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## Medical interventions for chronic rhinosinusitis in cystic fibrosis (Protocol)

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[Intervention Protocol]

# Medical interventions for chronic rhinosinusitis in cystic fibrosis

Tulasi Kota Karanth<sup>1</sup>, Veena KL Karanth<sup>2</sup>, Bryan K Ward<sup>3</sup>, Bradford A Woodworth<sup>4</sup>, Laxminarayan Karanth<sup>5</sup>

<sup>1</sup>Kasturba Medical College, Manipal University, Karnataka, India. <sup>2</sup>Department of Surgery, Kasturba Medical College and Hospital, Manipal, India. <sup>3</sup>Division of Otolaryngology, Neurotology and Skull Base Surgery, Johns Hopkins Hospital, Baltimore, Maryland, USA. <sup>4</sup>University of Alabama, Birmingham, USA. <sup>5</sup>Department of Obstetrics and Gynecology, Melaka Manipal Medical College, Melaka, Malaysia

Contact address: Tulasi Kota Karanth, Kasturba Medical College, Manipal University, Manipal, Karnataka, 576104, India. [karanthtk@gmail.com](mailto:karanthtk@gmail.com).

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## ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

The objective of this review is to compare the effects of different medical interventions in people diagnosed with CF and CRS.

## BACKGROUND

### Description of the condition

Cystic fibrosis (CF) is a genetic disorder primarily affecting the nasal cavities, paranasal sinuses (air spaces around eyes and nose), lungs and digestive system. CF is an autosomal recessively inherited condition which means that children of carrier parents have a 25% chance of having the disease and 50% chance of being a carrier. Carriers transmit the disease to the next generation without suffering from the disease themselves. It is a relatively common debilitating disorder with its incidence differing across different continents. The highest incidence is noted in Europe (ranging between 1 in 2000 to 1 in 3000 live births) and the lowest in Asia (ranging between 1 in 40,000 to 1 in 100,000 live births) ([WHO Human Genetics Programme 2004](#)).

The condition is caused by mutations in a gene on chromosome 7 that encodes the cystic fibrosis transmembrane conductance regulator (CFTR) protein ([Collins 1992](#); [Drumm 1993](#)). CFTR is an anion (a negatively-charged molecule, e.g. chloride (Cl<sup>-</sup>) and bicarbonate (HCO<sub>3</sub><sup>-</sup>)) channel usually present on the plasma membrane of epithelial cells lining the airway, pancreas, liver, intestines, sweat ducts, and epididymis (a tube located at the back of the testicles that stores and carries sperm) ([Guggino 2004](#)). The normal function of the anion channel promotes anion secretion to the airway surface (or into the extracellular lumen of the intestine and glandular ducts), which impacts the balance of water and electrolyte transport ([Johnson 1995](#); [Rowe 2005](#)).

The most common mutation is F508del, although more than 2000 different potentially disease-causing CFTR gene mutations have been listed in the Cystic Fibrosis Mutation Database ([Cystic Fibrosis Mutation Database 2011](#)). Six different classes of mutations have been identified, based on the way the defective CFTR

protein is produced. Class I mutations lead to defective protein production, which in turn leads to the premature termination of the mRNA and a complete absence of CFTR protein in the cell. Class II mutations are mutations in protein processing and trafficking and include the most common mutation - F508del. Class III mutations show defective regulation of CFTR channel gating (e.g. G551D). Class IV mutations reduce the duration of channel opening and also the rate of ion flow. Class V mutations have reduced quantities of normal CFTR protein due to abnormalities of mRNA splicing. Finally, class VI mutations have increased channel turnover at the cell surface due to instability, which results in decreased amounts of functional protein.

In a normal airway, hair-like projections from epithelial cells called cilia beat to move the overlying mucus out of the sinuses. The cilia are covered with 'thin' airway surface liquid (ASL) which is made up of a mucus layer overlying a periciliary fluid layer which is in direct contact with the epithelial cells. Normally, oxygen levels are equal throughout the depths of the ASL. In the airways of people with CF, defective chloride ion transport leads to the excessive absorption of sodium and water and consequently the dehydration of the ASL, resulting in a thin periciliary layer (Rowe 2005). Cilia are not able to function correctly in a thin periciliary layer and mucociliary clearance (the transport of mucus by the cilia towards the sinus openings) is impaired. Mucus is still produced and secreted forming a thick layer of static mucus which the cilia are not able to clear adequately and the thick secretions block the sinus openings. Ventilation of the sinuses decreases and hypoxia (low levels of oxygen in tissue) occurs; this hypoxia impairs mucociliary clearance even more by inhibiting chloride transport and further dehydrating ASL (Blount 2011).

*Pseudomonas aeruginosa* (*P aeruginosa*), *Staphylococcus aureus* (*S aureus*), *Haemophilus influenzae* (*H influenzae*), *Burkholderia cepacia* (*B cepacia*), *Achromobacter xylosoxidans* and *Stenotrophomonas maltophilia* are bacteria which commonly cause infection and inflammation (Brook 2016; Ramsey 1992). These bacteria further impair ciliary motion or co-ordination (or both), exacerbating impaired mucociliary clearance (Wilson 1987). Inflammation increases mucus secretion by mucosa (Mainz 2012), promotes the formation of neutrophil-predominant nasal polyps (Ryan 2008) and propagates the cycle of infection and inflammation.

Oxygen levels are highest near the surface of this mucus layer and lowest in its depths near the mucosa. *P aeruginosa* deposited on the surface penetrates into the hypoxic zones of mucus, adapts to the environment and forms microcolonies (Kim 2015). Hypoxic mucus with *P aeruginosa* microcolonies resists the natural defense mechanism in the lungs and sinuses, resulting in chronic airway infection.

A single type of mucosa (pseudostratified ciliated columnar epithelium) lines the nasal cavity through the sinuses, larynx, and trachea to the distal lungs (Krouse 2007). The pathophysiology of mucostasis (a mass of thick mucus over the mucosa which cannot be pushed away by cilia), infection and inflammation is the same

for upper and lower airway. The 'unified airway model' suggests that infection in the upper airway easily spreads to the lower airway and vice versa (Chang 2014; Illing 2014; Tos 1983). Therefore, chronic rhinosinusitis can lead to pulmonary exacerbations, a major cause of death in people with CF. Mucostasis with microcolonies of bacteria in sinuses form a reservoir of infection. If not adequately controlled or treated they can cause recurrent pulmonary infection and death. It has been shown that in people who have undergone surgery to open up sinuses and help drain the collected mucus, there is reduced pulmonary disease (Chang 2014; Holzmann 2004; Jones 1993; Rosbe 2001).

According to the International Consensus Statement on Allergy and Rhinology: Rhinosinusitis (Orlandi 2016) and the European Position Paper on rhinosinusitis and nasal polyps (Fokkens 2012), chronic rhinosinusitis (CRS) is diagnosed when a person presents for 12 weeks with two or more of: nasal obstruction, congestion, rhinorrhea, facial pain or pressure or reduction in olfaction (sense of smell); and has at least one of the following findings: nasal polyps, mucopurulent discharge (yellow-green sticky secretions of infected mucus), or mucosal edema.

## Description of the intervention

Medical intervention is one of the first steps in managing CRS in people with CF and can include oral and topical treatments which are usually given in combination for a long duration. Available treatment options include nasal saline irrigation, oral and topical antibiotics, oral and topical steroids, anti-inflammatory agents (such as ibuprofen), dornase alfa and CFTR modulators.

### Nasal saline irrigation

Nasal saline irrigation involves washing the nasal cavity with saline delivered via squeeze bottles and neti pots. It helps to soften dried mucous crusts and clears them out of the sinonasal cavity. It is usually used in two concentrations: hypertonic (more concentrated than serum, ranging from 3% to 7%); and isotonic (as concentrated as our serum, i.e. 0.9%).

### Corticosteroids

Corticosteroids break the infection-inflammation cycle, preventing the progression of CRS in people with CF. They are strong immunosuppressants and decrease the inflammatory response to the retained mucus or bacterial microcolonies. Oral corticosteroids are given as tablets, usually in the morning to match the circadian rhythm (bodily rhythm of morning and night). Topical corticosteroids are usually administered as nasal sprays inhaled in the morning. Topical application increases the local delivery of the drug and prevents the potential side effects that could arise by systemic administration.

## Antibiotics

Antibiotics are traditionally given as oral tablets or intravenous drips. In CF, nebulised tobramycin and colistin have been used to prevent the formation of bacterial micro-colonies in the mucus lining the sinuses.

## Dornase alfa

Dornase alfa (recombinant human DNase) is a relatively newly developed medicine which is administered topically. It breaks long DNA present in mucus and decreases its viscosity (stickiness). It enhances the clearance of mucus from the sinonasal cavities.

## CFTR modulators

CFTR modulators (e.g. ivacaftor and lumacaftor) are medicines that act on the cause of CF, the defective CFTR protein. They increase the efficacy of these proteins and thereby normalise their activity. They are specifically useful in individuals with G551D mutations, but have been expanded for use in people with other Class III and residual function mutations (Guigui 2016). Of these medical interventions, many interventions including saline irrigations, antibiotics and steroids are used empirically and have now become the standard of care.

## How the intervention might work

### Nasal saline irrigation

Nasal saline irrigation physically removes viscous mucus that impairs the clearance of debris and bacteria. Hypertonic saline could have the additional benefit of creating an osmotic gradient, where water is drawn into the mucus thus decreasing its viscosity. As water transfers from inflamed mucosa to the airway surface, edematous (swollen with fluid) mucosa shrink, thus acting as a decongestant (Kang 2015). Although hypertonic saline increases the osmotic gradient further and is the preferred saline in people with CF, it has been recognized to decrease the function of cilia (ciliostasis) (Boek 1999).

### Corticosteroids

Short courses of oral steroids in tapering doses are sometimes given with antibiotics in initial treatment, but their use is controversial. There is a risk of pulmonary exacerbation with the use of oral steroids in people with CF, although long-term oral steroids have been shown to slow the progression of lung disease, decrease hospitalization rates for respiratory exacerbations and improve quality of life with no effect on sino-nasal symptoms (Cheng 2015). The short-term use of oral steroids has not been analyzed.

Topical corticosteroids are commonly prescribed and have the advantage of enhanced local effects without systemic complications. Owing to their anti-inflammatory properties, topical corticosteroids have been used to decrease the burden associated with nasal polyps (Costantini 1990; Hadfield 2000). As inflammation decreases, edema improves and paranasal sinuses remain open longer, allowing secretions to clear.

## Antibiotics

Early aggressive anti-pseudomonal antibiotic therapy has been advocated to delay the onset of chronic *P aeruginosa* infection (Doring 2000; Langton Hewer 2017). The duration of antibiotic use for eradication is variable and depends on patient selection criteria, the source of respiratory secretion (upper versus lower airway) and the type of therapy (Gibson 2003). Ratjen reported a 12-month pathogen-free period after the use of an inhaled antibiotic (Ratjen 2001).

Anti-pseudomonal antibiotics are also used as maintenance therapy. These can include inhaled anti-pseudomonal antibiotics, oral quinolones and macrolides. Advantages of using an inhaled antibiotic, include a greater amount of drug reaching the nose and sinuses directly and limited systemic absorption and toxicity. Inhaled antibiotics that have been studied in people with CF include tobramycin (Ramsey 1999), colistin (Hodson 2002) and aztreonam (Fernandez 1994). Continuous anti-staphylococcal antibiotics are not used as they propagate the formation of methicillin-resistant *S aureus*, increase the colonisation of *P aeruginosa* and increase the formation of small colony variants (cell wall-deficient strains that have increased capability to survive defense mechanisms). Use of these antibiotics are appropriate only when they are given intermittently for respiratory symptoms (Gibson 2003).

Disease exacerbations are usually treated by targeting antibiotic therapy to the results of bacterial and antibiotic sensitivities. Antibiotics such as amoxicillin with clavulanic acid, second and third generation cephalosporins (such as cefuroxime axetil, cefprozil, cefixime, cefpodoxime proxetil and loracarbef) are chosen when culture grows *H influenzae*. Co-trimoxazole, doxycycline and minocycline are chosen when the culture grows *B cepacia*. Aminoglycosides are given once daily in order to achieve a high peak blood concentration to enhance anti-bacterial activity and a low trough blood concentration to minimise toxic effects to the ears and kidneys.

## Dornase alfa

The extensive neutrophil degradation observed in mucus from the CF airway results in the accumulation of long-chain, extracellular DNA. This increases the viscosity of the mucus, contributing to the disease. Dornase alfa targets the highly viscous mucus which lines the mucus membranes (Shak 1990); it cleaves the DNA and decreases the viscosity, helping in its clearance (Lindig 2013).

## CFTR modulators

Ivacaftor and lumacaftor are new drugs designed to target the CFTR protein. Ivacaftor is a CFTR potentiator that improves the open probability of the defective chloride channel in those with at least one copy of the mutant G551D-CFTR allele (Accurso 2010); this mutation is present in 4% to 5% of people with CF (Kaiser 2012). It has also been used successfully in people with other class III mutations such as G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, or G1349D (De Boeck 2014). Lumacaftor is a corrector which improves the folding and trafficking of some protein to the cell surface. It is used with ivacaftor as a combination treatment for people with CF aged 12 years or older with two copies of the F508del mutation (Castellani 2008; Liou 2001). The use of these medications improve the function of the CFTR protein. It increases chloride transport and thus decreases the viscosity of the mucus.

## Why it is important to do this review

Due to advancements in treating people with CF, many are surviving to an older age and CRS is common, reaching 100% when examined clinically or radiographically (Liang 2014). The unified airway model suggests that the lining of nose and sinuses is in continuity with that of lower respiratory tract. The bacteria that can be found in the upper airway, can also be found in the lower airway. Therefore, if there is an infection in the upper airway, it will easily spread to the lower airway; this can be life-threatening in people with CF (Tipirneni 2017).

Medical treatment is the initial management for people with CRS, and several treatment options are currently available. Given the diversity of treatments, it is important to know which combination of intervention and which method of delivery provides the best quality of life for people with CF.

This review will help provide high-quality information regarding medical interventions for CRS in people with CF to researchers, medical professionals, people with CF, parents and the public.

## OBJECTIVES

The objective of this review is to compare the effects of different medical interventions in people diagnosed with CF and CRS.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

We will include randomised controlled trials (RCTs), quasi-RCTs and cluster RCTs. We will also include RCTs of cross-over design if data from the first treatment phase are available. All included trials must have an adequate follow-up period (i.e. a minimum of three months).

We will exclude any trials that are randomised by the side of the nose.

#### Types of participants

Participants diagnosed with CF by sweat test or genetic testing for CFTR mutations and further diagnosed with CRS according to either the International Consensus Statement on Allergy and Rhinology: Rhinosinusitis (ICAR:RS) (Orlandi 2016) or the European Position Paper on Rhinosinusitis and Nasal Polyps (Fokkens 2012).

CRS will be defined as persistent sinonasal inflammation lasting at least 12 weeks, with two or more of the following symptoms: nasal blockage or obstruction or congestion; nasal discharge; facial discomfort; decreased sense of smell; and an objective finding by endoscopic or CT imaging showing nasal polyps or mucopurulent discharge or mucosal edema.

Asymptomatic individuals will be excluded from this analysis.

#### Types of interventions

We will include both short courses of treatment (up to 28 days) and long courses of treatment (longer than four weeks).

We will not evaluate the effect of medical interventions on surgical outcomes; the medical interventions that will be considered for this review are listed below.

- Nasal saline irrigation - isotonic (0.9%) saline, hypertonic saline (3% to 7%)
- Corticosteroids - oral or intravenous (e.g. prednisolone, hydrocortisone); or topical (e.g. beclomethasone, triamcinolone, budesonide, fluticasone, mometasone, betamethasone)
- Antibiotics - anti-staphylococcal (e.g. dicloxacillin, cephalixin, amoxicillin with clavulanic acid, macrolides (azithromycin, erythromycin, clarithromycin), nafcillin and vancomycin (for MRSA)), anti-pseudomonal (e.g. ciprofloxacin, inhaled tobramycin, inhaled colistin, ceftazidime, combination treatment of ticarcillin, piperacillin, imipenem, meropenem, aztreonam, amikacin), for treating *H influenzae* (e.g. amoxicillin with clavulanic acid, second and third generation cephalosporin (cefuroxime axetil, cefprozil, cefixime, cefpodoxime proxetil, loracarbef) and for treating *B cepacia* (e.g. co-trimoxazole, doxycycline, minocycline)
- Ibuprofen - high dose (more than 2400 mg/day)
- Dornase alfa
- CFTR modulators - ivacaftor, lumacaftor

Methods of delivery for topical application include nebulisers (jet or ultrasonic), soft mist, dry powder inhaler, pressured metered

dose inhaler, nasal drops, nasal spray, squeeze bottles and neti pots. We will compare the interventions listed above to no intervention, to placebo or to another medical intervention or class of medical intervention. We will also compare the same medical intervention given at a different dose, for a different duration or via a different route. We will also include comparisons of combinations of the treatments listed above. Concurrent treatments will be allowed if they are used in both treatment arms.

### Types of outcome measures

If a trial is found which measures outcomes other than those mentioned below, the trial will still be included if it has met our inclusion criteria and if the outcome has been measured objectively and is relevant to our review. The inclusion of any such additional outcomes will be noted as a post hoc change in the 'Difference between review and protocol' section.

#### Primary outcomes

1. QoL measured by questionnaires (e.g. Rhinosinusitis Outcome Measure-31 (Tipirneni 2017) and Sinonasal Outcome Test-22 (SNOT-22) (Tipirneni 2017) for adults; Sinonasal-5 for children (Tipirneni 2017))
2. Refractory to treatment - defined by persistent symptoms during intervention or recurrence of symptoms soon after stopping the intervention, requiring higher dose or concentration or more potent intervention to obtain any or sustained benefit as measured by Chronic Sinusitis Survey or visual analogue scale
3. Treatment-related adverse events
  - i) mild (an adverse event that does not require treatment, does not require the medication to be stopped, e.g. nausea)
  - ii) moderate (an adverse event that needs treatment, does not require the medication to be stopped; or needs the treatment to be stopped for a short duration, e.g. intractable vomiting)
  - iii) severe (an adverse event that is life-threatening and requires the medication to be stopped permanently, e.g. allergy to an antibiotic)

#### Secondary outcomes

1. Periods of improved symptoms (as measured by number of days of benefit)
2. Nasal endoscopic findings
  - i) nasal polyps
  - ii) mucopurulent discharge (discharge containing both mucus and pus)
  - iii) mucosal edema or change
3. Lund-Mackay scores
4. Pulmonary function tests (as measured by either a change from baseline, post-treatment values or both)
  - i) forced expiratory volume in one second (FEV<sub>1</sub>)
  - ii) functional vital capacity (FVC)

5. Change in nutritional status
  - i) height (cm) (in children)
  - ii) weight (kg) (in children)
  - iii) body mass index (BMI) (in adults)

Results will be reported at the end of treatment or at one month (or both), up to three months, three to six months, six to 12 months and over 12 months.

### Search methods for identification of studies

We will search for all relevant published and unpublished trials without restrictions on language, year or publication status.

#### Electronic searches

We will identify relevant studies from the Cochrane Cystic Fibrosis and Genetic Disorder Group's Cystic Fibrosis Trials Register using the term: sinusitis.

The Cystic Fibrosis Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of the Cochrane Library), weekly searches of MEDLINE, a search of Embase to 1995 and the prospective handsearching of two journals - *Pediatric Pulmonology* and the *Journal of Cystic Fibrosis*. Unpublished work is identified by searching the abstract books of three major cystic fibrosis conferences: the International Cystic Fibrosis Conference; the European Cystic Fibrosis Conference and the North American Cystic Fibrosis Conference. For full details of all searching activities for the register, please see the relevant section of the Cochrane Cystic Fibrosis and Genetic Disorders Group's [website](#).

We will search the following trial registries to identify unpublished and ongoing trials:

- ClinicalTrials.gov (<http://www.clinicaltrials.gov/>);
- WHO ICTRP (<http://apps.who.int/trialsearch/Default.aspx>); and
- European Union (EU) Clinical Trials Register (<https://www.clinicaltrialsregister.eu/>).

We will also search PubMed, Ovid Embase, the Cochrane Library and Google Scholar to retrieve trials and similar systematic reviews. See [Appendix 1](#) for the full search strategies.

#### Searching other resources

We will search the references listed in relevant trials and reviews to identify any further relevant RCTs. We will contact trial authors if we deem this to be necessary.

## Data collection and analysis

### Selection of studies

Two authors (TK and VK) will independently review all identified abstracts and reports retrieved from databases and other sources. If the reference appears relevant to the review topic, they will obtain a full text copy. The same two authors will assess and select any trials which they find to be relevant according to the review's inclusion and exclusion criteria. We will resolve any disagreements by discussion with a third author (BAW or LK). Any review author who is an investigator on a trial will not be active in the selection process for that trial.

### Data extraction and management

The review authors will create a data extraction sheet based on the 'Checklist of items to consider in data collection or data extraction' as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). Two review authors (TK and VK) will independently extract data from the included trials and resolve any disagreements by discussion with a third review author (BAW or LK). If a review author is an author on a trial, that author will not extract data for the trial.

The review authors will include key characteristics of the trial, such as trial design, setting, sample size, population, how outcomes were defined and collected in the trial. We will also collect baseline information on prognostic factors or effect modifiers, e.g. baseline symptom scores and Lund-Mackay scores. We will note down separately if participants were selected based on bacterial colonisation.

For any trials of multiple interventions, the review authors will make pair-wise summaries. If a common intervention group is present, we will split the sample size and mark this on the data extraction sheet.

For the outcomes of interest, the review authors will extract the findings of the trials on an available-case-analysis basis. We will include all participants from the point of randomisation, irrespective of the treatment they actually received.

The review authors will present all the results for each of the broad comparison groups (i.e. nasal saline irrigation, antibiotics, corticosteroids, etc.) together and will undertake subgroup analyses to look at the effects of individual agents to investigate any identified heterogeneity in the results (see below).

The review authors will extract the following statistics for each trial and each outcome:

- for dichotomous data - the number of participants experiencing an event and number of participants assessed at that time point;
- for continuous data - mean values, standard deviations (SDs) and number of participants in each treatment arm, if

available, we will report absolute values and change from baseline.

We will report results at the end of treatment or at one month (or both), up to three months, three to six months, six to 12 months and over 12 months; we will report the number of days of benefit both at the end of treatment and at one month.

### Assessment of risk of bias in included studies

Two review authors (TK and VK) will independently assess the risk of bias in each included trial based on the following six components: sequence generation, allocation concealment, blinding or masking, incomplete outcome data, selective outcome reporting, and other biases. For each of these components, we will assign a judgment regarding the risk of bias as high, low or unclear (Higgins 2011b). We will make these judgments separately for objectively and subjectively ascertained measures for the domains of blinding and incomplete outcome data. The review authors will record assessments in the standard risk of bias table for each included trial and use these assessments in making judgements on overall trial quality while preparing summary of findings tables (see below). When methodological details are unclear, the review authors will attempt to contact the trial authors for clarification. The review authors will resolve any differences by discussion.

We will include in the review any trials on which the authors themselves are investigators, if these are relevant to the review question, but will note this fact in the section on 'Declarations of interest'. In such cases, the review author who is also an investigator on the trial, will not make any risk of bias judgements for that trial.

### Measures of treatment effect

#### Dichotomous data

For dichotomous data, (refractory to treatment, presence or absence of abnormalities on nasal endoscopy and need for surgery, adverse events), we will present results as summary risk ratios (RR) with 95% confidence intervals (CI).

#### Continuous data

For continuous data (QoL measurements, pulmonary function tests, change in nutritional status and Lund-Mackay scores), we will calculate the mean difference (MD) between groups with 95% CIs if outcomes are measured in the same way in trials. When trials use different assessment scales, the authors will calculate the standardized mean difference (SMD) with 95% CIs.



## Unit of analysis issues

### Cluster-randomised trials

We will include cluster-randomized trials in this review along with individually randomized trials. We will use the methods described in the *Cochrane Handbook of Systematic Reviews of Interventions* to account for any unit of analysis error (Higgins 2011c). We will derive an estimate of the intracluster correlation co-efficient (ICC) from the trial, from a similarly designed trial or from a trial of a similar population. If we use ICCs from other sources in the review, we will report this and conduct a sensitivity analysis to recognise the effect of the variation of the ICCs. If we identify both cluster-randomized trials and individually-randomized trials with little heterogeneity between their methodology, and further if we consider an interaction between the effect of the intervention and choice of randomization unit is unlikely, we will pool the relevant information and combine the results. We will acknowledge any heterogeneity that may occur in the unit of randomization and will conduct a sensitivity analysis to investigate the effects of this.

### Cross-over trials

We will include the first phase of a cross-over trial if an adequate follow-up period (i.e. a minimum of three months) is available.

### Studies with multiple treatment groups

The authors will include multi-arm trials in the review if they can make pair-wise comparisons on the intervention groups and if when investigated alone, the comparison would meet the review's inclusion criteria. The authors will only analyze interventions or groups meeting the inclusion criteria in this review. The authors will assess the risk of bias based on the completeness of available data and absence of selective reporting of comparisons of intervention arms. The authors will attempt to overcome any unit of analysis errors by combining groups to create a single pair-wise comparison.

### Dealing with missing data

Whenever possible, we will contact original investigators to request missing data. We will assess missing data to try and establish if they are missing at random or if they had particular value. Where possible, we will extract data to allow an intention-to-treat analysis, where all randomised participants are analyzed in the groups to which they were originally assigned (Higgins 2011c). We will calculate discrepancies in the numbers randomized and numbers analyzed in each treatment group and report these as the percentage lost to follow-up. If more than 10% have been lost to follow-up for any trial, for dichotomous outcomes, we will assign the worst outcome and analyse the impact of this assignment using a sensitivity analysis.

If SDs are found to be missing in a small proportion of trials, we will impute these from other trials for which full data are available (Higgins 2011c). We will carry out sensitivity analyses to assess the impact of changing the assumptions made. If the majority of trials included in this review are missing SDs, we will not impute these values. We will not make any assumptions regarding loss to follow-up for continuous data and they will analyze the results for those who completed the trial.

### Assessment of heterogeneity

The review authors will assess heterogeneity between trials for the outcomes of interest both visually using a forest plot and using the  $I^2$  statistic as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). For multiple-intervention trials, we will split the sample size for the common intervention group in order to prevent a unit-of analysis error, to perform investigations of heterogeneity.

The interpretation of  $I^2$  will be as follows:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity (Higgins 2011b).

### Assessment of reporting biases

The review authors will use funnel plots to assess publication and reporting bias, if the number of trials permit this. We will measure funnel plot asymmetry with a linear regression approach on the logarithm scale of the RR. If the funnel plot is asymmetrical, we will explore alternative causes in addition to publication bias.

### Data synthesis

The review authors will carry out statistical analysis using the Review Manager software (Review Manager 2014). If we find that trials estimate the same underlying treatment effect, we will use a fixed-effect model to combine the data. Alternatively, if there is a high degree of heterogeneity between the trials' populations and methods, or if substantial statistical heterogeneity is detected ( $I^2$  lies between 60% and 90%), we will use a random-effects model and determine the average treatment effect to decide if the treatment effect is clinically meaningful. The review authors will treat the random-effects model summary as the average range of possible treatment effects and present the results as the average treatment effect with 95% CIs together with the estimates of  $I^2$ .

### Subgroup analysis and investigation of heterogeneity

If data permit, we will carry out subgroup analyses as follows:

- age (children - aged up to 18 years versus adults - aged more than 18 years);
- surgical status of participants (pre- and post-surgery);

- presence of co-morbidities (e.g. any other chronic disease such as diabetes and hypothyroidism);
- effects of each category of a type of medical intervention (e.g. fluticasone and mometasone; of inhaled corticosteroids).

### Sensitivity analysis

To ensure the conclusions drawn during the review process are robust and representative of reality, if there are sufficient comparable trials and if we identify methodological differences between trials, we will conduct sensitivity analyses excluding those trials with clearly inadequate randomisation, concealment of allocation or blinding (high risk of bias) (Deeks 2011).

We will also explore the impact of including trials with high levels of missing data in the overall assessment of treatment effect. As stated above, if more than 10% of participants have been lost to follow-up for any trial and we have assigned the worst outcome for dichotomous outcomes, we will analyze the impact of this assignment using a sensitivity analysis. We will also assess the effect of any imputed SDs we have used in the analyses.

Furthermore, if we use ICCs from other sources in the review, we will report this and conduct a sensitivity analysis to recognise the effect of the variation of the ICCs. We acknowledge heterogeneity that may occur in the randomization unit and will conduct a sensitivity analysis to investigate the effects of the randomization unit.

### Summary of findings table

The authors will create a summary of findings table for each comparison presented and use the GRADE approach to interpret the

findings. The authors will include in each table the following outcomes of this review:

1. QoL questionnaires;
2. refractoriness to treatment;
3. treatment-related adverse events;
4. periods of improved symptoms;
5. nasal endoscopic findings;
6. Lund-Mackay scores; and
7. pulmonary function test values.

For each, we will state the population, setting, intervention and comparison. We will assess the quality of the body of evidence by considering the overall risk of bias of the included trials, the directness of the evidence, the inconsistency of the results, the precision of the estimates, and the risk of publication bias (Schünemann 2011a; Schünemann 2011b).

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\* Indicates the major publication for the study

## APPENDICES

### Appendix I. Search Methods - Electronic Searching

Database or Resource	Search strategy
ClinicalTrials.gov ( <a href="http://www.clinicaltrials.gov/">www.clinicaltrials.gov/</a> )	(Cystic Fibrosis OR CFTR) AND (rhinitis OR sinusitis OR rhinosinusitis)
WHO ICTRP ( <a href="http://apps.who.int/trialsearch/Default.aspx">apps.who.int/trialsearch/Default.aspx</a> )	(Cystic Fibrosis OR CFTR) AND (rhinitis OR sinusitis OR rhinosinusitis)
European Union (EU) Clinical Trials Register ( <a href="http://www.clinicaltrialsregister.eu/">www.clinicaltrialsregister.eu/</a> )	(Cystic Fibrosis OR CFTR) AND (rhinitis OR sinusitis OR rhinosinusitis)
PubMed	(Cystic Fibrosis OR CFTR) AND (rhinitis OR sinusitis OR rhinosinusitis) AND (randomised control trial OR RCT OR review OR narrative review OR systematic review OR meta-analysis)
Ovid Embase	(Cystic Fibrosis OR CFTR) AND (rhinitis OR sinusitis OR rhinosinusitis) AND (randomised control trial OR RCT OR review OR narrative review OR systematic review OR meta-analysis)

(Continued)

Cochrane Library	(Cystic Fibrosis OR CFTR) AND (rhinitis OR sinusitis OR rhinosinusitis) AND (randomised control trial OR RCT OR review OR narrative review OR systematic review OR meta-analysis)
Google Scholar	(Cystic Fibrosis OR CFTR) AND (rhinitis OR sinusitis OR rhinosinusitis) AND (randomised control trial OR RCT OR review OR narrative review OR systematic review OR meta-analysis)

We will exclude search results with surgical interventions; all other articles will be studied in detail. We will check the reference lists in the articles to retrieve more articles.

## CONTRIBUTIONS OF AUTHORS

Task	Author(s) responsible
<b>Protocol stage:</b> draft the protocol	All five authors.
<b>Review stage:</b> select which trials to include (2 + 1 arbiter)	Tulasi Kota Karanth and Dr KVL Karanth will independently select trials. Disagreements will be discussed with Dr BA Woodworth and Dr L Karanth
<b>Review stage:</b> extract data from trials (2 people)	Tulasi Kota Karanth and Dr KVL Karanth will independently extract data from trials
<b>Review stage:</b> enter data into RevMan	Tulasi Kota Karanth.
<b>Review stage:</b> carry out the analysis	Dr L Karanth, Dr KVL Karanth, Tulasi Kota Karanth.
<b>Review stage:</b> interpret the analysis	Dr L Karanth, Dr KVL Karanth, Tulasi Kota Karanth.
<b>Review stage:</b> draft the final review	All five authors.
<b>Update stage:</b> update the review	All five authors.

## DECLARATIONS OF INTEREST

TK: none known.

VK: none known.

BKW has received payment from Oakstone, LLC. for providing educational reviews of recent medical literature on topics of interest to general otolaryngologists and has received reimbursement for attending a conference on inner ear disorders from Med-El Corporation.

BAW is a consultant for Olympus and Cook Medical and has grant support from the NHLBI and Cook Medical.

LK: none known

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