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Saline irrigation for allergic rhinitis

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ABSTRACT

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

To evaluate the effects of nasal saline irrigation in patients with allergic rhinitis.

BACKGROUND

Description of the condition

According to the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines (ARIA 2008), allergic rhinitis is defined clinically by nasal hypersensitivity symptoms induced by an immunologically mediated (most often IgE-dependent) inflammation of the nasal mucous membranes after exposure to an offending allergen. Common allergic triggers include house dust mites, pollens (from trees, grasses, shrubs and weeds), animal dander or fungi, which occur naturally in the environment. In addition, allergic rhinitis can be caused by triggers to which a person is exposed in the course of their work (occupational exposure). These may include vegetable proteins, enzymes and chemicals (BSACI 2008). Symptoms of allergic rhinitis may include nasal obstruction (blockage or congestion), rhinorrhoea (which can be anterior leading to nasal discharge, or posterior leading to post-nasal drip), nasal

itching and sneezing (ARIA 2008). In addition to nasal symptoms, some patients with allergic rhinitis also report ear symptoms such as pain, pressure or feeling of fullness; however, aural symptoms have also been reported as an adverse effect of nasal saline irrigation (Chusakul 2013). There is some evidence that people with allergic rhinitis may experience decreased quality of life due to issues such as loss of sleep, secondary daytime fatigue, impaired school and work performance, decreased cognitive functioning and decreased long-term productivity (Schoenwetter 2004).

Allergic rhinitis is commonly classified into 'intermittent' and 'persistent' disease. Intermittent allergic rhinitis is diagnosed when symptoms are present for less than four days per week or for less than four weeks. Persistent allergic rhinitis is diagnosed when symptoms are present more frequently than four days per week and for at least four consecutive weeks (ARIA 2008). The presence of intermittent or persistent disease may be related to the type of allergic triggers for allergic rhinitis, for example intermittent allergic rhinitis may be linked to the release of a certain type of tree

pollen (such as elm tree pollen) occurring once a year for a period of a few weeks.

Prior to 2008, allergic rhinitis was classified into 'seasonal', 'perennial' and 'occupational', based on the time of exposure. Seasonal allergic rhinitis was used to define mainly 'outdoor' allergens such as tree pollens, which were not present consistently throughout the year, whereas the term 'perennial' allergic rhinitis was used for 'indoor' allergens where exposure was thought to be consistent throughout the year. The [ARIA 2008](#) guidelines attempted to make the classification more useful in the real world by introducing the terms 'intermittent' and 'persistent' to classify the disease. The previous classification had been felt to be inadequate as it was noted that in certain situations a seasonal allergen may occur year round (e.g. grass pollen allergy in Southern California) or symptoms of perennial allergy may not always be present all year round (e.g. in the Mediterranean area where levels of house dust mite allergen are low in the summer). Thus the change to intermittent and persistent was made ([ARIA 2008](#)).

The ARIA guidelines further classify allergic rhinitis into 'mild' and 'moderate/severe' depending on the person's severity of symptoms and the impact of the condition on their quality of life. Moderate/severe allergic rhinitis is diagnosed when one or more of the following items are present: sleep disturbance; impairment of daily activities, leisure or sport; impairment of school or work; or troublesome symptoms ([ARIA 2008](#)).

The diagnosis of allergic rhinitis is based upon clinical symptoms combined with laboratory studies demonstrating the presence of allergen-specific IgE in the skin (skin prick test) or blood (serum IgE). A review of epidemiological studies estimated that 10% to 15% of adults have allergic rhinitis based on both the presence of symptoms and a positive skin prick test ([Mims 2014](#)). However, the number is higher when people reporting either just symptoms (up to 34%) or a positive skin prick test (up to 53.9%, testing 10 allergens) are considered ([Mims 2014](#)). There are a wide range of estimates for the prevalence of allergic rhinitis in children (10% to 40%). These differences in estimates may be attributable to both the geographical location of the study, the method of diagnosis used (whether a skin prick test was completed or whether the diagnosis was based on symptoms), or both ([Mims 2014](#)).

Traditionally there has appeared to be a higher prevalence of allergic rhinitis in countries with a 'western lifestyle' (USA and Europe), where reported prevalence rates vary between 10% and 30% ([ARIA 2008](#)). For areas outside these regions, [Katelaris et al](#) completed a review of global prevalence studies, which identified a great diversity in the prevalence estimates of allergic rhinitis both between and within countries ([Katelaris 2012](#)). The review concluded that "the prevalence of allergic rhinitis is increasing and its adverse impact on the quality of life of affected individuals is increasingly recognised" ([Katelaris 2012](#)). The increase in prevalence has been hypothesised as being due to increasing urbanisation and modification of lifestyles, which has led to reduced exposure to environmental allergens during early childhood resulting

in a weaker immune system and consequent development of allergies, commonly known as the 'hygiene hypothesis' ([ARIA 2008](#)). There is a well-established link between allergic rhinitis and asthma. A literature review identified that 40% of allergic rhinitis patients had asthma ([Kim 2008](#)). The proportion of asthmatic patients reporting symptoms of allergic rhinitis ranged from 30% to 80%. This connection is perhaps unsurprising as both allergic rhinitis and asthma are based on shared physiological immune responses to an identified foreign substance (allergen) ([Kim 2008](#)). Treatment options for allergic rhinitis include allergen avoidance, pharmacological therapy and immunotherapy. Pharmacological therapies include various classes of medications, including antihistamines, intranasal corticosteroids and anti-leukotrienes ([ARIA 2008](#)). Nasal saline has been used as a 'natural' remedy for centuries and recent Cochrane Reviews have evaluated its efficacy as a potential treatment or adjunct to pharmacological treatment for chronic rhinosinusitis and upper respiratory tract infections ([Chong 2016](#); [King 2015](#)).

Description of the intervention

Saline can be deposited in the nasal cavity in various forms, including sprays, drops, nebulisers and irrigations. The volume of nasal saline from sprays and nebulisers can vary greatly. These can be very low-volume devices (< 5 mL per nostril) through to squeeze bottles and Neti pots, which are usually high-volume devices (> 60 mL). While nasal saline sprays reach the nasal cavity adequately, there is some evidence to suggest that high pressure and volume saline is more effective in penetrating the adjacent sinus cavities ([Wormald 2004](#)).

The saline solutions available are hypotonic (with a concentration of less than 0.9% NaCl), physiologic (with a concentration of 0.9% NaCl) and hypertonic (with a concentration of greater than 0.9% NaCl). There is some evidence in other conditions that the tonicity of the saline solution alters its efficacy ([Berjis 2011](#); [Rabago 2005](#)). In addition, the pH of saline solutions has been investigated and there is some evidence that solutions buffered with sodium bicarbonate (increased alkalinity) may have an impact on the nasal symptoms of patients with allergic rhinitis ([Chusakul 2013](#)).

How the intervention might work

The physiological mechanisms underlying any benefit of the use of nasal saline are not fully understood but it is commonly proposed that the primary mechanism of action is mechanical ([Barham 2015](#)). This may include clearance of mucus (saline thins mucus and helps to clear it out) ([Elkins 2011](#)), and removal of inflammation mediators such as histamine ([Georgitis 1994](#)). There is some evidence to suggest that at some concentrations nasal saline may improve ciliary beat function ([Bonnomet 2016](#)) and mucociliary

function (Hermelingmeier 2012). Adverse effects of nasal saline irrigation are thought to be rare and generally mild but may include ear fullness, stinging of the nasal mucosa and epistaxis (Khianey 2012).

Why it is important to do this review

Allergic rhinitis is a highly prevalent condition with a large impact on patients and high healthcare costs: both direct, from the cost of repeat healthcare visits and of chronic medical therapy, and indirect, via absenteeism and lost productivity (Schoenwetter 2004). Nasal saline potentially represents a safe and inexpensive therapy for allergic rhinitis. Determining the effects (benefits and potential harms) has important implications for treatment recommendations.

Previous Cochrane Reviews have demonstrated some possible benefit of saline in patients with chronic rhinosinusitis (Chong 2016) and upper respiratory tract infections (King 2015). The two most recent systematic reviews identified on the use of nasal saline in allergic rhinitis had latest search dates of 2010 (Hermelingmeier 2012) and December 2011 (Khianey 2012). Khianey 2012 limited their inclusion criteria to studies published in English and also included studies in populations with a range of different sinonasal conditions including upper respiratory tract infection and chronic rhinosinusitis. Hermelingmeier 2012 specified the population as people with seasonal or perennial allergic rhinitis. This review looked at prospective trials (including before and after studies) and only included studies published in English or German. Both reviews identified potential benefits for patients in terms of symptom improvement and found that saline irrigation was well tolerated, but both reviews highlighted the need for further research in this area in order for definitive conclusions to be drawn. This review will include recently published studies and we will apply no restriction with regard to language of publication.

OBJECTIVES

To evaluate the effects of nasal saline irrigation in patients with allergic rhinitis.

METHODS

Criteria for considering studies for this review

Types of studies

We will **include** studies with the following design characteristics:

- randomised controlled trials, including cluster-randomised trials and quasi-randomised trials, and cross-over trials if the data from the first phase are available;
- patients were followed up for at least two weeks.

We will **exclude** studies with the following design characteristics:

- randomised patients by side of nose (within-patient controlled) because it is difficult to ensure that the effects of any of the interventions considered can be localised; or
- perioperative studies, where the sole purpose of the study was to investigate the effect of nasal saline irrigation on surgical outcomes.

Types of participants

Patients (adults and children) with clinical symptoms characteristic of allergic rhinitis with a positive radioallergen sorbent test (RAST) or skin prick test (SPT).

We will **exclude** studies that included a majority (more than 50%) of participants with:

- non-allergic rhinitis;
- chronic rhinosinusitis;
- acute sinusitis;
- cystic fibrosis;
- immunotherapy started within the prior year;
- any alteration of allergic rhinitis-specific pharmacotherapy (antihistamines, intranasal corticosteroids, anti-leukotrienes) during the trial;
- aspirin-exacerbated respiratory disease;
- surgery for turbinate reduction within three months prior to study.

Where a study includes a mixed group of participants, we will exclude it if more than 50% of the participants met the 'excluded' population criteria above, unless the study reports the results for the different populations separately. Similarly, where more than 50% of the people in the study have allergic rhinitis we will include the study but, where possible, we will only use the results for the population with allergic rhinitis.

Types of interventions

The use of saline, as an active treatment, delivered to the nose by any means (douche, irrigation, pulsed, spray or nebuliser).

Tonicity: we will include all concentrations of saline. 'Hypotonic' will be defined as a concentration of less than 0.9% NaCl, 'physiologic' as 0.9% NaCl and 'hypertonic' as greater than 0.9% NaCl.

Volume: we will include all volumes of saline treatments. 'Very low-volume' will relate to misting sprays or other delivery methods where the volume of application is likely to be less than 5 mL per nostril per application. 'Low-volume' will be defined as between 5 mL and 59 mL per nostril per application. 'High-volume' will be defined as a volume of 60 mL or greater per nostril per application.

We will include studies investigating 'buffered' saline solutions where the aim is to adjust the pH of the solution. We will exclude studies that used formulations of saline solution that contain other additives, such as xylitol, antibacterials and surfactants. We will also exclude studies using other formulations, such as lactated Ringer's solution.

There will be no minimum duration of treatment.

Comparisons

The main comparison pairs will be:

- nasal saline *versus* no treatment/placebo;
- nasal saline plus 'standard treatment' *versus* placebo or no treatment plus 'standard treatment'.

Other possible comparison pairs include:

- nasal saline *versus* 'standard' treatment'.

The term 'standard treatment' refers to commonly accepted treatments such as antihistamines and intranasal corticosteroids, as recommended by internationally accepted treatment guidelines, such as the ARIA guidelines (ARIA 2008).

Types of outcome measures

We will analyse the following outcomes in the review, but we will not use them as a basis for including or excluding studies.

Primary outcomes

- Disease severity, as measured by patient-reported symptom score (such as the Total Nasal Symptom Score (TNSS) questionnaire and visual analogue scales (VAS)).
- Significant local adverse effects: epistaxis.

Secondary outcomes

- Disease-specific health-related quality of life, using validated disease-specific health-related quality of life scores, such as the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ), Mini Rhinoconjunctivitis Quality of Life Questionnaire (MiniRQLQ) and Rhinitis Symptom Utility Index (RSUI).
- Individual symptom scores for the following symptoms:
 - anterior rhinorrhoea (runny nose): where a study reports 'rhinorrhoea' as the outcome, in the absence of a definition within the paper we will assume that this measures anterior rhinorrhoea. Where the authors report a combined outcome for anterior and posterior rhinorrhoea and we are not able to obtain individual results, we will record this as a combined 'anterior and posterior rhinorrhoea' category;
 - posterior rhinorrhoea (post-nasal drip);
 - nasal blockage or congestion or obstruction;
 - nasal itching;
 - sneezing.

- Generic health-related quality of life, using validated generic quality of life scores, such as the SF-36, EQ-5D and other well-validated instruments.

- Any other local adverse effects: local irritation, discomfort.
- Aural symptoms: ear pain, pressure or feeling of fullness.
- Endoscopic score (e.g. Lund-Mackay/Lund-Kennedy).

As both short-term and long-term effects are important we will evaluate efficacy outcomes at the following time points:

- up to four weeks from the start of treatment (particularly relevant for intermittent allergic rhinitis);
- from four weeks to six months;
- from six months to 12 months; and
- at more than 12 months (particularly relevant for persistent allergic rhinitis).

Where a study reports data for an outcome at more than one time point, we will include the data for the longest of each of the four time points above. For example, if a study reports outcomes at one week, three weeks and 12 weeks from the start of treatment, we will use the three-week results (for the up to four weeks time point) and the 12-week results (for the four weeks to six months time point). We will not report the results at one week. We will pay attention during the analysis to the prevention of 'double counting' of studies when presenting summary results.

We will not report data after the treatment has been discontinued as saline is not expected to have effects that continue past the end of the treatment duration.

For adverse effects, we will analyse data from the longest time periods available.

Search methods for identification of studies

The Cochrane ENT Information Specialist will conduct systematic searches for randomised controlled trials and controlled clinical trials. There will be no language, publication year or publication status restrictions. We may contact original authors for clarification and further data if trial reports are unclear and we will arrange translations of papers where necessary.

Electronic searches

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

- the Cochrane Register of Studies ENT Trials Register (search to date);
- Cochrane Register of Studies Online (search to date);
- 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);
- Ovid CAB abstracts (1910 to date);

- Ovid AMED (1985 to date);
- LILACS (search to date);
- KoreaMed (search to date);
- IndMed (search to date);
- PakMediNet (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);
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (search to date);
- ISRCTN, www.isrctn.com (search to date);
- Google Scholar (search to date);
- Google (search to date).

The subject strategies for databases will be modelled on the search strategy designed for CENTRAL ([Appendix 1](#)). Where appropriate, these will be combined with subject strategy adaptations of the highly sensitive search strategy designed by Cochrane 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. ([Handbook 2011](#))).

Searching other resources

We will scan the reference lists of identified publications for additional trials and contact trial authors if necessary. In addition, the Information Specialist will search Ovid MEDLINE, the *Cochrane Library* and Google to retrieve existing systematic reviews relevant to this systematic review, so that we can scan their reference lists for additional trials.

Data collection and analysis

Selection of studies

At least two review authors (KH and SG) will independently screen all titles and abstracts of the studies obtained from the database searches to identify potentially relevant studies. At least two review authors (KH and CP) will evaluate the full text of each potentially relevant study to determine whether it meets the inclusion and exclusion criteria for this review.

We will resolve any differences by discussion and consensus, with the involvement of a third author for clinical and/methodological input where necessary.

Data extraction and management

At least two review authors (KH and SG) will independently extract data from each study using a standardised data collection form (see [Appendix 2](#)). Whenever a study has more than one publication, we will retrieve all publications to ensure complete extraction of data. Where there are discrepancies in the data extracted by

different review authors, we will check these against the original reports and we will resolve differences by discussion and consensus, with the involvement of a third author or a methodologist where appropriate. We will contact the original study authors for clarification or for missing data whenever required. If differences are found between publications of a study, we will contact the original authors for clarification. We will use data from the main paper(s) if no further information is found.

We will include key characteristics of the studies, such as study design, setting, sample size, population and how outcomes were defined or collected in the studies. In addition, we will also collect baseline information on prognostic factors or effect modifiers. For this review, this will include:

- age of participants;
- intermittent or persistent allergic rhinitis;
- type of allergic trigger (e.g. mites, pollens, animals, etc.);
- severity of allergic rhinitis ('mild' or 'moderate/severe' as defined in [ARIA 2008](#)).

For the outcomes of interest to the review, we will extract the findings of the studies on an available case analysis basis; i.e. we will include data from all patients available at the time points based on the treatment randomised whenever possible, irrespective of compliance or whether patients had received the treatment as planned.

In addition to extracting prespecified information about study characteristics and aspects of methodology relevant to risk of bias, we will extract the following summary statistics for each trial and each outcome:

- For continuous data: the mean values, standard deviations and number of patients for each treatment group. Where endpoint data are not available, we will extract the values for change from baseline. We will analyse data from measurement scales such as RQLQ and EQ-5D as continuous data.
- For binary data: the numbers of participants experiencing an event and the number of patients assessed at the time point.
- For ordinal scale data: if the data appear to be approximately normally distributed or if the analysis that the investigators performed suggested parametric tests were appropriate, then we will treat the outcome measures as continuous data. Alternatively, if data are available, we plan to convert into binary data.

We have prespecified the time points of interest for the outcomes in this review ([Types of outcome measures](#)). While studies may have reported data at multiple time points, we will only extract the longest available data within the time points of interest. For example, if a study reports data at one, two and four weeks, we will only extract and analyse the data for the four-week follow-up.

Extracting data from figures

Where values for primary or secondary outcomes are shown as figures within the paper we will contact the study authors to try

to obtain the raw values. When the raw values are not provided, we will extract information from the graphs using an online data extraction tool (<http://arohatgi.info/WebPlotDigitizer/app/>), using the best quality version of the relevant figures available.

Assessment of risk of bias in included studies

KH and SG will undertake assessment of the risk of bias of the included trials independently, with the following taken into consideration, as guided by the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011):

- sequence generation;
- allocation concealment;
- blinding;
- incomplete outcome data;
- selective outcome reporting; and
- other sources of bias.

We will use the Cochrane 'Risk of bias' tool in RevMan 5.3 (RevMan 2014), which involves describing each of these domains as reported in the trial and then assigning a judgement about the adequacy of each entry: 'low', 'high' or 'unclear' risk of bias.

Measures of treatment effect

We will summarise the effects of dichotomous outcomes (e.g. proportion of patients with symptom resolution) as risk ratios (RR) with 95% confidence intervals (CIs). For the key outcomes that we will present in the 'Summary of findings' table, we will also express the results as absolute numbers based on the pooled results and compared to the assumed risk. We also plan to calculate the number needed to treat to benefit (NNTB) using the pooled results. The assumed baseline risk will typically be either (a) the median of the risks of the control groups in the included studies, this being used to represent a 'medium risk population' or, alternatively, (b) the average risk of the control groups in the included studies used to represent the 'study population' (Handbook 2011). If a large number of studies are available, and where appropriate, we also plan to present additional data based on the assumed baseline risk in (c) a low-risk population and (d) a high-risk population.

For continuous outcomes, we will express treatment effects as a mean difference (MD) with standard deviation (SD). If different scales are used to measure the same outcome we will use the standardised mean difference (SMD), and we will provide a clinical interpretation of the SMD values.

Unit of analysis issues

This review will not use data from phase II of cross-over studies or from studies where the patient is not the unit of randomisation, i.e. studies where the side of the nose (right versus left) was randomised.

If we find cluster-randomised trials, we will analyse these according to the methods in section 16.3.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011).

Dealing with missing data

We will contact study authors via email whenever the outcome of interest is not reported if the methods of the study suggest that the outcome had been measured. We will do the same if not all data required for meta-analysis are reported, unless the missing data are standard deviations. If standard deviation data are not available we will approximate these using the standard estimation methods from P values, standard errors or 95% CIs if these are reported, as detailed in the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011). Where it is impossible to estimate these, we will contact the study authors.

Apart from imputations for missing standard deviations, we will not conduct any other imputations. We will extract and analyse data for all outcomes using the available case analysis method.

Assessment of heterogeneity

We will assess clinical heterogeneity (which may be present even in the absence of statistical heterogeneity) by examining the included trials for potential differences between studies in the types of participants recruited (including age of participants), interventions or controls used and the outcomes measured.

We will assess statistical heterogeneity by visually inspecting the forest plots and by considering the Chi² test (with a significance level set at $P < 0.10$) and the I² statistic, which calculates the percentage of variability that is due to heterogeneity rather than chance, with I² values over 50% suggesting substantial heterogeneity (Handbook 2011).

Assessment of reporting biases

We will assess reporting bias as between-study publication bias and within-study outcome reporting bias.

Outcome reporting bias (within-study reporting bias)

We will assess within-study reporting bias by comparing the outcomes reported in the published report against the study protocol, whenever this can be obtained. If the protocol is not available, we will compare the outcomes reported to those listed in the methods section. If results are mentioned but not reported adequately in a way that allows analysis (e.g. the report only mentions whether the results were statistically significant or not), bias in a meta-analysis is likely to occur. We will try to find further information from the study authors. If no further information can be obtained, we will note this as being a 'high' risk of bias. Where there is insufficient information to judge the risk of bias we will note this as an 'unclear' risk of bias (Handbook 2011).

Publication bias (between-study reporting bias)

We plan to create funnel plots if sufficient trials (more than 10) are available for an outcome. If we observe asymmetry of the funnel plot, we plan to conduct more formal investigation using the methods proposed by Egger 1997.

Data synthesis

We will conduct all meta-analyses using Review Manager 5.3 (RevMan 2014). For dichotomous data, we plan to analyse treatment differences as a risk ratio (RR) calculated using the Mantel-Haenszel methods. We plan to analyse time-to-event data using the generic inverse variance method.

For continuous outcomes, if all the data are from the same scale, we will pool mean values obtained at follow-up with the change in outcomes (i.e. difference between pre- versus post-treatment values) and report this as a MD. However, if the SMD has to be used as an effect measure, we will not pool change and endpoint data.

When statistical heterogeneity is low, random-effects versus fixed-effect methods yield trivial differences in treatment effects. However, when statistical heterogeneity is high, the random-effects method provides a more conservative estimate of the difference.

Subgroup analysis and investigation of heterogeneity

Where data are available, we plan to conduct some subgroup analyses regardless of whether statistical heterogeneity is observed, as these are widely suspected to be potential effect modifiers. For this review, this includes the following.

- Volume of saline delivery (e.g. 'very low', 'low' and 'high' volume). There is evidence of a difference in effectiveness between high- and low-volume saline irrigation in patients with chronic sinonasal symptoms (Pynnonen 2007).
- Tonicity of saline solution (hypertonic, isotonic and hypotonic solutions). There is some evidence in other conditions that tonicity may have an effect on the efficacy of nasal saline (Berjis 2011; Rabago 2005).
- Alkalinity of saline solution. There is evidence that increased alkalinity of the saline solution improves some nasal symptoms (Chusakul 2013).
- Patient age (children, adults or mixed population). There may be differences in physiology that are unknown and compliance and volumes may well be quite different in the paediatric population compared to adults.

We plan to present the main analyses of this review according to the volume of saline delivery. We intend to present all other subgroup analysis results in tables.

In addition to the subgroups above, we plan to conduct the following subgroup analyses in the presence of statistical heterogeneity:

- method of delivery (e.g. nebuliser, sprays, irrigations);
- duration of treatment;

- frequency of allergic rhinitis symptoms (e.g. intermittent or persistent as defined by ARIA 2008), where an older study using the 'seasonal' and 'perennial' classification is used, we will interpret seasonal as 'intermittent' allergic rhinitis and 'perennial' as 'persistent' unless there is specific information in the paper that would make this inappropriate.
- severity of symptoms (mild, moderate/severe as defined by ARIA 2008).

When studies have a mixed group of patients, we plan to analyse the study as one of the subgroups (rather than as a mixed group) if more than 80% of the participants belong to one category. For example, if 81% of patients are over 18, we will analyse the study as though the participants were adults.

Sensitivity analysis

We plan to carry out sensitivity analyses to determine whether the findings are robust to the decisions made in the course of identifying, screening and analysing the trials. We plan to conduct sensitivity analysis for the following factors, whenever possible:

- impact of model chosen: fixed-effect versus random-effects model;
- risk of bias of included studies: evaluating the impact of missing data on the results of the studies due to participant attrition, to determine whether the missing outcome data for the participants in the trial could have influenced the results of the review;
- how outcomes were measured: we plan to investigate the impact of including data where the validity of the measurement instrument used was unclear.

If any of these investigations find a difference in the size of the effect or heterogeneity, we will mention this in the 'Effects of interventions' section.

GRADE and 'Summary of findings' table

Using the GRADE approach, at least two review authors (KH, SG) will independently rate the overall quality of evidence using the GDT tool (<http://www.guidelinedevelopment.org/>) for the main comparison pairs listed in the Types of interventions section. The quality of evidence reflects the extent to which we are confident that an estimate of effect is correct and we will apply this in the interpretation of results. There are four possible ratings: high, moderate, low and very low. A rating of high quality of evidence implies that we are confident in our estimate of effect and that further research is very unlikely to change our confidence in the estimate of effect. A rating of very low quality implies that any estimate of effect obtained is very uncertain.

The GRADE approach rates evidence from RCTs that do not have serious limitations as high quality. However, several factors can lead to the downgrading of the evidence to moderate, low or very

low. The degree of downgrading is determined by the seriousness of these factors:

- study limitations (risk of bias);
- inconsistency;
- indirectness of evidence;
- imprecision; and
- publication bias.

We will include a 'Summary of findings' table, constructed according to the recommendations described in Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011). We will include the following outcomes in the 'Summary of findings' table: patient-reported disease severity score, individual symptom scores, significant adverse events (epistaxis), disease-specific health-related quality of life and other ad-

verse events (local irritation/discomfort).

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* Indicates the major publication for the study

APPENDICES**Appendix I. Search strategies**

CRSO	MEDLINE (Ovid)	Embase (Ovid)	Web of Science (Web of Knowledge)
#1 MESH DESCRIPTOR Rhinitis	1 Rhinitis/	1 rhinitis/	#1 TOPIC:
#2 MESH DESCRIPTOR Conjunctivitis	2 Conjunctivitis/	2 conjunctivitis/	(rhinit* or Rhinoconjunctivitis or conjunctivitis)
#3 (rhinit* or Rhinoconjunctivitis or conjunctivitis):TI,AB, KY	3 (rhinit* or Rhinoconjunctivitis or conjunctivitis).ab,kf,ti	3 (rhinit* or Rhinoconjunctivitis or conjunctivitis).ab,kw,ti	Indexes=SCI-EXPANDED, CPCI-S Timespan=All years
#4 #1 OR #2 OR #3	4 1 or 2 or 3	4 1 or 2 or 3	#2 TOPIC: (allerg* or hypersensitivit* or perennial or non-season* or season* or pollen* or dust or hair* or dander or mite*)
#5 MESH DESCRIPTOR Allergens EXPLODE ALL TREES	5 exp Allergens/	5 exp allergen/	Indexes=SCI-EXPANDED, CPCI-S Timespan=All years
#6 MESH DESCRIPTOR Pollen EXPLODE ALL TREES	6 exp Pollen/	6 exp pollen/	#3 #2 AND #1
#7 MESH DESCRIPTOR Hypersensitivity EXPLODE ALL	7 exp Hypersensitivity/	7 exp hypersensitivity/	Indexes=SCI-EXPANDED, CPCI-S Timespan=All years
	8 (allerg* or hypersensitivit* or perennial or nonseason* or season* or pollen* or dust or hair* or dander or mite*).ab,kf,ti	8 (allerg* or hypersensitivit* or perennial or nonseason* or season* or pollen* or dust or hair* or dander or mite*).ab,kw,ti	#4 TOPIC: (hayfever or “hay fever” or pollenosis or polli-
	9 5 or 6 or 7	9 5 or 6 or 7 or 8	
	10 4 and 9	10 4 and 9	
	11 exp Rhinitis, Allergic/	11 exp allergic rhinitis/	
	12 exp Conjunctivitis, Allergic/	12 exp allergic conjunctivitis/	

(Continued)

<p>TREES #8 (allerg* or hypersensitivit* or perennial or nonseason* or season* or pollen* or dust or hair* or dander or mite*):TI,AB,KY #9 #5 OR #6 OR #7 OR #8 #10 #4 AND #9 #11 MESH DESCRIPTOR Rhinitis, Allergic EXPLODE ALL TREES #12 MESH DESCRIPTOR Conjunctivitis, Allergic EXPLODE ALL TREES #13 (hayfever or "hay fever" or pollenosis or pollinosis or SAR or PAR):TI,AB,KY #14 #10 OR #11 OR #12 OR #13 #15 MESH DESCRIPTOR Solutions #16 MESH DESCRIPTOR Hypertonic Solutions #17 MESH DESCRIPTOR Saline Solution, Hypertonic EXPLODE ALL TREES #18 MESH DESCRIPTOR isotonic solutions EXPLODE ALL TREES #19 MESH DESCRIPTOR Sodium Chloride EXPLODE ALL TREES #20 MESH DESCRIPTOR Mineral Waters EXPLODE ALL TREES #21 MESH DESCRIPTOR seawater EXPLODE ALL TREES #22 MESH DESCRIPTOR Hypotonic Solutions EXPLODE ALL TREES #23 (saline or "sodium chloride" or saltwater or hypertonic* or hypotonic* or isotonic* or hypersaline or "sea water" or seawater or ((salt* or thermal or mineral or sulfur* or bromic or iodine* or bromide and (water* or solution*)))):TI,AB,KY</p>	<p>13 (hayfever or "hay fever" or pollenosis or pollinosis or SAR or PAR).ab,kf,ti 14 10 or 11 or 12 or 13 15 Solutions/ 16 Hypertonic Solutions/ 17 exp Saline Solution, Hypertonic/ 18 exp isotonic solutions/ 19 exp Sodium Chloride/ 20 exp Mineral Waters/ 21 exp seawater/ 22 exp Hypotonic Solutions/ 23 (saline or "sodium chloride" or saltwater or hypertonic* or hypotonic* or isotonic* or hypersaline or "sea water" or seawater or ((salt* or thermal or mineral or sulfur* or bromic or iodine* or bromide or iodine or bromine and (water* or solution*))))).ab,kf,ti 24 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 25 Therapeutic Irrigation/ 26 exp Nasal Lavage/ 27 exp Administration, Inhalation/ 28 exp Administration, Intranasal/ 29 exp Nasal Sprays/ 30 exp Buffers/ 31 (douch* or spray* or lavag* or wash* or rinse* or rinsing* or irrigat* or pulsed or nebulise* or aerosol* or buffer* or atomiz* or atomiz* or (squeeze and bottle)).ab,kf,ti 32 (intranasal or inhalation* or irrigator).ab,kf,ti. 33 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 34 24 and 33 35 (sterimar or NeilMed or nasaline or navage or marimer or physiomer or Emcur or "simply saline" or "nasal mist" or ayr or salex or "otrovin saline" or</p>	<p>13 (hayfever or "hay fever" or pollenosis or pollinosis or SAR or PAR).ab,kw,ti 14 10 or 11 or 12 or 13 15 "solution and solubility"/ 16 exp hypertonic solution/ 17 exp sodium chloride/ 18 exp isotonic solution/ 19 exp mineral water/ 20 exp sea water/ 21 exp hypotonic solution/ 22 (saline or "sodium chloride" or saltwater or hypertonic* or hypotonic* or isotonic* or hypersaline or "sea water" or seawater or ((salt* or thermal or mineral or sulfur* or bromic or iodine* or bromide or iodine or bromine) and (water* or solution*))))).ab,kw,ti 23 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 24 lavage/ 25 exp nasal lavage/ 26 exp inhalational drug administration/ 27 exp intranasal drug administration/ 28 exp nose spray/ 29 exp buffer/ 30 (douch* or spray* or lavag* or wash* or rinse* or rinsing* or irrigat* or pulsed or nebulise* or aerosol* or buffer* or atomiz* or atomiz* or (squeeze and bottle)).ab,kw,ti 31 (intranasal or inhalation* or irrigator).ab,kw,ti. 32 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 33 23 and 32 34 (sterimar or NeilMed or nasaline or navage or marimer or physiomer or Emcur or "simply saline" or "nasal mist" or ayr or salex or "otrovin saline" or ISCS or Prorhinel or SSBI).ab,kw,ti</p>	<p>nosis) Indexes=SCI-EXPANDED, CPCI-S Timespan=All years #5 #4 OR #3 Indexes=SCI-EXPANDED, CPCI-S Timespan=All years #6 TOPIC: ((saline or "sodium chloride" or saltwater or hypertonic* or hypotonic* or isotonic* or hypersaline or "sea water" or seawater or ((salt* or thermal or mineral or sulfur* or bromic or iodine* or bromide or iodine or bromine) and (water* or solution*)))) Indexes=SCI-EXPANDED, CPCI-S Timespan=All years #7 TOPIC: ((douch* or spray* or lavag* or wash* or rinse* or rinsing* or irrigat* or pulsed or nebulise* or aerosol* or buffer* or atomiz* or atomiz* or (squeeze and bottle))) Indexes=SCI-EXPANDED, CPCI-S Timespan=All years #8 TOPIC: ((intranasal or inhalation* or irrigator)) Indexes=SCI-EXPANDED, CPCI-S Timespan=All years #9 #8 OR #7 Indexes=SCI-EXPANDED, CPCI-S Timespan=All years #10 #9 AND #6 Indexes=SCI-EXPANDED, CPCI-S Timespan=All years #11 TOPIC: ((sterimar or NeilMed or nasaline or navage or marimer or physiomer or Emcur or "simply saline" or "nasal mist" or ayr or salex or "otrovin saline" or ISCS or Prorhinel or SSBI)) Indexes=SCI-EXPANDED, CPCI-S Timespan=All years #12 TOPIC: ((nasal or intranasal or sinus or nose or sinonasal) NEAR/3 (irrigation*</p>
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<p>#24 #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23</p> <p>#25 MESH DESCRIPTOR Therapeutic Irrigation</p> <p>#26 MESH DESCRIPTOR Nasal Lavage EXPLODE ALL TREES</p> <p>#27 MESH DESCRIPTOR Administration, Inhalation EXPLODE ALL TREES</p> <p>#28 MESH DESCRIPTOR Administration, Intranasal EXPLODE ALL TREES</p> <p>#29 MESH DESCRIPTOR Nasal Sprays EXPLODE ALL TREES</p> <p>#30 MESH DESCRIPTOR Buffers EXPLODE ALL TREES</p> <p>#31 (douch* or spray* or lavag* or wash* or rinse* or rinsing or irrigat* or pulsed or nebulise* or aerosol* or buffer* or atomiz* or atomiz* or (squeeze and bottle):TI,AB,KY</p> <p>#32 (intranasal or inhalation* or irrigator):TI,AB,KY</p> <p>#33 #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32</p> <p>#34 #24 and #33</p> <p>#35 (sterimar or NeilMed or nasaline or navage or marimer or physiomer or Emcur or “simply saline” or “nasal mist” or ayr or salex or “otrovin saline” or ISCS or Prorhinel or SSBI):TI, AB,KY</p> <p>#36 (nasal or intranasal or sinus or nose or sinonasal) ADJ3 (irrigation* or rinsing or rinse* or wash* or lavage or douch* or hygiene):TI,AB,KY</p> <p>#37 MESH DESCRIPTOR Mineral Waters EXPLODE ALL TREES WITH QUALIFIERS TU</p> <p>#38 #34 or #35 or #36 or #37</p> <p>#39 #14 and #38</p>	<p>ISCS or Prorhinel or SSBI).ab, kf,ti</p> <p>36 ((nasal or intranasal or sinus or nose or sinonasal) adj3 (irrigation* or rinsing or rinse* or wash* or lavage or douch* or hygiene)).ab,kf,ti</p> <p>37 exp Mineral Waters/tu [Therapeutic Use]</p> <p>38 34 or 35 or 36 or 37</p> <p>39 14 and 38</p>	<p>35 ((nasal or intranasal or sinus or nose or sinonasal) adj3 (irrigation* or rinsing or rinse* or wash* or lavage or douch* or hygiene)).ab,kw,ti</p> <p>36 33 or 34 or 35</p> <p>37 14 and 36</p>	<p>or rinsing or rinse* or wash* or lavage or douch* or hygiene))</p> <p>Indexes=SCI-EXPANDED, CPCI-S Timespan=All years</p> <p>#13 #12 OR #11 OR #10</p> <p>Indexes=SCI-EXPANDED, CPCI-S Timespan=All years</p> <p>#14 #13 AND #5</p> <p>Indexes=SCI-EXPANDED, CPCI-S Timespan=All years</p>
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CINAHL (EBSCO)	ICTRP	ClinicalTrials.gov	LILACS
<p>S37 S14 AND S36 S36 S32 OR S33 OR S34 OR S35 S35 (MH "Mineral Water/TU") S34 TX (nasal or intranasal or sinus or nose or sinonasal) N3 (irrigation* or rinsing or rinse* or wash* or lavage or douch* or hygiene) S33 TX (sterimar or NeilMed or nasaline or navage or marimer or physiomer or Emcur or "simply saline" or "nasal mist" or ayr or salex or "otrovin saline" or ISCS or Prorhinel or SSBI) S32 S23 AND S31 S31 S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 S30 TX (intranasal or inhalation* or irrigator) S29 TX (douch* or spray* or lavag* or wash* or rinse* or rinsing or irrigat* or pulsed or nebulise* or aerosol* or buffer* or atomis* or atomiz* or (squeeze and bottle)) S28 (MH "Buffers+") S27 (MH "Administration, Intranasal+") S26 (MH "Administration, Inhalation+") S25 (MH "Nasal Lavage+") S24 (MH "Therapeutic Irrigation") S23 S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 S22 TX saline or "sodium chloride" or saltwater or hypertonic* or hypotonic* or isotonic* or hypersaline or "sea water" or seawater or ((salt* or thermal or mineral or sulfur* or bromic or iodid* or bromide or</p>	<p>rhinit* AND saline OR rhinit* AND salt AND water OR hayfever AND saline OR hayfever AND salt AND water</p>	<p>(rhinitis OR hayfever) AND (saline OR (salt AND water)) Interventional Studies</p>	<p>(TW:rhinit* OR TW:rinit OR TW:hayfever OR TW:"hay fever" OR TW:pollinosis OR TW:pollenosis) AND (TW:salin* OR TW:water* OR TW:Agua*)</p>

(Continued)

iodine or bromine) and (water* or solution*) S21 (MH "Hypotonic Solutions+") S20 (MH "Mineral Water") S19 (MH "Sodium Chloride+") S18 (MH "isotonic solutions+") S17 (MH "Saline Solution, Hypertonic+") S16 (MH "Hypertonic Solutions") S15 (MH "Solutions") S14 S10 OR S11 OR S12 OR S13 S13 TX hayfever or "hay fever" or pollenosis or pollinosis or SAR or PAR S12 (MH "Conjunctivitis, Allergic+") S11 (MH "Rhinitis, Allergic, Perennial") OR (MH "Rhinitis, Allergic, Seasonal") S10 S8 AND S9 S9 S4 OR S5 OR S6 OR S7 S8 S1 OR S2 OR S3 S7 TX allerg* or hypersensitivit* or perennial or nonseason* or season* or pollen* or dust or hair* or dander or mite*) S6 (MH "Hypersensitivity+") S5 (MH "Pollen+") S4 (MH "Allergens+") S3 TX rhinit* or Rhinoconjunctivitis or conjunctivitis S2 (MH "Conjunctivitis") S1 (MH "Rhinitis")			
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Appendix 2. Data extraction form

REF ID:	Study title:
Date of extraction:	Extracted by:

General comments/notes (internal for discussion):

Flow chart of trial	Flow chart of trial	
	Group A (Intervention)	Group B (Comparison)
No. of people screened		
No. of participants randomised - all		
No. randomised to each group		
No. receiving treatment as allocated		
No. not receiving treatment as allocated - Reason 1 - Reason 2		
No. dropped out (no follow-up data for any outcome available)		
No. excluded from analysis ¹ (for all outcomes) - Reason 1 - Reason 2		
¹ This should be the people who received the treatment and were therefore not considered 'dropouts' but were excluded from all analyses (e.g. because the data could not be interpreted or the outcome was not recorded for some reason)		
¹ This should be therefore not co analyses (e.g. be outcome was no		

Methods	X arm, double/single/non-blinded, [multicentre] parallel-group/cross-over/cluster-RCT, with x duration of treatment and x duration of follow-up
Participants	<p>Location: country, no. of sites etc.</p> <p>Setting of recruitment and treatment:</p> <p>Sample size:</p> <ul style="list-style-type: none"> • Number randomised: x in intervention, y in comparison • Number completed: x in intervention, y in comparison <p>Participant (baseline) characteristics:</p> <ul style="list-style-type: none"> • Age: • Gender: • Main diagnosis: <i>[as stated in paper]</i> • Type of allergic rhinitis: <i>[persistent or intermittent as per ARIA 2008 guidelines]</i> • Severity of allergic rhinitis: <i>[mild or moderate/severe as per ARIA 2008 guidelines]</i> • Type of allergic trigger: [e.g. mites, pollens, animals, etc.] • Other important effect modifiers, if applicable: (e.g. comorbidity of asthma): <p>Inclusion criteria: <i>[state diagnostic criteria used for allergic rhinitis, polyyps score if available]</i></p> <p>Exclusion criteria:</p>
Interventions	<p>Intervention (n = x): intervention name including tonicity, method of administration [including volume], frequency of administration, duration of treatment</p> <p>Comparator group (n = y):</p> <p>Use of additional interventions (common to both treatment arms):</p>
Outcomes	<p>Outcomes of interest in the review:</p> <p>Primary outcomes:</p> <ul style="list-style-type: none"> • Disease severity, as measured by patient-reported symptom score (such as the Total Nasal Symptom Score (TNSS) questionnaire and visual analogue scales) • Significant adverse effects: epistaxis <p>Secondary outcomes:</p> <ul style="list-style-type: none"> • Patient-reported individual symptom scores for the following symptoms: <ul style="list-style-type: none"> ○ nasal obstruction/blockage/congestion ○ nasal discharge (anterior or posterior rhinorrhoea - identify which one, or if both have been reported) ○ nasal itching ○ sneezing • Health-related quality of life, using <i>disease-specific</i> health-related quality of life scores, such as the Rhinoconjunctivitis

(Continued)

	<p>Quality of Life Questionnaire (RQLQ), Mini Rhinoconjunctivitis Quality of Life Questionnaire (MiniRQLQ) and Rhinitis Symptom Utility Index (RSUI)</p> <ul style="list-style-type: none"> • Health-related quality of life, using <i>generic</i> quality of life scores, such as the SF-36, EQ-5D and other well-validated instruments • Other local adverse effects: local irritation/discomfort, aural symptoms • Endoscopic score (e.g. Lund-Mackay/Lund-Kennedy) <p>Other outcomes reported by the study:</p> <ul style="list-style-type: none"> • <i>[List outcomes reported but not of interest to the review]</i>
Funding sources	'No information provided'/'None declared'/State source of funding
Declarations of interest	'No information provided'/'None declared'/State conflict
Notes	

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)		Quote: "..." Comment:
Allocation concealment (selection bias)		Quote: "..." Comment:
Blinding of participants and personnel (performance bias)		Quote: "..." Comment:
Blinding of outcome assessment (detection bias)		Quote: "..." Comment:
Incomplete outcome data (attrition bias)		Quote: "..." Comment:
Selective reporting (reporting bias)		Quote: "..." Comment:
Other bias (see section 8.15) Insensitive/non-validated instrument?		Quote: "..." Comment:
Other bias (see section 8.15)		Quote: "..." Comment:

Findings of study: continuous outcomes							Findings of study
Results (continuous data table)							Results (continued)
Outcome	Group A			Group B			Other summary stats/Notes
	Mean	SD	N	Mean	SD	N	Mean difference (95% CI), P values etc.
Disease-specific HRQL (<i>instrument name/range</i>) Time point:							
Generic HRQL (<i>instrument name/range</i>) Time point:							
Symptom score (overall) (<i>instrument name/range</i>) Time point:							
Added total - if scores reported separately for each symptom (<i>range</i>) Time point:							
Nasal blockage/obstruction/congestion (<i>instrument name/range</i>)							
Nasal discharge (anterior or posterior rhinorrhoea - specify which one if it is known) (<i>instrument</i>)							

(Continued)

<i>name/range)</i>									
Sneezing (instrument name/range)									
Nasal itching (instrument name/range)									
Endoscopic score (instrument name/range)									
Comments:									Comments:

Results (dichotomous data table)							Results (dichotomous data table)
Outcome	Intervention	Group A		Group B		Other summary stats/notes	
		No. of people with events	No. of people analysed	No. of people with events	No. of people analysed	P values, RR (95% CI), OR (95% CI)	
Epistaxis/ nosebleed	Nasal saline						
Local irritation (sore throat, oral thrush, discom- fort)	Nasal saline						
Local adverse ef- fects: Eustachian tube dysfunction	Nasal saline						
The following adverse effects will only be extracted if the comparison arm is one of the interventions indicated							The following adverse effects will only be extracted if the comparison arm is one of the interventions indicated
Os- teoporosis (min- imum 6 months)	INCS						

(Continued)

Stunted growth (children, minimum 6 months)	INCS					<i>Can also be measured as average height</i>
Mood disturbances	Oral steroids					
Gastrointestinal disturbances (diarrhoea, nausea, vomiting, stomach irritation)	Oral steroids Antibiotics					
Insomnia	Oral steroids					
Osteoporosis (minimum 6 months)	INCS Oral steroids					
Skin irritation	Antibiotics					
Anaphylaxis or other serious allergic reactions such as Stevens-Johnson syndrome	Antibiotics					
Antihistamine and decongestant adverse events: somnolence, irritability, insomnia, rhinitis medicamentosa, prolonged middle ear effusion	Antihistamines/ decongestants					
Comments:						Comments:

CONTRIBUTIONS OF AUTHORS

Karen Head drafted and revised the protocol.

Simon Glew, Claire Hopkins, Carl Philpott, Glenis Scadding, Anne Schilder and Kornkiat Snidvongs reviewed and edited the protocol.

DECLARATIONS OF INTEREST

Karen Head: none known.

Kornkiat Snidvongs: none known.

Simon Glew: none known.

Glenis Scadding: none known.

Carl Philpott: Carl Philpott has previously received consultancy fees from the companies Acclarent, Navigant, Aerin Medical and Entellus.

Claire Hopkins: Claire Hopkins has received financial support from several companies involved in producing instruments for sinus surgery.

Anne GM Schilder: Anne Schilder is joint Co-ordinating Editor of Cochrane ENT, but had no role in the editorial sign-off process for this review. Her evidENT team at UCL is supported by her NIHR Research Professorship award with the remit to develop a UK infrastructure and programme of clinical research in ENT, Hearing and Balance. She is a co-investigator on the NIHR PGfAR grant 'Defining best Management for Adults with Chronic Rhinosinusitis: the MACRO Programme.'

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