

Endoscopic sinus surgery in adult patients with Chronic Rhinosinusitis with nasal polyps (PolypESS) - statistical analysis plan for a multicentre randomised controlled trial*

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Abstract

Background: Chronic rhinosinusitis with nasal polyps (CRSwNP) afflicts 2-4% of the population and comes with a long time burden of disease and high societal costs. The current treatment consists of medical treatment alone or in combination with endoscopic sinus surgery. No consensus exists on the right timing and extent of disease that warrants surgery. Furthermore, there is lack of clinical knowledge about the benefit of surgery over medication only. The current study evaluates the clinical effectiveness and cost-effectiveness of endoscopic sinus surgery in addition to medical treatment versus medication alone in the adult patient group with nasal polyps (CRSwNP).

Methods: The PolypESS trial is designed as a prospective, randomised, multicentre trial in adult patients with CRSwNP selected for primary or revision endoscopic sinus surgery by their otorhinolaryngologist. Patients are randomly assigned to endoscopic sinus surgery in addition to medication or medical therapy only. This paper details the statistical analysis plan (SAP) of this trial and was submitted before outcome data were available.

Results: The primary outcome of the trial is disease-specific Health-Related Quality of Life quantified by the SNOT-22 at 12-months follow-up. Secondary outcomes consist of generic and disease-specific Health-Related Quality of Life, objective signs of disease and adverse events of treatment. Subgroup analyses will be performed to verify if treatment effects differ among patient phenotypes. Analyses will be completed according to this pre-specified SAP. The main analysis will be performed as a standard ITT analysis.

Discussion: The PolypESS trial will show whether addition of endoscopic sinus surgery to medical treatment improves the disease-specific Health-Related Quality of Life quantified by the SNOT-22 at 12-months follow-up. Unforeseen deviations from the SAP at the time of analysis will be motivated and discussed in the final publication of the primary outcome of this study.

Key words: paranasal sinus disease, sinusitis, nasal polyps, quality of life, endoscopic sinus surgery

Introduction

Patients with chronic rhinosinusitis with nasal polyps (CRSwNP) experience a significant impact on most aspects of their Health-related Quality of Life (HrQOL) ⁽¹⁻³⁾. Together with the high prevalence of disease (1-4%), the diagnosis and treatment give high healthcare costs ⁽⁴⁻⁶⁾. The current treatment exists of medical

treatment alone or in combination with endoscopic sinus surgery (ESS) ^(5, 7-11). It is unclear what the benefit is of the addition of surgical treatment on top of on-going medical treatment and at what time point in the disease course a patient should be offered surgery. The PolypESS study is the first multicentre, randomised controlled trial investigating the impact of ESS on

disease-specific HrQOL in adult patients suffering from CRSwNP in comparison to on-going medical treatment. Currently a large RCT comparing ESS with a prolonged course of Claritromycine in patients with chronic rhinosinusitis without nasal polyps (CRSsNP) and CRSwNP is conducted in the UK ⁽¹²⁾. Further details on the background of our current study are described in the previously published trial protocol ⁽¹³⁾.

Study objectives

The primary objective is to assess the effect of performing ESS in addition to medical treatment instead of medical treatment alone on patient health-related quality of life (HrQOL) and cost-effectiveness in adults with CRSwNP. Primary hypothesis is that the addition of ESS is better than medical treatment alone considering the mean difference (95% CI) in total SNOT-22 score at 12 months follow-up. We will test for superiority. The secondary hypotheses will be evaluated for risk difference (%) or mean difference (95% CI) between intervention groups. The following secondary hypotheses will be tested: ESS is better than medication only in improving generic HrQOL (as measured with the EQ-5D-5L), ESS is better in improving objective signs of disease (as measured with the nasal polyp score, Modified Lund-Kennedy score, Modified Lund- Mackay Postoperative Endoscopy score), ESS comes with better olfactory function (as measured with the Sniffin Sticks Test) and ESS gives higher improvement in nasal obstruction (as measured with the Peak Nasal Inspiratory Flow). Furthermore ESS comes with better disease control (as measured with the EPOS Control Test ⁽¹⁴⁾), better asthma control (as measured with the Asthma Control Test ⁽¹⁵⁾) and less symptomatic exacerbations requiring further treatment including ESS at 12 months follow-up. We will descriptively report (serious) adverse events in both treatment groups. We hypothesize more adverse events in the medical treatment group at 12 months follow-up. For more details on the process of data collection and a description of all secondary outcome measurements we refer to the published study protocol article ⁽¹³⁾.

Protocol developments

PolypESS is an investigator-initiated, prospective, open, multicentre randomised clinical superiority trial with parallel treatment groups. Participants are randomised to either ESS in addition to medical treatment or medical treatment alone. Medical treatment can be any treatment available for CRSwNP. The trial protocol is reviewed and approved by the Medical Ethics Committee (MEC) of the Amsterdam University Medical Centres, location AMC (Amsterdam, The Netherlands) and has been obtained for each participating centre. Written informed consent is obtained from all participants before any trial-related procedure is performed. The trial was registered in The Netherlands National Trial Register (<http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=4978>): NTR4978 on 27 November 2014.

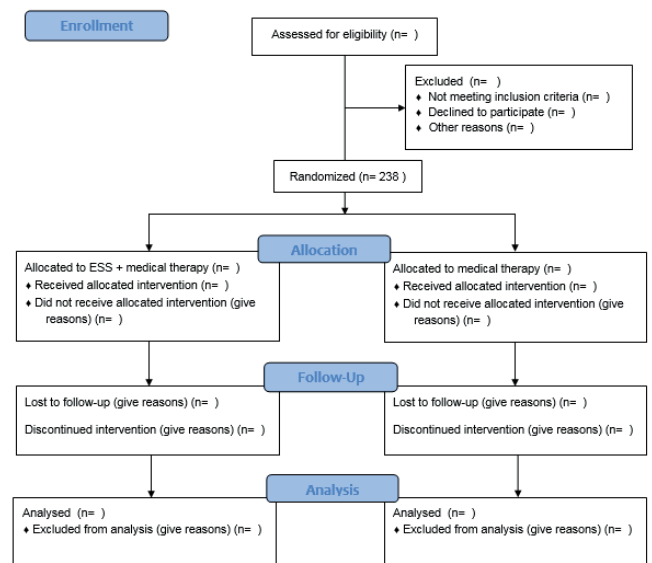


Figure 1. PolypESS CONSORT 2010 flow diagram.

There were no amendments apart from some small changes of wording in the patient letter and amendments concerning change of local investigators. In total 15 study centres (3 university centres and 12 otolaryngological hospital clinics) included patients in the trial. No changes were made regarding the sample size. The date of the inclusion of the first patient was 15-02-2015. The expected date of the completion of follow-up (24 months) for the last patient is 01-09-2021. The trial is conducted according to the principles of the Declaration of Helsinki ⁽¹⁶⁾ the Dutch law of Medical Research Involving Human Subjects (WMO) and GCP Guidelines (GCP).

Statistical Analysis Plan

General principles

The analyses will be done by the investigators of the study group supervised by an independent statistician. The analyses will be performed after data verification and validation have been carried out and after this SAP has been accepted for publication. The statistical programming and analysis to produce all tables and figures will use the SPSS v. 26 (IBM Corporation, Armonk, NY, USA) and the software environment R (latest version 4.0.3) ⁽¹⁷⁾. Descriptive statistics, means with SD for continuous normally distributed variables, medians and interquartile ranges for continuous skewed variables, and frequency counts with percentages for nominal variables will be used to summarize variables. Normality will be checked for with a Normal Q-Q plot and histogram. No statistical normality tests will be performed.

Patient flow diagram

A flow diagram of study participants will be displayed in line with the Consolidation Standard of Reporting Trials (CONSORT)

recommendations and finalized upon external peer review (Figure 1)⁽¹⁸⁾.

Treatment according to protocol and withdrawal

Treatment was regarded to have proceeded according to the study protocol if a patient had surgery or a discussion about additional medical treatment within 6 weeks after inclusion. All patients that attended the baseline visit will be included in the ITT population. Primary outcome is measured after 12 months, planned 12 months after the start of the allocated intervention. For all time points within or at 12 months of follow-up a window of 30 days before or after the scheduled time point is accepted. The numbers of losses to follow-up (withdrawal from follow-up) and dropouts (withdrawal from intervention) will be summarized by study arm. A line-by-line listing of reasons for withdrawal or loss to follow-up will be presented in an Appendix. A patient is considered lost to follow-up if both a scheduled study visit or replacement telephone visit could not be performed at 6 months follow-up and at 12 months follow-up (after at least three phone calls, two e-mails, sending postal questionnaires and a letter). If patients miss the 12 months visit, multiple imputations will be conducted if needed. A study visit is set to be missing if no SNOT-22 is obtained and the patient could not be contacted for study-related questions.

Definition of intention-to-treat, per-protocol and as-treated sets
The main analysis will follow the intention-to-treat (ITT) principle with all patients analysed in their randomisation group, irrespective of protocol adherence. This includes patients that crossed over to the other study treatment group during the course of the study (only possible from medication to ESS). Only patients with a protocol violation concerning eligibility are excluded from the ITT analysis. Protocol violation in eligibility refers to randomised patients who did not fulfil inclusion criteria or randomised patients who did meet an exclusion criterion. Baseline characteristics will be evaluated for these patients and compared to the ITT population. In addition, a per-protocol and as-treated analysis will be performed. Baseline characteristics will be compared between ITT, PP and as-treated with adjustment for confounding in the ITT and as treated analysis. The per-protocol analysis will include patients that were included and treated according to the study protocol. This means that patients who crossed over to the ESS treatment group will be excluded. The as-treated analysis includes patients that switched treatment (from medical to surgical). A summary of the inclusion and exclusion of patients in the analysis sets is displayed in Figure 2.

Representativeness of study sample

The total number of participants that were eligible will be reported including distribution of gender, age and when available disease-specific health-related quality of life (SNOT-22). To

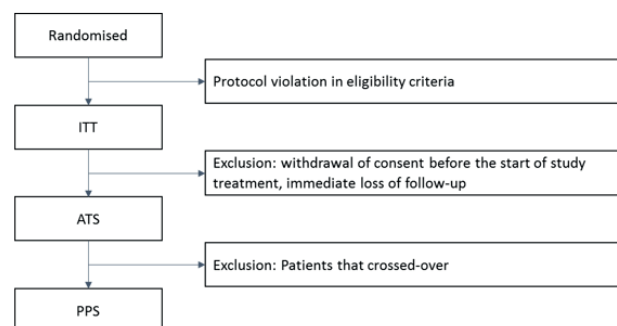


Figure 2. Summary of participant inclusion for the intention-to treat (ITT), as treated (ATS) and per-protocol set (PPS).

evaluate whether the randomised group is representative for all eligible patients, a comparison will be made between patients who declined to participate but were willing to fill in a SNOT-22 questionnaire and the randomised population. Mean age, percentage of males and mean or median disease-specific health-related quality of life, measured at baseline, will be compared.

Sample size

The power analysis is based on the literature-based assumption that the minimal clinically important difference (MCID) for the SNOT-22 is 8.9 points (SD 20.0)⁽¹⁹⁾. A two-group t-test with a two-sided p-value of 0.05, a power of 90% to detect a difference and an anticipated 10% loss of follow-up led to 238 patients needed for the main analysis.

Patient replacement and handling of missing data

Patients not fulfilling eligibility criteria resulting in the exclusion of the ITT analysis will not be replaced. An analysis of missing data will be performed to check for the assumptions regarding the missing data. In participants with missing data for the primary outcome (SNOT-22 at 12 months follow-up), multiple imputation will be used to predict the outcome if more than 60% of data is present ($\leq 40\%$ missing data). Considering the type of variables for which data could be missing and the nature of the trial, missing data will probably be missing at random and will be multiple imputed using chained equations (MICE). Results for the primary outcome at 12 months will be compared to complete cases.

Baseline characteristics

The mock-up of the baseline characteristics table can be found in Table 1. The baseline characteristics of all study participants will be presented in a table. Nominal variables will be presented as percentages and frequency counts for each category per treatment group. Categories will be displayed in the table if relevant. Continuous variables with a normal distribution will be summarized using means and standard deviations, whereas

Table 1. Baseline characteristics (data will be reported for both groups, total N=238).

Item	Description	Scale of measurement	Statistical analysis
Patient characteristics			
Gender	Males	Nominal	Percentage (and frequency count)
Age	Age in years	Discrete	Range, mean, SD or median and interquartile range in case of skewed data
Sensitisation for common aeroallergens	Proportion presence aero-allergy	Nominal	Percentage (and frequency count)
Total IgE	Total IgE expressed in kU/L	Continuous	Range, mean, SD or median and interquartile range in case of skewed data
Eosinophil count	Absolute count expressed in units 109/L	Continuous	Range, mean, SD or median and interquartile range in case of skewed data
Nasal polyp size (left and right)	0-8 points	Nominal	Percentage (and frequency count)
Lund-Mackay score	0-4 points 5-9 points 10-14 points 15-24 points	Nominal	Percentage (and frequency count)
Patient reported data			
Asthma	Presence	Nominal	Percentage (and frequency count)
NSAID-exacerbated respiratory disease	Presence	Nominal	Percentage (and frequency count)
Previous sinus surgery	Presence of previous sinonasal surgery	Nominal	Percentage (and frequency count)
Last sinus surgery	Proportion of years since last surgery 0-4 years 5-10 years > 10 years	Nominal	Percentage (and frequency count)
Smoking	Active smoker, former smoker	Nominal	Percentage (and frequency count)
Topical nasal corticosteroids	Proportion of current users	Nominal	Percentage (and frequency count)

medians and interquartile ranges will be used in case of non-normal distributions. Mean SNOT-22 scores will be dealt with as described above. Other missing data will not be imputed. The number of patients in the variable row will be reported when more than five patients have missing data for the variable of interest. We will not test for differences between study groups.

Assessment and analysis of primary outcome

The mock-up of the analysis of primary and secondary outcomes is shown in Table 2. For the primary outcome, SNOT-22 at 12 months, first a descriptive analysis will be performed. The mean difference with 95% CI will be reported for each treatment group.

Analyses will be stratified by baseline nasal polyp size, CT-sinus Lund-Mackay score, presence or absence of NSAID-Exacerbated Respiratory Disease (N-ERD) and tertiary care centres versus secondary care centres. If potential modification of the effect of ESS is suspected, subgroup analysis will be done further by multiple regression.

Assessment and analysis of secondary outcomes

Following the strategy for the primary outcome as described

above, secondary outcome measures will be analysed to further evaluate the added value of ESS over medication alone. These outcome measures are described in Table 2.

Analysis of safety outcomes

Safety outcomes are serious adverse events (SAE) and non-serious adverse events (AE). Both will be explored and reported for each treatment group, listed in a table, if they are related to study treatment or study activities.

Discussion

The aim of the PolypESS trial is to provide evidence regarding the effect of ESS in adult patients with CRSwNP. In this statistical analysis plan, we present the methods we will use to evaluate whether or not ESS is of additional value in the care of patients with CRSwNP. We have chosen the widely accepted SNOT-22 as primary outcome measure as it reflects our main interest: whether a patient reports a better HrQOL after surgery. In order to approach the real-life situation, patients from secondary and tertiary care hospitals are included whenever the treating otorhinolaryngologists would consider surgery to be indicated. Following the real-life dogma in which patients may need addi-

Table 2. The analysis of primary and secondary outcomes.

	Methods	Unit of measurement	Calculations or transformations	Timing of measurement	Primary analysis
Primary outcome					
Disease-specific HRQOL as measured with the Sinonasal Outcome Test 22 (SNOT-22)	The definition of the SNOT-22 is presented in the published study protocol	The difference / contrast in absolute SNOT-22 score between treatment groups and accompanying 95% CI. In addition, mean delta SNOT-22 will be reported (change from baseline)	Items on the SNOT-22 will be summed to calculate a total score (0-110). The delta will be calculated for each patient or for the treatment group depending on the amount of missing values.	Baseline and 12 months follow-up	Analysis in ITT and PP analysis. First a descriptive analysis will be performed. Mean difference with 95% CI will be reported.
Secondary outcomes					
Generic HRQOL as measured with the EQ-5D-5L	A questionnaire comprising five domains/questions: mobility, self-care, usual activities, pain or discomfort and anxiety or depression. The EQ-5D-5L can describe 3125 (55) unique health states. In addition, a VAS for health status is applied (0-100)	1. Difference between treatment groups in utility scores 2. Difference between treatment groups in VAS calculated from EQ-5D-5L	A health state index score will be calculated from individual health profiles using the Dutch time trade-off-based health utility algorithm for the EQ-5D-5L.	12 months follow-up	Analysis in ITT. Mean, standard deviation (SD) or median and interquartile range in case of skewed data will be provided for the study population by visit and by treatment.
CRS Symptoms	Total clinical symptoms, nasal blockage, symptoms of rhinorrhoea, symptoms of postnasal drip, facial pain / headache and loss of smell are measured with a Visual Analogue Scale (VAS) ranging from 0-10.	Difference between treatment groups in mean VAS scores	No calculations needed	12 months follow-up	Analysis in ITT. Mean, standard deviation (SD), or median and interquartile range in case of skewed data will be provided per item by treatment group if there is a relevant difference between treatment groups.
Asthma Control	Asthma Control Test (2002 TM Quality/Metric Incorporated) is used in the subpopulation of patients with asthma. It contains five individual questions (total score 5-25 points)	Difference between treatment groups in level of control.	Items on the five questions will be summed to calculate a total score which represents a category of control Level of control: <20 = uncontrolled asthma, 20-24= controlled asthma, 25 = well controlled asthma	12 months follow-up	Analysis in ITT. Percentage and frequency count will be reported.
Nasal polyp score	Left and right side of the nose is scored for size of nasal polyps (0-4 on both sides). For a description of the scoring system, see the published protocol.	Difference between treatment groups in percentage and count of each category.	Score of left and right side will be summed to get a total score.	12 months follow-up	Analysis in ITT. Percentage and frequency count will be reported.
Modified Lund-Kennedy endoscopy score (MLK)	Left and right side of the nose is scored for presence or absence of polyp, oedema and discharge (total score 0-12). For a description of the scoring system see, the published protocol.	Difference between treatment groups in mean total MLK score	Scores for three items on each side of the nose will be summed to calculate a total score.	12 months follow-up	Analysis in ITT. Range, mean, SD or median and interquartile range in case of skewed data will be reported.
Modified Lund Mackay Postoperative Endoscopy Score (MLMES)	Left and right maxillary, ethmoid, sphenoid, frontal sinuses and olfactory fossa are scored for mucosal inflammation, mucus and purulent discharge (total score 0-100). For a description of the scoring system see, the published protocol.	Difference between treatment groups in mean total MLMES scores. Only for patients that underwent ESS in the past or as part of the study treatment.	Scores for five items on each side of the nose will be summed to calculate a total score.	12 months follow-up	Analysis in ITT. Range, mean, SD or median and interquartile range in case of skewed data will be reported.

	Methods	Unit of measurement	Calculations or transformations	Timing of measurement	Primary analysis
Nasal obstruction	Peak nasal inspiratory flow method (PNIF) is used to quantify nasal obstruction. For a description of measurement, see the published protocol.	Difference between treatment groups in PNIF score	No calculations needed. Only the highest value will be used for an individual patient.	12 months follow-up	Analysis in ITT. Mean, SD or median and interquartile range in case of skewed data will be reported.
Olfactory function	The 'Sniffin' Sticks Identification test is used to assess olfactory performance by a 12-odor identification test. For a description of measurement, see the published protocol.	Difference between treatment groups in percentage of normosmic, hyposmic and anosmic patients.	Correctly identified odours will be summed and classified as normosmic (11-12 correct), hyposmic (7-10 correct) or anosmic (0-6 correct)	12 months follow-up	Analysis in ITT. Percentage and frequency count will be reported for the study population by visit and treatment.
Disease control of CRS	Control is evaluated as suggested by the European Position Paper on Chronic Rhinosinusitis (EPOS 2012). Symptoms of nasal blockage, rhinorrhoea/postnasal drip, facial pain/headache, olfactory function, sleep disturbance or fatigue will be evaluated together with nasendoscopic findings and any systemic medication needed to control disease.	Difference between treatment groups in percentage of controlled, partially controlled or uncontrolled patients.	Classification based on the answers for individual symptoms, findings during nasendoscopy or need for additional systemic medication. Scoring: <ul style="list-style-type: none"> • No symptoms and normal mucosa without need for systemic medication= controlled disease • ≥ 1 symptom or presence of diseased mucosa or need for systemic medication in the past 3 months = partially controlled disease. • ≥ 3 features of disease = uncontrolled disease. • Need for systemic medication in the past month= uncontrolled disease. 	12 months follow-up	Analysis in ITT. Percentage and frequency count will be reported.
Exacerbations of CRS	Symptoms of CRSwNP requiring further treatment (surgical or medical) collected in clinical practice.	Difference between treatment groups in count and percentage of exacerbations.	Number of episodes requiring intervention will be calculated for each patient between time points.	12 months follow-up	Analysis in ITT. Percentage and frequency count will be reported
Adverse events	Serious and non-serious adverse events related to treatment for CRSwNP (as defined by researcher) as measured by anamnesis and patient diaries.	Difference in (serious) adverse event rate (number and percentage) between treatment groups.	Adverse events will be summed between baseline and 12 months follow-up	12 months follow-up	Analysis in ITT. Percentage and frequency count of adverse events will be reported for the study population by treatment. Number of people with an event will be reported in both treatment arms. In the Appendix a line listing will be added of all adverse events per treatment group.
Daily nasal symptoms	Nasal symptoms will be recorded by patients each day 2 weeks before a visit until 2 weeks after a visit (score 0-3 for headache/ facial pain, rhinorrhoea, nasal congestion, loss of smell). For a description of scoring, see the published protocol.	Difference in weekly daily symptom scores between treatment groups	The main daily symptom sum-score is calculated for each patient as the sum of all individual symptom scores, representing the sum of the severity of the most common nasal symptoms (0-12)	12 months follow-up	Analysis in ITT. Only patients with ≥ 4 observations per week will be included. Mean, SD or median and interquartile range in case of skewed data will be reported.

	Methods	Unit of measurement	Calculations or transformations	Timing of measurement	Primary analysis
Medication compliance	Compliance to drug treatment for CRSwNP is measured with daily patient diaries filled in each day 2 weeks before a visit until 2 weeks after a visit	Difference between treatment groups in ratio between as administered daily dose/prescribed daily dose using the patient medical record.	Weekly ratio is calculated for each patient as the sum of daily ratios per medicine for CRSwNP	12 months follow-up	Analysis in ITT. Mean, SD or median and interquartile range in case of skewed data will be reported.

tional treatment over time, the study protocol enables crossover from medical treatment alone to the addition of surgery. Still, we will analyse the data primarily in an intention-to-treat fashion as described here. Unforeseen deviations from the SAP at the time of analysis will be motivated and discussed in the paper describing the primary and secondary outcomes.

List of abbreviations

CONSORT: CONSolidated Standards of Reporting Trials; CRSwNP: Chronic rhinosinusitis with nasal polyps; EPOS: European Position Paper on Chronic Rhinosinusitis; ESS: Endoscopic sinus surgery; HrQOL: Health related Quality of Life; ITT: Intention-to-treat; MICE: Multiple imputations using chained equations; SNOT-22: Sinonasal Outcome Test 22; ZonMw: Dutch Organization for healthcare research and healthcare innovation.

Authorship contribution

WJF is the principal investigator in the Academic Medical Centre and coordinating investigator with regard to all participating sites. ESL, SR and WJF prepared the manuscript. All authors read and approved the final manuscript.

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Conflict of interest

There are no conflicts of interest to report for this manuscript.

References

- Phillips KM, Speth MM, Shu ET, Talat R, Caradonna DS, Gray ST, et al. Validity of systemic antibiotics and systemic corticosteroid usage for chronic rhinosinusitis as metrics of disease burden. *Rhinology*. 2020;58(3):194-9.
- Zhang L, Zhang Y, Gao Y, Wang K, Lou H, Meng Y, et al. Long-term outcomes of different endoscopic sinus surgery in recurrent chronic rhinosinusitis with nasal polyps and asthma. *Rhinology*. 2020;58(2):126-35.
- Hastan D, Fokkens WJ, Bachert C, Newson RB, Bislumovska J, Bockelbrink A, et al. Chronic rhinosinusitis in Europe--an underestimated disease. A GA(2)LEN study. *Allergy*. 2011;66(9):1216-23.
- van Aghoven M, Uyl-de Groot CA, Fokkens WJ, van de Merwe JP, Busschbach JJ. Cost analysis of regular and filgrastim treatment in patients with refractory chronic rhinosinusitis. *Rhinology*. 2002;40(2):69-74.
- Fokkens WJ, Lund VJ, Hopkins C, Hellings PW, Kern R, Reitsma S, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2020. *Rhinology*. 2020;58(Suppl S29):1-464.
- Lourijsen ES, Fokkens WJ, Reitsma S. Direct and indirect costs of adult patients with chronic rhinosinusitis with nasal polyps. *Rhinology*. 2020;58(3):213-7.
- Fokkens WJ BE, van RM H, Sjogren E, Moret-Hartman M. CBO Richtlijn Chronische Rhinosinusitis en Neuspoliepen. 2010.
- Meltzer EO, Hamilos DL. Rhinosinusitis diagnosis and management for the clinician: a synopsis of recent consensus guidelines. *Mayo Clin Proc*. 2011;86(5):427-43.
- Park JJH, Seidel DU, Bachert C, Dazert S, Kostev K. Medication use in patients with chronic rhinosinusitis in Germany - a large retrospective patient-based study. *Rhinology*. 2019;57(2):94-100.
- Reitsma S, Adriaansen G, Cornet ME, van Haastert RM, Raftopoulos MH, Fokkens WJ. The Amsterdam Classification of Completeness of Endoscopic Sinus Surgery (ACCESS): a new CT-based scoring system grading the extent of surgery. *Rhinology*. 2020;58(6):538-43.
- Steiner UC, Bischoff S, Valaperti A, Ikenberg K, Starzyk J, Bucher S, et al. Endotypes of chronic rhinosinusitis with nasal polyps with and without NSAID aero" intolerance. *Rhinology*. 2020;58(6):544-9.
- Philpott C, le Conte S, Beard D, Cook J, Sones W, Morris S, et al. 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(1):246.
- Lourijsen ES, de Borgie CA, Vleming M, Fokkens WJ. Endoscopic sinus surgery in adult patients with chronic rhinosinusitis with nasal polyps (PolypESS): study proto-

- col for a randomised controlled trial. *Trials*. 2017;18(1):39.
14. Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2012. *Rhinology Supplement*. 2012;23:3 p preceding table of contents, 1-298.
 15. Nathan RA, Sorkness CA, Kosinski M, Schatz M, Li JT, Marcus P, et al. Development of the asthma control test: a survey for assessing asthma control. *J Allergy Clin Immunol*. 2004;113(1):59-65.
 16. WMA. Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects [Available from: <https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/>].
 17. Team RC. A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. 2018 [Available from: <https://www.R-project.org/>].
 18. Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. *Lancet*. 2001;357(9263):1191-4.
 19. Hopkins C, Gillett S, Slack R, Lund VJ, Browne JP. Psychometric validity of the 22-item Sinonasal Outcome Test. *Clin Otolaryngol*. 2009;34(5):447-54.

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