimistic recruitment projections.	• Consider higher scrutiny of feasibility forms and keeping recruitment projections realistic. • Contact local CRNs to query whether support staff are available (for NIHR portfolio trials).	• Staff support and availability continues to be an issue across clinical trials.
II. Anaesthetist equipoise		
Multifactorial choice of premedication. The decision on 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 co-morbidities 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 pre-medications important to healthcare professionals, patients and their caregivers.	• Consider complexities of trials that are multidisciplinary in nature (i.e. 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 pre-medications). • Large variation in prescribing practice amongst anaesthetists (e.g. use of dexmedetomidine).	• 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	• Variation in the degree of anaesthetist equipoise remains an ongoing issue within anaesthesia and perioperative trials.

Continued

Table 1 Continued

Issue encountered	Strategies to overcome	Challenge remains
• Disrupted equipoise among anaesthetists regarding interventions.	practices for anaesthetists across sites and within sites (i.e. survey more than one anaesthetist per site).	
New treatments becoming available • (e.g. 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 amongst 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 pre-medications 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 trial design stage is vital.
Equality, Diversion and Inclusivity (EDI) • Willingness to randomise some individuals (e.g. 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 pre-medications, 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: o A more diverse research workforce and recruiters within trials. o More inclusive patient and public involvement representation within trials.
III. 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 before surgery.	• Allow flexibility to randomise before the day of surgery wherever possible, whilst being mindful for the potential of post-randomisation dropouts • Consider using a range of staff to recruit patients (e.g. 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.
Paediatric assent • Requirement for assent even in children aged 5–7 yr old. • Made more challenging with the requirement to assent an already anxious population.	• Consider the practicalities of assenting younger children, anxious children, or both and whether it may be reasonable to seek parental-consent-only in certain situations. • Patient and public involvement (PPI) is crucial for input on 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.

Most trainees typically spend only 1–2 years as part of a network, some considerably less. In the context of a national study recruiting at many centres, this is a very short timescale, and the 'turnover' of local network membership may result in a shorter participation time, which affects consistent communication and engagement. The experience of MAGIC suggests that an alternative model for trainee engagement should be sought, if it is to provide the impact on research delivery which is truly transformative. The NIHR Associate Principal Investigator scheme may need to reconsider the minimum requirement for the duration of membership to allow trainees in these clinical disciplines to take part.

Limited recruiting sites and research staff

Lasagna's law states the incidence of patient availability sharply decreases when a clinical trial begins and returns to its original level as soon as the trial is completed.[19] It can be common for site research teams to overestimate recruitment capabilities.[23] When niche complexities of a trial emerge and competing alternative studies saturate, local resourcing can become scarce and recruitment numbers dwindle.[2,19]

NHS workload, organisational limitations of research nurse systems, and pressure on resources comprise major obstacles to trial recruitment.[14] Too few recruitment sites and recruiters, lack of staff engagement, administrative burdens, and time constraints have been identified as some of the major reasons for recruitment failure.[2] Within the MAGIC trial, those responsible for recruitment between anaesthetists, surgeons, and research nurses varied depending on resources and local standard practice at a site. The MAGIC trial experienced ongoing issues with local staff availability and engagement, both within and outside the COVID-19 pandemic.

In addition to the standard feasibility form completion, the MAGIC team asked sites to complete patient audits as part of feasibility and setup, to ascertain how many patients were typically prescribed a premedication. The study incorporated a 6 month 'pilot phase' for feasibility review, during which the

study team collected screening data for all paediatric patients treated who required a premedication, as opposed to only those patients approached for trial participation. This offered a more realistic, time-relevant overview of participant pools and flagged potential barriers to recruitment. However, it is worth noting these changes did not all necessarily bring about the improvements to recruitment required. The protocol mandated that premedication usage should be audited, for 1 month, at each site on three occasions: before trial commencement, during the pilot, and at 12 months. This was mandated in order to confirm that comparable proportions of patients were receiving premedication over the course of the trial, compared with the usual practice preceding trial commencement. No variation was seen.

Anaesthetist equipoise

Clinician equipoise is a well described problem in clinical trials.[2] A systematic review, undertaken before the commencement of MAGIC, touched on the differences in premedication selection by anaesthetists.[20] Further systematic reviews by Yang and colleagues[21] also highlighted variations in premedication selection. Issues identified are discussed below and include: anaesthetist equipoise and variation in clinical practice; choice of premedication being multifactorial; new medications becoming available (dexmedetomidine); and the use of multiple pre-medications.

Anaesthetist equipoise and other medications (two pre-medications and dexmedetomidine)

Equipoise regarding the effectiveness of trial interventions is a known barrier in research.[2,22] Lack of equipoise or 'Prejudice against effectiveness of trial interventions' is a key barrier to recruitment and is derived from multiple factors including: concerns of disadvantage to patients, questioning current practice, and loss of professional autonomy.[2] This issue appears to be particularly relevant to the anaesthetic and perioperative setting. We identified a wide variation in anaesthetist practice, which reduced the pool of anaesthetists involved in the trial and recruitment:

1. The study population included the most anxious children; however, this conflicted with some local guidelines where very anxious children, or children with complex neurological conditions, were routinely given two pre-medications.
2. We received anecdotal evidence that the use of an alternative premedication to midazolam, dexmedetomidine, was increasingly favoured at some sites, although a minority, it included the lead site. This change occurred after trial initiation and could not have been predicted.
3. Other local care processes, such as taking IMP in juice, conflicted with study procedures.

Variation in anaesthetist practice has also been noted by others[23]; these issues were difficult to address during the MAGIC trial. Whilst we had explored acceptability of the trial design during the grant application stage at six sites, no process identified these issues or predicted their emergence during trial implementation. We subsequently added direct questions around local prescribing practices in our site assessment template, and we recommend this as standard practice from the outset. Furthermore, we advocate this is explored beyond one anaesthetist per site, and involves several anaesthetists to accurately reflect individual prescribing practices.

Multifactorial decision-making in premedication selection and inclusivity

It became apparent that anaesthetist decisions on choice of premedication were not restricted to the anxiolytic properties of the drug. Factors influencing the choice of drug could include its pharmacological properties (e.g. anxiolysis *vs* sleepiness, predictability of child response, recollection, or both) and its palatability. Child factors such as clinical features and co-morbidities (e.g. neurodiversity or learning difficulties) and the likelihood of a child accepting a drug's route of administration (e.g. oral *vs* nasal) also influenced drug choice.

Children within the trial population frequently had additional needs and were deemed a 'fragile' research population whom clinicians were often reluctant to recruit. Neurodiverse children (e.g. those with autism, and children with learning disabilities) also proved a recruitment challenge, despite not being part of the exclusion criteria, as several site research teams were hesitant to recruit said children into a clinical trial feeling that participation may be 'too much'.[14]

These factors may affect future comparisons of premedications, as it may be difficult to ensure there is equipoise amongst healthcare professionals on trial treatments. The complexity in the decision-making process for premedication use in children may warrant a discrete choice of experiment to determine the attributes of pre-medications that are important to healthcare professionals, patients, and caregivers. Education is also recommended for future trials to ensure research teams are including a diverse population relevant to those routinely receiving these drugs in practice.

Recruitment setting

Day of surgery

Recruitment to paediatric trials has previously been identified as challenging.[24] Challenges are also well known in emergency trials regarding time sensitivity to recruit patients immediately whilst paradoxically giving enough time to digest relevant information.[9,25,26] Patients approached in inconvenient situations is also a known barrier to recruitment.[2] The requirement to ensure only the most anxious children entered MAGIC—and to enable maximum recruitment opportunities to approach anxious patients observed in the admissions unit on the day of surgery—consent, eligibility, and randomisation to the MAGIC trial remained limited to the day of surgery only. This, however, presented challenges of timings with local care teams, and ensuring participants and their parents had enough time to process the required study information and ask questions.

Mitigation strategies included trial information to be provided at preoperative assessments and research nurse-led informed consent, where it was clear the participant met the criteria for premedication for anxiety, to reduce burden on the day of surgery; however, eligibility was required to be reconfirmed. Despite being a drug trial, consent could also be taken by research nurses (with training), where approved by local Research and Development Governance Offices. Allowing research nurses to undertake the informed consent process supported capacity and enabled greater time flexibility to recruit patients.

Paediatric assent

Informed consent of study participants is a crucial part of Good Clinical Practice. For participants under 16 yr of age, receiving assent is considered good practice. However, there are circumstances where this is not practical within a clinical trial. The MAGIC trial recruited highly anxious children; by the very nature of anxiety, one could argue those children could be more unlikely to 'take in' the relevant information. Some children within our population were neurodiverse or had other learning difficulties. The trial also recruited children as young as 3 yr old. We found gaining assent was very difficult in this population and setting. We amended our protocol to provide a practical solution to ensure assent was sought whenever possible, however, where children were too anxious to confirm or decline entry into the trial, they could be enrolled by parental and principal investigator decision only. Trial information was also be provided via a short video animation (1 min) as opposed to a patient information sheet alone.

Future trials need to consider the practicalities of assenting anxious children, and it may be reasonable to seek only parental consent in certain situations.[27] Patient and public involvement in research is crucial for input on acceptability of trial procedures.

Discussion

Recruitment to trials within the perioperative and anaesthetic setting is challenging. We reviewed feedback from site teams and central teams through regular trial oversight meetings, monitoring visits, research nurse question and answer sessions, and qualitative pilot data review. From these sources, we identified barriers to recruitment as previously discussed.

Recruitment issues within RCTs are well documented, with a large body of research dedicated to evaluating methods to improve recruitment.[23,24,28–32] Unfortunately, despite implementing solutions, the MAGIC trial failed to recruit to its target. As highlighted, a key issue was research pharmacy availability conflicting with theatre list start times. A protocol amendment was submitted to allow randomisation before the day of surgery, to ease time pressures at site pharmacies. However, regulatory approval was severely delayed, and thus we do not know the impact of this amendment, although it was unlikely to improve recruitment to the level required.

It also must be recognised that, based on recruitment, projections during the pilot phase, even including the amendments to promote recruitment, were overly optimistic. However, it should be documented that despite not reaching the target recruitment, the MAGIC trial demonstrated a statistically and clinically significant result in favour of midazolam.[12]

This report gives an in-depth view into the ongoing challenges of running research within anaesthesia and perioperative medicine, which need to be addressed for the specialty to thrive within the research landscape. We believe this is the first account of difficulties specifically relating to the perioperative and anaesthetic field. However, our findings are limited to evidence received from multiple sources within a single trial. MAGIC also did not roll out the protocol amendment to allow recruitment before surgery, so it is difficult to gauge what effect this may have had. Some of our recommendations (e.g. discrete choice experiments) could not be tested within the trial and thus are suggestions only. Lastly, the trial was affected by the unique challenges of COVID-19; however, under-recruitment and its many causes were identified before these restrictions.

Before submitting the grant application, the trial design was discussed with six potential sites. Discussions included a flow diagram of the trial, inclusion and exclusion criteria, and some other key design questions (e.g. midazolam/melatonin product flavour and administration, targeting first and second on the list, would this work with research pharmacy). These discussions failed to identify the lack of enthusiasm for a trial of melatonin among some anaesthetists. This highlights how difficult it is to gauge enthusiasm for a trial. However, a full pilot trial before grant submission, is not feasible because of cost, time, and staffing issues amongst several other requirements, such as the need for ethical approval and external oversight. One possible compromise for this is a large survey of relevant clinicians. Having said this, there was enthusiasm for MAGIC amongst the active trial sites, and before final closure we had been contacted by a number of new sites wishing to join the trial.

The MAGIC trial emphasised the challenges of working within the field of paediatric perioperative medicine and anaesthesia. A 2018 Cochrane systematic review highlighted that the development and evaluation of recruitment interventions for use in paediatric trials is a priority.[24] The multidisciplinary nature of the trial (i.e. involving multiple care teams—surgical, anaesthetics, pharmacy, and research teams) gave added complexity and logistical challenges. The study also highlighted the vast variation within anaesthetic practice, at individual, local, and regional levels, which has been noted by others (e.g. the APRICOT study).[23]

Conclusions

Recruitment to perioperative and anaesthetic trials, particularly within the paediatric setting, is challenging. Future perioperative medicine trials could consider: funding for the research pharmacy outside of working hours; conducting risk assessments for study drugs to be held on theatre admission units; tailored design of site feasibility assessments, encompassing pre-trial engagement work (e.g. rapid ethnography), to help address variation in practice; and ensuring exploration of views from a number of health professionals at site to accurately gauge local clinical practices. Challenges remain ongoing for the feasibility of rotating anaesthetic trainees taking part in the Associate Principal Investigator scheme structure.

The MAGIC trial highlights variations within anaesthetic practice at individual, local, and regional levels. There is a need to explore the range of preferences and trade-offs on decisions around premedication choice in children, including the differing approach to pharmacological and non-pharmacological management of anxiety in children, and the unique challenges that these patients present to a relatively structured care delivery pathway. In conclusion, there continue to be significant challenges to delivering clinical trials in paediatric anaesthesia and perioperative medicine.

Authors' contributions

Produced the first draft of the manuscript: MCH (trial manager), DEP (CTRU lead), CD (chief investigator), RB (co-investigator), MJW (co-investigator)

Read and approved the final manuscript, offering critical feedback: all members of the authorship group: MCH, DEP, RB, MJW, MB, JC, EH, NI, JK, AL, ACN, CV, CD

Responsible for project level steering, national coordination, and data collection: the trial steering committee and data monitoring, and ethics committee
Responsible for ensuring adherence to hospital-level governance protocols and regional data collection: local leads
Revised the work critically for important intellectual content: all named authors
Involved in the final approval of the version to be published: all named authors

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Declarations of interest

The authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bjao.2024.100375.

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