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Intracapsular tonsillectomy in the treatment of recurrent and chronic tonsillitis in adults: a protocol of a prospective, single-blinded, randomised study with a 5-year follow-up (the FINITE trial)

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ABSTRACT

Introduction

The standard surgical treatment for recurrent or chronic tonsillitis is extracapsular tonsillectomy. Recent studies show that intracapsular tonsillectomy has the potential to reduce the postoperative morbidity of patients undergoing tonsil surgery. The Finnish Intracapsular Tonsillectomy (FINITE) trial aims to provide Level I evidence to support the hypothesis that the recovery time from tonsil surgery can be reduced with intracapsular tonsillectomy. Additionally, from this trial, major benefits in quality of life, reduction of postoperative complications, treatment costs, and throat symptoms might be gained.

Methods and analysis

The FINITE trial is a prospective, randomised, controlled, patient-blinded, three-arm clinical trial. It is designed to compare three different surgical methods being extracapsular monopolar tonsillectomy versus intracapsular microdebrider tonsillectomy versus intracapsular coblation tonsillectomy in the treatment of adult patients (16–65 years) suffering from recurrent or chronic tonsillitis. The study started in September 2019, and patients will be enrolled until a maximum of 200 patients are randomised. Currently, we are in the middle of the study with 125 patients enrolled as of February 28, 2022 and data collection is scheduled to be completed totally by December 2027. The primary endpoint of the study will be the recovery time from surgery. Secondary endpoints will be the postoperative pain scores and the use of analgesics during the first three weeks of recovery, postoperative haemorrhage, quality of life, tonsillar remnants, need for revision surgery, throat symptoms, treatment costs, and sick leave. A follow-up by a questionnaire at 1–21 days and at 1, 6, 24, and 60 months will be conducted with a follow-up visit at the 6-month time point.

Ethics and dissemination

Ethical approval was obtained from the Medical Ethics Committee of the Hospital District of Southwest Finland (reference number 29/1801/2019). Results will be made publicly available in peer-reviewed scientific journals.

Trial registration number

ClinicalTrials.gov (NCT03654742). First posted 31 August 2018.

KEYWORDS

Tonsillectomy, intracapsular tonsillectomy, partial tonsillectomy, subtotal tonsillectomy, intracapsular dissection tonsillectomy, recurrent tonsillitis, chronic tonsillitis, coblation, microdebrider

ARTICLE SUMMARY

Strengths and limitations of this study

- We use a clinical-based, randomised controlled trial (RCT) design to compare extracapsular monopolar tonsillectomy versus intracapsular microdebrider tonsillectomy versus intracapsular coblation tonsillectomy in the treatment of adult patients suffering from recurrent or chronic tonsillitis.
- The FINITE trial will provide original evidence showing whether an intracapsular tonsillectomy provides clinically significant reduction of recovery time after tonsil surgery in adults.
- We use a highly recommended assessment tool, The Brief Pain Inventory.
- This trial uses methods to assess the long-term outcomes in terms of quality of life, postoperative complications, treatment costs, and throat symptoms in patients

undergoing either intracapsular microdebrider or intracapsular coblation tonsillectomies.

INTRODUCTION

Recurrent tonsillitis and chronic tonsillitis are the most common indications for tonsil surgery in adults[1]. Extracapsular tonsillectomy (ECTE) is the gold-standard operative procedure for recurrent tonsillitis and chronic tonsillitis. In the United States, 737,000 outpatient ECTEs are performed annually[2], and in Finland, 7,000–9,000 annually[3]. However, ECTE causes substantial postoperative pain during the first two weeks after surgery[4] and includes a risk for primary and secondary haemorrhage[5].

The operative management of recurrent tonsillitis and chronic tonsillitis remains controversial. For decades, it was thought that an extracapsular removal of the palatine tonsils is required for effective symptom alleviation in patients suffering from tonsillitis. To reduce morbidity after ECTE, various instrumentation is suggested to be used including CO_2-laser[6], coblation[7], surgical scissors, monopolar electrocautery, bipolar forceps, and other instruments[8,9]. Tonsillotomy (TT) is a procedure for the partial removal of tonsils where only the protruding tonsillar tissue medial to the faucial pillars, which is approximately 50 to 70% of the total tissue, is reduced[10]. Other studies have suggested removal of up to 90 to 95% of tonsillar tissue, and this procedure is referred to as a type 2 TT or subtotal or intracapsular tonsillectomy (ICTE)[11,12]. In both TT and ICTE, the aim is to remove tonsillar tissue without injuring the underlying pharyngeal muscles and without violating the tonsillar capsule.

Concerning children, both TT and ICTE result in a faster return to normal daily activity and a reduction in postoperative pain and haemorrhage requiring medical intervention. Of course,

these benefits need to be balanced against their clinical effectiveness[13]. In the paediatric population, both TT and ICTE have been established in the treatment of sleep breathing disorders[14,15]. There are two systematic reviews that compare the postoperative morbidity and the effectiveness of ECTE to TT or ICTE in adults with tonsil-related symptoms[16,17]. To the best of our knowledge, seven randomised controlled trials (RCTs) have compared the postoperative morbidity between ECTE and TT or ICTE in the treatment of tonsil-related afflictions[18–26]. Compared to ECTE, TT and ICTE result in reduction of postoperative complications and a reduced use of analgesics in adults suffering from symptoms related to tonsillar hypertrophy. Two RCTs used the inclusion criteria of solely adults with recurrent tonsillitis or chronic tonsillitis[18,19].

The rationale of this proposal and the evidence gap that it may fill are that this Finnish Intracapsular Tonsillectomy (FINITE) trial will compare three different surgical methods in a prospective setting: ECTE (monopolar), ICTE (coblation), and ICTE (microdebrider) in the treatment of adult patients suffering from recurrent tonsillitis or chronic tonsillitis. The overall objective of the study is to fill existing gaps in knowledge about the effectiveness of different tonsillectomies and provide Level I evidence to support the hypothesis that the recovery time from tonsil surgery in adult patients with recurrent tonsillitis or chronic tonsillitis can be reduced with ICTE. Also, the complications, benefits, and costs will be assessed.

The primary endpoint will be the recovery time from surgery. Recovery from surgery will be defined as resolution of pain on a visual analogue scale (VAS 0–10) as pain <4 in rest and <6 on swallowing without regular use of analgesics. Secondary endpoints will be the postoperative pain scores and use of analgesics during the first three weeks of recovery, postoperative

haemorrhage, quality of life, tonsillar remnants, need for revision surgery, throat symptoms, treatment costs, and sick leave.

METHODS AND ANALYSIS

Trial design

The FINITE trial has been designed as a prospective, randomised, controlled, patient-blinded, three-arm clinical trial to compare extracapsular monopolar tonsillectomy versus intracapsular microdebrider tonsillectomy versus intracapsular coblation tonsillectomy in the treatment of recurrent tonsillitis and chronic tonsillitis in adults. The design of the trial is summarised in Figure 1 (see also Table 1 for an overview of the schedule). The trial is scheduled to be completed totally by December 2027.

Table 1. Study schedule.

Table 1 Study schedule							
	STUDY PERIOD						
	Enrolment	**Surgery**	**Postoperative course**				
TIME POINT	**-t1**	**t0: surgery**	**t1: days 1-21**	**t2: 1 month**	**t3: 6 months**	**t4: 24 months**	**t5: 60 months**
ENROLMENT:							
Eligibility	X						
Informed consent	X						
Randomisation	X						
Allocation	X						
INTERVENTIONS:							
Extracapsular monopolar tonsillectomy		X					

Intracapsular microdebrider tonsillectomy		X					
Intracapsular coblation tonsillectomy		X					
ASSESSMENTS:							
TOI-14	X				X	X	X
Perioperative data		X					
Brief Pain inventory			X				
NTSR 1-month				X			
NTSR 6, 24, and 60 months					X	X	X
GBI					X		
Clinical follow-up					X		
Sick leave					X	X	X
Case costs					X		X

NTSR, Nordic Tonsil Surgery Register; TOI-14, Tonsillectomy Outcome Inventory-14; GBI, Glasgow Benefit Inventory

Participants

Patients aged 16–65 years old and scheduled for tonsillectomy will be enrolled from the Turku University Hospital, Turku, Finland and Turunmaa Regional Hospital, Turku, Finland. The patient diagnosed with recurrent tonsillitis or chronic tonsillitis will be eligible for inclusion in the FINITE study. The study protocol will be described to eligible patients, and they will be invited to participate in the study. If they decide to participate, they will sign a written informed consent indicative of their approval. The inclusion of patients has been initiated in September 2019, and we have 125 enrolled as of early 2022.

Inclusion criteria

The inclusion criteria will be an age between 16 and 65 years and planned tonsil surgery due to clinical indication as a diagnosis of either: recurrent tonsillitis, which is defined as at least three acute occurrences of tonsillitis in the last 12 months, or chronic tonsillitis, which is defined as prolonged inflammation of the tonsils that affects daily activities and has lasted for at least three months. All included patients will give written informed consent.

Exclusion criteria

The exclusion criteria will be a peritonsillar abscess that occurred less than one month ago; an ongoing acute episode of tonsillitis; previous palatine tonsil surgery; a suspected tonsil malignancy; a high usage of anti-inflammatory analgesics, as defined by more than one defined daily dose during the previous four weeks, e.g., > 1.2 g ibuprofen/day or > 500 mg naproxen/day; severe obstructive sleep apnoea or ongoing continuous positive airway pressure (CPAP) therapy; untreated gastroesophageal reflux disease; anticoagulant medication; any condition of haemophilia, pregnancy, or lactation; and/or a current or positive history of a malignant disease with an ongoing active follow-up.

Registration procedure

With their written informed consent, all patients will be registered into a common electronic database (Research Electronic Data Capture, REDCap 10.6.9 ©2021 Vanderbilt University, Nashville, TN, United States) at the University of Turku[27]. The patients' names, electronic mail address, phone number, date of birth, and sex will be registered along with clinical information and baseline severity of symptoms.

Randomisation

Patients will be randomised with SAS (SAS Institute Inc., Cary, NC, United States) into permuted blocks of six patients. The randomisation will be performed in a 1:1:1 equal allocation ratio on the morning of or the day before surgery by the surgeon in the randomisation module of REDCap either to undergo extracapsular monopolar tonsillectomy, intracapsular microdebrider tonsillectomy, or intracapsular coblation tonsillectomy.

Blinding

The patients will remain unaware of their method of surgery until the 5-year follow-up is completed. The method of tonsil surgery will not be revealed in the hospital records. The clinical outcome at the 6-month follow-up visit will be evaluated by an otorhinolaryngologist (JP, LI, IM, EK, HS, TU), who will be blinded to the surgery method. The patients will be scheduled to visit another otorhinolaryngologist than the surgeon who performed the operation. The data analysis will be performed by an experienced statistician (TK) to ensure the blinding of the principal investigator.

Sample size calculation

Based on earlier study results, the average recovery time for ECTE is 12 days (SD = 3)[4]. If the recovery time for ICTE is three days shorter, we consider it as a clinically significant difference. In such a case, the effect size for a t-test is (12-9)/3 = 1. We aim to compare ICTE, in two groups, to ECTE. The level of significance is 5%, the Bonferroni correction is 2.5%, and the desired power is 90%. When expecting a total of 20% dropouts, the sample size is 27 patients per group. However, if the SD is 4, the sample size is 55. We intend to use a sample size of 55 patients per group and a maximum of 200 patients will be enrolled. The main

analyses will be based on the intention-to-treat principle, but both intention-to-treat and per-protocol analyses will be performed.

Interventions

All surgeries will be performed by one of the two surgeons (TU, HS), who both have experience in otorhinolaryngology with performing greater than 100 tonsillectomies. Prior to starting, each study centre will establish a uniform operative technique. We consider the learning curve of ICTE to be 10 procedures for a surgeon who has a routine skill level in TT and ECTE[28].

The surgical field in all techniques will be prepared with a tonsillectomy mouth gag. A pharyngeal round gaze sponge in saline solution will be used to prevent potential haemorrhage into the trachea. Velotraction with a suction catheter will be established for controlling the soft palate and especially the uvula. Intratonsillar injection of 1–2 millilitres of lidocaine-adrenaline will be administered for local haemostasis. The base of tongue will be left intact. Haemostasis is primarily achieved with compression with round gaze sponges soaked in lidocaine-adrenaline. When needed, small vessels will be coagulated. More profound vessels are, rarely, ligated to reduce the thermal effect to the operative area.

Extracapsular monopolar tonsillectomy (Control group)

A monopolar diathermy unit with 15-Watts power and spray settings will be used with a pen electrode and a blunt-needle tip. The tonsil will be grasped and pulled medially with forceps. Tonsillectomy will be performed by dissection in the peritonsillar plane. Parts of the upper and lateral palatal mucosal arches will be incised, and an extracapsular dissection for complete tonsil excision will be performed.

Intracapsular microdebrider tonsillectomy

The recommended settings of 1500 rounds-per-minute for a microdebrider ("Straightshot M4 handpiece," "12 degrees curved Tonsil blade," and "Integrated Power Console," Medtronic Ltd., Minneapolis, MN, United States) are used. Approximately 95% of the tonsillar tissue will be removed from an inferior to superior and from a posterior to anterior direction. The tonsil capsule will not be breached.

Intracapsular coblation tonsillectomy

Approximately 95% of the tonsillar tissue will be removed with a coblation wand ("Procise EZ" or "Evac 70 extra" Coblator II base unit, Smith & Nephew plc, Watford, United Kingdom). Power settings will be set to default and may be adjusted if needed. The tonsil capsule will not be breached.

Patient and public involvement

Patients will fill a semi-structured questionnaire one month after tonsil surgery regarding how their expectations were met. Their experience about the preoperative information will be analysed to detect any potential for improvement.

OUTCOME PARAMETERS

The primary endpoint

The primary endpoint of this trial is postoperative recovery time, which is defined as VAS pain, from 0–10 with <4 at rest and <6 on swallowing without regular use of analgesics. The regular use of analgesics is defined as a daily intake of 2 tablets of naproxen 500 mg and 3 or more tablets of tramadol-paracetamol 37.5/325 mg.

Secondary endpoints

The secondary endpoints will be the postoperative pain scores (VAS 0–10) and postoperative use of analgesics, early and late postoperative haemorrhage requiring a medical intervention, life quality, tonsil remnants, need for revision surgery, throat symptoms, treatment costs, and sick leave.

For the primary study endpoint, the duration of the postoperative recovery is a composite of three endpoints: pain at rest, pain on swallowing, and regular use of analgesics. The patients will be advised to a daily use of analgesics for the first postoperative week to ensure analgesia in all treatment arms.

Data collection

The trial consists of an intervention treatment, through tonsil surgery, with a 60-month follow-up. As shown in Table 1, data will be collected before the surgery, perioperatively, 1–21 days after surgery, and 1, 6, 24, and 60 months after surgery. Data collection from all patients participating in the trial will include the baseline severity of symptoms, perioperative data, and follow-up data. The perioperative data will be recorded using a report form (Table 2).

Table 2. Template for data collection during hospitalisation (FINITE trial).

Preoperative		**Intervention**		**Postoperative**
Medical history of gastroesophageal reflux disease, smoking, peritonsillar abscess		Technique and quantity used for haemostasis		Postoperative haemorrhage before release from ward (yes, no)

Number of courses of antibiotics for tonsillitis within 12 months		Problems related to haemostasis (yes, no)		Question used to ensure successful blinding of staff and patient: Was the surgical method used TE or ICTE?
Number of acute episodes of tonsillitis within 12 months		Blood loss, estimated (millilitres)		
Planned for day surgery or overnight stay		Time from insertion to removal of mouth gag including velotraction, intratonsillar infiltration, surgery, haemostasis, and photography of surgical area (minutes)		
Photograph of tonsils and tonsil grading using Brodsky Scale 1-4		Estimated residual tonsil tissue (0–100%)		
Indication for surgery (recurrent or chronic tonsillitis)		Subjective perceived difficulty level of operation (0–100%)		
Planned with adenoidectomy or not		Subjective perceived pleasantness of operation (0–100%)		
Number of sick leave days due to throat				

symptoms during previous 12 months				

Follow-up

Assessment of postoperative recovery, pain, and complications

Patients will use the Brief Pain Inventory (BPI) questionnaire in REDCap to record postoperative pain VAS scores, use of analgesics, nightly awakenings due to pain, and return to normal daily activities 1–21 days after tonsil surgery. The Finnish version of the form has been adapted from an earlier study[4]. One month after surgery, patients will fill out the Nordic Tonsil Surgery Register, 1-month questionnaire (NTSR 1-month) to report the following outcomes: occurrence of postoperative haemorrhage, the occurrence of an infection within 1 month, the need for a course of antibiotics, whether the patient contacted the health care system due to pain, in how many days after the surgery did the pain disappear, and in how many days after surgery did the patient resume his/her normal diet[29].

Assessment of tonsil remnants, quality of life, and patient satisfaction

Patients will record data preoperatively and 6, 24, and 60 months after tonsil surgery with the Tonsillectomy Outcome Inventory-14 (TOI-14) questionnaire, a disease-specific, quality-of-life instrument for throat-related symptoms. The total score can range between 0 (no problems) and 100 (most severe problems) and in patients with recurrent or chronic tonsillitis, a score of about 20.0 indicates mild symptoms, 30.0 indicates moderate symptoms, and 40.0 or higher intense symptoms. The minimum significant change is 10.0 points. The questionnaire has been validated into the Finnish language[30]. The Glasgow Benefit Inventory (GBI) is widely used in otorhinolaryngology to measure the change in quality of life associated with a surgical or pharmaceutical intervention. The individual responses are scored and added together to obtain

a total score from -100 (worst outcome) to 0 (no change) to +100 (best outcome). A Finnish version of the questionnaire has been validated[31]. Patients will fill the GBI questionnaire 6 months after surgery. The Nordic Tonsil Surgery Register questionnaire (NTSR 6, 24, and 60 months) collects data on whether the symptoms have alleviated after surgery and also whether the patient has experienced other symptoms[29]. In addition, patients will report the number of days on sick leave due to throat symptoms.

A clinical follow-up visit at 6 months after tonsil surgery will be performed by an otorhinolaryngologist (JP, LI, IM, EK, HS, TU). Data will be collected with a standardised report form (Table 3).

Table 3. Structured reporting template for the 6-month follow-up visit (FINITE trial)

Photograph of surgical area	Yes or no
Tonsil remnants present?	Yes or no
Tonsillitis symptoms during last 6 months? If yes, how many times?	Yes or no
Specific symptoms present? Change in taste Sensations of strictures or something extra in throat Symptoms of velopharyngeal insufficiency Painful swallowing (if yes; average on scale 0–10, 0=no pain, 10=most pain)	 Yes or no Yes or no Yes or no Yes or no
Has the patient contacted health care due to throat symptoms? If yes, how many times?	Yes or no
Question used to ensure successful blinding of the patient.	

The surgical method used was:	TE or ICTE
Question used to ensure successful blinding of the otorhinolaryngologist. The surgical method used was:	TE or ICTE (microdebrider) or ICTE (coblation)

Statistical analysis plan

The principal investigator (JP) will collect the study data, and it will be analysed by an experienced biostatistician (TK). All efficacy and safety variables and primary and secondary outcome variables will be listed and tabulated by time points and summarised using descriptive statistics. Both the absolute measured values and the change from baseline will be recorded. Reasons for discontinuations will be tabulated in detail. Analyses of outcome variables will be performed using generalised linear models. Model fit is evaluated by examining residuals. All results will be presented with 95% confidence intervals and P-values. A separate Statistical Analysis Plan (SAP) is prepared and contains a more detailed view of statistical analysis setup and variables. All analyses, tabulations, listings, and figures will be conducted using R version 4.0.3 or later (R Core Team).

Cost-benefit analysis and cost-effectiveness analysis

All tonsil surgery related direct medical costs will be estimated based on the actual input terms of resource use and personnel. Data of the costs will be provided by Auria Clinical Informatics from the information system of the Hospital District of Southwest Finland or determined in cooperation with the hospital administration. Operation time will be recorded in the case report forms. Indirect costs will arise from losses in productivity. These will be assessed by the BPI, in which the patient records when they consider themselves able to resume their normal daily activities, such as their work or studies after tonsil surgery. During the long-term follow-up,

the patient will report at time points of 6, 24, and 60 months the number of sick leave days due to persistent throat symptoms.

A cost-effectiveness analysis will be performed to compare the relative costs and outcomes between ECTE and ICTE, in terms of reduced symptoms measured with TOI-14 and benefit in quality of life measured with GBI.

Safety monitoring

Adverse events are defined as any undesirable experience occurring to a subject during a clinical trial whether or not these events are considered related to the investigational intervention. All adverse events reported by the patient, observed by the investigator, or the staff will be recorded. An interim analysis to ensure the safety of the ICTE will be performed after randomising 50–60 patients. We expect a 1% reoperation rate in all treatment groups.

Data collection and confidentiality

The researchers have created an online database where all patients evaluated for the study enrolment will be recorded after a written informed consent is obtained. REDCap is used as the online platform. All data will be handled confidentially, and the information in the datasets is non-identifiable. Data are gathered during hospitalisation, from clinical observations of the follow-up examination and from questionnaires filled in by the study patients. The information recorded from the non-participating patients will be used as data for a register-based study. The principal investigator (JP) will be in charge of the common database with full access to the data. The access to the data is otherwise strictly limited. The online database will not be used for other purposes during the trial, and all of the visits to the database will be recorded in the

database log. In order to prevent selection bias, we designed the study protocol to record data on all patients evaluated for eligibility.

Withdrawal

During the enrolment, patients will be informed of their right to withdraw from the study without explanation at any time.

Dissemination plan

The results of this trial will be disseminated by publication in international peer-reviewed scientific journals and by presentations at international and domestic conferences.

DISCUSSION

The hypothesis of the FINITE trial is that adult patients with recurrent or chronic tonsillitis can be treated effectively with ICTE with a faster recovery time and less morbidity compared to ECTE. This hypothesis is supported by previous randomised studies[18,19,23,24,26]. Recurrent and chronic tonsillitis affects quality of life[32]. In adults, ECTE reduces episodes of tonsillitis and sore throat compared to conservative treatment[31]. The quality of life, 6 months after ECTE, is improved in adult patients with recurrent tonsillitis[33]. However, the benefits must be balanced against the risks of the surgery, notably post-intervention haemorrhage and a painful recovery.

If this study can demonstrate the faster recovery time of ICTE, the need for any prolonged absence from work, studies, or other activities would substantially decrease.

Choice of the primary outcome

The recovery after ECTE, lasting an average of 12 to 14 days, is associated with moderate to severe pain, even with adequate pain medication[4,34,35]. Tonsillectomy leaves an open wound in the pharynx, which heals *per secundam.* After TT, in the age group of 16–25 year-olds, patients were able to return to their normal activity 4 days earlier compared to ECTE[21]. In three RCTs, adult patients were operated with ECTE on one tonsil and ICTE with coblation on the other tonsil[19,25,26]. Patients, after a 14-day follow-up, preferred the side that was performed with ICTE[19,25].

Wilson et al. compared ECTE with electrocautery versus ICTE with coblation or a microdebrider[23]. Patients (n = 156, age = 0.5–22 years old) with obstruction were randomly assigned to three treatment groups. The return to normal nutrition and normal daily activity after ICTE was on average 2 days faster when compared to ECTE.

Based on the available information, most of the patients seem to recover within the first 21 postoperative days, and it is therefore reasonable to use this timeframe for the primary endpoint evaluation.

Choice of the surgical instrumentation

In ECTE, there are no clinically relevant differences between different surgical instruments in terms of recovery time and pain scores[34,36]. Postoperative pain may be slightly reduced by using cold instrumentation, such as with cold steel dissection, and by minimising thermal energy conducted to the wound bed when using electrocautery for dissection and/or coagulating small vessels.

In clinical practice, the advantages of the reduced operation time and the ease of achieving intraoperative haemostasis have led many surgeons to use electrocautery. In this study, we wanted to include the most common instruments for ECTE and ICTE in the United States[37]. Thus, ECTE is performed with monopolar dissection and ICTE with either a microdebrider or a coblation wand.

Complications after tonsil surgery

Approximately 5 to 15 percent of patients need a medical intervention for postoperative complications after ECTE, which notably include pain, haemorrhage, dehydration, and poor nutrition[5]. The choice of the surgical method is an important factor regarding complications. The complication risk is known to be lower after TT[11,29] or ICTE[38]. In addition, a meticulous surgical technique is the key when trying to ease the postoperative recovery. Secondly, the choice of a surgical instrumentation, regardless of the extent of a surgery, may have an effect on the risk of postoperative haemorrhage. Cold instrumentation results in more primary haemorrhage, and the use of electrocautery results in more secondary haemorrhage[39,40].

Recurrent symptoms, quality of life, and tonsil remnants after tonsil surgery

Concerns have been raised regarding tonsillar remnants, which are always present after TT or ICTE and may, in theory, lead to persisting throat symptoms after operation[16]. With this prospect in mind, we aim to decrease tonsil volume as much as possible. A significant regrowth of tonsils in adults would be unexpected[20].

In a short-term follow-up of adult patients randomly assigned to undergo either ICTE or ECTE, both surgery methods result in a significant reduction of symptoms of recurrent or chronic tonsillitis, and the ICTE group needed less pain medication[18].

In this study, we will compare different surgical methods with an intention to reduce recovery time and postoperative complications. The presence of tonsil remnants both after the operation and at the 6-month follow-up will be documented. Throat symptoms, quality of life, and need for reoperation at 6, 24, and 60 months will also be recorded. These secondary endpoints are essential in determining the potential of ICTE in the treatment of adult patients with recurrent or chronic tonsillitis.

Direct and indirect costs to the public health care system

Tonsillitis and tonsil surgery place a substantial burden on health care resources[41]. The use of disposable instruments adds to the direct costs related to ICTE. On the other hand, differences between ICTE and ECTE related to the costs of instrumentation, operative time, use of analgesics, postoperative complications, reoperations, and loss of productivity may compensate for the expenses[42]. As part of this study, a cost-benefit analysis and a cost-effectiveness analysis will be conducted at 6-month and 5-year time points. We will consider both the direct and indirect costs related to ECTE and ICTE.

In summary, the FINITE trial is a prospective, randomised, three-arm clinical trial that compares extracapsular monopolar tonsillectomy with intracapsular microdebrider tonsillectomy and with intracapsular coblation tonsillectomy. The FINITE trial will provide new evidence to answer whether an intracapsular tonsillectomy provides a clinically significant reduction of recovery time after tonsil surgery in adults suffering from recurrent tonsillitis or chronic tonsillitis. Further, the different surgical methods will be evaluated in terms of primary and late complications, throat symptoms, tonsillar remnants, need for re-operation, quality of life, sick leave, and treatment costs.

AUTHORS' CONTRIBUTIONS

All of the following authors will contribute to multiple of the following aspects: Study design was done by: JP, TU, HS, LI, HJ, HK, EK, IM, JY, and JJ. Data collection will be performed by: JP, TU, HS, HJ, and JY. Statistical planning was done by: JP, TU, and TK. Statistical analysis will be done by: JP, TU, HS, JY, and TK. Operative procedures will be done by: TU and HS. Follow-up will be done by: JP, LI, EK, IM. JP was responsible for drafting this manuscript, which was refined by TU, HK, and HS. Critical review was performed by: LI, HJ, EK, TK, IM, JY, and JJ. All authors have read and approved the final manuscript. Supervision was and will be performed by: JP and JJ.

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COMPETING INTERESTS STATEMENT

The authors declare that they have no competing interests. TU has participated in a hands-on course for coblation by the manufacturer.

PATIENT AND PUBLIC INVOLVEMENT

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

PATIENT CONSENT FOR PUBLICATION

Not required.

ETHICS APPROVAL AND INFORMED CONSENT TO PARTICIPATE

The Medical Ethics Committee of the Hospital District of Southwest Finland, Turku has approved the protocol (reference number 29/1801/2019). The trial will be conducted in compliance with the principles of the Declaration of Helsinki. Prior to randomisation and surgery, all patients participating in the study will give a written informed consent.

PROVENANCE AND PEER REVIEW

Not commissioned; externally peer-reviewed.

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Figure 1. Study design and flow of participants.

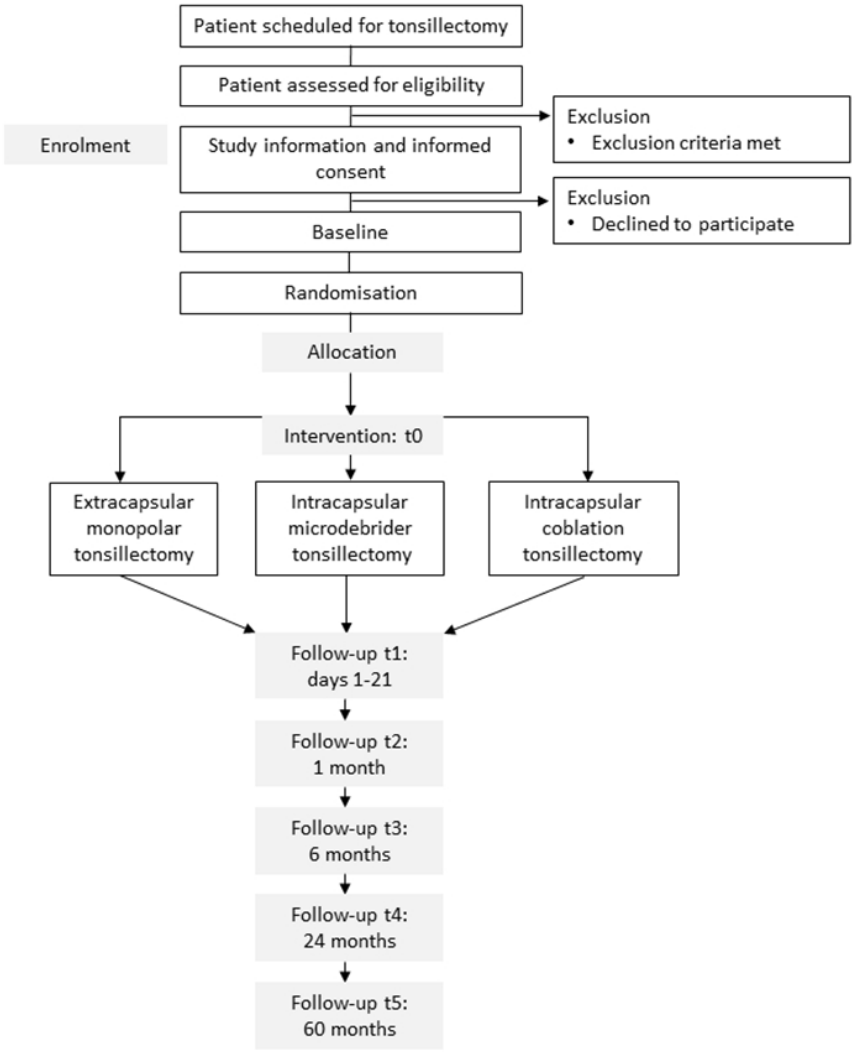

Figure 1. Study design and flow of participants.

67x82mm (300 x 300 DPI)

3

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	__1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	__3_____
	2b	All items from the World Health Organization Trial Registration Data Set	__3_____
Protocol version	3	Date and version identifier	__3_____
Funding	4	Sources and types of financial, material, and other support	__22_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	__1 and 22____
	5b	Name and contact information for the trial sponsor	__N/A_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	__N/A_____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	___N/A_____

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
	6b	Explanation for choice of comparators	19-21
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-11
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1 and table 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	___9_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	___7 and 9____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	___7_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	___8_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	___8_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	__9_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	___N/A_____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	___12-15_____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	___16_____

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	____16 -17____
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	___16____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	__N/A_____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	___16_____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	___N/A_____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	__17_____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	___17_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	___N/A_____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	____23_____
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	____N/A_____

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	__7_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	__N/A_____
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	__17_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	__22_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	___17_____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	___N/A_____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	___18_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	__22_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	__N/A_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	___N/A_____
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	___N/A_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Intracapsular tonsillectomy in the treatment of recurrent and chronic tonsillitis in adults: a protocol of a prospective, single-blinded, randomised study with a 5-year follow-up (the FINITE trial)

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Primary Subject Heading:	Ear, nose and throat/otolaryngology
Secondary Subject Heading:	Evidence based practice
Keywords:	Adult otolaryngology < OTOLARYNGOLOGY, Pain management < ANAESTHETICS, Paediatric otolaryngology < OTOLARYNGOLOGY

Intracapsular tonsillectomy in the treatment of recurrent and chronic tonsillitis in adults: a protocol of a prospective, single-blinded, randomised study with a 5-year follow-up (the FINITE trial)

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Word count: 295 (abstract), 4171 (without tables, statements and references)

ABSTRACT

Introduction

The standard surgical treatment for recurrent or chronic tonsillitis is extracapsular tonsillectomy. Recent studies show that intracapsular tonsillectomy has the potential to reduce the postoperative morbidity of patients undergoing tonsil surgery. The Finnish Intracapsular Tonsillectomy (FINITE) trial aims to provide Level I evidence to support the hypothesis that the recovery time from tonsil surgery can be reduced with intracapsular tonsillectomy. Additionally, from this trial, major benefits in quality of life, reduction of postoperative complications, treatment costs, and throat symptoms might be gained.

Methods and analysis

The FINITE trial is a prospective, randomised, controlled, patient-blinded, three-arm clinical trial. It is designed to compare three different surgical methods being extracapsular monopolar tonsillectomy versus intracapsular microdebrider tonsillectomy versus intracapsular coblation tonsillectomy in the treatment of adult patients (16–65 years) suffering from recurrent or chronic tonsillitis. The study started in September 2019, and patients will be enrolled until a maximum of 200 patients are randomised. Currently, we are in the middle of the study with 125 patients enrolled as of February 28, 2022 and data collection is scheduled to be completed totally by December 2027. The primary endpoint of the study will be the recovery time from surgery. Secondary endpoints will be the postoperative pain scores and the use of analgesics during the first three weeks of recovery, postoperative haemorrhage, quality of life, tonsillar remnants, need for revision surgery, throat symptoms, treatment costs, and sick leave. A follow-up by a questionnaire at 1–21 days and at 1, 6, 24, and 60 months will be conducted with a follow-up visit at the 6-month time point.

Ethics and dissemination

Ethical approval was obtained from the Medical Ethics Committee of the Hospital District of Southwest Finland (reference number 29/1801/2019). Results will be made publicly available in peer-reviewed scientific journals.

Trial registration number

ClinicalTrials.gov (NCT03654742). First posted 31 August 2018.

KEYWORDS

Tonsillectomy, intracapsular tonsillectomy, partial tonsillectomy, subtotal tonsillectomy, intracapsular dissection tonsillectomy, recurrent tonsillitis, chronic tonsillitis, coblation, microdebrider

ARTICLE SUMMARY

Strengths and limitations of this study

- This is a prospective, randomised, controlled, patient-blinded, three-arm clinical trial.
- Multiple standardised and validated questionnaires will be used during a 60-month follow-up period.
- Two surgeons will perform the surgeries with different levels of experience, and the follow-up evaluators will be blinded to the surgery method.
- Due to the sample size, the results will not likely show differences in post-tonsillectomy haemorrhage.
- The difference in postoperative pain between groups may be limited because we aim to decrease the tonsil volume as much as possible.

INTRODUCTION

Recurrent tonsillitis and chronic tonsillitis are the most common indications for tonsil surgery in adults[1]. Extracapsular tonsillectomy (ECTE) is the gold-standard operative procedure for recurrent tonsillitis and chronic tonsillitis. In the United States, 737,000 outpatient ECTEs are performed annually[2], and in Finland, 7,000–9,000 annually[3]. However, ECTE causes substantial postoperative pain during the first two weeks after surgery[4] and includes a risk for primary and secondary haemorrhage[5].

The operative management of recurrent tonsillitis and chronic tonsillitis remains controversial. For decades, it was thought that an extracapsular removal of the palatine tonsils is required for effective symptom alleviation in patients suffering from tonsillitis. To reduce morbidity after ECTE, various instrumentation is suggested to be used including CO_2-laser[6], coblation[7], surgical scissors, monopolar electrocautery, bipolar forceps, and other instruments[8,9]. Tonsillotomy (TT) is a procedure for the partial removal of tonsils where only the protruding tonsillar tissue medial to the faucial pillars, which is approximately 50 to 70% of the total tissue, is reduced[10]. Other studies have suggested removal of up to 90 to 95% of tonsillar tissue, and this procedure is referred to as a type 2 TT or subtotal or intracapsular tonsillectomy (ICTE)[11,12]. In both TT and ICTE, the aim is to remove tonsillar tissue without injuring the underlying pharyngeal muscles and without violating the tonsillar capsule.

Concerning children, both TT and ICTE result in a faster return to normal daily activity and a reduction in postoperative pain and haemorrhage requiring medical intervention[10,13,14]. Of course, these benefits need to be balanced against their clinical effectiveness[15]. In the paediatric population, both TT and ICTE have been established in the treatment of sleep breathing disorders[16,17]. Ericsson and Hultcrantz presented promising results after TT in

adolescent patients with both recurrent tonsillitis and symptoms related to tonsil hypertrophy[18].

In adults with tonsil-related symptoms, there are two systematic reviews that compare the postoperative morbidity and the effectiveness of ECTE to TT or ICTE ~~in adults with tonsil-related symptoms~~[19,20]. To the best of our knowledge, seven randomised controlled trials (RCTs) have compared the postoperative morbidity between ECTE and TT or ICTE in the treatment of tonsil-related afflictions[14,18,21–27]. Compared to ECTE, TT and ICTE result in reduction of postoperative complications and a reduced use of analgesics in adults suffering from symptoms related to tonsillar hypertrophy. Two RCTs used the inclusion criteria of solely adults with recurrent tonsillitis or chronic tonsillitis[21,22] and were focused on comparing the effectiveness of ECTE and ICTE.

The rationale of this proposal and the evidence gap that it may fill are that this Finnish Intracapsular Tonsillectomy (FINITE) trial will compare three different surgical methods in a prospective setting: ECTE (monopolar), ICTE (coblation), and ICTE (microdebrider) in the treatment of adult patients suffering from recurrent tonsillitis or chronic tonsillitis. The overall objective of the study is to fill existing gaps in knowledge about the effectiveness of different tonsillectomies and provide Level I evidence to support the hypothesis that the recovery time from tonsil surgery in adult patients with recurrent tonsillitis or chronic tonsillitis can be reduced with ICTE. Also, the complications, benefits, and costs will be assessed.

The primary endpoint will be the recovery time from surgery. Recovery from surgery will be defined as resolution of pain on a visual analogue scale (VAS 0–10) as pain <4 in rest and <6 on swallowing without regular use of analgesics. Secondary endpoints will be the postoperative pain scores and use of analgesics during the first three weeks of recovery, postoperative

haemorrhage, quality of life, tonsillar remnants, need for revision surgery, throat symptoms, treatment costs, and sick leave.

METHODS AND ANALYSIS

Trial design

The FINITE trial has been designed as a prospective, randomised, controlled, patient-blinded, three-arm clinical trial to compare extracapsular monopolar tonsillectomy versus intracapsular microdebrider tonsillectomy versus intracapsular coblation tonsillectomy in the treatment of recurrent tonsillitis and chronic tonsillitis in adults. The design of the trial is summarised in Figure 1 (see also Table 1 for an overview of the schedule). The trial is scheduled to be completed totally by December 2027.

Table 1. Study schedule.

Table 1 Study schedule							
	STUDY PERIOD						
	Enrolment	**Surgery**	**Postoperative course**				
TIME POINT	**-t1**	**t0: surgery**	**t1: days 1-21**	**t2: 1 month**	**t3: 6 months**	**t4: 24 months**	**t5: 60 months**
ENROLMENT:							
Eligibility	X						
Informed consent	X						
Randomisation	X						
Allocation	X						
INTERVENTIONS:							
Extracapsular monopolar tonsillectomy		X					

Intracapsular microdebrider tonsillectomy		X					
Intracapsular coblation tonsillectomy		X					
ASSESSMENTS:							
TOI-14	X				X	X	X
Perioperative data		X					
Brief Pain inventory			X				
NTSR 1-month				X			
NTSR 6, 24, and 60 months					X	X	X
GBI					X		
Clinical follow-up					X		
Sick leave					X	X	X
Case costs					X		X

NTSR, Nordic Tonsil Surgery Register; TOI-14, Tonsillectomy Outcome Inventory-14; GBI, Glasgow Benefit Inventory

Participants

Patients aged 16–65 years old and scheduled for tonsillectomy will be enrolled from the Turku University Hospital, Turku, Finland and Turunmaa Regional Hospital, Turku, Finland. The patient diagnosed with recurrent tonsillitis or chronic tonsillitis will be eligible for inclusion in the FINITE study. The study protocol will be described to eligible patients, and they will be invited to participate in the study. If they decide to participate, they will sign a written informed consent indicative of their approval. The inclusion of patients has been initiated in September 2019, and we have 125 enrolled as of early 2022.

Inclusion criteria

The inclusion criteria will be an age between 16 and 65 years and planned tonsil surgery due to clinical indication as a diagnosis of either: recurrent tonsillitis, which is defined as at least three acute occurrences of tonsillitis in the last 12 months, or chronic tonsillitis, which is defined as a prolonged tonsil-derived throat pain and at least one symptom or sign indicating that symptoms are tonsil-related (i.e., enlarged tonsils, tonsillar exudates, halitosis, tonsillar stones, enlarged and tender submandibular lymph nodes). In addition, these symptoms should affect the patient's daily activities and have lasted for at least three months. The diagnosis and treatment plans will be made by an otorhinolaryngologist. All included patients will give written informed consent.

Exclusion criteria

The exclusion criteria will be a peritonsillar abscess that occurred less than one month ago; an ongoing acute episode of tonsillitis; previous palatine tonsil surgery; a suspected tonsil malignancy; a high usage of anti-inflammatory analgesics, as defined by more than one defined daily dose during the previous four weeks, e.g., >1.2 g ibuprofen/day or >500 mg naproxen/day; severe obstructive sleep apnoea or ongoing continuous positive airway pressure (CPAP) therapy; reflux-derived pharyngalgia; anticoagulant medication; any condition of haemophilia, pregnancy, or lactation; and/or a current or positive history of a malignant disease with an ongoing active follow-up.

Registration procedure

With their written informed consent, all patients will be registered into a common electronic database (Research Electronic Data Capture, REDCap 10.6.9 ©2021 Vanderbilt University,

Nashville, TN, United States) at the University of Turku[28]. The patients' names, electronic mail address, phone number, date of birth, and sex will be registered along with clinical information and baseline severity of symptoms.

Randomisation

Patients will be randomised with SAS (SAS Institute Inc., Cary, NC, United States) into permuted blocks of six patients. The randomisation will be performed in a 1:1:1 equal allocation ratio on the morning of or the day before surgery by the surgeon in the randomisation module of REDCap either to undergo extracapsular monopolar tonsillectomy, intracapsular microdebrider tonsillectomy, or intracapsular coblation tonsillectomy.

Blinding

The patients will remain unaware of their method of surgery until the 5-year follow-up is completed. The method of tonsil surgery will not be revealed in the hospital records. The clinical outcome at the 6-month follow-up visit will be evaluated by an otorhinolaryngologist (JP, LI, IM, EK, HS, TU), who will be blinded to the surgery method. The patients will be scheduled to visit another otorhinolaryngologist than the surgeon who performed the operation. The data analysis will be performed by an experienced statistician (TK) to ensure the blinding of the principal investigator.

Sample size calculation

Based on earlier study results, the average recovery time for ECTE is 12 days (SD = 3)[4]. If the recovery time for ICTE is three days shorter, we consider it as a clinically significant difference. In such a case, the effect size for a t-test is (12-9)/3 = 1. We aim to compare ICTE, in two groups, to ECTE. The level of significance is 5%, the Bonferroni correction is 2.5%,

and the desired power is 90%. When expecting a total of 20% dropouts, the sample size is 27 patients per group. However, if the SD is 4, the sample size is 55. We intend to use a sample size of 55 patients per group and a maximum of 200 patients will be enrolled. The main analyses will be based on the intention-to-treat principle, but both intention-to-treat and per-protocol analyses will be performed.

Interventions

All surgeries will be performed by one of the two surgeons (TU, HS), who both have experience in otorhinolaryngology with performing greater than 100 monopolar electrocautery tonsillectomies and tonsillotomies. Prior to starting, each study centre will establish a uniform operative technique. We consider the learning curve of ICTE to be 10 procedures for a surgeon who has a routine skill level in TT and ECTE[29]. The surgeons will perform their duties at a 70:30 ratio.

The surgical field in all techniques will be prepared with a tonsillectomy mouth gag. A pharyngeal round gaze sponge in saline solution will be used to prevent potential haemorrhage into the trachea. Velotraction with a suction catheter will be established for controlling the soft palate and especially the uvula. Intratonsillar injection of 1–2 millilitres of lidocaine-adrenaline will be administered for local haemostasis. The base of tongue will be left intact. Haemostasis is primarily achieved with compression with round gaze sponges soaked in lidocaine-adrenaline. When needed, small vessels will be coagulated. More profound vessels are, rarely, ligated to reduce the thermal effect to the operative area. After haemostasis, the surgical field will be photographed with a smart phone for later reference, and the tonsil remnants will be noted.

Extracapsular monopolar tonsillectomy (Control group)

A monopolar diathermy unit with 15-Watts power and spray settings will be used with a pen electrode and a blunt-needle tip. The tonsil will be grasped and pulled medially with forceps. Tonsillectomy will be performed by dissection in the peritonsillar plane. Parts of the upper and lateral palatal mucosal arches will be incised, and an extracapsular dissection for complete tonsil excision will be performed.

Intracapsular microdebrider tonsillectomy

The recommended settings of 1500 rounds-per-minute for a microdebrider ("Straightshot M4 handpiece," "12 degrees curved Tonsil blade," and "Integrated Power Console," Medtronic Ltd., Minneapolis, MN, United States) are used. Approximately 95% of the tonsillar tissue will be removed from an inferior to superior and from a posterior to anterior direction. The tonsil capsule will not be breached.

Intracapsular coblation tonsillectomy

Approximately 95% of the tonsillar tissue will be removed with a coblation wand ("Procise EZ" or "Evac 70 extra" Coblator II base unit, Smith & Nephew plc, Watford, United Kingdom). Power settings will be set to default and may be adjusted if needed. The tonsil capsule will not be breached.

Patient and public involvement

Patients will fill a semi-structured questionnaire one month after tonsil surgery regarding how their expectations were met. Their experience about the preoperative information will be analysed to detect any potential for improvement.

OUTCOME PARAMETERS

The primary endpoint

The primary endpoint of this trial is postoperative recovery time, which is defined as VAS pain, from 0–10 with <4 at rest and <6 on swallowing without regular use of analgesics. The regular use of analgesics is defined as a daily intake of 2 tablets of naproxen 500 mg and 3 or more tablets of tramadol-paracetamol 37.5/325 mg.

For the primary study endpoint, the duration of the postoperative recovery will be dependent on three endpoints: pain at rest, pain on swallowing, and the regular use of analgesics. The patients will be advised for a daily use of analgesics for the first postoperative week to ensure analgesia use in all treatment arms[30]. The primary endpoint data will be collected within the 1–21-day time frame.

Secondary endpoints

The secondary endpoints will be the postoperative pain scores (VAS 0–10) and postoperative use of analgesics at 1–21 days, early and late postoperative haemorrhage requiring a medical intervention at 1 month, detection of tonsil remnants at 6 months, life quality assessment at 6, 24, and 60 months, need for revision surgery at 6, 24, and 60 months, throat symptoms at 6, 24, and 60 months, sick leave needed at 6, 24, and 60 months, and treatment costs at 6 and 60 months.

Data collection

The trial consists of an intervention treatment, through tonsil surgery, with a 60-month follow-up. As shown in Table 1, data will be collected before the surgery, perioperatively, 1–21 days after surgery, and 1, 6, 24, and 60 months after surgery. Data collection from all patients participating in the trial will include the baseline severity of symptoms, perioperative data, and follow-up data. The perioperative data will be recorded using a report form (Table 2).

Table 2. Template for data collection during hospitalisation (FINITE trial).

Preoperative		**Intervention**		**Postoperative**
Medical history of gastroesophageal reflux disease, smoking, peritonsillar abscess		Technique and quantity used for haemostasis		Postoperative haemorrhage before release from ward (yes, no)
Number of courses of antibiotics for tonsillitis within 12 months		Problems related to haemostasis (yes, no)		Question used to ensure successful blinding of staff and patient: Was the surgical method used TE or ICTE?
Number of acute episodes of tonsillitis within 12 months		Blood loss, estimated (millilitres)		
Planned for day surgery or overnight stay		Time from insertion to removal of mouth gag including velotraction, intratonsillar infiltration, surgery, haemostasis, and		

		photography of surgical area (minutes)		
Photograph of tonsils and tonsil grading using Brodsky Scale 1-4		Subjective estimated amount of residual tonsil tissue (0–100%)		
Indication for surgery (recurrent or chronic tonsillitis)		Subjective perceived difficulty level of operation (0–100%)		
Planned with adenoidectomy or not		Subjective perceived pleasantness of operation (0–100%)		
Number of sick leave days due to throat symptoms during previous 12 months				

Follow-up

Assessment of postoperative recovery, pain, and complications

Patients will use the Brief Pain Inventory (BPI) questionnaire in REDCap to record postoperative pain VAS scores, use of analgesics, nightly awakenings due to pain, and return to normal daily activities 1–21 days after tonsil surgery. The Finnish version of the form has been adapted from an earlier study[4]. One month after surgery, patients will fill out the Nordic Tonsil Surgery Register, 1-month questionnaire (NTSR 1-month) to report the following outcomes: occurrence of postoperative haemorrhage, the occurrence of an infection within 1 month, the need for a course of antibiotics, whether the patient contacted the health care system

due to pain, in how many days after the surgery did the pain disappear, and in how many days after surgery did the patient resume his/her normal diet[31].

Assessment of tonsil remnants, quality of life, and patient satisfaction

Patients will record data preoperatively and 6, 24, and 60 months after tonsil surgery with the Tonsillectomy Outcome Inventory-14 (TOI-14) questionnaire, a disease-specific, quality-of-life instrument for throat-related symptoms. The total score can range between 0 (no problems) and 100 (most severe problems) and in patients with recurrent or chronic tonsillitis, a score of about 20.0 indicates mild symptoms, 30.0 indicates moderate symptoms, and 40.0 or higher intense symptoms. The minimum significant change is 10.0 points. In a healthy population, the score is, in most cases, under 15.0, which is, in this study, used as a threshold score for significant efficacy (i.e. when a patient is cured). The questionnaire has been validated into the Finnish language[32]. The Glasgow Benefit Inventory (GBI) is widely used in otorhinolaryngology to measure the change in quality of life associated with a surgical or pharmaceutical intervention. The individual responses are scored and added together to obtain a total score from -100 (worst outcome) to 0 (no change) to +100 (best outcome). A Finnish version of the questionnaire has been validated[33]. Patients will fill the GBI questionnaire 6 months after surgery. The Nordic Tonsil Surgery Register questionnaire (NTSR 6, 24, and 60 months) collects data on whether the symptoms have alleviated after surgery and also whether the patient has experienced other symptoms[31]. In addition, patients will report the number of days on sick leave due to throat symptoms.

A clinical follow-up visit at 6 months after tonsil surgery will be performed by an otorhinolaryngologist (JP, LI, IM, EK, HS, TU). Data will be collected with a standardised report form (Table 3).

Table 3. Structured reporting template for the 6-month follow-up visit (FINITE trial)

Photograph of surgical area	Yes or no
Tonsil remnants present?	Yes or no
Tonsillitis symptoms during last 6 months? If yes, how many times?	Yes or no
Specific symptoms present? Change in taste Sensations of strictures or something extra in throat Symptoms of velopharyngeal insufficiency Painful swallowing (if yes; average on scale 0–10, 0=no pain, 10=most pain)	 Yes or no Yes or no Yes or no Yes or no
Has the patient contacted health care due to throat symptoms? If yes, how many times?	Yes or no
Question used to ensure successful blinding of the patient. The surgical method used was:	 TE or ICTE
Question used to ensure successful blinding of the otorhinolaryngologist. The surgical method used was:	TE or ICTE (microdebrider) or ICTE (coblation)

Statistical analysis plan

The principal investigator (JP) will collect the study data, and it will be analysed by an experienced biostatistician (TK). All efficacy and safety variables and primary and secondary outcome variables will be listed and tabulated by time points and summarised using descriptive statistics. Both the absolute measured values and the change from baseline will be recorded.

Reasons for discontinuations will be tabulated in detail. Analyses of outcome variables will be performed using generalised linear models. Model fit is evaluated by examining residuals. All results will be presented with 95% confidence intervals and P-values. In a separate Statistical Analysis Plan (SAP), a more detailed view of the statistical analysis setup and its variables are presented. All analyses, tabulations, listings, and figures will be conducted using R version 4.0.3 or later (R Core Team).

Cost-benefit analysis and cost-effectiveness analysis

All tonsil surgery related direct medical costs will be estimated based on the actual input terms of resource use and personnel. Data of the costs will be provided by Auria Clinical Informatics from the information system of the Hospital District of Southwest Finland or determined in cooperation with the hospital administration. Operation time will be recorded in the case report forms. Indirect costs will arise from losses in productivity. These will be assessed by the BPI, in which the patient records when they consider themselves able to resume their normal daily activities, such as their work or studies after tonsil surgery. During the long-term follow-up, the patient will report at time points of 6, 24, and 60 months the number of sick leave days due to persistent throat symptoms.

A cost-effectiveness analysis will be performed to compare the relative costs and outcomes between ECTE and ICTE, in terms of reduced symptoms measured with TOI-14 and benefit in quality of life measured with GBI.

Safety monitoring

Adverse events are defined as any undesirable experience occurring to a subject during a clinical trial whether or not these events are considered related to the investigational

intervention. All adverse events reported by the patient, observed by the investigator, or the staff will be recorded. An interim analysis to ensure the safety of the ICTE will be performed after randomising 50–60 patients. We expect a 1% reoperation rate in all treatment groups.

Data collection and confidentiality

The researchers have created an online database where all patients evaluated for the study enrolment will be recorded after a written informed consent is obtained. REDCap is used as the online platform. All data will be handled confidentially, and the information in the datasets is non-identifiable. Data are gathered during hospitalisation, from clinical observations of the follow-up examination, and from questionnaires filled in by the study patients. The information recorded from the non-participating patients will be used as data for a register-based study. The principal investigator (JP) will be in charge of the common database with full access to the data. The access to the data is otherwise strictly limited. The online database will not be used for other purposes during the trial, and all of the visits to the database will be recorded in the database log. In order to prevent selection bias, we designed the study protocol to record data on all patients evaluated for eligibility.

Withdrawal

During the enrolment, patients will be informed of their right to withdraw from the study without explanation at any time.

Ethics and dissemination plan

The present protocol and applied informed consent forms were approved by the Medical Ethics Committee of the Hospital District of Southwest Finland. The trial will be conducted with the

principles enunciated in the Declaration of Helsinki. Prior to randomisation and surgery, all patients participating in the study will give a written informed consent.

The results of this trial will be disseminated by publication in international peer-reviewed scientific journals and by presentations at international and domestic conferences.

DISCUSSION

The hypothesis of the FINITE trial is that adult patients with recurrent or chronic tonsillitis can be treated effectively with ICTE with a faster recovery time and less morbidity compared to ECTE. This hypothesis is supported by previous randomised studies[14,21,22,25,27]. Recurrent and chronic tonsillitis affects quality of life[34]. In adults, ECTE reduces episodes of tonsillitis and sore throat compared to conservative treatment[33]. The quality of life, 6 months after ECTE, is improved in adult patients with recurrent tonsillitis[35]. However, the benefits must be balanced against the risks of the surgery, notably post-intervention haemorrhage and a painful recovery.

If this study can demonstrate the faster recovery time of ICTE, the need for any prolonged absence from work, studies, or other activities would substantially decrease.

Choice of the primary outcome

The definition of recovery time can vary. In addition to measuring pain, tools to assess interference of pain with functional recovery should be utilized[36]. We defined the duration of the postoperative recovery to be dependent on three endpoints: pain at rest, pain on swallowing, and the regular use of analgesics.

The recovery after ECTE, lasting an average of 12 to 14 days, is associated with moderate to severe pain, even with adequate pain medication[4,37,38]. Tonsillectomy leaves an open wound in the pharynx, which heals *per secundam.* Most patients have significant pain, at rest with a VAS score >3 and during swallowing with a VAS score >5, during the first 6 mornings postoperatively even with analgesics. Without medication, most patients are willing to accept a pain level 3 at rest and 4 for dynamic pain[39]. Here, the threshold levels for recovery, being a VAS score <4 at rest and <6 on swallowing without the regular use of analgesics, are based on these earlier findings.

After TT, in the age group of 16–25 year olds, patients were able to return to their normal activity 4 days earlier compared to ECTE[18]. In three RCTs, adult patients were operated with ECTE on one tonsil and ICTE with coblation on the other tonsil[22,26,27]. Patients, after a 14-day follow-up, preferred the side that was performed with ICTE[22,26].

Wilson et al. compared ECTE with electrocautery versus ICTE with coblation or a microdebrider[14]. Patients (n = 156, age = 0.5–22 years old) with obstruction were randomly assigned to three treatment groups. The return to normal nutrition and normal daily activity after ICTE was on average 2 days faster when compared to ECTE. This trial presented here is original and will help determine whether results of earlier studies can be applied to adult tonsillitis patients.

Based on the available information, most of the patients seem to recover within the first 21 postoperative days, and it is therefore reasonable to use this timeframe for the primary endpoint evaluation.

Choice of the surgical instrumentation

In ECTE, there are no clinically relevant differences between different surgical instruments in terms of recovery time and pain scores[37,40]. Postoperative pain may be slightly reduced by using cold instrumentation, such as with cold steel dissection, and by minimising thermal energy conducted to the wound bed when using electrocautery for dissection and/or coagulating small vessels.

In clinical practice, the advantages of the reduced operation time and the ease of achieving intraoperative haemostasis have led many surgeons to use electrocautery. In this study, we wanted to include the most common instruments for ECTE and ICTE in the United States[41]. Thus, ECTE is performed with monopolar dissection and ICTE with either a microdebrider or a coblation wand.

Complications after tonsil surgery

Approximately 5 to 15 percent of patients need a medical intervention for postoperative complications after ECTE, which notably include pain, haemorrhage, dehydration, and poor nutrition[5]. The choice of the surgical method is an important factor regarding complications. The complication risk is known to be lower after TT[11,31] or ICTE[42]. In addition, a meticulous surgical technique is the key when trying to ease the postoperative recovery. Secondly, the choice of a surgical instrumentation, regardless of the extent of a surgery, may have an effect on the risk of postoperative haemorrhage. Cold instrumentation results in more primary haemorrhage, and the use of electrocautery results in more secondary haemorrhage[43,44].

Recurrent symptoms, quality of life, and tonsil remnants after tonsil surgery

Concerns have been raised regarding tonsillar remnants, which are always present after TT or ICTE and may, in theory, lead to persisting throat symptoms after operation[19]. With this prospect in mind, we aim to decrease tonsil volume as much as possible. A significant regrowth of tonsils in adults would be unexpected[23].

In a short-term follow-up of adult patients randomly assigned to undergo either ICTE or ECTE, both surgery methods result in a significant reduction of symptoms of recurrent or chronic tonsillitis, and the ICTE group needed less pain medication[21].

In this study, we will compare different surgical methods with an intention to reduce recovery time and postoperative complications. The presence of tonsil remnants (yes/no) both after the operation by the surgeon and at the 6-month follow-up by an otorhinolaryngologist will be documented. Throat symptoms, quality of life, and need for reoperation at 6, 24, and 60 months will also be recorded. These secondary endpoints are essential in determining the potential of ICTE in the treatment of adult patients with recurrent or chronic tonsillitis.

Direct and indirect costs to the public health care system

Tonsillitis and tonsil surgery place a substantial burden on health care resources[45]. The use of disposable instruments adds to the direct costs related to ICTE. On the other hand, differences between ICTE and ECTE related to the costs of instrumentation, operative time, use of analgesics, postoperative complications, reoperations, and loss of productivity may compensate for the expenses[46]. As part of this study, a cost-benefit analysis and a cost-effectiveness analysis will be conducted at 6-month and 5-year time points. We will consider both the direct and indirect costs related to ECTE and ICTE.

In summary, the FINITE trial is a prospective, randomised, three-arm clinical trial that compares extracapsular monopolar tonsillectomy with intracapsular microdebrider tonsillectomy and with intracapsular coblation tonsillectomy. The FINITE trial will provide new evidence to answer whether an intracapsular tonsillectomy provides a clinically significant reduction of recovery time after tonsil surgery in adults suffering from recurrent tonsillitis or chronic tonsillitis. Further, the different surgical methods will be evaluated in terms of primary and late complications, throat symptoms, tonsillar remnants, need for re-operation, quality of life, sick leave, and treatment costs.

AUTHORS' CONTRIBUTIONS

All of the following authors will contribute to multiple of the following aspects: Study design was done by: JP, TU, HS, LI, HJ, HK, EK, IM, JY, and JJ. Data collection will be performed by: JP, TU, HS, HJ, and JY. Statistical planning was done by: JP, TU, and TK. Statistical analysis will be done by: JP, TU, HS, JY, and TK. Operative procedures will be done by: TU and HS. Follow-up will be done by: JP, LI, EK, IM. JP was responsible for drafting this manuscript, which was refined by TU, HK, and HS. Critical review was performed by: LI, HJ, EK, TK, IM, JY, and JJ. All authors have read and approved the final manuscript. Supervision was and will be performed by: JP and JJ.

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Duodecim Association (N/A). The funding bodies played no role in the design and conduct of the study.

COMPETING INTERESTS STATEMENT

The authors declare that they have no competing interests. TU has participated in a hands-on course for coblation by the manufacturer.

PATIENT CONSENT FOR PUBLICATION

Not required.

ETHICS APPROVAL

The Medical Ethics Committee of the Hospital District of Southwest Finland, Turku has approved the protocol (reference number 29/1801/2019).

PROVENANCE AND PEER REVIEW

Not commissioned; externally peer-reviewed.

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Figure 1. Study design and flow of participants.

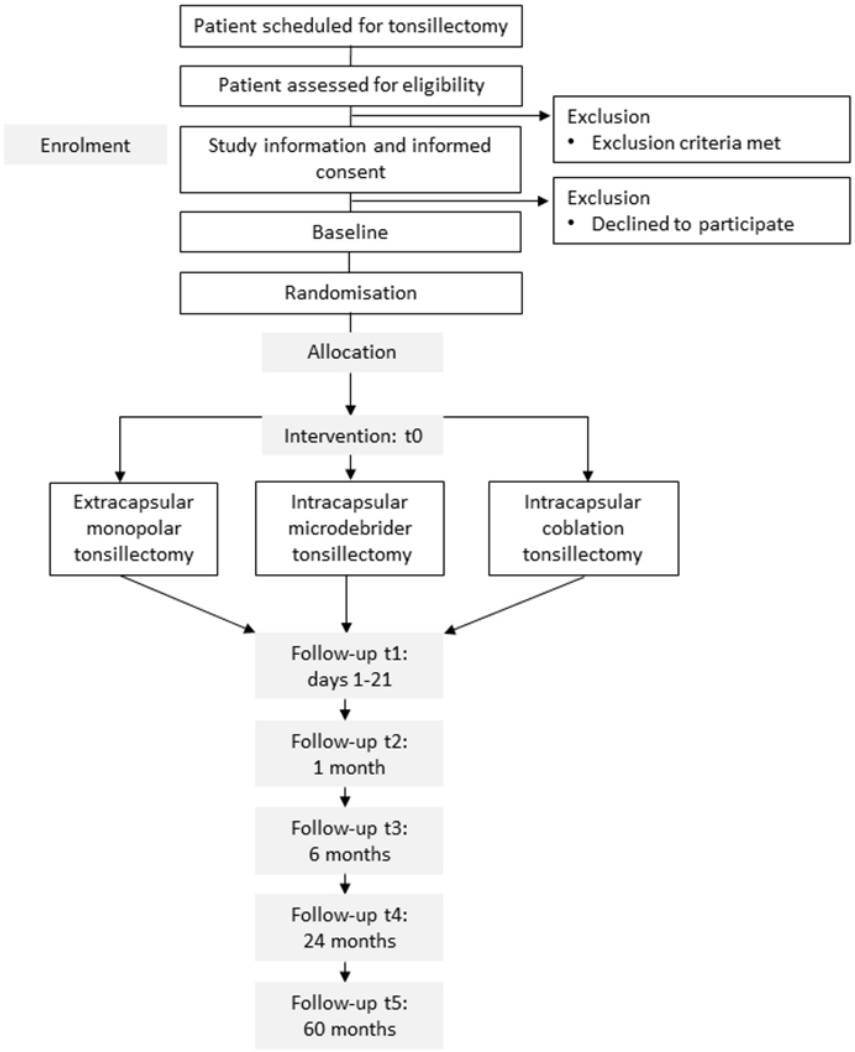

Figure 1. Study design and flow of participants.

67x82mm (300 x 300 DPI)

3

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	__1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	__3_____
	2b	All items from the World Health Organization Trial Registration Data Set	__3_____
Protocol version	3	Date and version identifier	__3_____
Funding	4	Sources and types of financial, material, and other support	__22_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	__1 and 22____
	5b	Name and contact information for the trial sponsor	__N/A_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	__N/A_____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	___N/A_____

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
	6b	Explanation for choice of comparators	19-21
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-11
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N/A
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1 and table 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	___9_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	___7 and 9____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	___7_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	___8_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	___8_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	__9_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	___N/A_____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	___12-15_____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	___16_____

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	____16 -17____
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	___16____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	__N/A_____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	___16_____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	___N/A_____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	__17_____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	___17_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	___N/A_____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	____23_____
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	____N/A_____

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	__7_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	__N/A_____
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	__17_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	__22_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	___17_____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	___N/A_____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	___18_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	__22_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	__N/A_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	___OK_____
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	___N/A_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.