BMJ Open  Intercostal nerve cryoablation versus thoracic epidural analgesia for minimal invasive Nuss repair of pectus excavatum: a protocol for a randomised clinical trial (ICE trial)

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ABSTRACT

Introduction  Epidural analgesia is currently considered the gold standard in postoperative pain management for the minimally invasive Nuss procedure for pectus excavatum. Alternative analgesic strategies (eg, patient-controlled analgesia and paravertebral nerve block) fail in accomplishing adequate prolonged pain management. Furthermore, the continuous use of opioids, often prescribed in addition to all pain management strategies, comes with side effects. Intercostal nerve cryoablation seems a promising novel technique. Hence, the primary objective of this study is to determine the impact of intercostal nerve cryoablation on postoperative length of hospital stay compared with standard pain management of young pectus excavatum patients treated with the minimally invasive Nuss procedure.

Methods and analysis  This study protocol is designed for a single centre, prospective, unblinded, randomised clinical trial. Intercostal nerve cryoablation will be compared with thoracic epidural analgesia in 50 young pectus excavatum patients (ie, 12–24 years of age) treated with the minimally invasive Nuss procedure. Block randomisation, including stratification based on age (12–16 years and 17–24 years) and sex, with an allocation ratio of 1:1 will be performed. Postoperative length of hospital stay will be recorded as the primary outcome. Secondary outcomes include (1) pain intensity, (2) operative time, (3) opioid usage, (4) complications, including neuropathic pain, (5) creatine kinase activity, (6) intensive care unit admissions, (7) readmissions, (8) postoperative mobility, (9) health-related quality of life, (10) days to return to work/school, (11) number of postoperative outpatient visits and (12) hospital costs.

Ethics and dissemination  This protocol has been approved by the local Medical Ethics Review Committee, METC Zuyderland and Zuyd University of Applied Sciences. Participation in this study will be voluntary and informed consent will be obtained. Regardless of the outcome, the results will be disseminated through a peer-reviewed international medical journal.

Trial registration number  NCT05731973.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This randomised controlled trial will evaluate the effect of intercostal nerve cryoablation, without the concomitant use of antiepileptics to prevent neuropathic pain, on the length of hospital stay.
⇒ This study will report on opioid usage, pain and mobility at different points in time.
⇒ This study will also provide detailed information on the influence of intercostal nerve cryoablation on patient recovery and health-related quality of life.
⇒ Limitations of this study include its open design and possible low response rates to questionnaires.

INTRODUCTION

Pectus excavatum is the most common congenital chest wall deformity. It is characterised by a posterior displacement of the sternum and often has a negative effect on cardiac function through compression. Currently, the Nuss procedure is considered the surgical treatment of choice for pectus excavatum. It is a minimally invasive surgical procedure that has proven its safety and efficacy, and comes with less morbidity than the conventional open Ravitch procedure. Pectus excavatum patients (ie, 12–24 years) are randomised, including stratification based on age (12–16 years and 17–24 years) and sex, with an allocation ratio of 1:1. Postoperative length of hospital stay will be recorded as the primary outcome. Secondary outcomes include (1) pain intensity, (2) operative time, (3) opioid usage, (4) complications, including neuropathic pain, (5) creatine kinase activity, (6) intensive care unit admissions, (7) readmissions, (8) postoperative mobility, (9) health-related quality of life, (10) days to return to work/school, (11) number of postoperative outpatient visits and (12) hospital costs.

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subvert its potential in effective pain management. As such, short-term complications (eg, urinary retention, hypotension and motor weakness in respectively 12%, 14% and 2% of the patients) occur considerably frequent.\(^8\)\(^9\) Furthermore, TEA-related long-term complications (eg, neurological injury) are rare but can be devastating for the patient. Moreover, a primary failure rate of 6%–35% for TEA has been reported,\(^10\)\(^11\) and the transition from TEA to oral pain medication can be challenging and impede discharge. Other treatment modalities such as patient-controlled analgesia (PCA), paravertebral nerve blocks (PVB) and pectoral nerves blocks (PECS II blocks) have failed to accomplish adequate pain control directly after the procedure and/or during prolonged postoperative pain management when applied without additional measures.\(^12\)\(^13\) The continuous use of opioids also comes with side effects, including severe nausea and obstruction.\(^14\) Thus, optimal pain management balancing adequate pain control on one hand and limiting side effects on the other hand remains a challenge.

A novel and promising alternative technique for postoperative analgesia may be intercostal nerve cryoablation (INC). This technique involves freezing of the intercostal nerves, causing Wallerian degeneration and thus temporary blocking of the transmission of pain signals.\(^15\) The patient will, however, experience pain of inflammatory nature in the first 12 hours after the procedure due to cell death in the frozen area. This pain can be managed by additional intercostal nerve blocks. The effect of INC lasts for several weeks to months.\(^16\) Prior studies comparing INC to other pain treatment modalities after pectus excavatum repair through the minimally invasive Nuss procedure report promising results.\(^17\)–\(^25\) Nevertheless, these studies pose significant limitations, including small sample sizes, a retrospective design with single arm or non-matched treatment groups, or contain considerable confounders (ie, use of concomitant treatments like PCA).

Financial impact related to INC is not clearly established yet. It is suggested that INC comes with higher costs related to additional equipment, use of disposables and prolonged operative time, but strongly reduces hospitalisation and opioid usage when compared with TEA. Five studies retrospectively reviewed patients that underwent the minimally invasive Nuss procedure along with INC and revealed a beneficial effect of INC on the hospital system.\(^16\)\(^18\)\(^26\)\(^29\)\(^30\) However, effects on recovery (eg, degree of mobilisation, days to return to work) and related financial impact, and quality of life are not reported in literature.

Hence, the primary objective of this study is to determine the impact of INC on length of hospital stay (LOHS) compared with our current protocol for pain management after the minimally invasive Nuss procedure for young pectus excavatum patients (<24 years of age), consisting of TEA. We hypothesise that INC is superior to TEA in terms of LOHS. Moreover, we will assess pain intensity, operative time, opioid usage, recovery (ie, degree of mobility, time required to return to work/school), complications (including neuropathic pain), creatine kinase (CK) activity, intensive care unit admissions, readmissions, changes in quality of life, number of postoperative outpatient visits and hospital costs.

**METHODS AND ANALYSIS**

**Study design**

This protocol is designed for a single-centre, prospective, unblinded randomised clinical trial comparing INC with TEA for young pectus excavatum patients treated by the minimally invasive Nuss procedure. The trial is designed as a parallel-group superiority trial on hospitalisation with an allocation ratio of 1:1, as presented in the Consolidated Standards of Reporting Trials Statement (CONSORT) flowchart (figure 1). The study will be conducted at Zuyderland Medical Center (Heerlen, the Netherlands), a tertiary referral centre for chest wall disorders and is registered at ClinicalTrials.gov (registry number: NCT05731973). The planned start date for the study is 8 December 2023 and the study is anticipated to conclude on 1 June 2025. We present our study protocol that is written in accordance with the CONSORT and the Standard Protocol Items: Recommendations for Interventional Trials Statement.\(^30\)\(^31\)

**Patient and public involvement**

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

**Patient selection**

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

1. Patients undergoing the minimally invasive Nuss procedure for surgical repair of pectus excavatum.
2. Young patients (12–24 years of age) according to the definition used by the WHO.\(^32\) This cut-off point has been chosen to create a more homogenous patient sample, as the thoracic cage is fully matured by the age of 24, in size and density, which will have an effect on postoperative pain.\(^33\)

A potential subject who meets any of the following criteria will be excluded from participation in this study:

1. A chest wall deformity other than pectus excavatum.
2. Opioid use in the 3 months prior to surgical repair of pectus excavatum.
3. Pain syndrome (eg, fibromyalgia) or neuropathic pain prior to surgical repair of pectus excavatum.
4. Connective tissue disease (eg, Marfan syndrome, Ehlers-Danlos syndrome).
5. Previous thoracic surgery or pectus excavatum repair.
6. Contraindication for INC or TEA (eg, patient refusal, infection at the site of cannulation, uncontrollable systemic infection, bleeding diathesis, increased intracranial pressure, mechanical spine obstruction).
8. Not mastering the Dutch language.
Participation in another clinical trial that may interfere with the current trial.

Sample size calculation
Sample size is determined based on the worst-case scenario reported in the meta-analysis by Daemen et al. In specific, the lower limit of the 95% CI of the mean reduction in hospitalisation was 2.15 days when INC was applied. An SD of 2 was derived from the article by de Loos et al., reporting the standard LOHS at our institution for patients who undergo the Nuss procedure. Significance level alpha is chosen at 0.05 and beta at 0.1 for 90% power. A sample size of 40 patients (n=20 per group) will have 90% power. A 20% follow-up loss per treatment arm is anticipated and therefore 50 patients are recruited. To improve the adherence to our follow-up programme and minimise the loss to follow-up, different
Treatments

In this study, INC (ie, intervention group) will be compared with TEA (ie, control group) as a treatment modality for postoperative pain following minimally invasive Nuss repair in pectus excavatum patients. INC is complemented with single-shot intercostal nerve blocks to overcome inflammatory pain due to cell death in the frozen area in the first period after cryoablation.

Both groups will receive medication conform a standardised pain management protocol (figure 2). If the standard pain medication is not sufficient and does not result in adequate pain control (ie, Numeric Rating Scale (NRS)>5), additional medication will be administered at the discretion of the pain management team.

Minimally invasive Nuss repair of pectus excavatum

All eligible patients will undergo pectus excavatum repair by the Nuss procedure. In brief, the following steps will be followed after intubation with a double lumen endotracheal tube, enabling bilateral single-lung ventilation: the deepest point of the sternal depression will be determined and guides the position of the lateral incisions, which will run from the anterior axillary line posteriorly for approximately 4 cm. A retropectoral tunnel will be created to the top of the edge of the sternal depression. Midaxillary, a port will be introduced in the fourth intercostal space on the right side and a 5 mm 30° videoscope will be inserted, allowing all next steps to be performed under thoracoscopic vision. A stainless-steel wire suture is placed transversally through the anterior sternal cortex at the level of the deepest point of the pectus deformity and attached to the crane system (Thompson Surgical Instruments, Traverse City, Michigan, USA). Sternal elevation is then applied until the point of maximum correction or anterior chest wall lift. A tunnel will be created between the sternum and the pericardium from the right to the left side of the thorax using the Nuss introducer. Subsequently, an umbilical tape will be fixed to the introducer, with the latter being pulled back out of the patient from left to right, leaving the umbilical tape behind. The appropriately sized prebent metal bar will then be pulled from left to right into the retrosternal tunnel using the umbilical tape, with the convexity of the bar faced dorsally. The bar will be flipped using a Lorenz pectus flipper so the convexity pushes against the sternum. Bar ends will only be adjusted with the bar bender when necessary. One or more bar stabilisers will be placed on one (left) or both ends of the bar as appropriate to prevent bar dislocation postoperatively. If required (eg, severe depression), a second or even third bar will be inserted as previously described. Air will be evacuated from the chest by applying manual compression on the chest and wounds are closed in multiple layers using absorbable sutures.

Figure 2 Pain management protocol. TEA, thoracic epidural analgesia.

<table>
<thead>
<tr>
<th>CRYO</th>
<th>TEA</th>
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</thead>
<tbody>
<tr>
<td><strong>Preoperative care unit:</strong></td>
<td>- Paracetamol 1000 mg PO</td>
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<tr>
<td><strong>Intraoperative:</strong></td>
<td>- Dexamethasone 4 mg IV prior to incision</td>
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<tr>
<td></td>
<td>- Diclofenac 75 mg IV</td>
</tr>
<tr>
<td></td>
<td>- Thoracoscopic assisted cryoablation of intercostal level T3-T9, bilaterally</td>
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<tr>
<td></td>
<td>- Intercostal nerve blocks with bupivacaine 5%, 2.3 ml at level T3-T9, bilaterally</td>
</tr>
<tr>
<td><strong>Postoperative:</strong></td>
<td>- Paracetamol 1000 mg PO, every 6 hours</td>
</tr>
<tr>
<td></td>
<td>- Diclofenac 50 mg PO, every 8 hours</td>
</tr>
<tr>
<td><strong>Discharge medication:</strong></td>
<td>- Paracetamol 1000 mg PO, every 6 hours</td>
</tr>
<tr>
<td></td>
<td>- Diclofenac 50 mg PO, every 8 hours</td>
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<tr>
<td><strong>Optional:</strong></td>
<td>- Oxycodone 5 mg PO, every 6 hours</td>
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<tr>
<td></td>
<td>- Oxycodone with prolonged discharge 10 mg, every 12 hours</td>
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<tr>
<td>Patients are instructed how to wean off pain medication</td>
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|                        | - Diclofenac 50 mg PO, every 8 hours |
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|                        | - Oxycodone with prolonged discharge 10 mg, every 12 hours |
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|                        | - Oxycodone with prolonged discharge 10 mg, every 12 hours |
Intercostal nerve cryoablation

When a patient is allocated to the intervention group, cryoablation will be performed prior to bar placement. In brief, cryoablation will be performed at the level T3–T9, bilaterally. For this, the cryoprobe (cryoICE, Atricure, Mason, Ohio, USA) will be inserted under video guidance through the existing thoracic incisions made for bar placement. Where feasible, these thoracic incisions will also serve for video guidance on the left side of the thorax eliminating the need for creating a second portal access. The cryoprobe will be placed at the inferior aspect of the ribs, posterior to the midaxillary line, directly on the neurovascular bundle. One freezing cycle takes 2 min, and a temperature of −60°C will be applied. The probe will be warmed to room temperature before removing it from the pleura to prevent additional trauma. Furthermore, INC will be combined with single shot bupivacaine (1.25 mg/mL, 2–3 mL per intercostal space) intercostal nerve blocks placed just anterior to the site of the cryoablation.

Thoracic epidural analgesia

Prior to surgery, an anaesthesiologist will place the thoracic epidural at T3–T6 or T6–T7 interspace in the awake patient. After correct placement, a local continuous infusion with sufentanil (1 µg/mL) and bupivacaine (1.25 mg/mL) will be started. On the third postoperative day, TEA will be ceased and transitioned to oral pain medication at discretion of the pain management team. In general, opioids (oxycodone with prolonged discharge 10 mg orally every 12 hours and oxycodone 5 mg every 6 hours as needed) will be provided 12 hours before TEA is ceased.

Concomitant care

Neuropathic pain will be treated with antiepileptic drugs such as gabapentin or pregabalin. However, these will not be routinely given as it is associated with psychiatric and behavioural side effects in adolescents, and dizziness and somnolence, as well as peripheral oedema in adult patients. Therefore, antiepileptics will only be started on indication after consulting a dedicated pain specialist based on a DN4 score of >4. The DN4 is a validated questionnaire that is used to estimate the probability of neuropathic pain.

Consultation with the physiotherapist for breathing exercises and supervised mobilisation is standard care and will be applied to both treatment groups.

Outcomes

Besides the primary and secondary outcomes, the following patient and procedural characteristics will be collected: (1) age, (2) sex, (3) body mass index, (4) preoperative Haller Index, (5) numbers of bars implanted, (6) number of stabilisers and (7) blood loss.

Primary outcome

The primary outcome of this study is LOHS, defined as the number of days of hospital admittance after the Nuss procedure. Standard LOHS at our institution for patients who undergo the Nuss procedure and receive TEA for the management of postoperative pain is 5 days (±2 SD). For both study arms, discharge criteria are evaluated daily and include:
1. No conditions requiring medical attention or treatment.
2. Ability to mobilise and engage in self-care.
3. Adequate pain control with oral analgesia.
4. Tolerance of oral intake.
5. Ability to urinate spontaneously.
6. Adequate bowel function with no conditions requiring medical attention.
7. Ability to mobilise and engage in self-care.
8. Adequate pain control with oral analgesia.
10. Ability to urinate spontaneously.

Secondary outcomes

1. Pain intensity at rest and during mobilisation. Pain scores will be rated on the NRS and obtained in the preoperative care unit before surgery, in the morning on postoperative day 1 and 2, and 7 days, 14 days, 3 months and 6 months postoperatively.
2. Operative time in minutes. Duration of cryoablation will be assessed separately. Operative time will not include the time needed for the placement of the thoracic epidural as placement will be performed in the preoperative care unit.
3. (a) Intraoperative administered opioids; (b) Opioid usage during postoperative days 0, 1 and 2 at the recovery unit and surgical ward and (c) Opioid usage within the first 2 weeks after surgery. Opioid usage will be converted to oral morphine milligram equivalents.
4. Complications graded according to the Clavien-Dindo classification. The most common procedure-related and analgesia-related complications are defined in online supplemental tables 1 and 2. Occurrence of neuropathic pain will be actively monitored during the hospitalisation period and during all follow-up appointments.
5. CK activity. CK level will be assessed prior to the surgical procedure (ie, baseline measurement during routine blood evaluation on the day of surgery) and on postoperative day 1. CK levels will be denoted in U/L.
6. Number and length of intensive care unit admissions due to the occurrence of perioperative complications denoted as absolute numbers.
7. Number and length of readmissions denoted as absolute numbers.
8. Degree of mobility measured on a 4-point scale (ie, 1—on the bed, 2—to the chair, 3—to the toilet and 4—outside the patient’s hospital room) during postoperative days 1 and 2.
9. HRQOL measured by the Dutch versions of the Pectus evaluation questionnaire (PEEQ). Short Form Health Survey (SF-36) and EuroQol 5 Dimensions 5 Levels (EQ-5D-5L). The PEEQ is a validated disease-specific questionnaire evaluating the quality of life in pectus excavatum patients. The SF-36 is a generic questionnaire that assesses health in eight dimensions. For the EQ-5D-5L, participants will rate their health in five dimensions on five levels and
will give an overall score of their health on a Visual Analogue Scale. The PEEQ, SF-36 and EQ-5D-5L will be completed before surgery as a baseline measurement, and at 2 weeks, 3 months and 6 months after the surgical procedure.

10. Days to return to work/school reported as days between day of surgery and return to work or school. This will be assessed at all follow-up appointments.

11. Number of postoperative outpatient visits and telephone appointments denoted as absolute numbers in the first 6 months after the surgical procedure.

12. Hospital costs reported as hospital costs during initial hospitalisation (e.g., medication, patient care supply, surgical equipment) and hospital costs after discharge until 6 months follow-up (e.g., medications, outpatient visits, (opioid-related) readmissions).

**Randomisation, treatment allocation and blinding**

**Randomisation and allocation**

Random allocation, including stratification based on sex and age (12–16 years, 17–24 years), will be performed prior to the Nuss procedure using a computer-generated block randomisation scheme (4 patients per block) using the Electronic Data Capture tool of Research Manager (Deventer, the Netherlands). This will ensure that the 1:1 allocation ratio is handled with equal distribution of patient characteristics. The randomisation scheme is unavailable to those who enrol patients or assign the intervention. Randomisation will be performed by delegated members of the research team, after obtaining informed consent from the patient.

**Blinding**

Due to the nature of treatments compared in this study, it is not possible to blind the healthcare professionals or participants to the allocation of a treatment group.

**Participant timeline**

Participants will be enrolled during their preoperative visit to our outpatient clinic by a trial physician, researcher or thoracic surgeon. At the day of surgery, participants allocated to the TEA group will receive an epidural at the preoperative care unit, and participants allocated to the INC group will undergo cryoablation during surgery, prior to bar placement. On discharge, subjects in the epidural group will be prescribed opioids for 9 days, and subjects in the cryoablation group will be prescribed opioids on indication. Opioid usage and the need for a refill prescription will be assessed via a telephone appointment. Furthermore, in context of CK activity assessment, patients will be asked to not conduct any high intensity (sports) activities (e.g., sport training or matches) within 1 week prior to each measurement and no moderate activities (e.g., walking long (>5 km) distances) within 48 hours prior to each measurement.

**Figure 3** represents the participant timeline for data collection throughout our study.

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons. Subjects withdrawn from treatment will receive follow-up as part of standard care.

**Data collection**

Data will be extracted from the electronic patient file, coded by participant ID and stored by our research team.

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**Figure 3** Participant timeline. BMI, body mass index; HI, Haller Index; HRQOL, health-related quality of life; ICU, intensive care unit; NRS, Numeric Rating Scale; POD, postoperative day.
in our secured database in Research Manager Software (Research Manager, Deventer, the Netherlands) for 15 years. Records containing personal identifiers will be stored separate from study records and will only be accessible to the principal investigator and research coordinator. All informed consent forms will be stored at the study site for 15 years.

**Statistical analysis**

A normal probability plot chart and histogram will be generated to assess if the data are normally distributed in combination with the Kolmogorov-Smirnov test. The analysis will be performed as a per-protocol analysis. An intention-to-treat analysis will be run to test the robustness of the findings. Statistical methods for dealing with missing data (eg, multiple imputation) will be chosen based on the reason for missing data.

Categorical and nominal variables will be reported in absolute numbers and percentages, and tested with a Pearson’s χ² test or Fisher’s exact test where appropriate. Proportions will be presented as percentage with 95% CI. Continuous variables will be reported as mean and SD in case of normally distributed data and will be analysed with a paired or unpaired t-test where appropriate. If skewed, data will be presented as median and IQR, and statistical significance will be determined by a Wilcoxon signed-rank test or Mann-Whitney U test where appropriate. However, if the outcome is based on repeated observations (eg, the outcome pain intensity) then a repeated measures analysis of variance or Friedman test will be applied where appropriate. Multivariable analysis will also be performed to correct for any covariates. A p<0.05 is considered statistically significant and further post hoc testing is not prespecified.

Analysis will be performed using SPSS statistics (IBM, IBM SPSS statistics for MacOS, V.27.0).

Our research group intends to perform a cost-effectiveness analysis on data gathered during this study and will disseminate the statistical analysis in a separate protocol.

**ETHICS AND DISSEMINATION**

**Ethical considerations**

This study protocol follows the recommendations determined by the Declaration of Helsinki (as revised in 2013). The protocol has been reviewed and approved by the local Medical Ethics Review Committee, METC Zuyderland and Zuyd, (registry number: METCZ20230011; acceptance date: 17 October 2023) in accordance with the Dutch Law Medical Research Involving Human Subjects Act (WMO). Patients will be consecutively recruited during their preoperative appointment at our outpatient clinic by a trial physician, researcher or thoracic surgeon who will inform the patient about the objectives of the study. Participants will also receive study information prior to their preoperative appointment and have the possibility to ask questions. After all information is provided, subjects will be given sufficient time (at least 48 hours) to consider their decision before their informed consent is obtained. An independent expert will be assigned to this project, who can be contacted by the subjects in case they want further information. For this study, all subjects will be informed in Dutch and provide written consent using a Dutch informed consent form (online supplemental material form 1). If under the age of 16 years, additional parental/legal guardian consent is received (online supplemental material form 2). The written informed consent form will also be signed by the trial physician, researcher or thoracic surgeon who provided the study information. Participation is on voluntary basis and participants are allowed to withdraw at any time. Furthermore, the Netherlands Association for Paediatric Medicine’s (NVK) code of conduct for dealing with subjects’ expressions of objection in the course of the research will be adhered to. Patients will have no benefit from participation in this study other than a possible higher perceived mobility and diminished pain intensity and anxiety. Risks related to study participation are minimal.

**Dissemination**

Regardless of the outcome, the results of this study will be disseminated through a suitable peer-reviewed international medical journal and cannot be traced to individual participants. After completion of the study, participants will receive information on their personal and overall study results on request. All authors are eligible to participate in dissemination.

**Contributors**

NJ: conceptualisation; data curation; project administration; methodology; writing—original draft. JHTD: conceptualisation; data curation; methodology; writing—review and editing. AJPMF: conceptualisation; data curation; methodology; writing—review and editing. EJvP: conceptualisation; data curation; project administration; writing—review and editing. LMvR: conceptualisation; methodology; writing—review and editing. KWEH: conceptualisation; methodology; writing—review and editing. YvC: conceptualisation; methodology; writing—review and editing. ERdL: conceptualisation; methodology; writing—review and editing. The final version of the manuscript has been fully reviewed and approved by all authors.

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**Competing interests**

None declared.

**Patient and public involvement**

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication**

Not applicable.

**Provenance and peer review**

Not commissioned; externally peer reviewed.

**Supplemental material**

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