The clinical effectiveness of clarithromycin versus endoscopic sinus surgery for adults with chronic rhinosinusitis with and without nasal polyps (MACRO): a pragmatic, multicentre, three-arm, randomised, placebo-controlled phase 4 trial

Carl Philpott, David J Beard, Elnaz Saeedi, Jonathan A Cook, Stephen Jones, Caroline S Clarke, Lucinda Teoh, Mike Thomas, Paul Little, Jane Vennik, Valerie Lund, Anne G M Schilder, Fei Long, Stephen Durham, James Boardman, Claire Hopkins, on behalf of the MACRO Collaborative and MACRO Programme Team*

Lancet 2025; 406: 926–39

See **Comment** page 887

*Additional members of the MACRO Collaborative are listed at the end of the Article

Norwich Medical School, University of East Anglia, Norwich, UK (Prof C Philpott MD); **James Paget University Hospital, Norfolk & Waveney ENT Service, Norfolk, UK** (Prof C Philpott); **Surgical Intervention Trials Unit** (Prof D J Beard DPhil, S Jones BA Hons) **and Oxford Clinical Trials Research Unit** (E Saeedi MSc, Prof J A Cook PhD), **University of Oxford, Oxford, UK; NHMRC CTC, University of Sydney, Camperdown, NSW, Australia** (Prof D J Beard); **Research Department of Primary Care and Population Health** (C S Clarke PhD, L Teoh PhD) **and Ear Institute** (Prof Dame V Lund MS, Prof A G M Schilder PhD, F Long MSc), **University College London, London, UK; University of Southampton, Southampton, UK** (Prof M Thomas PhD, Prof P Little FRCGP, J Vennik PhD); **Faculty of Medicine, National Heart and Lung Institute, Imperial College London, London, UK** (Prof S Durham MD); **SmellTaste, Bicester, UK** (J Boardman BSc); **ENT Department, Guy's and St Thomas' NHS Foundation Trust, London, UK** (Prof C Hopkins DM)

Correspondence to: Prof Carl Philpott, Norwich Medical School, University of East Anglia, Norwich NR4 7TJ, UK
C.Philpott@uea.ac.uk

Summary

Background A paucity of evidence regarding use of endoscopic sinus surgery and antibiotics in managing chronic rhinosinusitis has contributed to a five-times variation in endoscopic sinus surgery rates, as well as variation in the use of antibiotics. The main aim of the present trial was to compare the clinical effectiveness of endoscopic sinus surgery or 3 months of clarithromycin treatment alongside intranasal medication in adults with chronic rhinosinusitis with or without nasal polyps.

Methods In this pragmatic, three-arm, randomised, placebo-controlled phase 4 trial, participants were recruited from 20 secondary and tertiary care sites in the UK. Adults (aged ≥18 years) with chronic rhinosinusitis remaining symptomatic following appropriate medical therapy (intranasal corticosteroids, saline nasal irrigations, and a short course of antibiotics) were randomly assigned (1:1:1) to receive endoscopic sinus surgery (within 6 weeks of randomisation if waiting lists allowed) plus intranasal medication, clarithromycin (250 mg twice a day for 2 weeks then 250 mg once a day for 10 weeks) plus intranasal medication, or placebo plus intranasal medication. Intranasal medication comprised intranasal corticosteroids and saline irrigations. Participants were allocated with an automated, web-based secure randomisation system in permuted blocks of varying size (block sizes of three and six), stratified by the presence of polyps and trial site. Participants and site teams were masked to the clarithromycin and placebo allocations, including for outcome assessment. The primary outcome measure was the total score on the 22-item Sino-Nasal Outcome Test (SNOT-22) quality-of-life questionnaire at 6 months after randomisation, with analysis by intention to treat (ITT; available-case basis). Adverse reactions were assessed in the safety population (clarithromycin and placebo), and serious adverse events in the ITT population (all groups). The trial was registered on the ISRCTN registry, ISRCTN36962030, and EudraCT, 2018-001100-11, and is complete, with optional long-term follow-up ongoing.

Findings Between Nov 1, 2018, and Oct 13, 2023, 514 participants (181 [35%] female and 333 [65%] male), with chronic rhinosinusitis with nasal polyps (n=410) or chronic rhinosinusitis without nasal polyps (n=104), were recruited and randomly assigned to receive endoscopic sinus surgery (n=171), clarithromycin (n=172), or placebo (n=171), all with intranasal medication. SNOT-22 scores at 6 months after randomisation were significantly lower (at the 98·33% confidence level after Bonferroni adjustment) in the endoscopic sinus surgery group than in the clarithromycin group (adjusted mean difference –18·13 [98·33% CI –24·26 to –11·99], p<0·0001) and placebo group (–20·44 [–26·42 to –14·46], p<0·0001). 6-month SNOT-22 scores did not differ significantly between participants randomly assigned to clarithromycin versus placebo (–3·11 [–8·56 to 2·33], p=0·17). Ten serious adverse events occurred in nine participants (two events in two [1%] of 172 participants allocated to clarithromycin, three events in three [2%] of 171 allocated to placebo, and five events in four [2%] of 171 allocated to endoscopic sinus surgery), none of which were fatal.

Interpretation The MACRO trial shows that endoscopic sinus surgery has clinical effectiveness in patients with chronic rhinosinusitis, providing significantly improved disease-specific quality of life at 6 months. Conversely, the trial findings do not support routine long-term use of low-dose clarithromycin. Endoscopic sinus surgery should be recommended if intranasal medication alone is unable to achieve symptom control.

Funding National Institute for Health and Care Research Programme Grants for Applied Research.

Research in context

Evidence before this study

Our previous Cochrane systematic reviews on chronic rhinosinusitis treatments found good evidence of efficacy of topical intranasal corticosteroids and nasal saline irrigations, but a paucity of evidence on the efficacy for longer-term macrolide antibiotics and endoscopic sinus surgery. In one of our reviews on systemic and topical antibiotics for chronic rhinosinusitis (*Cochrane Database Syst Rev* 2016; **4:** CD011994), the following was concluded: "We found very little evidence that systemic antibiotics are effective in patients with chronic rhinosinusitis. We did find moderate quality evidence of a modest improvement in disease-specific quality of life in adults with chronic rhinosinusitis without polyps receiving 3 months of a macrolide antibiotic. The size of improvement was moderate (0·5 points on a 5-point scale) and only seen at the end of the 3-month treatment; by 3 months later no difference was found. Despite a general understanding that antibiotics can be associated with adverse effects, including gastrointestinal disturbances, the results in this review were very uncertain because the studies were small and few events were reported." In another review on surgical versus medical interventions for chronic rhinosinusitis with nasal polyps (*Cochrane Database Syst Rev* 2014; **12:** CD006991), the following was concluded: "The evidence relating to the effectiveness of different types of surgery versus medical treatment for adults with chronic rhinosinusitis with nasal polyps is of very low quality. The evidence does not show that one treatment is better than another in terms of patient-reported symptom scores and quality-of-life measurements. The one positive finding from amongst the several studies examining a number of different comparisons must be treated with appropriate caution, in particular when the clinical significance of the measure is uncertain. As the overall evidence is of very low quality (serious methodological limitations, reporting bias, indirectness and imprecision) and insufficient to draw firm conclusions, further research to investigate this problem, which has significant implications for quality of life and health-care service usage, is justified." No additional literature search was performed as these reviews were relevant at the time of commencing the present trial; however, any new published studies since that time have been commented on in the Discussion section of this Article.

Added value of this study

This study shows the clinical effectiveness of endoscopic sinus surgery at 6 months after treatment allocation in reducing relevant symptoms, when compared with low-dose long-term (3-month) clarithromycin and topical nasal medication. The results do not support the use of macrolide antibiotics in an unselected group of patients with chronic rhinosinusitis. There was a large effect size of endoscopic sinus surgery, with 148 (97%) of 153 participants with available data in the endoscopic sinus surgery group having a minimum clinically important difference in disease-specific quality of life at 6 months.

Implications of all the available evidence

General practitioners and ear, nose, and throat specialists should be aware of the implications of the present findings for patients with chronic rhinosinusitis who they see and treat. Patients could be advised of the high potential to benefit from endoscopic sinus surgery in terms of symptom relief when being counselled about how to manage their chronic rhinosinusitis. Streamlining of clinical pathways will help to reduce unnecessary visits and consultations and save on health-care resources.

Introduction

Chronic rhinosinusitis represents a common source of ill health, with a pooled prevalence of approximately 9% among adults during 1980–2021, based on a global meta-analysis.[1] Symptoms, including nasal obstruction, nasal discharge, facial pain, anosmia, and sleep disturbance, have a major effect on quality of life, with this negative effect reportedly being greater in several domains of the Short Form-36 Health Survey than for angina or chronic respiratory disease.[2,3] Acute exacerbations, uncontrolled symptoms, and respiratory disease exacerbation are common. At least one in three patients with chronic rhinosinusitis attending ear, nose, and throat (ENT) clinics are considered to have had an inadequate response to appropriate medical therapy with intranasal corticosteroids, short courses of antibiotics, and saline rinses, and are therefore considered for endoscopic sinus surgery.[4–7] Longer-term antibiotic use remains controversial due to conflicting evidence from two previous randomised controlled trials (RCTs), with calls for further trials.[8,9] In 2023 in England, secondary care electronic health records from the National Consultant Information Programme portal showed that approximately 12 090 sinus operations were performed,[10] in addition to an estimated 120 000 outpatient consultations;[11] in the USA, more than 250 000 endoscopic sinus surgeries are performed annually.[12] Insufficient evidence to define the role of surgery contributes to a five-times variation in surgical intervention rates across England.[13] The *European Position Paper on Rhinosinusitis and Nasal Polyps 2020* published treatment and research guidance, emphasising when limited evidence restricts care and highlighting the paucity of RCTs on rhinosinusitis treatments.[14] A previous systematic review of endoscopic sinus surgery identified the need for high-quality studies comparing surgery with medical treatment.[15] Two 2014 Cochrane systematic reviews of medical and surgical management also concluded that further studies were urgently needed.[16,17]

The MACRO trial sought to address this evidence gap, with a primary objective to establish the comparative clinical effectiveness of endoscopic sinus surgery or a prolonged course of antibiotics (clarithromycin) alongside standard medical care (intranasal medication) in adult patients with chronic rhinosinusitis, in terms of participant-reported symptomatic improvement at 6 months after being assigned treatment. Secondary objectives of the trial were to measure clinical effectiveness using additional subjective self-report ratings as well as objective clinical measures; compare clinical effectiveness according to chronic rhinosinusitis phenotype (ie, with and without nasal polyps); record the incidence and details of adverse events in all treatment groups; embed a mixed-methods process evaluation into the main trial to identify factors and processes necessary for implementation of trial findings; and obtain informed consent for participants to be followed up over a longer period (5 years).

Methods

Study design

The MACRO trial was a pragmatic, three-arm, parallel group, randomised, placebo-controlled phase 4 trial conducted at secondary and tertiary care centres in the UK, each with a dedicated consultant rhinologist as the local principal investigator. 21 sites were open for recruitment with 20 centres recruiting participants; the trial sites are listed in the appendix (p 5). The end of the main trial was 6 months from randomisation (reported herein), with optional long-term follow-up for up to 5 years. A flowchart of the trial design is provided in the protocol (appendix) and has been published.[18] A 6-month internal recruitment pilot phase involving six sites that included an embedded qualitative study (the MACRO conversation study[19]) was done as part of the pilot phase to identify and address recruitment challenges. A nested qualitative process evaluation involving semi-structed interviews with a purposeful sample of patients and trial clinicians was also conducted, with an aim to identify barriers and facilitators to the implementation of trial findings. The results of this nested evaluation will be reported elsewhere. The trial was managed by the Surgical Intervention Trials Unit team at the University of Oxford (Oxford, UK) with trial management meetings once every 2 weeks involving the joint chief investigators (CP and CH) and co-opted members of the MACRO Programme Management Group. Independent oversight was provided by the Programme steering committee that included a Chair, four methodologists, and two lay representatives. An independent data monitoring committee met before each steering committee meeting and included academic ENT surgeons and methodologists not involved in the trial; the Oxford Surgical Intervention Trials Unit team were also called into data monitoring committee meetings.

See Online for appendix

Ethical approval was granted by the North East—Newcastle and North Tyneside 2 Research Ethics Committee (reference 18/NE/0210). The trial protocol has been published[18] and protocol version dated Sept 1, 2023, is provided in the appendix. The trial was registered on the ISRCTN registry, ISRCTN36962030 (registered on Oct 17, 2018) and EudraCT, 2018-001100-11 (registered on June 8, 2018), and is complete, with optional long-term follow-up ongoing (ending in October, 2028). Changes to the protocol after trial commencement are summarised in the appendix (p 3). This Article has been written in accordance with the CONSORT 2010 guidelines for RCTs.

Participants

Eligible patients were adults (aged ≥18 years) with chronic rhinosinusitis, in whom symptom control had not been achieved following appropriate medical therapy (intranasal corticosteroids, saline nasal irrigations, and a short-course [≤3 weeks] of antibiotics; appendix p 3), with insufficient symptom response determined by the local principal investigator or co-investigator, and who were considered suitable candidates for further treatment including surgery. Chronic rhinosinusitis was diagnosed based on European guidelines[14,20] (minimum of 12 weeks' history of two or more symptoms, one of which should be nasal blockage, obstruction, or congestion and/or nasal discharge [anterior or posterior nasal drip], and one additional symptom of facial pain or pressure and/or reduction or loss of smell). Other criteria included nasal endoscopy (within the past 3 months) to confirm chronic rhinosinusitis diagnosis and phenotype (chronic rhinosinusitis with nasal polyps or chronic rhinosinusitis without nasal polyps); non-contrast CT scan (within the past 12 months) to determine Lund–Mackay score and confirm suitability for endoscopic sinus surgery; and moderate-to-severe symptoms as confirmed by a 22-item Sino-Nasal Outcome Test (SNOT-22) score of at least 20 (within the past 3 months).[21] Patients were also required to have a sufficient understanding of the English language to understand written and verbal information about the trial, its consent process, and study questionnaires.

Exclusion criteria were Lund–Mackay CT scan score below 4; macrolide antibiotic treatment for longer than 3 continuous weeks' duration within the past 12 months; endoscopic sinus surgery in the previous 6 months or visible, open frontoethmoidal sinus cavities; oral, intravenous, or intramuscular corticosteroids within a month of the baseline (randomisation) visit; active treatment with biologic therapies which might modulate disease severity in chronic rhinosinusitis; rare or complex sinus conditions (eg, secondary chronic rhinosinusitis or suspected malignancy); allergic fungal rhinosinusitis confirmed or suspected on CT imaging necessitating immediate surgery; severe asthma (requiring high doses of inhaled steroids—ie, >1·5 mg per day); known

immunodeficiency states including HIV and multiple selective antibody deficiency states; severe septal deviation preventing endoscopic examination; contraindications to surgery (significant medical comorbidity, generally defined by an American Society of Anesthesiologists grade of 4–5 and ascertained by local site assessment); any absolute contraindications to clarithromycin (including history of ischaemic heart disease, prolonged QT interval on electrocardiogram, or any medications known to interact with clarithromycin); known allergies to clarithromycin or other macrolide antibiotics or excipients of clarithromycin and placebo; female patients who were pregnant or breastfeeding; female patients of reproductive potential not prepared to use a reliable means of contraception; inability to give consent (significant cognitive impairment or language issues), or to understand and comply with trial instructions; or participation in another randomised clinical trial in the past 4 months. A screening and consent flow diagram is presented in the protocol (appendix).

Randomisation and masking

Following consent, once trial eligibility was confirmed, participants were randomly allocated (1:1:1) to receive: endoscopic sinus surgery plus intranasal medication, clarithromycin plus intranasal medication, or placebo plus intranasal medication. These groups are referred to as the endoscopic sinus surgery, clarithromycin, and placebo groups hereafter. Randomisation was done with an automated, web-based secure randomisation system (the Registration/Randomisation and Management of Product system, version 3.4.12) provided by the Oxford Clinical Trials Research Unit. The algorithm stratified by the presence of polyps and trial centre, using permuted blocks of block sizes three and six, with the allocations generated by the trial statistician who was unmasked to allocation and throughout the trial.

Centrally managed randomisation ensured allocation concealment and prevented selection bias. The participants' identifiable information was recorded on the randomisation form and was uploaded to an encrypted, separate database at the University of Oxford. Participants allocated to receive placebo or clarithromycin were allocated a treatment pack number for the corresponding medication, which was randomly generated to ensure allocation concealment and masking. Participants allocated to receive endoscopic sinus surgery were consented for surgery and booked on to the local principal investigator's waiting list.

Masking of participants and site teams was maintained for the comparison of clarithromycin through an identical placebo. Participants and medical staff were not masked to allocation to endoscopic sinus surgery. Outcome assessors were therefore masked to allocations to clarithromycin and placebo but not endoscopic sinus surgery. At the end of each trial participant's follow-up period of 6 months after randomisation, the participant returned to normal National Health Service care. Participants who remained symptomatic at that point received further treatment as defined by their ENT clinician, which included being offered steroids, antibiotics, or endoscopic sinus surgery, depending on which arm of the trial they were in. Participants who were allocated to either placebo or clarithromycin were not told of their allocation at the end of their 6-month trial period.

Procedures

In the clarithromycin group, study treatment comprised an initial 2-week course of clarithromycin 250 mg capsules twice daily starting on the day of randomisation, followed by a 10-week course of clarithromycin 250 mg capsules once daily. In the placebo group, treatment comprised an initial 2-week course of placebo capsules twice daily starting at baseline, followed by a 10-week course of placebo capsules once daily. The rationale for the choice and dose of clarithromycin is provided in our published protocol.[18] UK-licensed clarithromycin 250 mg standard-release tablets were over-encapsulated and provided in two bottles with a masked label compliant with Annex 13 of the EU Good Manufacturing Practice guidelines; identical encapsulated placebo tablets were provided in matching bottles (Guy's and St Thomas' and Royal Free Hospitals pharmacies, London, UK). Tablets were taken orally and compliance with medical treatment was recorded in weekly compliance diaries completed by the participants.

In the endoscopic sinus surgery group, surgery within 6 weeks of randomisation (if waiting lists allowed) was performed or supervised by consultant rhinologists according to the techniques described by Stammberger, Lund, and Kennedy,[14] with surgery proceeding in a stepwise fashion through polypectomy (when present), uncinectomy, maxillary antrostomy, ethmoidectomy, frontal sinusotomy, and sphenoidotomy. The extent of surgery was decided at an individual participant level by the operating surgeon in agreement with the consenting participant, and recorded by the surgeon.

Participants in all three groups also received intranasal medication, defined as intranasal corticosteroids as per local formulary guidelines and saline irrigations (non-investigational medicinal products) throughout all 6 months of the trial. Saline irrigation packs were provided by NeilMed Pharmaceuticals (Harrow, UK). Further details of the treatment schedule are provided in the protocol (appendix).[18]

In the case of acute exacerbations of rhinosinusitis, all participants received appropriate additional medical treatment as decided by the ENT surgeon or their ENT clinician or general practitioner. The prespecified additional treatments were oral steroids or full-dose broad-spectrum or culture-directed antibiotics. Concomitant medications were captured in a

participant-reported resource use questionnaire completed at baseline and at 3 and 6 months.

Baseline variables collected by the site teams included age, sex, and ethnicity (ethnicity was recorded from 2021 onwards); skin prick allergy test (or inhalant radioallergosorbent test [RAST]; minimum allergens tested: house dust mite, mixed grass, mixed tree, mixed mould, dog, and cat); blood tests (full blood count and total IgE concentration); CT scan Lund–Mackay score; history of COVID-19 and other respiratory diseases; and a participant-reported resource use questionnaire that included details of additional treatments (eg, oral steroids or antibiotics), health-care visits to primary and secondary care, and days of work or usual activities missed. Sex and ethnicity were self-reported by participants. Further information on baseline assessments and the post-baseline visit schedule and follow-up assessments are detailed in the protocol (appendix).[18]

Outcomes

The primary outcome was disease-specific health-related quality of life measured as SNOT-22 score (score range 0 to 110; with lower score indicating better sinonasal-related quality of life).[22] The primary endpoint was 6 months after randomisation. The trial endpoint was set at 6 months due to stability of SNOT-22 scores between 6 months and 5 years.[23] Prespecified analyses of SNOT-22 score at 6 weeks and 3 months after randomisation were conducted as supportive analyses of the primary outcome. This outcome was also measured at baseline (day of randomisation).

The secondary outcomes included: Short Form-12 (SF-12; version 2) generic health-related quality of life reported as physical component score (PCS) and mental component score (MCS); utility scores calculated from EuroQol 5-Dimension 5-Level (EQ-5D-5L) generic health-related quality-of-life responses with use of Hernández Alava mapping[24] (maximum of 1, anchored at 0 for dead) and EQ-5D-5L visual analogue scale (VAS) scores (0 to 100); Lund–Kennedy endoscopic score (LKES; 0 to 20); Lildholdt polyp score (LPS; 0=no polyposis to 3=severe polyposis, scored for each nasal side and as a total bilateral score out of 6); Sniffin' Sticks TDI score (odour threshold [T], discrimination [D], and identification [I]); upper and lower respiratory function in terms of peak nasal inspiratory flow rate (PNIF) and peak expiratory flow rate (PEFR), measured in L/min using handheld meters; need for further treatment (eg, oral steroids or antibiotics) as recorded in the resource use participant questionnaire; Asthma Control Test questionnaire score (range 5 [worst] to 25 [best], only in individuals with asthma confirmed at baseline); and adverse events, including serious adverse events and adverse reactions. Serious adverse events were defined as any untoward medical occurrence that resulted in death, were life-threatening, required inpatient hospitalisation or prolongation of existing hospitalisation, resulted in persistent or significant disability/incapacity, or consisted of a congenital anomaly or birth defect. Adverse reactions were defined as any untoward and unintended responses to study medication (clarithroymcin or placebo). Adverse events were coded according to the Medical Dictionary for Regulatory Activities (version 21.0).

There were no changes to the outcome measures after the trial commenced. All secondary outcome measures were captured at baseline, 3 months, and 6 months. The SF-12 and EQ-5D-5L measures were also taken at 6 weeks after randomisation. Participant questionnaires (SNOT-22, EQ-5D-5L, and SF-12) and need for further treatment were electronically completed when possible. Need for further treatment was recorded as a current need for treatment at each assessment point. Adverse events were recorded systematically by site teams in an adverse event case report form up to 6 months after randomisation. Secondary outcomes pertaining to cost-effectiveness, including information on health-care resource use, days off work, and quality-adjusted life-years, over the full 5-year follow-up period will be reported separately in due course.

Statistical analysis

The original sample size target was 600, which was chosen to enable secondary analyses of treatment according to the presence of polyps. The calculation assumed an even number of participants with chronic rhinosinusitis with nasal polyps and those without nasal polyps (1:1 ratio). However, as the trial progressed, the ratio became 4:1 and hence the sample size was reduced in agreement with the MACRO Programme steering committee and funder (appendix pp 3–4). The revised sample size was 510 participants, which was based on achieving at least 80% statistical power at a two-sided 1·67% significance level. A significance level of 1·67% was selected to allow for three pairwise treatment group comparisons on the basis of Bonferroni adjustment (conventional 5% level divided by 3=1·67% per comparison). The minimum clinically important difference for SNOT-22 score has been estimated to be 8·9 points.[22] An 8·9-point difference in SNOT-22 equivalent to 0·45 SD (Cohen's *d*; assuming SD=20) is considered a median effect size and an important difference for this type of outcome.[25] Previous research suggested that a larger effect of endoscopic sinus surgery versus alternative treatment is plausible, as large as 13·8 for the mean difference in SNOT-22 score.[22,26] Offsetting this larger effect size is the possibility of clustering within the surgical arm (which would affect the pairwise comparisons involving endoscopic sinus surgery) and the need to perform subgroup analysis by phenotype (polyps or not). Allowing for clustering at the surgeon level (intracluster correlation coefficient of 0·05 and 17 clusters of equal size based on the estimated intracluster correlation coefficient for similar outcomes in previous studies[27] and the number of sites originally

anticipated) in the endoscopic sinus surgery group, 153 participants per group (459 overall) allowed detection of a target mean difference for each pairwise comparison of 10·0 points with 90% power, or 8·9 points with 80% power. Corresponding clarithromycin versus placebo calculations both had over 90% power. Allowing for 10% missing data increased the target sample size to 510.

The statistical analysis plan (version 2.0; Sept 25, 2023) is provided in the appendix. For the primary outcome, SNOT-22 scores at 6 months after randomisation were summarised by intervention arm as the mean and SD. For each pairwise comparison (clarithromycin *vs* placebo, endoscopic sinus surgery *vs* placebo, endoscopic sinus surgery *vs* clarithromycin), a mixed-effects linear model adjusting for phenotype (chronic rhinosinusitis with nasal polyps *vs* chronic rhinosinusitis without nasal polyps) and baseline SNOT-22 score as fixed effects as well as treatment as a fixed effect, and for recruiting centre as a random effect, was used to compare the two groups. The models which included the endoscopic sinus surgery group data also accounted for clustering by surgeon in the endoscopic sinus surgery arm by including surgeon as a random effect. For each model, the appropriateness of the assumption of approximate normality of the residuals was assessed graphically. The models accounting for clustering by surgeon were considered the main analysis. The adjusted mean difference (with 98·33% CI, allowing for three pairwise treatment comparisons) and associated p value for each comparison were reported. These analyses were reported for the intention-to-treat (ITT; as randomised) population on an available-case basis. The primary outcome and select baseline characteristics are also presented descriptively by sex, age, and ethnicity, as requested during the review process.

As a sensitivity analysis, the impact of missing outcome data on the results for the primary outcome was investigated using a pattern-mixture approach under missing not at random assumptions implemented with use of the rctmiss command in Stata (version 18.0; with a simplified linear regression model using only 6-month data adjusted for SNOT-22 at baseline and for trial centre). Complier average causal effect (CACE) analyses were also performed in the ITT population (available cases) for each of the three comparisons using an instrumental variables approach (ivregress command in Stata), with compliance included as a model variable (rather than to exclude data), defined as receipt of at least 75% of the trial capsules for clarithromycin, and receipt of surgery within 3 months after randomisation for endoscopic sinus surgery.

As a secondary analysis, trends over time in SNOT-22 score from baseline to 6 months after randomisation were presented graphically and summarised at 6 weeks, 3 months, and 6 months as means and SDs. For each comparison, a repeated measures mixed-effects linear model was used to explore changes in treatment effect over time. The models included repeated measures (level 1) nested within participants (level 2) within recruiting centre (level 3). Models were adjusted for the presence or absence of polyps and baseline SNOT-22 score as fixed effects, included a treatment-by-time interaction, and also accounted for clustering by surgeon in the endoscopic sinus surgery arm as described earlier. Adjusted mean differences with 98·33% CIs and associated p values were calculated for each comparison at each timepoint.

For the continuous secondary outcome measures of SF-12 (MCS and PCS), EQ-5D-5L (utility scores from the Hernández Alava mapping algorithm[24] and VAS scores), LKES, TDI score, PEFR, PNIF, and LPS, results in each group were summarised at each timepoint as means with SDs. Repeated measures mixed-effects linear models were used to perform pairwise comparisons (clarithromycin *vs* placebo, endoscopic sinus surgery *vs* placebo, endoscopic sinus surgery *vs* clarithromycin). The models included the aforementioned repeated measures and nested levels. The assumptions of the model were tested by examining residual plots for normality. Outcomes were summarised for the pairwise comparisons at each timepoint as adjusted mean differences along with associated 98·33% CIs and p values. Need for further treatment was considered a binary outcome at 3 months and 6 months after randomisation. The number and percentage of participants in each group requiring further treatment at each timepoint were summarised and for each comparison, a repeated measures mixed-effects logistic model analogous to the aforementioned linear model for the continuous outcomes was used to compare the intervention groups. Odds ratios (ORs) and associated 98·33% CIs and p values comparing each pair of interventions at each timepoint were presented. Details of what types of further treatment were required in each group were also summarised. Asthma Control Test scores at each timepoint were summarised by intervention group for relevant participants. Serious adverse event rates were compared by calculating risk differences with associated 98·33% CIs. All secondary outcome analyses and assessments, excluding assessment of adverse reactions, were performed for the ITT population on an available-case basis. Adverse reactions were assessed in the clarithroymcin and placebo groups at 3 and 6 months in participants confirmed to have taken their allocated treatment and with corresponding safety data available. Serious adverse events were summarised for the ITT population.

We also conducted prespecified subgroup analyses (of SNOT-22 score, LPS score, TDI score, and need for further treatment, at 6 months after randomisation, according to polyp status, and SNOT-22 score at 6 months according to IgE concentration and eosinophil counts) and four post-hoc subgroup analyses (of SNOT-22 score at 6 months

according to baseline asthma status, global allergen status determined by skin prick test or inhalant RAST, and COVID-19 history, plus an analysis of SNOT-22 score at 6 months according to SNOT-22 score-based symptom categorisation at baseline, requested by a reviewer). For pairwise comparisons in subgroup analyses, the comparisons were done at the 98·33% confidence level and were considered exploratory. Treatment-by-subgroup interactions estimated differences in treatment effects between the subgroups.

Statistical significance was assessed at the 1·67% level for all tests. All analyses were done with Stata (version 18.0).

Role of the funding source

The funder of the study approved the study design but had no role in the study design, nor in data collection, data analysis, data interpretation, or writing of the report.

Results

The MACRO trial was open for recruitment from Nov 1, 2018, to Oct 13, 2023. The recruitment target for the trial was 510 participants; a total of 1948 patients were screened, of whom 514 (26·4%) were randomly assigned to receive clarithromycin (n=172), placebo (n=171), or endoscopic sinus surgery (n=171), all with intranasal medication. 410 (80%) participants had chronic rhinosinusitis with nasal polyps and 104 (20%) had chronic rhinosinusitis without nasal polyps. 485 (94%) participants received the allocated treatment (figure 1, appendix p 7). Important protocol deviations (ie, deviations considered to have an impact on the scientific integrity of the study or patient safety), including cases when unassigned treatment was received, are detailed in the appendix (p 24), with a total of 39 important protocol deviations overall. In the endoscopic sinus surgery group, 148 participants underwent the allocated surgery, 92 (62%) of whom received complete surgery that included surgery to all of the sinuses, and all 148 (100%) participants received surgery within 6 months (appendix pp 8–9).

The trial population comprised 333 (65%) male participants and 181 (35%) female participants, and 271 participants (92% of 296 with ethnicity data) self-identified as White. The baseline similarity of the three intervention groups was considered, in terms of

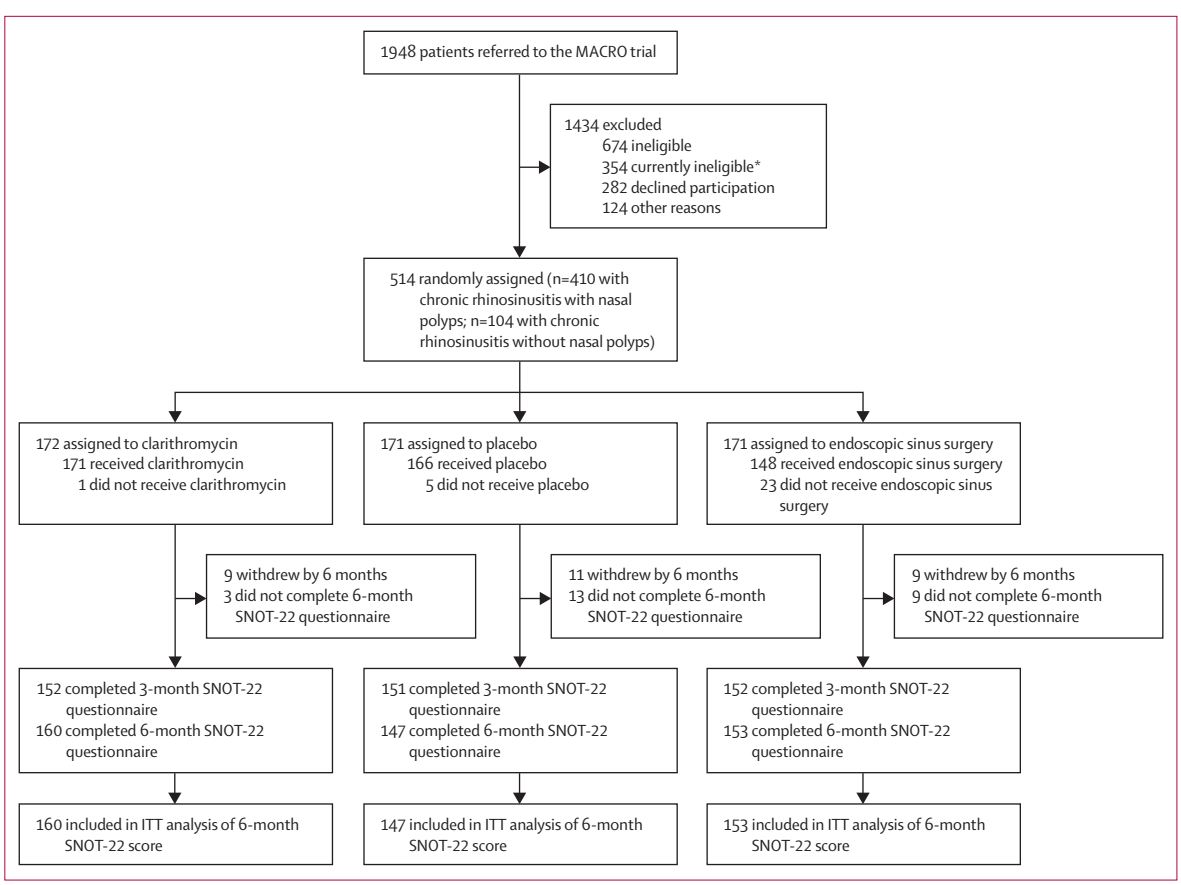

Figure 1: **Consort flowchart**

Participants in all three groups also received intranasal corticosteroids and saline irrigations. SNOT-22 score at 6 months after randomisation (primary outcome) was analysed by ITT on an available-case basis. ITT=intention to treat. SNOT-22=22-item Sino-Nasal Outcome Test. *Reason for exclusion was transient (eg, being within 1 month of a course of corticosteroids).

	Endoscopic sinus surgery (N=171)	Clarithromycin (N=172)	Placebo (N=171)	Total (N=514)
Age, years	n=171; 52·5 (13·8)	n=172; 53·0 (12·9)	n=171; 52·5 (14·5)	n=514; 52·6 (13·8)
Sex				
Female	59 (35%)	60 (35%)	62 (36%)	181 (35%)
Male	112 (65%)	112 (65%)	109 (64%)	333 (65%)
Ethnicity				
Asian or Asian British: Bangladeshi	0	1/100 (1%)	0	1/296 (<1%)
Asian or Asian British: Indian	2/98 (2%)	1/100 (1%)	1/98 (1%)	4/296 (1%)
Asian or Asian British: Other Asian	1/98 (1%)	2/100 (2%)	1/98 (1%)	4/296 (1%)
Asian or Asian British: Pakistani	1/98 (1%)	0	1/98 (1%)	2/296 (1%)
Black or Black British: African	2/98 (2%)	2/100 (2%)	0	4/296 (1%)
Black or Black British: Caribbean	0	0	3/98 (3%)	3/296 (1%)
Mixed: White and Asian	2/98 (2%)	1/100 (1%)	0	3/296 (1%)
Other: Chinese	0	1/100 (1%)	0	1/296 (<1%)
Other: any Other group	1/98 (1%)	2/100 (2%)	0	3/296 (1%)
White: Other	9/98 (9%)	6/100 (6%)	4/98 (4%)	19/296 (6%)
White: British	80/98 (82%)	83/100 (83%)	86/98 (88%)	249/296 (84%)
White: Irish	0	1/100 (1%)	2/98 (2%)	3/296 (1%)
History of COVID-19				
No	63/112 (56%)	51/113 (45%)	55/108 (51%)	169/333 (51%)
Yes	49/112 (44%)	62/113 (55%)	53/108 (49%)	164/333 (49%)
History of other respiratory diseases				
No	91 (53%)	101 (59%)	86/169 (51%)	278/512 (54%)
Yes	80 (47%)	71 (41%)	83/169 (49%)	234/512 (46%)
Asthma				
No	97 (57%)	103 (60%)	90/170 (53%)	290/513 (57%)
Yes	74 (43%)	69 (40%)	80/170 (47%)	223/513 (43%)
Chronic obstructive pulmonary disease				
No	167 (98%)	168 (98%)	167/170 (98%)	502/513 (98%)
Yes	4 (2%)	4 (2%)	3/170 (2%)	11/513 (2%)
Bronchiectasis				
No	168 (98%)	169 (98%)	169/170 (99%)	506/513 (99%)
Yes	3 (2%)	3 (2%)	1/170 (1%)	7/513 (1%)
Other respiratory disease				
No	168 (98%)	170 (99%)	166/170 (98%)	504/513 (98%)
Yes	3 (2%)	2 (1%)	4/170 (2%)	9/513 (2%)
Depression or anxiety				
No	141 (82%)	136 (79%)	123/169 (73%)	400/512 (78%)
Yes	30 (18%)	36 (21%)	46/169 (27%)	112/512 (22%)
Taking antidepressant medication in those with depression or anxiety				
No	14/30 (47%)	13/36 (36%)	26/46 (57%)	53/112 (47%)
Yes	16/30 (53%)	23/36 (64%)	20/46 (43%)	59/112 (53%)
Gastro-oesophageal reflux				
No	137 (80%)	136 (79%)	131/168 (78%)	404/511 (79%)
Yes	34 (20%)	36 (21%)	37/168 (22%)	107/511 (21%)
Taking reflux medication in those with gastro-oesophageal reflux				
No	5/29 (17%)	6/29 (21%)	13/34 (38%)	24/92 (26%)
Yes	24/29 (83%)	23/29 (79%)	21/34 (62%)	68/92 (74%)
Previous sinus surgery or nasal polypectomy				
No	102 (60%)	100 (58%)	108/169 (64%)	310/512 (61%)
Yes	69 (40%)	72 (42%)	61/169 (36%)	202/512 (39%)

(Table 1 continues on next page)

	Endoscopic sinus surgery (N=171)	Clarithromycin (N=172)	Placebo (N=171)	Total (N=514)
(Continued from previous page)				
Number of previous surgeries (sinus surgery or nasal polypectomy)				
One surgery	38 (22%)	33 (19%)	27 (16%)	98 (19%)
Two surgeries	21 (12%)	25 (14·5%)	17 (10%)	63 (12%)
At least three surgeries	10 (6%)	14 (8%)	17 (10%)	41 (8%)
No surgery	102 (60%)	100 (58%)	108 (64%)	310 (61%)
Global allergy status*				
Negative	69/129 (53%)	56/132 (42%)	64/124 (52%)	189/385 (49%)
Positive	60/129 (47%)	76/132 (58%)	60/124 (48%)	196/385 (51%)
Blood total IgE, IU/mL	n=121; 191·7 (405·3)	n=119; 259·2 (421·9)	n=120; 216·3 (438·8)	n=360; 222·2 (421·9)
Bloods eosinophils, cells × 10^9/L	n=126; 0·6 (2·8)	n=126; 0·4 (0·3)	n=123; 0·4 (0·3)	n=375; 0·5 (1·7)
Type 2 inflammatory status				
IgE ≥100 IU/mL or eosinophils ≥0·15 × 10^9/L	105/120 (88%)	112/119 (94%)	108/117 (92%)	325/356 (91%)
IgE <100 IU/mL and eosinophils <0·15 × 10^9/L	15/120 (13%)	7/119 (6%)	9/117 (8%)	31/356 (9%)

Data are n; mean (SD), n (%), or n/N (%), where N represents participants with available data. *Based on either a positive skin prick test or a positive radioallergosorbent inhalant screen test. Participants who had either form of allergy testing had multiple allergens tested. Minimum allergens tested: house dust mite, mixed grass, mixed tree, mixed mould, dog, and cat. Specific allergens were acceptable in place of mixed tree, mixed grass, or mixed mould.

Table 1: **Patient demographics and medical history by intervention group**

	6-month SNOT-22 score: n; mean (SD)	Comparison*	Adjusted mean difference (98·33% CI)	p value
Clarithromycin	n=160; 42·8 (26·1)	Clarithromycin *vs* placebo	−3·11 (−8·56 to 2·33)	0·17
Endoscopic sinus surgery	n=153; 24·3 (17·8)	Endoscopic sinus surgery *vs* clarithromycin	−18·13 (−24·26 to −11·99)	<0·0001
Placebo	n=147; 46·8 (22·3)	Endoscopic sinus surgery *vs* placebo	−20·44 (−26·42 to −14·46)	<0·0001

SNOT-22=22-item Sino-Nasal Outcome Test. *Reference group is treatment group B, for comparison A versus B.

Table 2: **Comparison between intervention groups of SNOT-22 scores at 6 months after randomisation (main analysis)**

randomisation stratification factors (appendix p 5), demographic and clinical characteristics and medical history (table 1), and outcome measures at baseline (appendix p 6). Randomisation was successful in ensuring balance for the stratification factors of trial site and phenotype (polyps or not) across the three groups (appendix p 5).

The main analysis of SNOT-22 scores at 6 months after randomisation was performed in the ITT population on an available-case basis and summarised by intervention group (table 2). We observed a large and statistically significant (at the 98·33% confidence level) mean difference in 6-month SNOT-22 score in favour of endoscopic sinus surgery compared with the other two randomised groups (adjusted mean difference *vs* clarithromycin −18·13 [98·33% CI −24·26 to −11·99], p<0·0001; and adjusted mean difference *vs* placebo −20·44 [−26·42 to −14·46], p<0·0001). We found no evidence of a difference between clarithromycin and placebo with an adjusted mean difference of −3·11 (−8·56 to 2·33; p=0·17). The appendix (p 22) shows the comparison of baseline versus 6-month SNOT-22 symptom severity levels for all three treatment groups combined. The primary outcome and select baseline characteristics according to sex, age, and ethnicity are also presented in the appendix (pp 26–28).

Trends over time in SNOT-22 score were summarised and compared based on measurements at 6 weeks, 3 months, and 6 months after randomisation (table 3, appendix p 30). Figure 2 displays the mean (observed) SNOT-22 scores for each treatment group over time, showing continued improvement in the endoscopic sinus surgery group compared with the clarithromycin and placebo groups up to 6 months. Comparing with baseline data in those with available measurements, the proportion of participants who improved by 8·9 SNOT-22 points (minimum clinically important difference[22]) at 3 months was 106 (70%) of 152 in the clarithromycin group, 101 (68%) of 149 in the placebo group, and 123 (81%) of 152 in the endoscopic sinus surgery group (appendix p 29). Corresponding numbers at 6 months were 106 (66%) of 160, 102 (70%) of 145, and 148 (97%) of 153, respectively.

The appendix (pp 10–12) presents the results of the analyses of the continuous secondary outcomes by timepoint. Quality-of-life outcomes (SF-12 MCS and PCS, and EQ-5D-5L utility and VAS scores) were generally quite similar across the intervention groups, although some significant differences in favour of endoscopic sinus surgery at 6 months after randomisation were detected. LKES and LPS showed a similar pattern to the primary outcome, with significant effects in favour of endoscopic sinus surgery, and no clear evidence of a difference

	6-month SNOT-22 score: n; mean (SD)	Comparison*	Adjusted mean difference (98·33% CI)†	p value
6 weeks				
Clarithromycin	n=155; 41·8 (21·8)	Clarithromycin *vs* placebo	−4·58 (−9·49 to 0·33)	0·026
Endoscopic sinus surgery	n=155; 44·9 (20·8)	Endoscopic sinus surgery *vs* clarithromycin	3·09 (−2·00 to 8·17)	0·14
Placebo	n=152; 48·1 (19·8)	Endoscopic sinus surgery *vs* placebo	−1·82 (−6·86 to 3·22)	0·38
3 months				
Clarithromycin	n=152; 41·3 (24·3)	Clarithromycin *vs* placebo	−3·22 (−8·15 to 1·72)	0·12
Endoscopic sinus surgery	n=152; 34·0 (22·9)	Endoscopic sinus surgery *vs* clarithromycin	−8·39 (−13·49 to −3·28)	<0·0001
Placebo	n=151; 46·9 (20·2)	Endoscopic sinus surgery *vs* placebo	−11·93 (−17·00 to −6·87)	<0·0001
6 months				
Clarithromycin	n=160; 42·8 (26·1)	Clarithromycin *vs* placebo	−3·52 (−8·43 to 1·40)	0·087
Endoscopic sinus surgery	n=153; 24·3 (17·8)	Endoscopic sinus surgery *vs* clarithromycin	−18·50 (−23·57 to −13·43)	<0·0001
Placebo	n=147; 46·8 (22·3)	Endoscopic sinus surgery *vs* placebo	−22·22 (−27·29 to −17·14)	<0·0001

SNOT-22=22-item Sino-Nasal Outcome Test. *Reference group is treatment group B, for comparison A versus B. †This secondary analysis used repeated measures mixed-effects linear models incorporating all timepoints (6 weeks, 3 months, and 6 months). The primary analysis (table 2) used mixed-effects linear models based on 6-month data only, hence the minor differences in adjusted mean differences at 6-months between the two analyses. 6-week and 3-month results are presented to aid interpretation of the results at 6 months.

Table 3: **Comparison between intervention groups of SNOT-22 scores from 6 weeks to 6 months after randomisation (secondary analysis)**

between the clarithromycin and placebo groups. In general, PEFR and PNIF did not show any clear evidence of differences between the groups, albeit with some indication of significantly better outcome with surgical or medical intervention versus placebo. TDI score was significantly improved in favour of endoscopic sinus surgery compared with the placebo group. With regard to the need for further treatment (appendix pp 15–16), no significant differences were identified between the groups at 3 or 6 months. Asthma control test scores were similar across follow-up (appendix p 17).

Assessment of the primary outcome using a pattern-mixture model approach suggested robustness of the findings to the presence of missing data, with mean differences at 6 months in favour of endoscopic sinus surgery remaining across a range of scenarios (appendix pp 31–33). Additionally, the CACE analysis of SNOT-22 scores supported a large effect at 6 months with endoscopic sinus surgery versus clarithromycin or placebo (appendix p 12).

Prespecified subgroup data and analyses are shown in the appendix (pp 13–15). The significant beneficial effect of endoscopic sinus surgery on 6-month SNOT-22 score was observed in both phenotype subgroups (participants with or without polyps). Phenotype did not appear to affect the other key outcomes for which this subgroup comparison was prespecified except for LPS score, for which comparisons with ESS had significant treatment-by-subgroup interactions. Prespecified subgroup analysis of SNOT-22 at 6 months by baseline IgE and eosinophil status did not find differential subgroup treatment differences based on treatment-by-subgroup interaction terms, although uncertainty was substantial (appendix p 15).

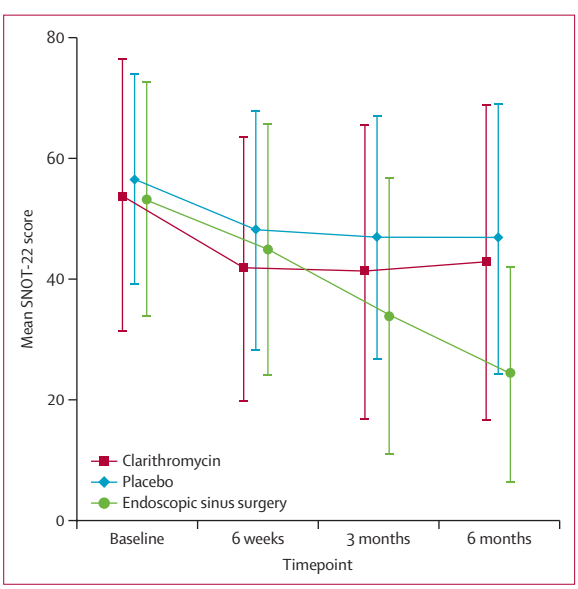

Figure 2: **Trends over time in unadjusted mean SNOT-22 score by treatment group**
Error bars represent SD. The x-axis is not on a linear scale.

Three post-hoc subgroup analyses of SNOT-22 score at 6 months were performed according to baseline asthma status, global allergen status, and COVID-19 history (appendix pp 21–22). The results indicated no statistically significant difference in the mean difference between treatments by subgroup, based on 98·33% CIs for the treatment-by-subgroup interaction terms, when

comparing participants with versus without asthma, and those with versus without allergies. With regard to baseline COVID-19 history, the treatment-by-subgroup interaction was significant for endoscopic sinus surgery versus clarithromycin, suggesting a larger treatment effect among participants with a history of COVID-19. In a fourth post-hoc subgroup analysis, those who had severe SNOT-22 symptoms at baseline had significantly greater benefit (reduction in 6-month SNOT-22 score) than those with non-severe symptoms for the comparison of endoscopic sinus surgery versus clarithromycin, but not for the other two comparisons (appendix p 25).

Serious adverse events were infrequent and occurred at similar rates across the groups. Overall, ten serious adverse events occurred in nine participants (two events in two [1%] of 172 participants allocated to clarithromycin, three events in three [2%] of 171 allocated to placebo, and five events in four [2%] of 171 allocated to endoscopic sinus surgery), none of which were fatal (appendix pp 17, 23). Adverse reactions in the clarithromycin and placebo groups are summarised in the appendix (pp 18–20). The most common adverse reactions were abdominal pain and diarrhoea at 3 months.

Discussion

This study highlights the clinical effectiveness of surgery in the management of chronic rhinosinusitis in adults, with endoscopic sinus surgery having superiority over continued medical care with intranasal medication alone, or with intranasal medication and 3 months of low-dose clarithromycin. Compliance with allocation was high, with 337 (98%) of 343 participants receiving allocated treatment with clarithromycin or placebo, and 148 (87%) of the 171 participants allocated to endoscopic sinus surgery receiving surgery, all within 6 months. Mean SNOT-22 score at 6 months after randomisation was substantially and significantly lower in the endoscopic sinus surgery group than in the clarithromycin and placebo groups, with no clear difference in mean SNOT-22 between the clarithromycin and placebo groups. These findings appeared to be robust to missing data and non-compliance. LKES and LPS showed a similar pattern to the primary outcome. Other generic quality-of-life outcomes were generally similar in all three groups with some results in favour of endoscopic sinus surgery at 6 months.

As a pragmatic trial, the protocol was not prescriptive about the choice of intranasal corticosteroid given previous Cochrane review evidence.[28] It was also not prescriptive about the procedural details of endoscopic sinus surgery undertaken by the individual sites, however all surgeons had a subspecialty practice in rhinology.

The trial had intended to recruit individuals with chronic rhinosinusitis with nasal polyps and chronic rhinosinusitis without nasal polyps in a 1:1 ratio; however, as recruitment progressed, especially after the COVID-19 pandemic, the ratio progressed from 2:1 to 4:1 and, therefore, the prespecified chronic rhinosinusitis without nasal polyps subgroup was underpowered to address the effect of clarithromycin in this phenotype specifically. Analysing by endotypes to compare subgroups by eosinophil count or by total IgE concentration as markers for type 2 inflammation also yielded a small subgroup with non-type 2 inflammation, and was therefore underpowered to detect differing effectiveness. Ultimately the completed trial was not large enough with respect to the chronic rhinosinusitis without nasal polyps phenotype or non-type 2 endotype to show a definitive result.

As a surgical trial, there was no specific sham or placebo surgery comparison; instead the trial compared endoscopic sinus surgery with a different routine treatment not involving surgery. Direct conclusions about the fundamental effectiveness of surgery (compared to no treatment) are therefore not possible, but the inference of benefit is persuasive. The screening process required participants to be deemed suitable for endoscopic sinus surgery at the point of randomisation, and as such we might have excluded some individuals with chronic rhinosinusitis for whom medical management (with clarithromycin) might have been effective.

There was under-representation of non-White ethnic groups in the study population, which might limit generalisability to those groups (in our study, 25 [8%] of 296 participants self-identified as belonging to non-White ethnic groups, compared with 18% in the last UK Census[29]). Due to the effect of the COVID-19 pandemic, we were unable to collect secondary outcomes on some participants due to the lockdown, with more than 20% of data missing for some secondary outcomes.

A previous systematic review of endoscopic sinus surgery identified the need for high-quality studies comparing surgery with medical treatment.[15] Two 2014 Cochrane systematic reviews of medical and surgical management also concluded that further studies were urgently needed.[16,17] A paucity of evidence regarding the effectiveness of endoscopic sinus surgery has in the past led to its inclusion on lists of procedures of limited clinical effectiveness, and reluctance in considering surgery both in primary care and in ENT clinics.[30] Our results should give doctors confidence in offering surgery to adults with chronic rhinosinusitis with persistent symptoms despite use of intranasal medication.

Since the MACRO Programme commenced, a pragmatic, multicentre RCT in the Netherlands has been published,[31] which compared endoscopic sinus surgery plus medical therapy versus medical therapy alone in adult participants with chronic rhinosinusitis with nasal polyps. The study also showed greater effectiveness with surgery, but the difference between the two groups did not meet the minimum clinically important difference for SNOT-22 at 6 months (mean difference between groups in SNOT-22 of –7·1 (95% CI –12·7 to –1·5). The study similarly recruited patients in whom appropriate

medical therapy had been unsuccessful. Medical therapy comprised of any medical treatment considered suitable by the participant's otorhinolaryngologist, including intranasal corticosteroids, systemic antibiotics, and systemic corticosteroids, with no standardisation. This Dutch study recruited only patients with chronic rhinosinusitis with nasal polyps; our prespecified subgroup analysis indicated a similar effect on SNOT-22 score between participants with chronic rhinosinusitis with nasal polyps and those without nasal polyps (with surgery significantly more effective than clarithromycin or placebo in both subgroups). The Dutch study had a higher crossover rate to surgery (23 [20%] of 117) than in the current trial (six [2%] of 343 participants in the clarithromycin and placebo groups; appendix p 7). The absence of improvement in the medical groups in our trial might reflect that participants had shown inadequate response to appropriate medical therapy before referral from primary care, and therefore further treatment was likely to be unsuccessful.

Our study showed that treatment with 12 weeks of low-dose clarithromycin did not provide a clinically significant improvement in SNOT-22 scores. Two previous RCTs in adults with chronic rhinosinusitis evaluated outcomes after 12 weeks of treatment with macrolide antibiotics compared with placebo; roxithromycin[8] was shown to have efficacy with regard to improvements in disease-specific quality of life, while azithromycin[32] was not. The roxithromycin trial only included individuals with chronic rhinosinusitis without nasal polyps, with a greater effect observed in participants with likely non-type 2 disease. Although our group of participants with chronic rhinosinusitis without nasal polyps was small, there was no evidence of a significantly greater response in disease-specific quality of life when stratifying by phenotype. The subgroup analysis of endotype (type 2 inflammatory status), although not statistically significant, is consistent with findings of the roxithromycin trial, with clarithromycin having greater effectiveness than placebo in non-type 2 disease (19·10-point mean difference in 6-month SNOT-22 score, p=0·074; appendix p 15). As mentioned, this analysis had limited precision due to a small subgroup size, and further evaluation might be warranted. There might be a different response with different macrolide preparations. However, roxithromycin is not available in the UK and was not an option for this trial. Macrolides might be beneficial in patients with non-type 2 disease, but our results suggest that long-term macrolides should not be used routinely in the management of undifferentiated chronic rhinosinusitis in a primary care setting. Of note, there was a lower rate of antibiotic use other than clarithromycin reported in the clarithromycin group than in the other treatment groups at 3 months (appendix p 16), which could suggest reductions in acute exacerbations while on active treatment, which did not persist beyond the 12-week course of treatment.

Loss of sense of smell is a prevalent symptom for chronic rhinosinusitis with and without nasal polyps. We observed significantly greater improvement in TDI scores at 3 months and 6 months after randomisation in the surgical group compared with in the placebo group. However, mean differences did not reach the minimum clinically important difference (5·5 points in TDI score[33]) in psychophysical testing of olfactory function in any of the pairwise comparisons, highlighting a limitation of the tested treatments. The effect was similar to that reported in other studies,[34,35] with a small and significant improvement after surgery but no significant improvement with intranasal corticosteroids.

Our primary endpoint was improvement in disease-specific quality of life at 6 months after randomisation. It has been shown that SNOT-22 scores remain stable from 6 months to 5 years;[23] however long-term disease recurrence rates are high[36,37] and there is a progressive increase in revision surgery rates.[7] We therefore plan to re-evaluate our trial participants on an annual basis and will publish long-term outcomes in 2029 once all registered participants have completed 5 years of follow-up from randomisation.

Antibiotic resistance is considered one of the most important threats to patient safety in Europe.[38] In addition, potential cardiovascular side-effects of macrolide antibiotics have been highlighted.[39] Our study findings do not support the routine use of long-term clarithromycin in adult patients with chronic rhinosinusitis, although we acknowledge that long waiting times for ENT outpatients and for endoscopic sinus surgery might influence medical treatment practice patterns. In contrast, surgery achieves significant improvements in disease-specific quality of life at 6 months in this group. The ongoing long-term follow-up will factor in the effect of symptom recurrence and revision surgery in the surgical group, as well as endoscopic sinus surgery undertaken in the clarithromycin group.

The majority of participants within the MACRO trial had complete surgery, reflecting the high disease burden detected on preoperative CT scans. The MACRO trial had a pragmatic design and recruited participants characteristic of the typical patient population. It also formed part of a larger programme of work, the overarching aim of which is to address the major deficiencies in the evidence base for chronic rhinosinusitis management, establish best practice for the management of adults with chronic rhinosinusitis, and design the ideal patient pathway across primary and secondary care. The present findings, if implemented in a care pathway, could reduce unnecessary antibiotic prescriptions and reduce the time taken for patients with chronic rhinosinusitis with nasal polyps to access endoscopic sinus surgery for those wanting surgical intervention, with potential cost-savings from reduced consultations and prescriptions.

MACRO Collaborative

UK H Kariyawasam, S Gane (University College London Hospital, London), H Saleh (Charing Cross Hospital, London), H Khalil (University Hospitals Plymouth NHS Trust, Plymouth), I Hathorn (Edinburgh Royal Infirmary, Edinburgh), I Syed (Lewisham Hospital, London), M Lechner (Homerton Hospital, London), N Tan (Royal Cornwall Hospital, Truro), P Nix (Leeds General Infirmary, Leeds), P White (Ninewells Hospital, Dundee), Peter Prinsley (Norfolk and Norwich University Hospital, Norwich), R Bhalla (Manchester Royal Infirmary, Manchester), R Salib (University Hospital Southampton, Southampton), R Green (Ninewells Hospital, Dundee), R Talwar (Luton and Dunstable University Hospital, Luton), R Sharma (Addenbrookes Hospital, Cambridge), R Almeyda (Royal Berkshire Hospital, Reading), S Sunkaraneni (Royal Surrey County Hospital, Guildford), S Carrie (Freeman Hospital, Newcastle), S Ahmed (Queen Elizabeth Hospital, Birmingham), Yujay Ramakrishnan (Queens Medical Centre, Nottingham), Helen Blackshaw (University College London, London)

Contributors

CP: chief investigator of the trial, site principal investigator for James Paget University Hospital, joint lead grant applicant for the MACRO Programmme; study design, data collection, data analysis, data interpretation, manuscript writing. DJB: grant co-applicant; study design, funding acquisition, data interpretation, manuscript writing. MT: grant co-applicant; study design, funding acquisition, data interpretation, manuscript writing. PL: grant co-applicant; study design, funding acquisition, data interpretation, manuscript writing. JV: grant co-applicant; study design, funding acquisition, data interpretation, manuscript writing. VL: grant co-applicant; study design, data interpretation, manuscript writing. AGMS: grant co-applicant: study design and delivery, grant management, data interpretation, manuscript writing. JB: patient and public involvement grant co-applicant; study design and delivery, trial management, data interpretation. ES: trial statistician; accessed and verified the data, data analysis, data interpretation, manuscript writing. JAC: grant co-applicant, trial statistician; study design and methodology, accessed and verified the data, data analysis, data interpretation, manuscript writing. CSC: grant co-applicant, health economics lead; study design, data collection design, data analysis, data interpretation, manuscript writing. LT: trial health economist; data analysis, data interpretation, manuscript writing. FL: programme manager. SJ: trial manager. SD: grant co-applicant: study design and delivery, grant management, data interpretation, manuscript writing. CH: co-chief investigator, site principal investigator for Guy's and St Thomas' Hospital, joint lead grant applicant; study design, data collection, data analysis, data interpretation, manuscript writing. All authors had full access to all the data through the MACRO Programme Management Group meetings. All authors had final responsibility for the decision to submit for publication.

Declaration of interests

CP has received grants from the UK National Institute for Health and Care Research (NIHR) and Engineering and Physical Sciences Research Council, consultancy fees from GSK, Sanofi, Medtronic, and Stryker including advisory board work for all four companies, and royalties from Thieme. CP is a trustee of the charity SmellTaste and President of the UK Semiochemistry Network. CH is on the advisory board for Medtronic and is Secretary General for the European Rhinologic Society. VL has received royalties, honoraria, or consulting fees from Elsevier, Thieme, Novartis, Sanofi, Evidera, Alcimed, GSK, the European Forum for Research and Education in Allergy and Airway Diseases, Mayo Foundation, Cancer Research, InTouch, Medcrowd, and Medscape, and has been an advisory board member for GSK and Sanofi. All other authors declare no competing interests. CP, CH, JB, CSC, JAC, PL, VL, AGMS, DJB, SD, MT, and JV were applicants or co-applicants on the NIHR MACRO Programme Grant received in 2016. FL, LT, SJ and JV were employed or received salary through the NIHR Programme Grant.

Data sharing

Individual participant data that underlie the results reported in this Article, after de-identification, will be available upon reasonable request. Data for sharing will be held by Oxford Clinical Trials Research Unit, and will be available from Dec 31, 2025 to Dec 31, 2028, upon reasonable request (to octrutrialshub@ndorms.ox.ac.uk) subject to agreement of the study sponsor. Data requestors will need to sign a data access agreement. The study protocol (version 8.0; Sept 1, 2023) and statistical analysis plan (version 2.0; Sept 25, 2023) are provided in the appendix.

Acknowledgments

This trial was funded by an NIHR Programme Grant for Applied Research (grant number RP-PG-0614–20011). The views expressed are those of the author(s) and not necessarily those of the NIHR or the UK Department of Health and Social Care. This study has been conducted as part of the portfolio of trials in the registered UKCRC Oxford Clinical Trials Research Unit at the University of Oxford. We thank Steffi le Conte, Edmund Wyatt, Laura Lloyd Jones, and Surjeet Singh from the Oxford Surgical Intervention Trials Unit, wider members of the MACRO Programme Team, NeilMed Pharmaceuticals for provision of the sinus irrigation bottles for the trial, Nikkayla Dixon as sponsor representative for University College London, and Jane Woods and Teresa Ferreira for research nurse feedback on trial set up.

References

1 Min HK, Lee S, Kim S, et al. Global incidence and prevalence of chronic rhinosinusitis: a systematic review. *Clin Exp Allergy* 2025; **55**: 52–66.

2 Gliklich RE, Metson R. The health impact of chronic sinusitis in patients seeking otolaryngologic care. *Otolaryngol Head Neck Surg* 1995; **113:** 104–09.

3 Erskine SE, Hopkins C, Clark A, et al. Chronic rhinosinusitis and mood disturbance. *Rhinology* 2017; **55:** 113–19.

4 Pynnonen MA, Venkatraman G, Davis GE. Macrolide therapy for chronic rhinosinusitis: a meta-analysis. *Otolaryngol Head Neck Surg* 2013; **148:** 366–73.

5 Cervin A, Wallwork B. Efficacy and safety of long-term antibiotics (macrolides) for the treatment of chronic rhinosinusitis. *Curr Allergy Asthma Rep* 2014; **14:** 416.

6 Head K, Chong LY, Piromchai P, et al. Systemic and topical antibiotics for chronic rhinosinusitis. *Cochrane Database Syst Rev* 2016; **4:** CD011994.

7 Orlandi RR, Kingdom TT, Smith TL, et al. International Consensus Statement on Allergy and Rhinology: Rhinosinusitis 2021. *Int Forum Allergy Rhinol* 2021; **11:** 213–739.

8 Wallwork B, Coman W, Mackay-Sim A, Greiff L, Cervin A. A double-blind, randomized, placebo-controlled trial of macrolide in the treatment of chronic rhinosinusitis. *Laryngoscope* 2006; **116:** 189–93.

9 Videler WJ, Badia L, Harvey RJ, et al. Lack of efficacy of long-term, low-dose azithromycin in chronic rhinosinusitis: a randomized controlled trial. *Allergy* 2011; **66:** 1457–68.

10 NHS England. National Consultant Information Programme (NCIP). https://gettingitrightfirsttime.co.uk/associated_projects/ncip/ (accessed March 20, 2025).

11 NHS England. Hospital Episode Statistics (HES). https://digital.nhs.uk/services/hospital-episode-statistics (accessed March 20, 2025).

12 Bhattacharyya N. Ambulatory sinus and nasal surgery in the United States: demographics and perioperative outcomes. *Laryngoscope* 2010; **120:** 635–38.

13 Hopkins C, McCombe A, Philpott C, et al. Commissioning guide: rhinosinusitis. ENT UK and The Royal College of Surgeons of England, 2013.

14 Fokkens WJ, Lund VJ, Hopkins C, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2020. *Rhinology* 2020; **58** (suppl S29)**:** 1–464.

15 Dalziel K, Stein K, Round A, Garside R, Royle P. Endoscopic sinus surgery for the excision of nasal polyps: a systematic review of safety and effectiveness. *Am J Rhinol* 2006; **20:** 506–19.

16 Rimmer J, Fokkens W, Chong LY, Hopkins C. Surgical versus medical interventions for chronic rhinosinusitis with nasal polyps. *Cochrane Database Syst Rev* 2014; **12:** CD006991.

17 Sharma R, Lakhani R, Rimmer J, Hopkins C. Surgical interventions for chronic rhinosinusitis with nasal polyps. *Cochrane Database Syst Rev* 2014; **11:** CD006990.

18 Philpott C, le Conte S, Beard D, et al, and the MACRO Programme Team. Clarithromycin and endoscopic sinus surgery for adults with chronic rhinosinusitis with and without nasal polyps: study protocol for the MACRO randomised controlled trial. *Trials* 2019; **20:** 246.

19 McDermott C, Vennik J, Philpott C, et al. Maximising recruitment to a randomised controlled trial for chronic rhinosinusitis using qualitative research methods: the MACRO conversation study. *Trials* 2021; **22:** 54.

20 Fokkens WJ, Lund VJ, Mullol J, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2012. *Rhinol Suppl* 2012; **23:** 1–298.

21 Toma S, Hopkins C. Stratification of SNOT-22 scores into mild, moderate or severe and relationship with other subjective instruments. *Rhinology* 2016; **54:** 129–33.

22 Hopkins C, Gillett S, Slack R, Lund VJ, Browne JP. Psychometric validity of the 22-item Sinonasal Outcome Test. *Clin Otolaryngol* 2009; **34:** 447–54.

23 Soler ZM, Smith TL. Quality-of-life outcomes after endoscopic sinus surgery: how long is long enough? *Otolaryngol Head Neck Surg* 2010; **143:** 621–25.

24 Hernández Alava M, Pudney S, Wailoo A. Estimating the relationship between EQ-5D-5L and EQ-5D-3L: results from a UK population study. *Pharmacoeconomics* 2023; **41:** 199–207.

25 Cook JA, Hislop J, Adewuyi TE, et al. Assessing methods to specify the target difference for a randomised controlled trial: DELTA (Difference Elicitation in Trials) review. *Health Technol Assess* 2014; **18:** v–vi, 1–175.

26 Chong LY, Head K, Hopkins C, et al. Saline irrigation for chronic rhinosinusitis. *Cochrane Database Syst Rev* 2016; **4:** CD011995.

27 Cook JA, Bruckner T, MacLennan GS, Seiler CM. Clustering in surgical trials—database of intra-cluster correlations. *Trials* 2012; **13:** 2.

28 Chong LY, Head K, Hopkins C, Philpott C, Schilder AG, Burton MJ. Intranasal steroids versus placebo or no intervention for chronic rhinosinusitis. *Cochrane Database Syst Rev* 2016; **4:** CD011996.

29 Office for National Statistics. Census-based statistics UK: 2021. June 27, 2025. https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/datasets/censusbasedstatisticsuk2021 (accessed Aug 14, 2025).

30 Vennik J, Eyles C, Thomas M, et al. Management strategies for chronic rhinosinusitis: a qualitative study of GP and ENT specialist views of current practice in the UK. *BMJ Open* 2018; **8:** e022643.

31 Lourijsen ES, Reitsma S, Vleming M, et al. Endoscopic sinus surgery with medical therapy versus medical therapy for chronic rhinosinusitis with nasal polyps: a multicentre, randomised, controlled trial. *Lancet Respir Med* 2022; **10:** 337–46.

32 Videler WJ, Badia L, Harvey RJ, et al. Lack of efficacy of long-term, low-dose azithromycin in chronic rhinosinusitis: a randomized controlled trial. *Allergy* 2011; **66:** 1457–68.

33 Gudziol V, Lötsch J, Hähner A, Zahnert T, Hummel T. Clinical significance of results from olfactory testing. *Laryngoscope* 2006; **116:** 1858–63.

34 Banglawala SM, Oyer SL, Lohia S, Psaltis AJ, Soler ZM, Schlosser RJ. Olfactory outcomes in chronic rhinosinusitis with nasal polyposis after medical treatments: a systematic review and meta-analysis. *Int Forum Allergy Rhinol* 2014; **4:** 986–94.

35 Mattos JL, Schlosser RJ, Storck KA, Soler ZM. Understanding the relationship between olfactory-specific quality of life, objective olfactory loss, and patient factors in chronic rhinosinusitis. *Int Forum Allergy Rhinol* 2017; **7:** 734–40.

36 DeConde AS, Mace JC, Levy JM, Rudmik L, Alt JA, Smith TL. Prevalence of polyp recurrence after endoscopic sinus surgery for chronic rhinosinusitis with nasal polyposis. *Laryngoscope* 2017; **127**: 550–55.

37 Vlaminck S, Vauterin T, Hellings PW, et al. The importance of local eosinophilia in the surgical outcome of chronic rhinosinusitis: a 3-year prospective observational study. *Am J Rhinol Allergy* 2014; **28:** 260–64.

38 Lodato EM, Kaplan W. Priority medicines for Europe and the world "a public health approach to innovation": background paper 6.1 antimicrobial resistance. World Health Organization, 2013.

39 Gibbins NE, Theokli C, Hopkins C. Time to reconsider guidelines on clarithromycin in chronic rhinosinusitis? *BMJ* 2013; **346:** f2678.