Chronic Rhinosinusitis

Executive summary:

To identify areas of priority for new evidence syntheses and updates in patients with chronic rhinosinusitis (CRS) we conducted a scoping exercise, which included identifying current reviews, comprehensive searches and discussions with clinical experts. We looked at Cochrane reviews and HTA reports, and we also conducted searches to identify the number of new trial abstracts in order to estimate the amount of new evidence available.

There are no NICE guidelines on the management of CRS, but a commissioning guideline from the Royal College of Surgeons of England and ENT UK is available. The uptake of the EPOS guideline (European Position Paper on Rhinosinusitis and Nasal Polyps, EPOS 2012) is variable, particularly in general practice. Most CRS patients are managed in primary care and have never seen a specialist to establish accurately whether or not they have nasal polyps. Topical steroids are the standard treatment, but many patients are also treated with short courses of antibiotics despite the lack of evidence in this area. In addition, many patients may use local decongestants, either on prescription or obtained over the counter.

There are currently 10 published Cochrane reviews, covering a range of topics from topical steroids to the safety and effectiveness of various surgical techniques. Most of the evidence focuses on pharmacological interventions and nasal irrigation with saline. Although most of these reviews have been updated within the past five years, many of them are based on an historical protocol and are focused specifically on evidence for either (a) patients with nasal polyps (CRSwNP) or (b) patients without nasal polyps (CRSsNP); only studies that recruited one type of patients were included. This reflects how patients are grouped in international guidelines such as EPOS and how they are assessed and treated in secondary care, but *not* how patients are managed in primary care. These reviews need to be restructured and standardised.

Taking into account current UK clinical practice, the evidence base and the potential impact of reviews, we propose the following:

1. Include in Cochrane CRS reviews studies that recruited patients with CRS, *regardless of whether these patients had nasal polyps*, as the distinction is not usually made in primary care where most management decisions are made. We will investigate the effects of interventions among patients with various phenotypes of CRS diagnosis as subgroups in the analysis.

2. Review the evidence for pharmacological interventions: topical steroids, oral steroids, antibiotics (short- and long-term) and nasal (saline) irrigations.

   A review of the evidence for surgical interventions is of lower priority. A review was completed at the end of 2014 and found little (RCT) evidence on the relative effectiveness of surgical interventions *versus* medical interventions. Variations in surgical techniques are the subject of a few Cochrane reviews, but we consider this topic to be of lower priority in terms of its impact on the NHS and therefore we will not review it.

We have also considered other 'up and coming' interventions such as monoclonal antibodies to IL-5, anti-IgE and leukotriene antagonists. In addition, we have also identified agents that have either been shown to be ineffective or should not be used for CRS, but are widely used inappropriately. If time and budget allow, we will also deliver reviews of antifungals and local decongestants. However, if this is impossible, the Cochrane ENT group will commit to undertake these reviews as part of their programme.

3. Use a common set of outcome measures of effectiveness across all the reviews based on those that are important to patients (patient-rated symptom scores, quality of life), so that the results of the interventions are comparable. At the same time, we will consider the potential harms to be assessed based on the characteristics of the interventions considered. In this we have been informed by the preliminary findings of a research project examining patient-relevant outcomes in CRS recently conducted at University College London (UCL).

We will not review CRS in special populations (e.g. patients with cystic fibrosis) and special phenotypes of CRS (e.g. Samter's triad), as the evidence from these populations is generally not applicable to the wider population.

An experienced systematic reviewer and a clinical expert will lead all the reviews to ensure clinical relevance, high methodological quality and timely completion of the reviews. We will involve junior doctors whenever possible, to provide training opportunities and exposure to evidence-based medicine.

1 THE REMIT

A review of the evidence for all methods of managing CRS in people with and without nasal polyps.

2 CLINICAL NEED FOR THE REVIEW OF EVIDENCE

2.1 EPIDEMIOLOGY/BURDEN OF DISEASE

2.1.1 Description of populations and impact (outcomes)

CRS represents a common source of ill health; 11% of UK adults reported CRS symptoms in a worldwide population study[1]. Symptoms, including nasal obstruction, nasal discharge, facial pain, anosmia and sleep disturbance, have a major impact on quality of life, reportedly greater in several domains of the SF-36 than angina or chronic respiratory disease[2]. Acute exacerbations, inadequate symptom control and respiratory disease exacerbation are common. Complications are rare, but may include visual impairment and intracranial infection.

Longitudinal data from the Clinical Practice Research Datalink (CPRD) shows that 1% of UK adults receive treatment for CRS from their GP each year, averaging four GP visits; they receive multiple medications with 91% receiving an antibiotic prescription[3]. Data from Hospital Episode Statistics (HES) for 2012-13 show that approximately 40,000 sinus operations were performed in England and Wales, in addition to an estimated 120,000 outpatient consultations[4]. A worldwide study demonstrated that one in three CRS patients in primary care have poorly controlled symptoms[5]. The socio-economic cost of CRS is significant: 57% of patients reported absenteeism and 28% associated anxiety and depression in a Swedish study[6].

2.2 CURRENT PRACTICE

2.2.1 Description of interventions

Pharmacological interventions commonly used include:

- Intranasal corticosteroids (INCS)
- Systemic steroids
- Antibiotics

The types of surgery used for the management of CRS include:

- Endoscopic sinus surgery; this approach may include a variety of surgical instruments including balloon sinuplasty and surgery of differing extent
- Open approaches to the sinuses (rarely used)

Other interventions used (or misused):

- Nasal irrigations, including high- and low-volume irrigations, differing solutions (such as saline or buffered saline), differing strength of solutions and irrigations with additives such as surfactants or xylitol
- Antifungals, either topical or systemic
- Local decongestants

2.2.2 How different interventions work

Although the aetiology of CRS is not fully understood, CRS may involve abnormalities in the host response to irritants, commensal and pathogenic organisms and allergens, obstruction of sinus drainage pathways, abnormalities of normal mucociliary function, loss of the normal mucosal barrier or infection. Two typical profiles may be observed with respect to inflammatory mediators; in eosinophilic CRS, which is typically associated with nasal polyps, high levels of eosinophils, IgE and IL-5 may be found, while in neutrophilic CRS, more often associated with CRS without polyps, neutrophils predominate, with elevated IFN gamma, IL8 and TNF.

Interventions may therefore address any of these aspects: surgery achieves clearance of inflamed tissue (e.g. polyps), restores drainage to blocked sinuses and improves access for topical treatments. Nasal irrigation may improve mucociliary function. Antibiotics may have a direct antibacterial action but some classes, such as macrolides, also have an anti-inflammatory effect. Some researchers had proposed that CRS is an IgE independent immune response to the presence of fungus on the mucosal surfaces and the use of antifungals has therefore been proposed[7].

Due to the differences in mechanisms of action and the pathology of different subgroups of CRS patients, some novel treatments, such as monoclonal antibodies to IL-5, are only likely to be effective in subgroups of patients, while other treatments, such as intranasal steroids (which have anti-inflammatory properties), are likely to have effects in all groups.

2.3 CLINICAL ISSUES/VARIATIONS IN CURRENT PRACTICE

The European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) was published in 2012, but the uptake of EPOS is variable. There are no NICE guidelines on CRS but various sources of guidance, such as the ENT-UK Commissioning Guideline and the Clinical Knowledge Summaries (CKS), are also available for clinicians.

There are several areas where major variation in practice had been identified. In relation to antibiotics, the results of existing trials are conflicting. While the ENT-UK commissioning guideline has recommended that antibiotics are not used in primary care, GPs often prescribe repeated courses. The strength of recommendation to use long-term antibiotics in secondary care is weak.

A second area where uncertainty occurs is regarding whether patients with CRS should receive surgery, and when/how severe their symptoms have to be before surgery is provided. If surgery is provided, what is the best technique? The uncertainty and variation in practice has a 'high-volume' and 'high-cost' impact. At least one in three CRS patients attending ENT clinics are considered to have failed current medical treatment and are considered for surgery. There is also a five-fold variation in UK intervention rates[7], and symptom duration before surgery varies from under one year to over 10 years. Such

uncertainty has resulted in the inclusion of endoscopic sinus surgery in the NICE Database of Treatment Uncertainties (DUETS).

2.3.1 Description of where the evidence is

We conducted scoping searches for randomised controlled trials (RCTs), using the methods established in the existing Cochrane reviews, in PubMed, CENTRAL and EMBASE (from 2010 to March 2015); and we developed a new combined strategy for CRS with/without polyps for CENTRAL and Ovid Medline (see further details in Appendix 2). We also searched for existing evidence from clinical guidelines, Cochrane reviews and HTA reports. We reviewed the results to identify all the interventions where RCTs have been identified and where better evidence would support clinical decision-making.

There are 10 existing Cochrane reviews[9-18] published in *The Cochrane Library*. Five of these looked at various pharmacological interventions (nasal steroids, oral steroids, antibiotics and antifungals): two reviewed CRS patients with established nasal polyps[11,18]; two reviewed those without[12,15]; and the other reviewed antifungals[13]. Two reviews looked at the effectiveness of surgery versus medical treatment[10,17], and two others reviewed the different surgical techniques[9,14]. The last review looked at nasal saline irrigation for any CRS patient[16].

Although most of these reviews have been updated within the past five years, many are based on historical protocols, which were developed over time by different author teams. Substantial work is required to bring them into line with new Cochrane minimum standards and current clinical practice in the UK. Standardisation of the methods and outcomes measured in these reviews is needed to allow for (indirect) comparison of the different interventions available for CRS patients. Each of these reviews developed their own population, intervention and comparison criteria; therefore we have also identified some possible gaps where certain populations and intervention-comparison pairs were not covered by any of the current reviews.

By far the largest body of evidence is on topical steroids. This is currently covered by two existing Cochrane reviews. CRSwNP (2012)[11] included 40 studies and CRSsNP (2011)[12] included 10 studies. These reviews are restricted to studies that specifically identified whether patients had nasal polyps or not and despite the large number of studies identified, only seven (small) studies provided data for the main analysis in the review of 40 studies, and even fewer data were available for meta-analysis in the other review. Our scoping searches have identified at least 102 (CRSwNP) and 159 (CRSsNP) new RCT abstracts to screen, based on the scope of the current protocols. As we will expand the scope of these reviews to include all CRS patients, it is possible that more RCTs will be identified. With the limited amount and quality of evidence currently available, any newly identified evidence in this area could have a substantial impact on the evidence base for topical steroids in CRS patients.

Three studies were included in the review of oral steroids in CRSwNP that was published in 2010. Our scoping searches have retrieved 433 new abstracts. The 2010 Cochrane review on systemic antibiotics in CRSsNP included one study. Our scoping searches have identified 546 new abstracts to screen. We plan to expand both of these reviews to include all studies in CRS patients. For antifungals, the 2011

review included six studies, and a preliminary search identified 50 new abstracts to screen if this review is updated.

The oldest review (2006) on nasal saline irrigation in CRS (with/without nasal polyps) included eight studies. Subsequent searches have identified 540 new abstracts to screen.

Our scoping work has identified five additional pharmacological interventions that are not covered by existing Cochrane reviews: leukotriene antagonists, anti-IL-5, anti-IgE, local decongestants and antihistamines. The scoping searches retrieved 381 abstracts on leukotriene antagonists, 624 abstracts on anti-IL-5 and 471 abstracts on anti-IgE. In addition, capsaicin had also been mentioned in the EPOS guideline and our searches retrieved 59 abstracts.

The HTA commissioned systematic review of sinus surgery (published in 2003) identified the need for high-quality studies to compare functional endoscopic surgery with medical treatment[19]. Despite this, recent Cochrane reviews have found little new evidence. Two recent (2014) Cochrane systematic reviews of medical and surgical management concluded that further studies are urgently needed[9,10].

2.3.2 Description of which areas most require an updated evidence synthesis (why is it important to do this review)

Topical steroids, or intranasal corticosteroids, are the mainstay and currently recommended treatment for CRS. However, despite the seemingly large number of studies found, only very few data could be meta-analysed. Therefore, any new studies could still potentially contribute data that affect our confidence in the relative benefits and harms of this treatment.

Similarly, oral steroids are widely used as a form of add-on therapy, but the evidence base is lacking, both in quantity and detail. An up to date systematic review could detect whether our understanding changes with new available evidence and also pinpoint areas for research.

Nasal (saline) irrigation is commonly used as a treatment for CRS, based on the evidence available in a previous review. Despite the relatively low quality of evidence showing its effectiveness, the treatment has been widely adopted, based on the presumption that it does not do patients any harm. However, evidence about the optimal method of delivery, and whether other concentrations of sodium chloride or other types of solutions are as effective, is lacking. An update of the systematic review provides an opportunity to find further evidence to fill these gaps. The effectiveness of the treatment should also be confirmed; although 'harmless', these interventions can have a cost for patients.

One of the most common treatments prescribed to patients with CRS is antibiotic therapy, despite conflicting evidence to support its use. Inappropriate use of antibiotics risks an increase in antibiotic resistance and therefore this area of research is a priority. Although the hypothesis that fungus is an aetiological agent in CRS has been largely rejected [13], antifungals continue to be used. Similarly, topical decongestants are not recommended for the treatment for of CRS, but can be readily obtained without prescription and may be even prescribed by some practitioners. Systematic review of the evidence will be important to serve as an evidence base to discourage the inappropriate use of these agents.

Other pharmacological therapies being evaluated are 'newer' treatments. An up to date synthesis of the evidence available to date is important, both for the detection of potentially useful treatments and to

highlight the insufficiency of current evidence to support their wide adoption. However, reviews of these 'newer' treatments are likely to be of a lower priority than reviews of those agents that are commonly used, or potentially misused.

3 PROPOSED SCOPE OF REVIEWS

This scope defines what the reviews will (and will not) examine. This scope is based on the remit from the NIHR. The areas that will be addressed by the suite of reviews are described in the following sections.

3.1 SETTING

We will include evidence from all healthcare settings.

There will be no limits on the language or year of publication or the country where the research was conducted.

3.2 POPULATION

3.2.1 Populations that will be included:

We will include studies of patients with CRS, whether with polyps (CRSwNP) or without polyps (CRSsNP), in the reviews.

3.2.2 Populations that will not be included:

We will not include special populations and certain phenotypes of CRS in this suite of reviews:

- Allergic fungal rhinosinusitis/eosinophilic fungal/mucinous rhinosinusitis (except for the review(s) on antifungals)
- Aspirin-exacerbated respiratory disease (aka Samter's triad)
- Cystic fibrosis

We will exclude studies that specifically recruited these populations or studies where these populations formed the majority of patients from the reviews. It is very likely that the effects of the interventions observed for these groups are different from most patients with CRS; therefore the results of these studies cannot be pooled or applied to the other groups.

We will not include studies that recruit perioperative patients; these studies assess the effectiveness of therapy that is adjunctive to (sinus) surgery and the data will not be generalisable to other patients.

3.3 INTERVENTIONS

Taking into consideration the uncertainties in current practice, the amount of evidence potentially to be found, and the currency and relevance of recent reviews, we have prioritised the interventions that are likely to make the most impact.

3.3.1 Types interventions to be included in reviews

1. Topical steroids
2. Oral steroids
3. Antibiotics (both topical and oral)
4. Saline irrigation
5. Antifungals
6. Local decongestants
7. Nasal (saline) irrigation
8. Anti-IL-5
9. Anti-leukotrienes
10. Anti-IgE
11. Capsaicin
12. Antihistamines

We will produce reviews on the efficacy and relative effectiveness of interventions 1 to 4, which are most commonly used, as part of this grant, within the timelines stipulated and the funding provided. Our estimation of budget and timelines indicates that there is a risk that the other reviews may only be completed outside the timelines and budget provided. Should this be the case, the Cochrane ENT group will commit to completing these reviews (in the order of priority shown) using their own resources.

3.3.2 Types of interventions to be excluded from the reviews

We will not assess surgical interventions, variations in surgical technique and perioperative procedures as part of this suite of reviews.

Other than capsaicin, we will not review any other herbal, complementary or alternative therapies.

3.4 MAIN OUTCOMES

We will use three outcomes across all the reviews (core outcomes) to allow for comparability across reviews:

1. Disease severity, as measured by patient-reported symptom score (such as the Chronic Sinusitis Survey (CSS), Lund-Mackay scale, visual analogue scales).
2. Health-related quality of life, using disease-specific health-related quality of life scores, such as the Sino-Nasal Outcome Test-22 (SNOT-22), Rhinosinusitis Outcome Measures-31 (RSOM-31) and SNOT-20.
3. Health-related quality of life, using generic quality of life scores, such as the SF-36, EQ-5D and other well-validated instruments.

The choice of patient-reported outcomes allowable for each type of outcome will be guided by the domains covered and the validity of the instrument for the outcome[20,21].

We will choose other outcomes based on the population, intervention and comparisons assessed. Depending on these factors, these outcomes may include:

1. Recurrence of symptoms
2. Endoscopic appearances

3. Complications or adverse effects from treatment; for example: epistaxis, infection, orbital complications, intracranial complications.
4. Objective physiological measures: nasal peak flow, nasal volume, nasal cross-sectional area, nasal nitric oxide (nNO), ciliary function (including saccharine clearance time).
5. Olfactory tests.

4 REVIEW QUESTIONS

Table 1 lists the reviews to be conducted, with details of the types of patient (population), intervention and comparison to be included. We will prioritise reviews **1 to 6** in this project and we will deliver these within the timeline stipulated and within the grant provided. If there is insufficient time and funding, the other reviews will be completed by the Cochrane ENT Group in the order of priority shown, outside the grant for this project.

Table 1: List of populations, interventions and comparisons for the suite of reviews and in which reviews these are likely to be presented.

Key: **INCS** Intranasal corticosteroids

CRS Patients with chronic rhinosinusitis with or without nasal polyps

(Tentative) Review short name[1]	Pair	Population[2]	Intervention[3]	Comparison
1. INCS	1.	CRS	INCS	Placebo/no intervention
2. Relative effectiveness of INCS	2.	CRS	INCS type A	INCS type B
	3.	CRS	INCS delivery method A	INCS delivery method B
	4.	CRS	High-dose INCS	Low-dose INCS
3. Oral steroids (short course)	5.	CRS	Oral steroids	Placebo/no intervention
	6.	CRS	Oral steroids	Other pharmacological treatments[4]
4. Oral steroids (short course) as an add-on therapy	7.	CRS, currently using INCS	Oral steroids + INCS	INCS + placebo/no intervention
	8.	CRS currently using INCS plus antibiotics	Oral steroid + INCS + antibiotics	INCS + antibiotics + placebo/no intervention
5. Antibiotics (systemic and topical)	9.	CRS	Antibiotics	Placebo
	10.	CRS	Antibiotics A	Antibiotics B
	11.	CRS, currently using INCS	Antibiotics + INCS	Placebo + INCS
	12.	CRS, currently using INCS	Antibiotics + oral steroids + INCS	Oral steroids + INCS

[1] This reflects the tentative organisation of different comparison pairs in the reviews. The organisation of information into different reviews may need to be changed, depending on the number of studies eventually included and the clinical relevance of the available comparisons.

[2] Characteristics of populations to be explored as subgroups by the status of surgery (never had surgery, had surgery before, mixed or unknown) and presence of polyps (with polyps, without polyps, mixed or unknown). Where relevant, we will also consider diagnostic criteria for inclusion.

[3] We will explore the effects of the type of active intervention (within a class), method of delivery, dose and duration of intervention and comparisons using subgroup analysis where appropriate.

[4] This can be any other treatments; we will analyse these separately as different comparisons.

6. Saline irrigation	13.	CRS	Saline irrigation	Placebo
	14.	CRS	Saline irrigation A	Other types or volume of nasal irrigation
	15.	CRS, on standard therapy	Saline irrigation + standard therapy[5]	Placebo + standard therapy
7. Antifungals (systemic and topical)	16.	CRS[6]	Antifungals	Placebo
	17.	CRS	Antifungal A	Antifungal B
8. Local decongestants	18.	CRS	Local decongestants	Placebo
	19.	CRS	Local decongestants + standard therapy	Placebo/no intervention + standard therapy
9. Anti-IL-5	20.	CRS[7]	IL-5	Placebo
	21.	CRS	IL-5 + standard therapy	Standard therapy
10. Leukotriene antagonists	22.	CRS	Leukotriene antagonists	Placebo
	23.	CRS	Leukotriene antagonists + standard therapy	Standard therapy
11. Anti-IgE monoclonal antibodies	24.	CRS	Anti Ig E	Placebo
	25.	CRS	Anti IgE + standard therapy	Standard therapy
12. Capsaicin	26.	CRS	Capsaicin	Placebo
	27.	CRS	Capsaicin + standard therapy	Standard therapy
13. Antihistamines	28.	CRS	Antihistamines	Placebo
	29.	CRS	Antihistamines	Standard therapy

[5] Standard therapy refers to intranasal corticosteroids or topical steroids or other regimens where patients may also have additional therapy such as oral corticosteroids.

[6] For antifungals, we will analyse studies which specifically recruited patients with allergic fungal rhinosinusitis as a separate subgroup

[7] Anti-IgE, anti-IL-5 and leukotriene antagonists are only expected to work in CRSwNP. We will not pool data from CRSwNP and CRSsNP patients.

5 REVIEW METHODS

We will use the standard methodology expected in Cochrane reviews, in accordance with the *Cochrane Handbook*[22]. In addition, we will also ensure that the formulation of review questions and interpretation of effects are in line with the recommendations of GRADE and with the NICE guidelines manual[23].

5.1 SEARCHES

The Cochrane Ear, Nose and Throat Disorders Group Trial Search Co-ordinator will conduct systematic searches for randomised controlled trials and controlled clinical trials.

Published, unpublished and ongoing studies will be identified by searching the following databases from their inception:

- the Cochrane Register of Studies ENT Disorders Group Trials Register (search to date);
- the Cochrane Central Register of Controlled Trials (CENTRAL, current issue);
- Ovid Medline (1946 to date) Ovid Medline (In-Process & Other Non-Indexed Citations); PubMed (as a top up to searches in Ovid Medline));
- Ovid EMBASE (1974 to date);
- EBSCO CINAHL (1982 to date);
- LILACS (search to date);
- Web of Knowledge, Web of Science (1945 to date);
- ClinicalTrials.gov, www.clinicaltrials.gov (search via the Cochrane Register of Studies to date);
- ICTRP (search to date);
- ISRCTN, www.isrctn.com (search to date);
- Google Scholar (search to date).

We will combine the subject strategy for CRS patients detailed in Appendix 2 (table 7.1) with adaptations of the existing strategies developed for the present Cochrane intervention reviews. We will develop new strategies for the new reviews.

5.2 TYPES OF RESEARCH DESIGNS CONSIDERED FOR REVIEW

We will include randomised controlled trials, including cluster-randomised trials. We will include quasi-randomised trials.

We will consider cross-over trials for pharmacological interventions, if there is sufficient evidence to suggest that the condition of patients was stable and the washout period was adequate. Otherwise, we will only use the first phase of cross-over trials.

We will exclude studies that randomised patients by side of nose (within-patient controlled). It is difficult to ensure that the effects of any of the interventions considered can be localised.

We will only include studies where patients were followed up for at least three months, to reflect the importance of focusing on long-term outcomes for a chronic condition.

5.3 DATA EXTRACTION AND MANAGEMENT

All the reviews will share a common set of outcome measures of effectiveness (symptom score, health-related quality of life) to ensure comparability between reviews. We will determine any other relevant outcomes and potential harms based on the characteristics of the interventions and comparisons being reviewed. We will define these outcomes *a priori* and list them in a protocol. When we perform data extraction, we will only extract outcomes that are of interest and will use a standardised data extraction form. Unless data extraction or risk assessment have already been completed (e.g. the study has been assessed in a previous Cochrane review), at least two review authors will independently extract data and assess the risk of bias. We will resolve any discrepancies through discussion, with the involvement of an expert clinician and methodologist as required.

5.4 RISK OF BIAS ASSESSMENT

We will summarise binary (yes/no) data using risk ratios (RR) and present them with 95% confidence intervals (95% CI). Where appropriate, we will calculate the absolute risk values using the GRADEpro Guideline Development Tool (GDT), using the median risk in the control group as the baseline risk. We will summarise differences in continuous outcomes using the mean difference (MD) or standardised mean difference (SMD) with 95% CI.

5.5 ANALYSIS AND POOLING OF EVIDENCE

We will choose analysis methods, assess heterogeneity and manage missing data or unit of analysis issues using standard Cochrane methods. We will only conduct subgroup and sensitivity analysis when pre-specified in the review protocols, and we will be highlight and justify any exceptions.

One key feature of the suite of reviews proposed in this document is the inclusion of patients with the two main types of CRS (with and without nasal polyps - CRSwNP, CRSsNP) within the same review. We will explore the differences in response based on the diagnostic groups in subgroup analyses in the topical and oral steroids, antibiotics, local decongestants and nasal saline irrigation reviews. However, anti-IgE, anti-IL-5 and leukotriene antagonists are only expected to work in CRSwNP; we will therefore not pool data from CRSwNP and CRSsNP patients in these reviews and we will analyse these data separately.

To avoid multiplicity of analysis or reviewer bias, we will predetermine the time points for analysis for each outcome, and we will only use the longest available data from the study within the specified period in the analysis. We will specify the time points for data analysis in the protocol for each intervention and take into consideration both the mechanisms of actions of the intervention-comparison pair involved and the natural history of CRS.

5.6 RATING OF QUALITY OF EVIDENCE

We will rate the quality of evidence using the GRADE criteria. We will use the GRADE criteria for systematic reviews. However, we will take particular care to consider the issue of clinically significant effect sizes and to highlight these in the reviews. [§§]

5.7 OUTPUT OF THE EVIDENCE REVIEW

All of the reviews will be published as Cochrane reviews.

An indirect benefit of conducting this suite of reviews is the development of systematic review methodology that is specific for CRS (e.g. choice of outcomes and whether different ways of measuring an outcome can be pooled), which can then be used as guidance for future reviews in this area. Methodological issues are a significant challenge in reviewing the evidence in CRS (large number of possible outcomes and methods and measuring, uncertainty in validity and clinical interpretation); the availability of this guidance will allow future reviews in the area to be produced more quickly and to a higher quality.

[§§] There are two main differences between the approaches used for systematic reviews versus clinical guidelines:

1. Imprecision rating: Systematic reviews consider where the confidence intervals cross the line of no difference (i.e. RR = 1, or MD = 0); i.e. confidence in whether the effect of the intervention will be higher or lower compared to the control group is assessed. In contrast, guideline panels need to consider whether an effect size is of clinical significance (for example, a 25% increase, RR 1.25 is considered to be the minimum desirable or acceptable in order to consider it worthwhile to use an intervention). Confidence intervals that include this minimal important difference value (e.g. 95% CI of RR 1.02 to 1.3) will be considered imprecise.
2. Indirectness rating: Systematic reviews typically do not downgrade the evidence for indirectness since the evidence is only included if it satisfies the criteria. However, clinical guidelines can downgrade evidence for indirectness (lack of applicability) if the evidence has originated from a setting or population that is very different (and the effects of the interventions may be different) from the population to which the evidence will be applied, or certain characteristics in the intervention, comparison and outcomes measured affect its applicability.

6 APPENDIX 1

Existing list of Cochrane reviews.

Review title	Date of last search	Number of included RCTs	Estimated number of abstracts***
CRS			
1. Steroid-eluting sinus stents for improving symptoms in chronic rhinosinusitis patients undergoing functional endoscopic sinus surgery	14/05/2015	0	n/a
2. Functional endoscopic balloon dilation of sinus ostia for chronic rhinosinusitis	19/12/2010	1	79
3. Functional endoscopic sinus surgery for chronic rhinosinusitis	17/11/2008	3	162
4. Nasal saline irrigations for chronic rhinosinusitis	16/11/2006	8	212
CRSwNP			
5. Surgical versus medical interventions for chronic rhinosinusitis with nasal polyps	20/02/2014	4	852
6. Surgical interventions for chronic rhinosinusitis with nasal polyps	20/02/2014	0	852
7. Topical steroids for nasal polyps	10/04/2012	40	102
8. Oral steroids for nasal polyps	11/10/2010	3	433
CRSsNP			
9. Topical steroid for chronic rhinosinusitis without polyps	08/07/2010	10	159
10. Systemic antibiotics for chronic rhinosinusitis without nasal polyps in adults	09/06/2010	1	546
Allergic fungal rhinosinusitis			
11. Topical and systemic antifungal therapy for the symptomatic treatment of chronic rhinosinusitis	07/03/2011	6	50

*** The scoping search was conducted in March 2014 using the previous search strategies and without deduplication.

7 APPENDIX 2

Where applicable we combined the searches with the highly sensitive search strategy designed by The Cochrane Collaboration for identifying randomised controlled trials and controlled clinical trials (as described in the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0, Box 6.4.b.

7.1 SEARCHES FOR CONDITION ALONE

CENTRAL	Ovid Medline	EMBASE (Ovid)
#1 MeSH descriptor: [Sinusitis] explode all trees #2 MeSH descriptor: [Rhinitis] this term only #3 MeSH descriptor: [Rhinitis, Atrophic] this term only #4 MeSH descriptor: [Rhinitis, Vasomotor] this term only #5 MeSH descriptor: [Paranasal Sinus Diseases] this term only #6 MeSH descriptor: [Paranasal Sinuses] explode all trees #7 rhinosinusitis or nasosinusitis or pansinusitis or ethmoiditis or sphenoiditis #8 kartagener* near syndrome* #9 inflamm* near sinus* #10 (maxilla* or frontal*) near sinus* #11 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 #12 MeSH descriptor: [Chronic Disease] explode all trees #13 MeSH descriptor: [Recurrence] explode all trees #14 chronic or persis* or recurrent* #15 #12 or #13 or #14 #16 #11 and #15 #17 CRSsNP #18 (sinusitis or rhinitis) near (chronic or persis* or recurrent*) **#19 #16 or #17 or #18** #20 MeSH descriptor: [Nasal Polyps] explode all trees #21 MeSH descriptor: [Nose] explode all trees #22 MeSH descriptor: [Nose	1. exp Sinusitis/ 2. paranasal sinus diseases/ or rhinitis/ or rhinitis, atrophic/ or rhinitis, vasomotor/ 3. exp Paranasal Sinuses/ 4. (rhinosinusitis or nasosinusitis or pansinusitis or ethmoiditis or sphenoiditis).ab,ti. 5. (kartagener* adj3 syndrome*).ab,ti. 6. (inflamm* adj5 sinus*).ab,ti. 7. ((maxilla* or frontal*) adj3 sinus*).ab,ti. 8. 1 or 2 or 3 or 4 or 5 or 6 or 7 9. exp chronic disease/ 10. exp Recurrence/ 11. (chronic or persis* or recurrent*).ab,ti. 12. 9 or 10 or 11 13. 8 and 12 14. CRSsNP.ab,ti. 15. ((sinusitis or rhinitis) adj3 (chronic or persis* or recurrent*)).ab,ti. **16. 13 or 14 or 15** 17. exp Nasal Polyps/ 18. exp Nose/ or exp Nose Diseases/ 19. exp Polyps/ 20. 30 and 31 21. ((nose or nasal or rhino* or rhinitis or sinus* or sinonasal) adj3 (papilloma* or polyp*)).ab,ti. 22. (rhinopolyp* or CRSwNP).ab,ti. **23. 17 or 20 or 21 or 22** **24. 16 or 23**	1. exp sinusitis/ or paranasal sinus disease/ 2. rhinitis/ or atrophic rhinitis/ or chronic rhinitis/ or rhinosinusitis/ or vasomotor rhinitis/ 3. exp paranasal sinus/ 4. (rhinosinusitis or nasosinusitis or pansinusitis or ethmoiditis or sphenoiditis).tw. 5. (kartagener* adj3 syndrome*).tw. 6. (inflamm* adj5 sinus*).tw. 7. ((maxilla* or frontal*) adj3 sinus*).tw. 8. 1 or 2 or 3 or 4 or 5 or 6 or 7 9. exp chronic disease/ 10. exp recurrent disease/ 11. (chronic or persis* or recurrent*).tw. 12. 9 or 10 or 11 13. 8 and 12 14. CRSsNP.tw. 15. ((sinusitis or rhinitis) adj3 (chronic or persis* or recurrent*)).tw. **16. 13 or 14 or 15** 17. exp nose polyp/ 18. exp nose disease/ or exp nose/ 19. exp polyp/ 20. 18 and 19 21. ((nose or nasal or rhino* or rhinitis or sinus* or sinonasal) adj3 (papilloma* or polyp*)).tw. 22. (rhinopolyp* or CRSwNP).tw. **23. 17 or 20 or 21 or 22** **24. #16 or #23**

Diseases] explode all trees #23 #21 or #22 #24 MeSH descriptor: [Polyps] explode all trees #25 #23 and #24 227 #26 (nose or nasal or rhino* or rhinitis or sinus* or sinonasal) near (papilloma* or polyp*) #27 rhinopolyp* or CRSwNP **#28 #20 or #25 or #26 or #27** **#29 #19 or #29**		

7.2 Searches by intervention (2010 to March 2015):

7.2.1 Topical steroids

7.2.1.1 CRSwNP

CENTRAL	**PubMed**	**EMBASE (Ovid)**
#1 STEROIDS explode all trees (MeSH) #2 ANTI-INFLAMMATORY AGENTS explode all trees (MeSH) #3 ANTI-INFLAMMATORY AGENTS, NON-STEROIDAL explode all trees (MeSH) #4 #2 NOT #3 #5 GLUCOCORTICOIDS single term (MeSH) #6 steroid* OR corticosteroid* #7 glucocorticoid* OR corticoid* #8 beclomethason* OR beclamet OR beclocort OR beclometasone OR becotide #9 betamethason* OR betametasone OR betadexamethasone OR flubenisolone #10 hydrocortison* OR cortisol OR celesto* #11 dexamethason* OR dexamethason* OR hexadecadrol OR decadron OR dexasone OR hexadrol #12 budesonid* OR horacort OR	#1 “Nasal Polyps” [Mesh] OR rhinopolyp* #2 “Nose” [Mesh] OR nose [ti] OR nasal [ti] OR rhino* [ti] #3 “polyps” [MeSH] OR polyp* OR papilloma* #4 #2 AND #3 #5 1 OR #4 #6 Steroids” [Mesh] OR “ADRENAL CORTEX HORMONES” [Mesh] OR “Glucocorticoids” [Mesh] #7 “Anti-Inflammatory Agents “ [MeSH] NOT “Anti-Inflammatory Agents, Non-Steroidal” [MeSH] #8 triamclinolon* OR nasacort OR tri next nasal OR aristocort OR volon OR fluticason* OR flonase OR flounce OR mometason* OR nasonex OR flunisolid* OR nasalide OR millicorten OR oradexon OR budesonid* OR horacort OR pulmicort OR rhinocort OR methylfluorprednisolone OR dexamethason* OR dexamethason* OR	1 exp steroid/ 2 exp antiinflammatory agent/ 3 exp nonsteroid antiinflammatory agent/ or OCULAR-ANTIINFLAMMATORY-AGENT/ 4 2 not 3 5 (STEROID* or CORTICOSTEROID* or GLUCOCORTICOID* or CORTICOID*).mp. 6 BETAMETHASONE.mp. or 378-44-9.rn. or BETAMETASONE.mp. or BETADEXAMETHASONE.mp. or FLUBENISOLONE.mp. or CELESTO*.mp. 7 (HYDROCORTISONE or CORTISOL).mp. or 50-23-7.rn. 8 DEXAMETHASONE.mp. or 50-02-2.rn. or DEXAMETASONE.mp. or HEXADECADROL.mp. or DECADRON.mp. or DEXACORT.mp. or DEXASONE.mp. or HEXADROL.mp. or METHYLFLUORPREDNISOLONE.mp. or MILLICORTEN.mp. or ORADEXON.mp. 9 BUDESONIDE.mp. or 51333-22-3.rn. or HORACORT.mp. or PULMICORT.mp. or

pulmicort OR rhinocort OR methylfluorprednisolone #13 flunisolid* OR nasalide OR millicorten OR oradexon #14 fluticason* OR flonase OR flounce OR mometason* OR nasonex #15 triamclinolon* OR nasacort OR tri next nasal OR aristocort OR volon #16 #1 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 #17 NASAL POLYPS single term (MeSH) #18 rhinopolyp* #19 POLYPS single term (MeSH) #20 polyp* or papilloma* #21 #19 OR #20 #22 NOSE explode all trees (MeSH) #23 nose* OR nasal* OR nasi OR intranasal* OR sinonasal* OR paranasal* #24 #22 OR #23 #25 #21 AND #24 #26 #17 OR #18 OR #25 #27 #16 AND #26 #28 ADMINISTRATION, TOPICAL explode all trees (MeSH) #29 NEBULIZERS AND VAPORIZERS explode all trees (MeSH) #30 ADMINISTRATION, INTRANASAL explode all trees (MeSH) #31 spray* or aerosol or powder or inhal* or solution or turbuhaler or intranasal* or intra-nasal or topical* #32 #28 OR #29 OR #30 OR #31 #33 #27 AND #30	hexadecadrol OR decadron OR dexasone OR hexadrol OR hydrocortison* OR cortisol OR celesto* OR betamethason* OR betametasone OR betadexamethasone OR flubenisolone OR beclomethason* OR beclamet OR beclocort OR beclometasone OR becotide OR steroid* OR corticosteroid* OR glucocorticoid* OR corticoid* #9 #6 OR #7 OR #8 #10 #5 AND #9 #11 “ADMINISTRATION, TOPICAL” [Mesh] OR “NEBULIZERS AND VAPORIZERS” [Mesh] OR “ADMINISTRATION, INTRANASAL” [Mesh] OR spray* [tiab] OR aerosol [tiab] OR powder [tiab] OR inhal* [tiab] OR solution [tiab] OR turbuhaler [tiab] OR intranasal* [tiab] OR intra-nasal [tiab] OR topical* [tiab] #12 #10 AND #11	RHINOCORT.mp. 10 FLUNISOLIDE.mp. or 3385-03-3.rn. or NASALIDE.mp. or NASAREL.mp. or RHINALAR.mp. 11 FLUTICASONE.mp. or 90566-53-3.rn. or 80474-14-2.rn. or FLONASE.mp. or FLOUNCE.mp. or FLIXONASE.mp. 12 MOMETASONE.mp. or 105102-22-5.rn. or NASONEX.mp. 13 ((TRIAMCINOLONE.mp. or 124-94-7.rn. or NASACORT.mp. or TRI.mp.) adj NASAL.mp.) or ARISTOCORT.mp. or VOLON.mp. 14 BECLOMETHASONE.mp. or 4419-39-0.rn. or BECLAMET.mp. or BECLOCORT.mp. or BECOLMETASONE.mp. or BECOTIDE.mp. or BECONASE.mp. or VANCENASE.mp. 15 1 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 16 nose polyp/ 17 polyp/ or polyposis/ 18 (polyp* or papillom*).tw. 19 17 or 18 20 exp *nose/ 21 (NOSE* or NASAL* or NASI or INTRANASAL* or SINONASAL* or PARANASAL*).tw. 22 20 or 21 23 19 and 22 24 rhinopolyp*.tw. 25 16 or 23 or 24 26 15 and 25 27 exp intranasal drug administration/ 28 nebulization/ or nebulizer/ 29 (spray* or aerosol or powder or inhal* or solution or turbuhaler or intranasal* or intra-nasal or topical*).tw. 30 27 OR 28 OR 29 31 26 AND 30

7.2.1.2 CRSsNP

CENTRAL	PubMed	EMBASE (Ovid)
#1 PARANASAL SINUS DISEASES	#1 "Paranasal Sinus	1 rhinosinusitis/

single term (MeSH) #2 SINUSITIS explode all trees (MeSH) #3 RHINITIS explode all trees (MeSH) #4 (sinusiti* OR rhinosinusiti* OR rhiniti* OR nasosinusiti* OR pansinusiti* OR ethmoiditis OR antritis OR sphenoiditis):ti #5 ((sinus* OR sinonasal OR endonasal OR paranasal or nose or nasal or rhinosinus*) NEAR (inflammation OR inflamed OR pain* OR ache OR aching OR infect* OR pressure OR purulen* OR obstruct* OR block* OR drainage OR discharge* OR symptom* OR disease*)):ti #6 #1 OR #2 OR #3 OR #4 OR #5 #7 CHRONIC DISEASE explode all trees (MeSH) #8 RECURRENCE explode all trees (MeSH) #9 chronic* OR persist* OR recur* OR reoccur* #10 #7 OR #8 OR #9 #11 #6 AND #10 #12 "STEROIDS explode all trees (MeSH) #13 ANTI-INFLAMMATORY AGENTS explode all trees (MeSH) #14 ANTI-INFLAMMATORY AGENTS, NON-STEROIDAL explode all trees (MeSH) #15 #13 NOT #14 #16 GLUCOCORTICOIDS single term (MeSH) #17 steroid* OR corticosteroid* OR glucocorticoid* OR corticoid* OR beclomethason* OR beclamet OR beclocort OR beclometasone OR becotide OR betamethason* OR betametasone OR betadexamethasone OR flubenisolone OR hydrocortison* OR cortisol OR celesto* #18 dexamethason* OR	Diseases"[Mesh:NoExp] #2 "SINUSITIS" [Mesh] OR "RHINITIS" [Mesh] OR sinusiti* [ti] OR rhinosinusiti* [ti] OR rhiniti* [ti] OR nasosinusiti* [ti] OR pansinusiti* [ti] OR ethmoiditis [ti] OR antritis [ti] OR sphenoiditis [ti] OR ((sinus* [ti] OR sinonasal [ti] OR endonasal [ti] OR paranasal [ti] or nose [ti] or nasal [ti] or rhinosinus* [ti]) AND (inflammation [ti] OR inflamed [ti] OR pain* [ti] OR ache [ti] OR aching [ti] OR infect* [ti] OR pressure [ti] OR purulen* [ti] OR obstruct* [ti] OR block* [ti] OR drainage [ti] OR discharge* [ti] OR symptom* [ti] OR disease* [ti])) #3 #2 OR #1 #4 "CHRONIC DISEASE" [Mesh] OR "RECURRENCE" [Mesh] OR chronic* [tiab] OR persist* [tiab] OR recur* [tiab] OR reoccur* [tiab] #5 #3 AND #4 #6 "STEROIDS" [Mesh] OR "GLUCOCORTICOIDS" [Mesh] OR steroid* [tiab] OR corticosteroid* [tiab] OR glucocorticoid* [tiab] OR corticoid* [tiab] OR beclomethason* [tiab] OR beclamet [tiab] OR beclocort [tiab] OR beclometasone [tiab] OR becotide [tiab] OR betamethason* [tiab] OR betametasone [tiab] OR betadexamethasone [tiab] OR flubenisolone [tiab] OR hydrocortison* [tiab] OR cortisol [tiab] OR celesto* [tiab] OR dexamethason* [tiab] OR dexamethason* [tiab] OR hexadecadrol [tiab] OR decadron [tiab] OR dexasone [tiab] OR hexadrol [tiab] OR budesonid* [tiab] OR horacort [tiab] OR	2 (sinusiti* or rhinosinusiti* or rhiniti* or nasosinusiti* or pansinusiti* or ethmoiditis or antritis or sphenoiditis or ((sinus* or sinonasal or endonasal or paranasal or nose or nasal or rhinosinus*) and (inflammation or inflamed or pain* or ache or aching or infect* or pressure or purulen* or obstruct* or block* or drainage or discharge* or symptom* or disease*))).ti. 3 chronic disease/ 4 recurrent disease/ 5 (chronic* or persist* or recur* or reoccur*).tw. 6 1 or 2 7 3 or 4 or 5 8 6 and 7 9 exp steroid/ 10 exp antiinflammatory agent/ 11 exp nonsteroid antiinflammatory agent/ 12 10 not 11 13 (steroid* or corticosteroid* or glucocorticoid* or corticoid* or beclomethason* or beclamet or beclocort or beclometasone or becotide or betamethason* or betametasone or betadexamethasone or flubenisolone or hydrocortison* or cortisol or celesto* or dexamethason* or dexamethason* or hexadecadrol or decadron or dexasone or hexadrol or budesonid* or horacort or pulmicort or rhinocort or methylfluorprednisolone or flunisolid* or nasalide or millicorten or oradexon or fluticason* or flonase or flounce or mometason* or nasonex or triamclinolon* or nasacort or tri next nasal or aristocort or volon).tw.

dexamethason* OR hexadecadrol OR decadron OR dexasone OR hexadrol OR budesonid* OR horacort OR pulmicort OR rhinocort OR methylfluorprednisolone OR flunisolid* OR nasalide OR millicorten OR oradexon OR fluticason* OR flonase OR flounce OR mometason* OR nasonex OR triamclinolon* OR nasacort OR tri next nasal OR aristocort OR volon #19 #12 OR #15 OR #16 OR #17 OR #18 #20 #11 AND #19 #21 ADMINISTRATION, TOPICAL explode all trees (MeSH) #22 NEBULIZERS AND VAPORIZERS explode all trees (MeSH) #23 ADMINISTRATION, INTRANASAL explode all trees (MeSH) #24 spray* or aerosol or powder or inhal* or solution or turbuhaler or intranasal* or intra-nasal or topical* #25 #21 or #22 or #23 or #24 #26 #20 and #25	pulmicort [tiab] OR rhinocort [tiab] OR methylfluorprednisolone [tiab] OR flunisolid* [tiab] OR nasalide [tiab] OR millicorten [tiab] OR oradexon [tiab] OR fluticason* [tiab] OR flonase [tiab] OR flounce [tiab] OR mometason* [tiab] OR nasonex [tiab] OR triamclinolon* [tiab] OR nasacort [tiab] OR tri next nasal [tiab] OR aristocort [tiab] OR volon [tiab] #7 "ANTI-INFLAMMATORY AGENTS" [Mesh] NOT "ANTI-INFLAMMATORY AGENTS, NON-STEROIDAL" [Mesh] #8 #6 OR #7 #9 #5 AND #8 #10 “ADMINISTRATION, TOPICAL” [Mesh] OR “NEBULIZERS AND VAPORIZERS” [Mesh] OR “ADMINISTRATION, INTRANASAL” [Mesh] OR spray* [tiab] OR aerosol [tiab] OR powder [tiab] OR inhal* [tiab] OR solution [tiab] OR turbuhaler [tiab] OR intranasal* [tiab] OR intra-nasal [tiab] OR topical* [tiab] #11 #9 AND #10	14 9 or 12 or 13 15 8 and 14 16 exp topical drug administration/ or exp topical treatment/ 17 exp inhalational drug administration/ or exp inhaler/ 18 exp intranasal drug administration/ 19 nebulization/ or nebulizer/ 20 (spray* or aerosol or powder or inhal* or solution or turbuhaler or intranasal* or intra-nasal or topical*).tw. 21 16 or 17 or 18 or 19 or 20 22 15 and 21

7.2.2 Oral steroids

CENTRAL	PubMed	Embase
#1 NASAL POLYPS single term (MeSH) #2 POLYPS explode all trees (MeSH) #3 (polyp* OR papilloma*) #4 NOSE explode all trees (MeSH) #5 (nose* OR nasal* OR nasi OR intranasal* OR sinonasal* OR paranasal*) #6 (#2 OR #3) #7 (#4 OR #5) #8 (#6 AND #7) #9 rhinopolyp*	#1 “NASAL POLYPS” [Mesh] OR rhinopolyp* [tiab] #2 “POLYPS” [Mesh] OR POLYP* [tiab] OR PAPILLOMA* [tiab] #3 “NOSE” [Mesh] OR NOSE* [tiab] OR NASAL* [tiab] OR NASI [tiab] OR INTRANASAL* [tiab] OR SINONASAL* [tiab] OR PARANASAL* [tiab] #4 #1 OR (#2 AND #3) #5 “STEROIDS” [Mesh] OR “ADRENAL CORTEX HORMONES” [Mesh] OR “GLUCOCORTICOIDS” [Mesh]	1 nose polyp/ 2 polyp/ or polyposis/ 3 (polyp* or papillom*).tw. 4 2 or 3 5 exp *nose/ 6 (NOSE* or NASAL* or NASI or INTRANASAL* or SINONASAL* or PARANASAL*).tw. 7 5 or 6 8 4 and 7 9 rhinopolyp*.tw. 10 1 or 8 or 9 11 exp Corticosteroid/ 12 (STEROID* or

#10 (#1 OR #8 OR #9) #11 STEROIDS explode all trees (MeSH) #12 ADRENAL CORTEX HORMONES explode all trees (MeSH) #13 GLUCOCORTICOIDS explode all trees (MeSH) #14 (steroid* OR glucocorticoid* OR corticosteroid* OR glucosteroid* OR cyclocosteroid*) #15 (beclomethasone OR beclometasone OR beclamet OR beclocort OR becotide) #16 (betamethasone OR betadexamethasone OR flubenisolone OR celeston* OR cellestoderm OR betnelan OR oradexon) #17 (dexamethasone OR dexameth OR dexone OR dexametasone OR decadron OR dexasone OR hexadecadron OR hexadrol OR methylfluorprednisolone OR millicorten) #18 (flunisolide OR fluticasone OR hydrocortisone OR cortisol OR cortifair OR cortril OR hyrocortone OR cortef OR epicortisol OR efcortesol) #19 (methylprednisolone OR medrol OR metripred OR urbason) #20 (mometasone OR prednisolone OR precortisyl OR deltacortril OR deltastab OR prednesol OR deltasone OR prednisone OR cortan OR liquid NEXT pred OR meticorten) #21 (paramethasone OR triamcinolone OR aristocort OR volon OR atolone OR kenacort OR orasone OR panasol OR prednicen) #22 (#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 or #18 or	#6 STEROID*[tiab] OR GLUCOCORTICOID*[tiab] OR CORTICOSTEROID*[tiab] OR GLUCOSTEROID*[tiab] OR CYCLOSTEROID*[tiab] #7 BECLOMETASONE[tiab] OR BECLAMET[tiab] OR BECLOCORT[tiab] OR BECOTIDE[tiab] OR BETADEXAMETHASONE[tiab] OR FLUBENISOLONE[tiab] OR CELESTON$1[tiab] OR CELLESTODERM[tiab] OR BETNELAN[tiab] OR DEXAMETH[tiab] OR DEXONE[tiab] OR DEXAMETASONE[tiab] OR DECADRON[tiab] OR DEXASONE[tiab] OR HEXADECADRON[tiab] OR HEXADROL[tiab] OR ETHYLFLU[tiab] ORPREDNISOLONE[tiab] OR MILLIC[tiab] ORTEN[tiab] OR[tiab] ORADEXON[tiab] OR CORTISOL[tiab] OR CORTIFAIR[tiab] OR CORTRIL[tiab] OR HYROCORTONE[tiab] OR CORTEF[tiab] OR EPICORTISOL[tiab] OR EFCORTESOL[tiab] OR MEDROL[tiab] OR METRIPRED[tiab] OR URBASON[tiab] OR MOMETASONE[tiab] OR PRECORTISYL[tiab] OR DELTACORTRIL[tiab] OR DELTASTAB[tiab] OR PREDNESOL[tiab] OR DELTASONE[tiab] OR CORTAN[tiab] OR “LIQUID PRED”[tiab] OR METICORTEN[tiab] OR ORASONE[tiab] OR PANASOL[tiab] OR PREDNICEN [tiab] #8 PARAMETHASONE[tiab] OR	GLUCOCORTICOID* or CORTICOSTEROID* or GLUCOSTEROID* or CYCLOSTEROID*).tw. 13 (BECLOMETASONE or BECLAMET or BECLOCORT or BECOTIDE or BETADEXAMETHASONE or FLUBENISOLONE or CELESTON* or CELLESTODERM or BETNELAN or DEXAMETH or DEXONE or DEXAMETASONE or DECADRON or DEXASONE or HEXADECADRON or HEXADROL or ETHYLFLU ORPREDNISOLONE or MILLIC ORTEN or ORADEXON or CORTISOL or CORTIFAIR or CORTRIL or HYROCORTONE or CORTEF or EPICORTISOL or EFCORTESOL or MEDROL or METRIPRED or URBASON or MOMETASONE or PRECORTISYL or DELTACORTRIL or DELTASTAB or PREDNESOL or DELTASONE or CORTAN or (LIQUID adj PRED) or METICORTEN or ORASONE or PANASOL or PREDNICEN).tw. 14 (PARAMETHASONE or ARISTOCORT or VOLON or ATOLONE or KENACORT or BECLOMETHASONE or 4419-39-0 or BETAMETHASONE or 378-44-9 or BUDESONIDE or 51333-22-3 or CORTISONE or 53-06-5 or DEXAMETHASONE or 50-02-2 or FLUNISOLIDE or 3385-03-3 or FLUTICASONE or 90566-53-3 or (FLUTICASONE adj PROPIONATE) or 80474-14-2 or HYDROCORTISONE or CORTISOL or 50-23-7 or METHYLPREDNISOLONE or 83-43-2 or MOMETASONE or 105102-22-5 or PREDNISOLONE or 50-24-8 or PREDNISONE or 53-03-2 or TRIAMCINOLONE or 124-94-7).tw. 15 11 or 12 or 13 or 14

#19 or #20 or #21) #23 (#10 AND #22)	ARISTOCORT[tiab] OR VOLON[tiab] OR ATOLONE[tiab] OR KENACORT[tiab] OR BECLOMETHASONE[tiab] OR 4419-39-0[tiab] OR BETAMETHASONE[tiab] OR 378-44-9 [tiab] OR BUDESONIDE[tiab] OR 51333-22-3 [tiab] OR CORTISONE[tiab] OR 53-06-5[tiab] OR DEXAMETHASONE[tiab] OR 50-02-2 [tiab] OR FLUNISOLIDE[tiab] OR 3385-03-3[tiab] OR FLUTICASONE[tiab] OR 90566-53-3[tiab] OR "FLUTICASONE PROPIONATE" [tiab] OR 80474-14-2[tiab] OR HYDROCORTISONE[tiab] OR CORTISOL[tiab] OR 50-23-7[tiab] OR METHYLPREDNISOLONE[tiab] OR 83-43-2 [tiab] OR MOMETASONE[tiab] OR 105102-22-5 [tiab] OR PREDNISOLONE[tiab] OR 50-24-8 [tiab] OR PREDNISONE[tiab] OR 53-03-2[tiab] OR TRIAMCINOLONE[tiab] OR 124-94-7 [tiab] #9 #5 OR #6 OR #7 OR #8 #10 #4 AND #9	16 10 and 15

7.2.3 Systemic antibiotics

CENTRAL	PubMed	EMBASE (Ovid)
#1 MeSH descriptor Sinusitis explode all trees #2 rhinosinusitis OR nasosinusitis OR sinusitis OR pansinusitis OR ethmoiditis OR antritis OR sphenoiditis #3 (kartagener* near syndrome) #4 (inflamm* near sinus*) #5 (#1 OR #2 OR #3 OR #4) #6 MeSH descriptor Chronic Disease explode all trees #7 MeSH descriptor Recurrence explode all trees #8 (chronic* OR persist* OR recur*)	#1 "PARANASAL SINUS DISEASES" [Mesh] OR "SINUSITIS" [Mesh] OR "RHINITIS" [Mesh] OR sinusiti* [ti] OR rhinosinusiti* [ti] OR rhiniti* [ti] OR nasosinusiti* [ti] OR pansinusiti* [ti] OR ethmoiditis [ti] OR antritis [ti] OR sphenoiditis [ti] OR ((sinus* [ti] OR sinonasal [ti] OR endonasal [ti] OR paranasal [ti] or nose [ti] or nasal [ti] or rhinosinus* [ti]) AND (inflammation [ti] OR inflamed [ti] OR pain* [ti] OR ache [ti] OR aching [ti] OR infect*	1 rhinosinusitis/ 2 paranasal sinus disease/ 3 (sinusiti* or rhinosinusiti* or rhiniti* or nasosinusiti* or pansinusiti* or ethmoiditis or antritis or sphenoiditis).ti. 4 ((sinus* or sinonasal or endonasal or paranasal or nose or nasal or rhinosinus*) and (inflammation or inflamed or pain* or ache or aching or infect* or pressure or purulen* or obstruct* or block* or drainage or discharge* or symptom* or disease*)).ti.

#9 (#6 OR #7 OR #8) #10 (#5 AND #9) #11 MeSH descriptor Anti-Bacterial Agents explode all trees #12 MeSH descriptor Antibiotic Prophylaxis explode all trees #13 MeSH descriptor Lactams explode all trees #14 MeSH descriptor Quinolones explode all trees #15 MeSH descriptor Macrolides explode all trees #16 ANTIBIOT* OR ANTI NEXT BIOT* OR ANTIMICROBIAL* OR ANTI NEXT MICROBIAL* OR BACTERIOCID* OR ANTIBACTERIAL* OR ANTI NEXT BACTERIAL* #17 PENICILLIN* OR AMOXICILLIN OR AMPICILLIN OR CLAVULANIC NEXT ACID OR AMOXICLAV OR AUGMENTIN OR TICARCILLIN OR TIMENTIN OR FLUCLOXACILLIN OR FLUAMPICIL OR MAGNAPEN OR PIPERACILLIN OR TAZOCIN OR CEPHALOSPORIN* OR CEFACLOR OR DISTACLOR OR CEFADROXIL OR BAXAN OR CEFALEXIN OR CEPOREX OR KEFLEX OR CEFAMANDOLE OR KEFADOL OR CEFAZOLIN* OR KEFZOL OR CEFIXIME OR SUPRAX OR CEFOTAXIME OR CLAFORAN OR CEFOXITIN OR MEFOXIN OR CEFPIROME OR CEFROM OR CEFPODOXIME OR ORELOX OR CEFPROZIL OR CEFZIL OR CEFRADINE OR VELOSEL OR CEFTAZIDIM OR FORTUM OR KEFADIM OR CEFTRIAXONE OR ROCEPHIN OR CEFUROXIME OR ZINACEF OR ZINNAT OR CEFONICID OR AZTREONAM OR AZACTAM OR IMIPENEM OR CILASTATIN OR PRIMAXIN OR MEROPENEM OR TETRACYCLINE* OR DETECLO OR	[ti] OR pressure [ti] OR purulen* [ti] OR obstruct* [ti] OR block* [ti] OR drainage [ti] OR discharge* [ti] OR symptom* [ti] OR disease* [ti])) #2 "CHRONIC DISEASE" [Mesh] OR "RECURRENCE" [Mesh] OR chronic* [tiab] OR persist* [tiab] OR recur* [tiab] OR reoccur* [tiab] #3 #1 AND #2 #4 "Anti-Bacterial Agents" [Mesh] OR "Antibiotic Prophylaxis" [Mesh] OR "Lactams" [Mesh OR "Quinolones" [Mesh] OR "Macrolides" [Mesh] #5 ANTIBIOT* [tiab] OR (ANTI [tiab] AND BIOT* [tiab]) OR ANTIMICROBIAL* [tiab] OR (ANTI [tiab] AND MICROBIAL* [tiab]) OR BACTERIOCID* [tiab] OR ANTIBACTERIAL* [tiab] OR "ANTI BACTERIAL*" [tiab] OR PENICILLIN* [tiab] OR AMOXICILLIN [tiab] OR AMPICILLIN [tiab] OR (CLAVULANIC [tiab] AND ACID [tiab]) OR AMOXICLAV [tiab] OR AUGMENTIN [tiab] OR TICARCILLIN [tiab] OR TIMENTIN [tiab] OR FLUCLOXACILLIN [tiab] OR FLUAMPICIL [tiab] OR MAGNAPEN [tiab] OR PIPERACILLIN [tiab] OR TAZOCIN [tiab] OR CEPHALOSPORIN* [tiab] OR CEFACLOR [tiab] OR DISTACLOR [tiab] OR CEFADROXIL [tiab] OR BAXAN [tiab] OR CEFALEXIN [tiab] OR CEPOREX [tiab] OR KEFLEX [tiab] OR CEFAMANDOLE [tiab] OR KEFADOL [tiab] OR CEFAZOLIN* [tiab] OR KEFZOL [tiab] OR CEFIXIME [tiab] OR SUPRAX [tiab] OR CEFOTAXIME [tiab] OR CLAFORAN [tiab] OR CEFOXITIN [tiab] OR MEFOXIN [tiab] OR	5 1 or 2 or 3 or 4 6 chronic disease/ 7 recurrent disease/ 8 (chronic* or persist* or recur* or reoccur*).ti. 9 6 or 7 or 8 10 5 and 9 11 exp antibiotic agent/ 12 antibiotic prophylaxis/ 13 exp lactam/ 14 exp quinolone derivative/ 15 exp macrolide/ 16 (ANTIBIOT* or (ANTI and BIOT*) or ANTIMICROBIAL* or (ANTI and MICROBIAL*) or BACTERIOCID* or ANTIBACTERIAL* or "ANTI BACTERIAL*" or PENICILLIN* or AMOXICILLIN or AMPICILLIN or (CLAVULANIC and ACID) or AMOXICLAV or AUGMENTIN or TICARCILLIN or TIMENTIN or FLUCLOXACILLIN or FLUAMPICIL or MAGNAPEN or PIPERACILLIN or TAZOCIN or CEPHALOSPORIN* or CEFACLOR or DISTACLOR or CEFADROXIL or BAXAN or CEFALEXIN or CEPOREX or KEFLEX or CEFAMANDOLE or KEFADOL or CEFAZOLIN* or KEFZOL or CEFIXIME or SUPRAX or CEFOTAXIME or CLAFORAN or CEFOXITIN or MEFOXIN or CEFPIROME or CEFROM or CEFPODOXIME or ORELOX or CEFPROZIL or CEFZIL or CEFRADINE or VELOSEL or CEFTAZIDIM or FORTUM).tw. 17 (KEFADIM or CEFTRIAXONE or ROCEPHIN or CEFUROXIME or ZINACEF or ZINNAT or CEFONICID or AZTREONAM or AZACTAM or IMIPENEM or CILASTATIN or PRIMAXIN or MEROPENEM or TETRACYCLINE* or DETECLO or DEMECLEOCYCLIN or LEDERMYCIN or DOXYCYCLINE or

DEMECLEOCYCLIN OR LEDERMYCIN OR DOXYCYCLINE OR VIBRAMYCIN OR MINOCYCLINE OR MINOCINE OR OXYTETRACYCLINE OR TERRAMYCIN OR MACROLIDE* OR ERYTHROMYCIN OR ERYMAX OR ERYTHROCIN OR ERYTHROPED OR AZITHROMYCIN OR ZITHROMAX OR CLARITHROMYCIN OR KLARICID OR TELITHROMYCIN OR KETEK OR TRIMOXAZOLE OR SEPTRIN OR TRIMETHOPRIM OR MONOTRIM OR TRIMOPAN OR METRONIDAZOLE OR FLAGYL OR METROLYL OR PHENOXYMETHYLPENICILLIN OR SULFAMETHOXAZOLE OR OXACILLIN OR CEPHALOTHIN OR SULBACTAM OR OFLOXACIN OR CLINDAMYCIN OR GENTAMYCIN OR VANCOMYCIN #18 (#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17) #19 (#10 AND #18)	CEFPIROME [tiab] OR CEFROM [tiab] OR CEFPODOXIME [tiab] OR ORELOX [tiab] OR CEFPROZIL [tiab] OR CEFZIL [tiab] OR CEFRADINE [tiab] OR VELOSEL [tiab] OR CEFTAZIDIM [tiab] OR FORTUM [tiab] #6 KEFADIM [tiab] OR CEFTRIAXONE [tiab] OR ROCEPHIN [tiab] OR CEFUROXIME [tiab] OR ZINACEF [tiab] OR ZINNAT [tiab] OR CEFONICID [tiab] OR AZTREONAM [tiab] OR AZACTAM [tiab] OR IMIPENEM [tiab] OR CILASTATIN [tiab] OR PRIMAXIN [tiab] OR MEROPENEM [tiab] OR TETRACYCLINE* [tiab] OR DETECLO [tiab] OR DEMECLEOCYCLIN [tiab] OR LEDERMYCIN [tiab] OR DOXYCYCLINE [tiab] OR VIBRAMYCIN [tiab] OR MINOCYCLINE [tiab] OR MINOCINE [tiab] OR OXYTETRACYCLINE [tiab] OR TERRAMYCIN [tiab] OR MACROLIDE* [tiab] OR ERYTHROMYCIN [tiab] OR ERYMAX [tiab] OR ERYTHROCIN [tiab] OR ERYTHROPED [tiab] OR AZITHROMYCIN [tiab] OR ZITHROMAX [tiab] OR CLARITHROMYCIN [tiab] OR KLARICID [tiab] OR TELITHROMYCIN [tiab] OR KETEK [tiab] OR TRIMOXAZOLE [tiab] OR SEPTRIN [tiab] OR TRIMETHOPRIM [tiab] OR MONOTRIM [tiab] OR TRIMOPAN [tiab] OR METRONIDAZOLE [tiab] OR FLAGYL [tiab] OR METROLYL [tiab] OR PHENOXYMETHYLPENICILLIN [tiab] OR SULFAMETHOXAZOLE [tiab] OR OXACILLIN [tiab] OR CEPHALOTHIN [tiab] OR	VIBRAMYCIN or MINOCYCLINE or MINOCINE or OXYTETRACYCLINE or TERRAMYCIN or MACROLIDE* or ERYTHROMYCIN or ERYMAX or ERYTHROCIN or ERYTHROPED or AZITHROMYCIN or ZITHROMAX or CLARITHROMYCIN or KLARICID or TELITHROMYCIN or KETEK or TRIMOXAZOLE or SEPTRIN or TRIMETHOPRIM or MONOTRIM or TRIMOPAN or METRONIDAZOLE or FLAGYL or METROLYL or PHENOXYMETHYLPENICILLIN or SULFAMETHOXAZOLE or OXACILLIN or CEPHALOTHIN or SULBACTAM or OFLOXACIN or CLINDAMYCIN or GENTAMYCIN or VANCOMYCIN).tw. 18 11 or 12 or 13 or 14 or 15 or 16 or 17 19 10 and 18

	SULBACTAM [tiab] OR OFLOXACIN [tiab] OR CLINDAMYCIN [tiab] OR GENTAMYCIN [tiab] OR VANCOMYCIN [tiab] #7 #4 OR #5 OR #6 #8 #3 AND #7	

7.2.4 Nasal saline

CENTRAL	PubMed	EMBASE
#1 MeSH descriptor: [Nose] explode all trees #2 MeSH descriptor: [Nasal Cavity] explode all trees #3 MeSH descriptor: [Nasal Mucosa] explode all trees #4 MeSH descriptor: [Nasal Obstruction] explode all trees #5 MeSH descriptor: [Nasal Polyps] explode all trees #6 MeSH descriptor: [Rhinitis] explode all trees #7 MeSH descriptor: [Sinusitis] explode all trees #8 MeSH descriptor: [Paranasal Sinuses] explode all trees #9 MeSH descriptor: [Paranasal Sinus Diseases] explode all trees #10 MeSH descriptor: [Nose Diseases] explode all trees #11 nose OR nasal* OR sinus* OR rhinosinus* OR paranasal* OR rhinitis* OR nasosinus* OR pansinus* #12 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 #13 MeSH descriptor: [Hypertonic Solutions] explode all trees #14 MeSH descriptor: [Isotonic Solutions] explode all trees #15 MeSH descriptor: [Solutions] explode all trees #16 MeSH descriptor: [Hypotonic Solutions] explode all trees #17 MeSH descriptor: [Sodium Chloride] explode all trees	#13 #3 AND #12 #12 #10 OR #11 #11 irrigation #10 #6 AND #9 #9 #7 OR #8 #8 (douch* [tiab] OR spray* [tiab] OR lavag* [tiab] OR wash* [tiab] OR rinse* [tiab] OR rinsing [tiab] OR irrigat* [tiab]) #7 "Administration, Intranasal"[Mesh] #6 #4 OR #5 #5 (saline [tiab] OR "sodium chloride" [tiab] OR "salt water" [tiab] OR saltwater [tiab] OR hypertonic* [tiab] OR isotonic* [tiab] OR hypotonic* [tiab]) #4 "HYPERTONIC SOLUTIONS" [Mesh] OR "HYPOTONIC SOLUTIONS" [Mesh] OR "ISOTONIC SOLUTIONS" [Mesh] OR "SOLUTIONS" [Mesh] OR"SALINE SOLUTION HYPERTONIC" [Mesh] OR "SODIUM CHLORIDE" [Mesh] #3 #1 OR #2 #2 (nose [tiab] OR nasal* [tiab] OR sinus* [tiab] OR ethmoid* [tiab] OR rhinosinus* [tiab] OR paranasal* [tiab] OR rhiniti* [tiab] OR nasosinus* [tiab] OR pansinus* [tiab]) #1 "NOSE" [Mesh] OR "NASAL CAVITY" [Mesh] OR "NASAL MUCOSA" [Mesh] OR "PARANASAL SINUSES" [Mesh] OR "PARANASAL SINUS DISEASES" [Mesh] OR	1 nose/ 2 nose cavity/ 3 exp nose mucosa/ 4 exp paranasal sinus/ 5 paranasal sinus disease/ 6 exp sinusitis/ 7 exp rhinitis/ 8 nose polyp/ 9 nose obstruction/ 10 (nose or nasal* or sinus* or rhinosinus* or paranasal* or rhiniti* or nasosinus* or pansinus*).tw. 11 6 or 3 or 7 or 9 or 2 or 8 or 1 or 4 or 10 or 5 12 HYPERTONIC SOLUTION/ 13 SODIUM CHLORIDE/ 14 (saline or (sodium adj chloride) or (salt adj water) or hypertonic* or isotonic*).tw. 15 13 or 12 or 14 16 11 and 15 17 (douch* or spray* or wash* or rinse* or rinsing or irrigat*).tw. 18 16 and 17

#18 saline or sodium chloride or salt water or saltwater or hypertonic* or hypotonic* or isotonic* #19 #13 or #14 or #15 or #16 or #17 or #18 #20 #12 and #19 #21 MeSH descriptor: [Therapeutic Irrigation] explode all trees #22 douch* or spray* or lavag* or wash* or rinse* or rinsing or irrigat* #23 #22 or #21 #24 #20 and #23	"SINUSITIS" [Mesh] OR "RHINITIS" [Mesh] OR "NASAL POLYPS" [Mesh] OR "NASAL OBSTRUCTION" [Mesh] OR "NOSE DISEASES" [Mesh]	

7.2.5 Leukotriene antagonists

CENTRAL	PubMed	EMBASE
#1 PARANASAL SINUS DISEASES single term (MeSH) #2 SINUSITIS explode all trees (MeSH) #3 RHINITIS explode all trees (MeSH) #4 NASAL POLYPS single term (MeSH) #5 NASAL OBSTRUCTION single term (MeSH) #6 sinusiti* OR rhinosinusiti* OR rhiniti* OR nasosinusiti* OR pansinusiti* OR ethmoiditis OR antritis OR sphenoiditis OR rhinorrhoea OR rhinorrhea OR rhinorroea OR rhinorrea OR facial NEAR (pain OR congestion OR pressure) #7 (sinus* or nose or nasal or rhinosinus*) NEAR (inflammation OR inflamed OR pain* OR ache OR aching OR infect* OR pressure OR purulen* OR obstruct* OR block* OR drainage OR discharge*) #8 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 #9 LEUKOTRIENE ANTAGONISTS single term (MeSH) #10 leukotriene* NEAR	#14 #9 AND #13 #13 #10 OR #11 OR #12 #12 montelukast [tiab] OR singulair* [tiab] OR zafirlukast [tiab] OR pranlukast [tiab] OR nalukast [tiab] OR pomilukast [tiab] OR accolate* [tiab] OR onon* [tiab] OR accoleit* [tiab] OR vanticon* [tiab] #11 (leucotriene* [tiab] OR leukotriene* [tiab]) AND (antagonist* [tiab] OR inhibitor* [tiab]) #10 "Leukotriene Antagonists"[Mesh] #9 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 #8 (sinus* [tiab] or nose [tiab] or nasal [tiab] or rhinosinus* [tiab]) AND (inflammation* [tiab] OR inflamed [tiab] OR pain* [tiab] OR ache* [tiab] OR aching [tiab] OR infect* [tiab] OR pressure [tiab] OR purulen* [tiab] OR obstruct* [tiab] OR block* [tiab] OR drainage [tiab] OR discharg* [tiab]) #7 facial [tiab] AND (pain [tiab] OR congestion [tiab] OR pressure [tiab])	1 exp Paranasal Sinus Disease/ 2 exp Sinusitis/ 3 exp Rhinitis/ 4 Nose Polyp/ 5 Nose Obstruction 6 (sinusiti* or rhinosinusiti* or rhiniti* or nasosinusiti* or pansinusiti* or ethmoiditis or antritis or sphenoiditis or rhinorrhoea or rhinorrhea or rhinorroea or rhinorrea).tw 7 (facial and (pain or congestion or pressure)).ti 8 ((sinus* or nose or nasal or rhinosinus*) and (inflammation* or inflamed or pain* or ache or aching or infect* or pressure or purulen* or obstruct* or block* or drainage or discharg*)).ti 9 6 or 3 or 7 or 2 or 8 or 1 or 4 or 5 10 exp Leukotriene Receptor Blocking Agent/ 11 ((leucotriene* or leukotriene*) and (antagonist* or inhibitor*)).tw. 12 (montelukast or singulair* or zafirlukast or pranlukast or nalukast or pomilukast or accolate* or onon* or accoleit*

antagonist* OR leukotriene* NEAR inhibitor* OR leucotriene* NEAR antagonist* OR leucotriene* NEAR antagonist* #11 montelukast OR singulair* OR zafirlukast OR pranlukast OR nalukast OR pomilukast OR accolate* OR onon* OR accoleit* OR vanticon* #12 #9 OR #10 OR #11 #13 #8 AND #12	#6 (sinusiti* [tiab] OR rhinosinusiti* [tiab] OR rhiniti* [tiab] OR nasosinusiti* [tiab] OR pansinusiti* [tiab] OR ethmoiditis [tiab] OR antritis [tiab] OR sphenoiditis [tiab] OR rhinorrhoea [tiab] OR rhinorrhea [tiab] OR rhinorroea [tiab] OR rhinorrea [tiab]) #5 "NASAL OBSTRUCTION"[Mesh] #4 "NASAL POLYPS"[Mesh] #3 "Rhinitis"[Mesh] #2 "Sinusitis"[Mesh] #1 "Paranasal Sinus Diseases"[Mesh]	or vanticon*).tw 13 11 or 10 or 12 14 9 and 13

7.2.6 Antifungal therapy

CENTRAL	PubMed	EMBASE
#1 MeSH descriptor Sinusitis explode all trees #2 Paranasal Sinuses/explode all trees with qualifiers: MI,TH #3 nasosinusit* OR sinusit* OR pansinusit* OR ethmoidit* OR sphenoidit* OR sinusitid* OR rhinosinusit* #4 #1 OR #2 OR #3 #5 MeSH descriptor Mycoses explode all trees with qualifiers: TH #6 MeSH descriptor Venturicidins explode all trees #7 MeSH descriptor Trimetrexate explode all trees #8 MeSH descriptor Triacetin explode all trees #9 MeSH descriptor Tolnaftate explode all trees #10 MeSH descriptor Tomatine explode all trees #11 MeSH descriptor Thymol explode all trees #12 MeSH descriptor Sodium Benzoate explode all trees #13 MeSH descriptor Sirolimus explode all trees #14 MeSH descriptor Salicylic	#1 "Sinusitis"[Mesh] #2 ("Paranasal Sinuses/microbiology"[Mesh] OR "Paranasal Sinuses/therapy"[Mesh]) #3 nasosinusit* [tiab] OR sinusit* [tiab] OR pansinusit* [tiab] OR ethmoidit* [tiab] OR sphenoidit* [tiab] OR sinusitid* [tiab] OR rhinosinusit* [tiab] #4 #1 OR #2 OR #3 #5 "Antifungal Agents"[Mesh] #6 "Antifungal Agents"[Pharmacological Action] #7 "Amphotericin B"[Mesh] #8 "Antimycin A"[Mesh] #9 "Azaserine"[Mesh] #10 "Benzoates"[Mesh] #11 "Brefeldin A "[Mesh] #12"Candicidin"[Mesh] #13 "Cerulenin"[Mesh] #14"Clotrimazole"[Mesh] #15 "Cycloheximide"[Mesh] #16 "Cyclosporine"[Mesh] #17 "Dichlorophen"[Mesh] #18 "Echinocandins"[Mesh] #19 "Econazole"[Mesh] #20 "Filipin"[Mesh] #21 "Fluconazole"[Mesh]	1 exp *sinusitis/ 2 exp paranasal sinus disease/th [Therapy] 3 (nasosinusit* or sinusit* or pansinusit* or ethmoidit* or sphenoidit* or sinusitid* or rhinosinusit*).ti. 4 1 or 2 or 3 5 exp antifungal agent/ 6 (antifung* or acivicin or ajoene or amorolfin or Amphotericin or anidulafungin or Antimycin or artemether or aureobasidin or Azaserine or bafilomycin or Benzoates or bifonazole or blasticidin or Brefeldin or butenafine or butoconazole).tw. 7 (Candicidin or candidin or captax or caspofungin or Cerulenin or ciclopirox or cilofungin or Clotrimazole or compactin or cordycepin or cryptophycin or Cycloheximide or Cyclosporine or (decanoic adj acid) or (diallyl adj trisulfide) or Dichlorophen or diucifon or echinocandin or Echinocandins or Econazole or Ethonium).tw. 8 (fenticonazole or ferroin or

Acid explode all trees #15 MeSH descriptor Rutamycin explode all trees #16 MeSH descriptor Pentamidine explode all trees #17 MeSH descriptor Nystatin explode all trees #18 MeSH descriptor Nifuratel explode all trees #19 MeSH descriptor Natamycin explode all trees #20 MeSH descriptor Mycobacillin explode all trees #21 MeSH descriptor Monensin explode all trees #22 MeSH descriptor Miconazole explode all trees #23 MeSH descriptor Mepartricin explode all trees #24 MeSH descriptor Lucensomycin explode all trees #25 MeSH descriptor Ketoconazole explode all trees #26 MeSH descriptor Itraconazole explode all trees #27 MeSH descriptor Hexetidine explode all trees #28 MeSH descriptor Griseofulvin explode all trees #29 MeSH descriptor Flucytosine explode all trees #30 MeSH descriptor Fluconazole explode all trees #31 MeSH descriptor Filipin explode all trees #32 MeSH descriptor Econazole explode all trees #33 MeSH descriptor Echinocandins explode all trees #34 MeSH descriptor Dichlorophen explode all trees #35 MeSH descriptor Cyclosporine explode all trees #36 MeSH descriptor Cycloheximide explode all trees #37 MeSH descriptor Clotrimazole explode all trees #38 MeSH descriptor Cerulenin	#22 "Flucytosine"[Mesh] #23 "Griseofulvin"[Mesh] #24 "Hexetidine"[Mesh] #25 "Itraconazole"[Mesh] #26 "Ketoconazole"[Mesh] #27 "Lucensomycin"[Mesh] #28 "Mepartricin"[Mesh] #29 "Miconazole"[Mesh] #30 "Monensin"[Mesh] #31 "Mycobacillin"[Mesh] #32 "Natamycin"[Mesh] #33 "Nifuratel"[Mesh] #34 "Nystatin"[Mesh] #35 "Pentamidine"[Mesh] #36 "Rutamycin"[Mesh] #37 "Salicylic Acid "[Mesh] #38 "Sirolimus"[Mesh] #39 "Sodium Benzoate "[Mesh] #40 "Thymol"[Mesh] #41 "Tomatine"[Mesh] #42 "Tolnaftate"[Mesh] #43 "Triacetin"[Mesh] #44 "Trimetrexate"[Mesh] #45 "Venturicidins"[Mesh] #46 "Mycoses"[Mesh] #47 antifung* [tiab] OR acivicin [tiab] OR ajoene [tiab] OR amorolfin [tiab] OR “Amphotericin B” [tiab] OR “amphotericin B-deoxycholate” [tiab] OR anidulafungin [tiab] OR “Antimycin A” [tiab] OR artemether [tiab] OR “aureobasidin A” [tiab] OR Azaserine [tiab] OR “bafilomycin A1” [tiab] OR Benzoates [tiab] OR bifonazole [tiab] OR “blasticidin S” [tiab] OR “Brefeldin A” [tiab] OR butenafine [tiab] OR butoconazole [tiab] #48 Candicidin [tiab] OR candidin [tiab] OR captax [tiab] OR caspofungin [tiab] OR Cerulenin [tiab] OR ciclopirox [tiab] OR cilofungin [tiab] OR Clotrimazole [tiab] OR compactin [tiab] OR cordycepin [tiab] OR	Filipin or Fluconazole or Flucytosine or glyphosate or Griseofulvin or hamycin or Hexetidine or hydroxyitraconazole or (ICI adj "195739") or isoconazole or Itraconazole or iturin or jasplakinolide or Ketoconazole or lactoferricin or lapachol or lawsone or leptomycin or Lucensomycin).tw. 9 (Mepartricin or methylamphotericin or micafungin or Miconazole or miltefosine or Monensin or monorden or mucidin or muconaldehyde or Mycobacillin or myxothiazol or n-hexanal or naftifine or Natamycin or Nifuratel or nikkomycin or nitroxoline or Nystatin or oxiconazole or papulacandin or (pelargonic adj acid) or Pentamidine or polygodial or (polyoxin adj D) or posaconazole or (potassium adj iodate) or pradimicin or protegrin-1 or purothionin or pyochelin or pyrithione or Pyrrolnitrin).tw. 10 (rhizoxin or Rutamycin or (salicylhydroxamic adj acid) or (Salicylic adj Acid) or saperconazole or (Sch adj "39304") or sertaconazole or sinefungin or Sirolimus or (Sodium adj Benzoate) or squalestatin or sulconazole or terbinafine or terconazole or thermozymocidin or Thymol or tioconazole or Tolnaftate or Tomatine or Triacetin or trichostatin or Trimetrexate or troclosene or (usnic adj acid) or Venturicidins or vibunazole or voriconazole or wortmannin).tw. 11 5 or 6 or 7 or 8 or 9 or 10 12 4 and 11

explode all trees #39 MeSH descriptor Candicidin explode all trees #40 MeSH descriptor Brefeldin A explode all trees #41 MeSH descriptor Benzoates explode all trees #42 MeSH descriptor Azaserine explode all trees #43 MeSH descriptor Antimycin A explode all trees #44 MeSH descriptor Amphotericin B explode all trees #45 MeSH descriptor Antifungal Agents explode all trees #46 rhizoxin OR Rutamycin OR salicylhydroxamic NEXT acid OR Salicylic NEXT Acid OR saperconazole OR Sch NEXT 39304 OR sertaconazole OR sinefungin OR Sirolimus OR Sodium NEXT Benzoate OR squalestatin NEXT 1 OR sulconazole OR terbinafine OR terconazole OR thermozymocidin OR Thymol OR tioconazole OR Tolnaftate OR Tomatine OR Triacetin OR trichostatin NEXT A OR Trimetrexate OR troclosene OR usnic NEXT acid OR Venturicidins OR vibunazole OR voriconazole OR wortmannin #47 Mepartricin OR methylamphotericin NEXT B OR micafungin OR Miconazole OR miltefosine OR Monensin OR monorden OR mucidin OR muconaldehyde OR Mycobacillin OR myxothiazol OR n-hexanal OR naftifine OR Natamycin OR Nifuratel OR nikkomycin OR nitroxoline OR Nystatin OR oxiconazole OR papulacandin NEXT B OR pelargonic NEXT acid OR Pentamidine OR polygodial OR polyoxin NEXT D OR posaconazole OR potassium	cryptophycin [tiab] OR Cycloheximide [tiab] OR Cyclosporine [tiab] OR “decanoic acid” [tiab] OR diallyl trisulfide [tiab] OR Dichlorophen [tiab] OR diucifon [tiab] OR “echinocandin B” [tiab] OR Echinocandins [tiab] OR Econazole [tiab] OR Ethonium [tiab] #49 fenticonazole [tiab] OR ferroin [tiab] OR Filipin [tiab] OR Fluconazole [tiab] OR Flucytosine [tiab] OR glyphosate [tiab] OR Griseofulvin [tiab] OR hamycin [tiab] OR Hexetidine [tiab] OR hydroxyitraconazole [tiab] OR “ICI 195739” [tiab] OR isoconazole [tiab] OR Itraconazole [tiab] OR “iturin A” [tiab] OR jasplakinolide [tiab] OR Ketoconazole [tiab] OR “lactoferricin B” [tiab] OR lapachol [tiab] OR lawsone [tiab] OR “leptomycin B” [tiab] OR Lucensomycin [tiab] #50 Mepartricin [tiab] OR “methylamphotericin B” [tiab] OR micafungin [tiab] OR Miconazole [tiab] OR miltefosine [tiab] OR Monensin [tiab] OR monorden [tiab] OR mucidin [tiab] OR muconaldehyde [tiab] OR Mycobacillin [tiab] OR myxothiazol [tiab] OR n-hexanal [tiab] OR naftifine [tiab] OR Natamycin [tiab] OR Nifuratel [tiab] OR nikkomycin [tiab] OR nitroxoline [tiab] OR Nystatin [tiab] OR oxiconazole [tiab] OR “papulacandin B” [tiab] OR “pelargonic acid” [tiab] OR Pentamidine [tiab] OR polygodial [tiab] OR “polyoxin D” [tiab] OR posaconazole [tiab] OR “potassium iodate” [tiab] OR “pradimicin A” [tiab] OR protegrin-1 [tiab] OR purothionin [tiab] OR pyochelin [tiab] OR	

NEXT iodate OR pradimicin NEXT A OR protegrin-1 OR purothionin OR pyochelin OR pyrithione OR Pyrrolnitrin #48 fenticonazole OR ferroin OR Filipin OR Fluconazole OR Flucytosine OR glyphosate OR Griseofulvin OR hamycin OR Hexetidine OR hydroxyitraconazole OR ICI NEXT 195739 OR isoconazole OR Itraconazole OR iturin NEXT A OR jasplakinolide OR Ketoconazole OR lactoferricin NEXT B OR lapachol OR lawsone OR leptomycin NEXT B OR Lucensomycin #49 Candicidin OR candidin OR captax OR caspofungin OR Cerulenin OR ciclopirox OR cilofungin OR Clotrimazole OR compactin OR cordycepin OR cryptophycin OR Cycloheximide OR Cyclosporine OR "decanoic acid" OR diallyl trisulfide OR Dichlorophen OR diucifon OR echinocandin NEXT B OR Echinocandins OR Econazole OR Ethonium #50 antifung* OR acivicin OR ajoene OR amorolfin OR Amphotericin NEXT B OR amphotericin NEXT B-deoxycholate OR anidulafungin OR Antimycin NEXT A OR artemether OR aureobasidin NEXT A OR Azaserine OR bafilomycin NEXT A1 OR Benzoates OR bifonazole OR blasticidin NEXT S OR Brefeldin NEXT A OR butenafine OR butoconazole #51 #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29	pyrithione [tiab] OR Pyrrolnitrin [tiab] #51 rhizoxin [tiab] OR Rutamycin [tiab] OR "salicylhydroxamic acid" [tiab] OR "Salicylic Acid" [tiab] OR saperconazole [tiab] OR "Sch 39304" [tiab] OR sertaconazole [tiab] OR sinefungin [tiab] OR Sirolimus [tiab] OR "Sodium Benzoate" [tiab] OR "squalestatin 1" [tiab] OR sulconazole [tiab] OR terbinafine [tiab] OR terconazole [tiab] OR thermozymocidin [tiab] OR Thymol [tiab] OR tioconazole [tiab] OR Tolnaftate [tiab] OR Tomatine [tiab] OR Triacetin [tiab] OR "trichostatin A" [tiab] OR Trimetrexate [tiab] OR troclosene [tiab] OR "usnic acid" [tiab] OR Venturicidins [tiab] OR vibunazole [tiab] OR voriconazole [tiab] OR wortmannin [tiab] #52 #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 #53 #4 AND #52	

OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 #52 #4 AND #51		

7.2.7 Anti-IL-5

Combined with condition searches in 7.1

CENTRAL	Ovid Medline	EMBASE
#1 MeSH descriptor: [Antibodies, Monoclonal, Humanized] explode all trees #2 MeSH descriptor: [Interleukin-5] explode all trees #3 MeSH descriptor: [Receptors, Interleukin-5] this term only 4. (IL near ("5" or five)) 5. (Interleukin near ("5" or five)) 6. (humanized near (mAb or monoclonal)) 7. (reslizumab or IL5 or mepolizumab) 8. #1 or #2 or #3 or #4 or #5 or #6 or #7	1. exp Antibodies, Monoclonal, Humanized/ 2. exp Interleukin-5/ 3. Receptors, Interleukin-5/ 4. (IL adj3 ("5" or five)).ab,ti. 5. (Interleukin adj3 ("5" or five)).ab,ti. 6. (humanized adj3 (mAb or monoclonal)).ab,ti. 7. (reslizumab or IL5 or mepolizumab).ab,ti. 8. 1 or 2 or 3 or 4 or 5 or 6 or 7	1. exp monoclonal antibody/ 2. exp interleukin 5/ 3. exp interleukin 5 receptor/ 4. (IL adj3 ("5" or five)).tw. 5. (Interleukin adj3 ("5" or five)).tw. 6. (humanized adj3 (mAb or monoclonal)).tw. 7. (reslizumab or IL5 or mepolizumab).tw. 8. 1 or 2 or 3 or 4 or 5 or 6 or 7

7.2.8 Anti-IgE

Combined with condition searches in 7.1

CENTRAL	Ovid Medline	EMBASE
#1 MeSH descriptor: [Antibodies, Anti-Idiotypic] explode all trees #2 MeSH descriptor: [Antibodies, Monoclonal, Humanized] explode all trees #3 anti next (IgE* or Idiotyp*) #4 omalizumab* #5 (humanized near (mAb or monoclonal)) #6 Antiglobulin* #7 ("anti gamma" or Antigamma) near Globulin #8 #1# or #2 or #3 or #4	1. exp Antibodies, Anti-Idiotypic/ 2. exp Antibodies, Monoclonal, Humanized/ 3. (anti adj3 (IgE* or Idiotyp*)).ab,ti. 4. "omalizumab*".ab,ti. 5. (humanized adj3 (mAb or monoclonal)).ab,ti. 6. "Antiglobulin*".ab,ti. 7. (("anti gamma" or Antigamma) adj3 Globulin).ab,ti. 8. 1 or 2 or 3 or 4 or 5 or 6 or 7	1. exp Antibodies, Anti-Idiotypic/ 2. exp Antibodies, Monoclonal, Humanized/ 3. (anti adj3 (IgE* or Idiotyp*)).ab,ti. 4. "omalizumab*".ab,ti. 5. (humanized adj3 (mAb or monoclonal)).ab,ti. 6. "Antiglobulin*".ab,ti. 7. (("anti gamma" or Antigamma) adj3 Globulin).ab,ti. 8. 1 or 2 or 3 or 4 or 5 or 6 or 7

8 APPENDIX 3

Number of abstracts identified across the condition

	Total number of abstracts (all years)
CRS (CRSsNP/CRSwNP)	9377
CRSsNP	7578
CRSwNP	3273

Number of abstracts identified for each intervention

	Included in previous reviews	**New abstracts to screen (2010-2015)**
Topical steroids	50	261
Oral steroids	3	433
Systemic antibiotics	1	546
Nasal saline	8	540
Antifungal therapy	6	50
Leukotriene antagonists	n/a	348
Anti-IL-5	n/a	624
Anti-IgE	n/a	471
Local decongestants	n/a	n/a

9 APPENDIX 4

N/A

10 REFERENCES

1. Hastan D, Fokkens WJ, Bachert C, et al. Chronic rhinosinusitis in Europe - an underestimated disease. A GA(2) LEN study. Allergy 2011;**66**(9):1216-23.
2. Gliklich RE, Metson R. The health impact of chronic sinusitis in patients seeking otolaryngologic care. Otolaryngol Head Neck Surg 1995;**113**(1):104-9.
3. Gulliford MC, Dregan A, Moore MV, et al. Continued high rates of antibiotic prescribing to adults with respiratory tract infection: survey of 568 UK general practices. BMJ open 2014;**4**(10):e006245.
4. Hospital Episode Statistics: Department of Health, 2012.
5. Lange B, Holst R, Thilsing T, et al. Quality of life and associated factors in persons with chronic rhinosinusitis in the general population: A prospective questionnaire and clinical cross-

sectional study. Clinical otolaryngology : official journal of ENT-UK ; official journal of Netherlands Society for Oto-Rhino-Laryngology & Cervico-Facial Surgery 2013;38(6):474-80.
6. Sahlstrand-Johnson P, Ohlsson B, Von Buchwald C, et al. A multi-centre study on quality of life and absenteeism in patients with CRS referred for endoscopic surgery. Rhinology 2011;49(4):420-8.
7. Ponikau JU, Sherris DA, Kern EB. The diagnosis and incidence of allergic fungal sinusitis. Mayo Clinic Proceedings 1999;74:877-84.
8. Hopkins C, McCombe A, Philpott C, et al. Commissioning Guide: Rhinosinusitis: ENT UK/Royal College of Surgeons of England, 2013.
9. Sharma R, Lakhani R, Rimmer J, et al. Surgical interventions for chronic rhinosinusitis with nasal polyps. Cochrane Database Syst Rev 2014;11:CD006990.
10. Rimmer J, Fokkens W, Chong LY, et al. Surgical versus medical interventions for chronic rhinosinusitis with nasal polyps. Cochrane Database Syst Rev 2014;12:CD006991.
11. Kalish L, Snidvongs K, Sivasubramaniam R, et al. Topical steroids for nasal polyps. Cochrane Database Syst Rev 2012;12:CD006549.
12. Snidvongs K, Kalish L, Sacks R, et al. Topical steroid for chronic rhinosinusitis without polyps. Cochrane Database Syst Rev 2011(8):CD009274.
13. Sacks PL, Harvey RJ, Rimmer J, et al. Topical and systemic antifungal therapy for the symptomatic treatment of chronic rhinosinusitis. Cochrane Database Syst Rev 2011(8):CD008263.
14. Ahmed J, Pal S, Hopkins C, et al. Functional endoscopic balloon dilation of sinus ostia for chronic rhinosinusitis. Cochrane Database Syst Rev 2011(7):CD008515.
15. Piromchai P, Thanaviratananich S, Laopaiboon M. Systemic antibiotics for chronic rhinosinusitis without nasal polyps in adults. Cochrane Database Syst Rev 2011(5):CD008233.
16. Harvey R, Hannan SA, Badia L, et al. Nasal saline irrigations for the symptoms of chronic rhinosinusitis. Cochrane Database Syst Rev 2007(3):CD006394.
17. Khalil HS, Nunez DA. Functional endoscopic sinus surgery for chronic rhinosinusitis. Cochrane Database Syst Rev 2006(3):CD004458.
18. Martinez-Devesa P, Patiar S. Oral steroids for nasal polyps. Cochrane Database of Systematic Reviews 2011, Issue 7. Art. No.: CD005232. DOI: 10.1002/14651858.CD005232.pub3
19. Dalziel K, Stein K, Round A, et al. Systematic review of endoscopic sinus surgery for nasal polyps. Health technology assessment 2003;7(17):iii, 1-159.
20. Johnston BC, Patrick DL, Busse JW, et al. Patient-reported outcomes in meta-analyses--Part 1: assessing risk of bias and combining outcomes. Health and quality of life outcomes 2013;11:109.
21. Johnston BC, Patrick DL, Thorlund K, et al. Patient-reported outcomes in meta-analyses-part 2: methods for improving interpretability for decision-makers. Health and quality of life outcomes 2013;11:211.

22. Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org

23. National Institute for Health and Clinical Excellence. The guidelines manual 2012. National Institute for Health and Clinical Excellence, 2012 Available from: http://www.nice.org.uk/article/pmg6/resources/non-guidance-the-guidelines-manual-pdf