

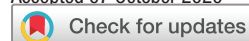
# BMJ Open Randomised controlled trial to assess the effectiveness of apnoeic oxygenation in adults using low-flow or high-flow nasal cannula with head side elevation versus usual care to prevent desaturation during endotracheal intubation in the emergency department (ApOxED): study protocol

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## ABSTRACT:

**Introduction** Apnoeic oxygenation is a process of delivering continuous oxygen through nasal cannula during direct laryngoscopy. The oxygen that is delivered through these nasal cannulas is either low flow or high flow. Although the effectiveness of apnoeic oxygenation has been shown through systematic reviews and randomised controlled trials, a comparison of high-flow versus low-flow oxygen delivery has not been tested through a superiority study design. In this study we propose to assess the effectiveness of giving low-flow oxygen with head side elevation versus high-flow oxygen with head side elevation against the usual practice of care in which no oxygen is provided during direct laryngoscopy.

**Methods and analysis** This will be a three-arm study instituting a block randomisation technique with a sample size of 46 in each arm (see [table 1](#)). Due to the nature of the intervention, no blinding will be introduced. The primary outcomes will be lowest non-invasive oxygen saturation measurement during direct laryngoscopy and during the 2 min after the placement of the tube and the first pass success rate. The intervention constitutes head side elevation up to 30° for improving glottis visualisation together with low-flow or high-flow oxygen delivery through nasal cannula to increase safe apnoea time for participants undergoing endotracheal intubation. Primary analysis will be intention to treat.

**Ethics and dissemination** The study is approved by the Ethical Review Committee of Aga Khan University Hospital (2019-0726-2463). The project is an institution University Research Committee grant recipient 192 002ER-PK. The results of the study will be disseminated among participants, patient communities and healthcare professionals in the institution through seminars, presentations and emails. Further, the findings will be published in a highly accessed peer-reviewed medical

## Strengths and limitations of this study

- Testing efficacy of apnoeic oxygenation through a superior design in emergency.
- High flow versus low flow as a means for apnoeic oxygenation in low-resource setting.
- Combining head side elevation with apnoeic oxygenation in achieving safe airway.
- A three-arm parallel assignment study instituting block randomisation.
- Blinding is not possible due to nature of intervention.

journal and will be presented at both national and international conferences.

**Trial registration number** ClinicalTrials.gov Registry (NCT04242537).

## INTRODUCTION

Critically ill patients undergoing endotracheal intubation in the emergency department (ED) face hypoxemia, an important risk factor for peri-intubation cardiac arrest and death.<sup>1 2</sup> As a standard of care, preoxygenation has a pivotal role in rapid sequence intubation, which is defined as placing a patient on supplemental oxygen with a goal of administering 100% fraction of inspired oxygen (FiO<sub>2</sub>) for 3 min prior to administration of induction and paralytic agents.<sup>1-3</sup> This is based on the idea of increasing the amount of oxygen present in the functional residual capacity of the lungs, to prolong

maintenance of acceptable oxygen saturation during the apnoeic phase of endotracheal intubation.<sup>4,5</sup>

Apnoeic oxygenation is a technique that was developed to prevent the occurrence of desaturation during direct laryngoscopy by prolonging safe apnoea time.<sup>6</sup> In this technique, the patient is kept on nasal cannula during direct laryngoscopy when visualising the vocal cords. Studies have shown its effectiveness through trials. However, few have been tested in the emergency room. In order to improve glottis visualisation, head side elevation during endotracheal intubation improves first pass success rate.<sup>7–10</sup> Famous studies namely: ‘Facilitating Endotracheal intubation by Laryngoscopy technique’, ‘Apneic Oxygenation Within the intensive care unit’ and ‘Emergency Department use of Apneic Oxygenation vs Usual Care During Rapid Sequence Intubation’ found this technique superior to the standard of care.<sup>11</sup>

While the effectiveness of apnoeic oxygenation has been established, there is a debate surrounding high-flow versus low-flow oxygenation among experts. High-flow nasal cannula delivers warm humidified oxygen at flow rates up to 70 L/min. Heating and humidification are critical for tolerance of these higher oxygen flow rates.<sup>2</sup> Transnasal Humidified Rapid Insufflation Ventilatory Exchange is a technique that maintains oxygen saturation for a significant period of time after the commencement of apnoea in surgical patients and prevents the rise of carbon dioxide over time.<sup>12</sup> Low-flow nasal cannula technique on the contrary improves oxygenation without impairing ventilation by delivering oxygen in low-flow rates. A recently published systematic review renders the apnoeic oxygenation technique safe with no adverse effects on patient outcomes.<sup>13</sup>

There is a lack of data on airway management procedures from low/middle-income countries (LMICs) comparing high-flow versus low-flow oxygen delivery through nasal cannula for increasing safe apnoea time and improving oxygenation during endotracheal intubation in the ED. Additionally, the effectiveness of head side elevation on glottis visualisation and improving first pass success rate among patients undergoing endotracheal intubation has not been assessed. By combining high-flow or low-flow oxygen delivery with head side elevation to 30°, we aim to assess the effectiveness of these two measures in improving oxygenation and first pass success rate among adults during endotracheal intubation in the ED. The apnoeic oxygenation technique can pave the way for improving airway management algorithms in the ED for better patient outcomes. This study is the first of its kind that will be conducted in the ED of an LMIC. This study therefore aims to assess the effectiveness of giving low-flow oxygen with head side elevation versus high-flow oxygen with head side elevation against the usual practice of care when no oxygen is provided during direct laryngoscopy through parallel group, 1:1:1 allocation ratio, non-inferiority, randomised controlled trial on adult patients’ oxygenation level and first pass success rate.

## STUDY HYPOTHESIS

Oxygen delivery through nasal cannula during endotracheal intubation in patients in the ED will improve oxygenation by 15%–30%.

## STUDY OBJECTIVES

1. To compare the effectiveness of low-flow versus high-flow nasal oxygen delivery during direct laryngoscopy to prevent desaturation during endotracheal intubation compared with usual practice of care in ED of a tertiary care hospital.
2. To compare the effectiveness of low-flow versus high-flow nasal oxygen delivery during direct laryngoscopy to increase safe apnoea time for patients undergoing endotracheal intubation compared with the usual practice of care in ED of a tertiary care hospital.
3. To compare the effectiveness of low-flow versus high-flow nasal oxygen delivery with head side elevation on improving the first pass success rate.

## METHODS AND ANALYSIS

### Study design and setting

This will be an individually randomised controlled trial with parallel assignment and treatment allocation ratio of 1:1:1. This study will be conducted in the ED of the Aga Khan University Hospital which is a 550-bedded large tertiary care teaching facility located in Karachi, Pakistan. The ED is a 62-bedded facility that receives 60 000 patients annually.

## OPERATIONAL DEFINITIONS

**Desaturation** is defined as a decrease in oxygen saturation of greater than 3% from induction to lowest oxygen saturation (eg, 93%–90%).

**Induction:** time of induction of hypnosis (giving of the sedation agent) followed by the paralysis agent.

**Safe apnoea time:** time measured in seconds after induction (includes hypnosis followed by paralysis) followed by cessation of breathing until the peripheral arterial oxygen saturation (SpO<sub>2</sub>) declines to 3% or above from the baseline (1–2). The safe apnoea time will be recorded in seconds after the sedating and paralyzing agent are given in rapid succession to the participant as per the rapid sequence intubation step.

**First pass success** is defined as placement of endotracheal tube in the trachea after the first insertion of the laryngoscope into the oral cavity without the use of other devices.

**High-flow oxygen** is defined as delivery of oxygen through nasal cannula (large or medium nasal cannula as per participant nostril) at a rate of 40 L/min for 4 min in which the gas undergoes humidification and is heated to approximately normal body temperature.<sup>11</sup>

**Low-flow oxygen** is defined as delivery of oxygen through nasal cannula (large or medium nasal cannula as

per participant nostril) at a rate of 20 L/min for 4 min in which the gas undergoes humidification and is heated to approximately normal body temperature.<sup>13</sup>

### INCLUSION CRITERIA

1. Adult patients (18 years and above) requiring endotracheal intubation in the ED of Aga Khan University Hospital.
2. Intubation performed by emergency medicine physicians who are postgraduate trainees year IV and above. The year IV and above cut-off is taken because at this level the trainees have done more than 20 endotracheal intubations. The operators are assessed through direct supervision and confirmation through filing of their procedural log books.

### EXCLUSION CRITERIA

1. Supervisor or operator feels specific intraprocedural oxygenation technique will be required.
2. Patients presenting with cardiac arrest.
3. Pregnant patients (as the patients are at risk of aspiration and high oxygen delivery can have adverse effects on the fetus).
4. Patients with 'Do not resuscitate' order.
5. Morbidly obese on assessment as such patients may need pre-intubation preparation of the head side and more controlled settings.
6. Patients who are shifted from another hospital post-intubation.
7. Patients with interstitial lung disease or lung tumour.
8. Neck trauma (expanding neck haematoma).
9. Neck and oral cavity cancers, or patients with cancers of the neck and oral cavity who have undergone surgery or post-radiation.
10. Pulse oximetry <90% in ambient air.
11. Body mass index >35 kg/m<sup>2</sup>.

### STUDY OUTCOMES

#### Primary

1. The lowest non-invasive oxygenation value in any time between administration of sedation and/or neuromuscular blockade to successful endotracheal intubation.
2. First pass success rate: single successful attempt for the placement of endotracheal tube during direct laryngoscopy.

#### Secondary

1. The time from the administration of sedation and/or neuromuscular blockade to successful endotracheal intubation (safe apnoea time).
2. Need for additional airway equipment/number of times additional equipment was required.
3. Grade of laryngoscopic view on first attempt.
4. Incidence of non-hypoxia complications (eg, arrhythmia, hypotension, tracheal rupture, vocal cord injury).

5. Incidence of post-intubation tube malposition on chest X-ray.

### STUDY ARMS

Patients meeting the eligibility criteria will be randomised to one of the following arms:

1. High-flow oxygen delivery through nasal cannula with head side elevation to 30° during direct laryngoscopy.
2. Low-flow oxygen delivery through nasal cannula with head side elevation to 30° during direct laryngoscopy.
3. Standard practice of care when no oxygen is provided during direct laryngoscopy.

### RANDOMISATION AND TREATMENT ALLOCATION

Randomisation technique will be block randomisation. Randomisation will occur in blocks of unequal size of 3, 6 or 9. Randomisation sequence generation will be performed by an independent statistician in the department of emergency medicine. It will be generated using random selection method before commencing the study. Randomisation sequence number will be printed and sealed in opaque envelopes which will be kept in the ED. Those envelopes will be available in the distribution/equipment bay to the ED physicians when patient is enrolled and it is determined that endotracheal intubation will be performed. The envelopes will be opened by ED physicians in front of patient/next of kin who provide consent. The treatment assignment will be logged in treatment log of enrolled patients against their identifying codes.

### BLINDING

Due to the nature of treatment assignment (either nasal cannula for oxygen delivery during the entire procedure or no provision of a nasal cannula during the airway management procedure), this trial cannot be blinded.

### RECRUITMENT

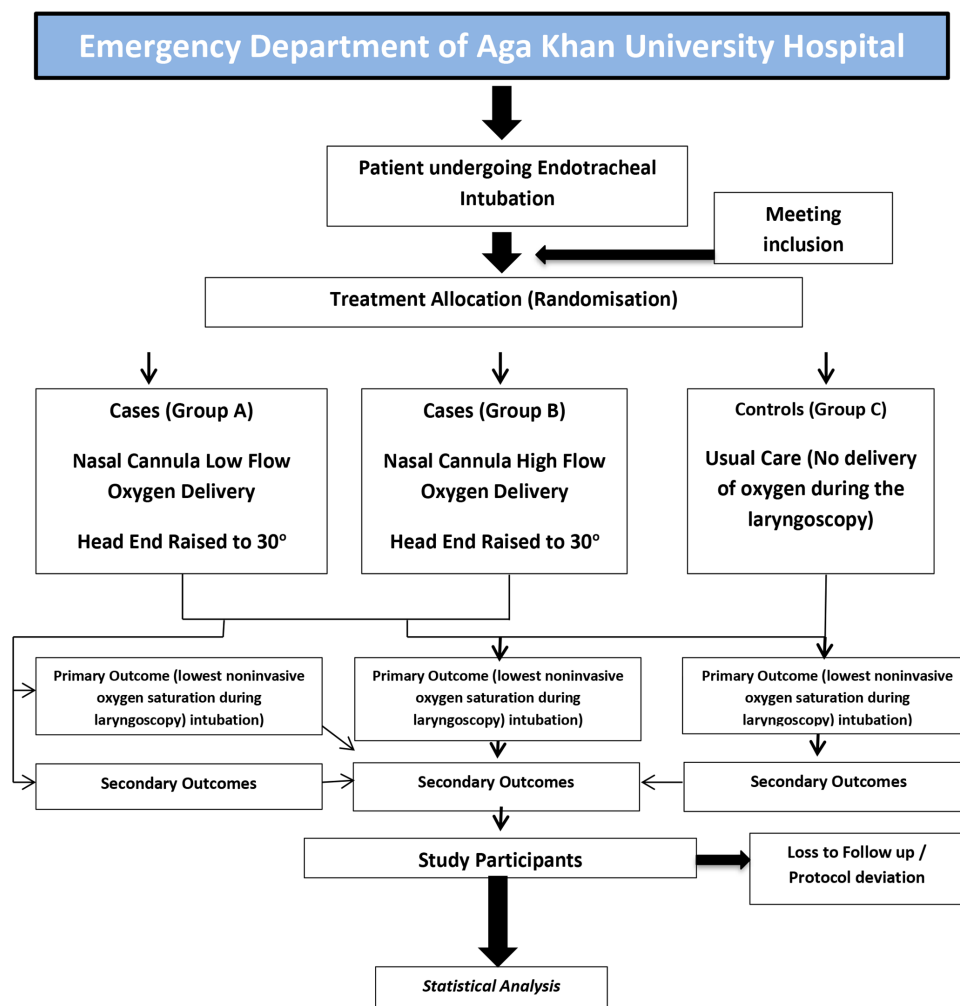
All adult patients presenting to emergency and requiring intubation will be screened for eligibility as per the inclusion and exclusion criteria by the on-call ED physician. If eligible, the patient will be enrolled by research staff by logging their entry in case record forms. Simultaneously ED staff as per routine protocol will proceed to the distribution/equipment bay to collect intubation supplies and pick randomisation envelope. The ED staff will hand over equipment and randomisation envelope to the ED physician, who will open the envelope in front of research staff and will inform about the treatment allocation.

### PROCEDURE

#### Intervention (high flow and low flow)

The participants, after fulfilling the eligibility criteria, will be randomly assigned to the respective arm (high

## Apnoeic Oxygenation in the Emergency Department (ApOxED) – Study Procedures.



**Figure 1** Apnoeic oxygenation in the emergency department—study procedures.

flow, low flow or standard) (figure 1). For procedure, depending on the arm, the head side of the patient bed will be elevated up to 30° (the 30° of the beds that are placed in the resuscitation room of the ED will be precalibrated with the help of a ‘D’, that will mark the bed that is to be raised to achieve 30° height) in order to better visualise glottis. The participant in the high-flow oxygen delivery through nasal cannula preoxygenation will be set for 4 min at 20 L/min through humidified and heated pure oxygen (FiO<sub>2</sub> 100%, 37°C). Similarly, participant in the low-flow oxygen delivery through nasal cannula preoxygenation will be set for 4 min at 10 L/min through humidified and heated pure oxygen (FiO<sub>2</sub> 100%, 37°C). The size of the cannula, medium or large, will be chosen according to the patient’s nostril size in order to limit air contamination. Throughout the procedure, the high-flow nasal cannula or low-flow nasal cannula will be maintained trying to achieve a continuous oxygen in the participant that will be spontaneously breathing during direct laryngoscopy of rapid sequence intubation. The steps are listed in the checklist in the online supplemental appendix 1.

### Standard arm

In the standard arm, the head end of the bed will not be raised to 30°. Instead the whole bed is raised up to the operator belly button in order to ease glottis visualisation. In the standard group the patient will be preoxygenated for 4 min or until achievement of a peripheral oxygen saturation greater than 95% with a face mask (the size of which will be adapted to fit the patient and ensure air tightness) that will be connected to the oxygen port at 10 L/min. During the direct laryngoscopy, there will be no insufflation of oxygen through nasal cannula or face mask.

### DATA COLLECTION

Research staff involved in collecting data will be independent from the primary research team in order to minimise observer bias. Research staff will record the time, steps of intubation and oxygen saturation while intubation will be undertaken by ED physician. The oxygen saturations will be recorded using pulse oximetry

(through a standard infrared oximetry tape) exclusively used for research purposes and time will be recorded using a stopwatch (Casio Digital Stopwatch) during and after the procedure. The operator will report to research staff about all subjective assessments of difficulty of intubation and airway complications during the procedure on the data collection tool. If the operator experiences a difficult airway (Corkman Lehman grade III/IV) while performing direct laryngoscopy, he may decide to use adjuncts in the face of an anticipated difficult intubation and will inform research staff for protocol deviation. Intubation attempts (number of times the patient had the endotracheal tube placed in their mouth) would be counted for each patient. In those patients where first pass failed and subsequent attempts were made without assisted ventilation, the apnoea time will be noted as mentioned above. In those attempts in which the first pass intubation fails and the patient was ventilated prior to subsequent attempt (ie, the laryngoscope was taken out of the mouth and the patient ventilated), the apnoea time will be defined as the time of first look to the time of assisted ventilation. To confirm the accuracy of data collected by the research staff, the primary investigators will conduct a concurrent assessment of the same outcomes for a convenience sample of 10% of enrolled patients. The study questionnaire will also be pilot tested before the start of the study. All protocol amendments will be communicated to ethics committee, clinical trial unit and lead investigators committee of the project.

### PROCEDURE VARIABLES

The information that will be collected during the procedure: date and time of sedative and or neuromuscular blocker administration, saturation at time of sedation and or neuromuscular blocker administration, sedative agent, neuromuscular blocker agent, need of bag mask ventilation between induction and laryngoscopy, tube characteristics (size), route (oral), laryngoscope type (size) and size, total number of attempts of direct laryngoscopy, tube taping level, confirmation of placement technique (calorimetric, auscultation), airway grade, airway difficulty (score), rescue device use and complications.

Baseline demographic information will be recorded in case record form for the following variables: age, gender, height, weight, race, presenting complaint, admitting diagnosis (pneumonia, sepsis and so on), active comorbidities, mean arterial pressure (MAP), vasopressor use prior to intubation, lowest oxygen saturation at presentation, lowest oxygen saturation in the safe apnoea time, oxygen saturation 2 hours after placement of the endotracheal tube, arterial blood gases (pH, partial pressure of arterial oxygen, partial pressure of arterial carbon dioxide), indication for intubation, re-intubation, preoxygenation technique, operator job position/title and additional personnel available. All other data on baseline characteristics, pre-laryngoscopy and post-laryngoscopy

management and clinical outcomes will be collected from the medical record of the personnel.

### Follow-up information from 0 to 6 hours after intubation

Lowest oxygen saturation after passing of the endotracheal tube, post-intubation imaging, post-intubation events like hypotension, cardiac arrest, saturation of arterial oxygen, peak end expiratory pressure and MAP at 1 and 6 hours after intubation.

### PROCEDURE CONSISTENCE

Prior to the start of the study, a workshop will be undertaken for the emergency physicians, healthcare staff and nursing physicians on airway management about a structured approach for airway management and how to use the low-flow and high-flow nasal cannula techniques for airway management. This Emergency Advanced Airway Workshop will be mandatory to attend for all the physicians of the ED before the start of the study. In this workshop the steps of endotracheal intubation and the standard algorithm will be taught, and pre-assessment and post-assessment will be undertaken. The proposal will be discussed with the physicians and the recording variables will be introduced to the physician. The low-flow and high-flow techniques will also be taught in this workshop and tested through simulation.

The physician who will be performing the procedure will be resident year IV and above. In order to be eligible for the study as an operator, the physician has to give his/her consent and has to get a sign off in the workshop and on the emergency floor before being able to perform the procedure in the ED.

### SAMPLE SIZE ESTIMATION

Study by Jaber *et al.*<sup>11</sup> According to this study the statistics of intubation procedure of SpO<sub>2</sub> values were found significantly higher in the intervention groups as compared with the reference groups: median (IQR) was (100 (95–100) % vs 96 (92–99) %, p=0.029). For the given calculation of median (IQR) converted in term of mean±SD through using the formula given by Wan *et al.*<sup>14</sup> see table 1.

$$X(\text{mean}) = \frac{q1+m+q3}{3}$$

$$S \approx \frac{q3-q1}{\frac{20^{-1}(0.75n-0.125)}{(n+0.25)}}$$

A sample size of 46 patients would be required in each arm. Therefore, we derived a maximum required sample

**Table 1** Sample size calculation

Group	Median (IQR)	Mean±SD (calculation)	Intervention versus reference
Intervention	100 (95–100)	98.33±3.75	Total=138 (46 in each arm)
Reference	96 (92–99)	95.67±5.25	



size for the study as  $n=138$ , that is, 46 in each arm; with 80% power and 5% level of significance.

## PLAN OF ANALYSIS

### Analysis principle

Primary analysis will be intention to treat (all patients will be analysed as per the assigned treatment arm). All hypothesis tests will be two sided with an alpha of 0.05. All analysis will be performed on Stata V.12. Student's t-test will be used to compare (statistically significant difference between) non-invasive lowest oxygenation in two groups. Mann-Whitney U test will be used to compare (statistically significant difference between) safe apnoea in two groups.

### Baseline comparisons and assessment of randomisation

To assess distribution of patient characteristics by arm, we will summarise baseline and demographic characteristics. Categorical variables will be reported as frequencies and percentages, and continuous variables as either means with SD or medians with IQRs. Variables reported will include demographics (age, gender, race, body mass index), indication for intubation, re-intubation status, active illness at the time of intubation, active comorbidities complicating intubation (vomiting, upper gastrointestinal bleeding and so on), respiratory status pre-intubation (non-invasive ventilation use, lowest  $O_2$  saturation,  $FiO_2$ ) and airway management procedure (preoxygenation technique, saturation at time of induction, induction medication, neuromuscular blocker, laryngoscope type).

### Secondary analysis

The difference between categorical variables (namely sex, grade of laryngoscopy, postgraduate trainee level, ED physician designation and so on) of the two study arms will be analysed using Fisher's exact test and for continuous variables, Mann-Whitney U test or t-test will be used. Subgroup analysis will be repeated for the following variables:

1. Grade of view on first attempt (Mann-Whitney U test).
2. Number of attempts required for tube placement (Mann-Whitney U test).
3. Incidence of need for a second operator (Fisher's exact test).
4. Incidence of non-hypoxia complications—composite of all recorded complications (Fisher's exact test).
5. Incidence of post-intubation tube malposition on chest X-ray (Fisher's exact test).
6. We will assess the impact of apnoeic oxygenation (low flow and high flow) versus no apnoeic oxygenation on in-hospital mortality using Fisher's exact test.
7. We will assess the impact of apnoeic oxygenation versus no apnoeic oxygenation in intensive care unit free days and number of days on ventilator using Mann-Whitney U test.

## MISSING DATA

In the initial analysis, cases with data missing for the primary endpoint will not be included. As sensitivity analysis, the primary analysis will be repeated with missing data by multiple imputation technique.

## ETHICS AND DISSEMINATION

Ethical approval has been sought from Ethics Review Committee of Aga Khan University Hospital (2019-0726-2463). The project is an institution University Research Committee grant recipient 192002ER-PK. Apnoeic oxygenation and intubation without administration of oxygen during laryngoscopy are both common in our current practice and written informed consent is not obtained. The study meets criteria for waiver of pre-intervention consent due to life-threatening condition that necessitates engagement of clinical protocol. There are no existing national guidelines and as per institutional policy we would be obtaining post-procedure signature as the procedure meeting Food and Drug Administration 21 CFR 50.24 criteria of emergency care research.<sup>6 11 12</sup> The consent form can be found as a standard online supplemental file 1. Privacy and confidentiality will be maintained, study participation will be voluntary. The data collected will be kept confidential and no personal identifiers will be used in the study. The data collected will be retained for up to 7 years as per the Aga Khan University data retention policy. The filled study questionnaires will be kept safely locked. The results will be published in a highly accessed international peer-reviewed journal. The findings will be disseminated within the institution through seminars, conferences and presentations during grand rounds. Additionally, the findings will be incorporated into the institutional airway management in the ED guidelines. The burden of the intervention was assessed by the project team and no cost of the intervention materials will be borne by the participants.

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**Contributors** SW conceived the study and was involved in writing the project. MFK is the subject expert and involved in reviewing the manuscript. SMK and AR provided statistical and methodological expertise in clinical trial design. NNK and RN helped with the implementation and management of the trial. All authors contributed to the refinement of the study protocol and approved the final manuscript.

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**Competing interests** None declared.

**Patient and public involvement statement** Patients were not involved in the design and conception of this study. Refer to the 'Methods and design' section for further details.

**Patient consent for publication** Not required.

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