NCCHTA

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Research Protocol

The safety and effectiveness of different methods of ear wax removal: a systematic review and economic evaluation

September 2008

1 Project title

The safety and effectiveness of different methods of ear wax removal: a systematic review and economic evaluation

2 Details of project team

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3 Plain English Summary

Ear wax is a natural secretion which can build up and block ears. Methods of removal include drops, flushing with water in general practice, and removal with suction or probes in specialist clinics. The relative safety and benefits of the different methods of removal are not known for certain.

We propose to systematically search for published and unpublished evidence on the removal of ear wax, using standard methods. Data from individual studies will be combined statistically (by meta-analysis) where possible and appropriate to do so. Also, we will aim to develop an economic model using data from this review and other relevant sources to estimate the relative costs and benefits of different methods. The project will aim to establish the safety, clinical and cost effectiveness of the alternative methods of removing ear wax, preventing its recurrence and improving hearing. We anticipate that there may be important questions to which the answers remain unknown. In that case we will try to specify the most useful new research that could be done in the future.

4 Planned investigation

4.1 Background

4.1.1 Description of the condition and epidemiology

Wax (cerumen) is a normal secretion in the external ear canal, produced as a protective layer by small glands in the outer ear. Its purpose is to trap particles, whether dirt, dead skin or other fragments, and prevent them from entering the deeper part of the ear. Normally the wax moves these particles to the outer ear at a rate that prevents significant build up. However, build up of wax may occur causing blockage in the ear canal, with the possibility of impaction. People with ear wax may suffer from hearing loss, discomfort and, on occasions, infection. Blockage of the ear may cause hearing loss of over 5dB or more.[1] A study has reported that 34% of people had an improvement in hearing of more than 10dB after wax was removed.[2] Also, it may present problems in assessing hearing, blocking the view of the ear drum during medical examination and interfering with the fitting or function of hearing aids. Different groups may be at a higher

risk of suffering from accumulation of ear wax. For example, the use of hearing aids, small ear canals, or skin conditions may increase the risk of a build up of ear wax. Some people suffer recurrence of the problem and may require and/or undergo regular treatment.

The consequences of the build up of ear wax in the ear canal are thought to be a common reason for consultation in general practice.[1] Although data on the incidence, prevalence, natural history and long term impact of treatment are thought to be limited, available studies have shown varying rates of occurrence. It has been suggested that up to a third of older people suffer from the symptoms of impacted wax.[3-5] Sharp and colleagues estimated in 1990 that GPs were syringing about two ears per week, and that the incidence rate of ear wax needing removal in the Lothian population was about 67 per thousand population per year.[1] Local experience in two Hampshire practices has shown incidence rates of 24 and 38 per thousand (R Coppin and S Fraser, personal communications). This suggests that health professionals perform up to two million ear irrigations in England and Wales per year.[4] These figures are likely to underestimate the incidence and prevalence of the disorder in the community because many people may not seek treatment.

4.1.2 Treatment

There are several different methods for removing ear wax, which may involve one or more technologies. The approach taken will depend upon the severity of the condition, any comorbidities present and the practitioner and setting involved. The different interventions available for removing wax include ear drops, irrigation, and mechanical removal with a probe, hook or micro-suction.

Drops

Simple remedies and proprietary drops can be used with a view to softening wax ready for syringing, or to removing wax in their own right.[6;7] The British National Formulary (BNF) lists the following preparations:

Almond Oil	Olive Oil
Sodium Bicarbonate drops	Cerumol®
Exterol®	Molcer®
Otex®	Waxsol®

It is thought that the various preparations may operate in different ways, either through lubricating the wax for it to dissipate itself (e.g. almond or olive oils), or to allow easier removal with other technologies or to dissolve the wax itself (e.g. sodium bicarbonate). The particular preparation used may depend upon how hard and compacted the wax appears, as well as whether the person has any comorbidities. Although it is suggested that these drops may differ in their mode of action, evidence on the effectiveness of the different preparations appears limited,[7-9] although some adverse effects have been noted. These preparations offer people the opportunity to self-treat, although people should be cautious if they intend to use these in combination with swabs as they may inadvertently damage their ear canal or drum.

Irrigation

The long established means of flushing wax out of the ear is with warm water in a metal piston syringe (e.g. the Reiner-Alexander Ear Syringe[4]). Syringes are less frequently used now, with electronic irrigators more commonly used in primary care.[10] This may reflect the move from general practitioners to practice nurses performing the procedure. The electronic devices include an oral jet irrigator or nebuliser (e.g. Propulse) and a DeVilbis ear irrigator.[4;11] Increasingly nurses in general practice undertake ear irrigation, with staff costs in the UK thought to be around £4 million per year (R Coppin, personal communication). Although concerns have been expressed about the safety of irrigation, there appear to be limited data on the safety or efficacy of either type of device. Reported harms of irrigation are pain, infection and injury to the ear (including perforation of the drum).[12] Perforation is the most serious adverse event from syringing/irrigation. The rate of perforation remains uncertain. Blake and colleagues reported 38 perforations in New Zealand over a 17 month period in 1993.[12] Ogunleye and Awobem found a rate of 0.2% among a cohort of 622 people in Nigeria.[13] Irrigation is contraindicated in people with perforated ear drums, history of ear surgery or chronic ear conditions (e.g. tinnitus).

Self treatment using irrigation has become an option outside the UK. Soft bulb syringes to flush out a person's own ears have been used and can be purchased over the counter at pharmacies in many European countries and in the US (R Coppin, personal communication). However, whilst these were previously supported by organizations such as the American Academy of Otolaryngology-Head and Neck Surgery[11], guidance has changed and self treatment with soft bulb syringes is no longer recommended

(http://www.entnet.org/healthinfo/ears/earwax.cfm). Usually drops are used at least 5 days before irrigation to try and soften the wax prior to irrigation. Their value over irrigation alone is uncertain.

Other treatments
Several proprietary, self-use devices to treat ear wax are available from several sources, including pharmacies and the internet. These include Audiclean (a cleansing spray containing isotonic sea water), Earol (pump spray containing olive oil) and the Real McCoy and Ear Blaster plastic piston syringes for self irrigation. Whilst most people requiring removal are treated in general practice, some require more specialist treatment. Those with contraindications to irrigation, such as pre-existing perforation of the ear drum or suspicion of significant disease of the ear drum (e.g. cholestesteotoma), require clearance of wax under direct microscopic vision. This is normally carried out in secondary care using suction or by curetting.

4.1.3 Current UK practice

Practice varies in the UK and has continued to change over recent years. Traditionally, people requiring ear wax removal have had their ears syringed by general practitioners. Syringing has largely been replaced by the use of electric irrigation, with practice nurses undertaking the procedure. Often district nurses care for those people unable to attend the surgery. A survey by Coppin and colleagues in 2004 suggested that in most (86%) practices ear wax was removed by nurses. Nurses chose to use electric irrigators rather than piston syringes in 90% of cases. GPs were slightly more attached to their piston syringes, but only 28% of them used it most or all of the time.[10] Drops are almost always advised before irrigation to soften and lubricate the wax, with Coppin and colleagues identifying 50% of professionals recommending olive oil.[10] Anecdotally people are being encouraged to self treat with drops over a period of weeks, only attending general practice after treating for a period of weeks with no resolution.

4.1.4 Existing evidence

Preliminary scoping searches of key databases (Medline, CCRCT and Cinahl) were undertaken in January 2007 as part of the original application, identifying over 80 references. These will be updated as part of the research programme (see Section 4.4 Research Methods). The preliminary scoping searches identified one existing evidence summary of a range of treatments[8] and two systematic reviews of drops.[7;9] The last dates that literature databases were searched for each of these are 2005, 2004 and 2003 respectively. Two 'mini-reviews'[14;15] that used systematic methods, one on ear syringing and the other on the value of drops to facilitate syringing were also identified. They were published in 2002 and 2005 but search dates are not stated.

The reviews identify a total of 20 controlled trials of drops. The published trials are generally small and of poor quality. The existing reviews suggest that there is weak evidence for the benefit of drops over no treatment for wax removal, but insufficient evidence to indicate greater effectiveness of one type of drop over another. For wax softening before irrigation, there was also very weak evidence of benefit over no treatment. One review also summarises the results of in vitro studies of drops to disperse wax.[14] This suggests that most preparations, including water could soften wax, although it is unclear how they would work in clinical practice.

From the preliminary scoping searches no additional trials were identified. There appear to be no published trials of ear irrigation versus other technologies or versus no treatment. There appear to be no trials of mechanical removal of wax with probes, hooks or suction. Three unpublished studies were identified on the National Research Register (of ongoing trials). One (led by co-applicant RC) compares bulb syringing with routine treatments, another assesses the effect of wax removal on hearing, and a third assesses the adverse effects of irrigation.

Adverse events, particularly perforation are relatively rare with treatment of ear wax.[8;10] The rate from ear syringing is likely to be lower than 1%, although one study examining the effect of electric pumps on ear drums post mortem reported a perforation rate of 6%.[4;16] The trials and reviews identified in this preliminary search do not provide a meaningful estimate of the harms from treatment. Observational studies will therefore be included in our search for evidence of harm.

The five reviews all use different methods to search, assess studies for eligibility, and only one review pools data quantitatively.[9] In view of this variation and the unreliable quality of the included studies, these reviews will be used as a source of primary studies.

4.1.5 Rationale for the study

There are a number of different methods for removing ear wax and the existing evidence has concentrated only on assessing the clinical effectiveness of topical preparations, either as sole treatment or to facilitate irrigation. Due to the large numbers of people attending primary care practices with ear wax it is important for clinicians to know the effectiveness and harms of each of these methods and currently no systematic reviews have examined the effectiveness of methods of irrigation, suction and/or surgical instruments. In particular there do not appear to be any evaluations of the cost-effectiveness of any methods of ear wax removal.

An up to date systematic review of the clinical and cost effectiveness of all current technologies for the removal of ear wax is required. The development of a de novo economic model will provide an assessment of the cost effectiveness of the different technologies for removing ear wax within the UK setting. This will allow several important questions to be considered, including:

- How safe, effective and cost-effective is irrigation of ears in primary care compared to the gold standard of removal in a specialist clinic under direct vision? Which is the most suitable method of irrigating ears and who should undertake the procedure?
- Is there a benefit to treating ear wax with drops prior to syringing and which regime is more effective?
- Is self-care, using drops or syringing, safe and clinically and cost-effective compared to irrigation in primary care? If possible, we will examine the cost-effectiveness of self-care to assess whether a switch from primary care would be appropriate.
- What are the important research needs in this topic and what is the most appropriate study design to address them? As the quantity and quality of existing research may be variable, we will give recommendations on future research.

4.2 Research Aim

The aim of this project is to evaluate the clinical and cost effectiveness of the different methods for removing ear wax in adults and children, including drops, irrigation, mechanical and other methods. The project also aims to identify adverse events associated with the different methods of removing ear wax. The project will identify future research needs and use value of information approaches to assist in prioritising these needs to help inform appropriate study designs.

4.3 Objectives

The main objectives will be as follows:

- To conduct a systematic review of the evidence assessing the clinical and cost effectiveness of the interventions currently available for softening and/or removing ear wax in children or adults;
- To systematically search for, appraise and summarise clinical trial and observational evidence for the harms or adverse events associated with interventions for softening or removing ear wax;
- To construct, if appropriate, a de novo economic model for the UK to estimate the relative cost effectiveness of those interventions considered clinically effective;
- To identify future cost effective research in the management of ear wax through a value of information analysis, specifying key elements in the design of future studies.

4.4 Research Methods

4.4.1 Systematic Review

A systematic review will be undertaken in accordance with the NHS Centre for Reviews and Dissemination guidelines,[17] published guidelines on meta-analysis,[18] and criteria for appraising economic evaluations.[19;20]

Literature searches

Literature will be identified from several sources including electronic databases, bibliographies of articles, grey literature and consultation with experts in the area. A comprehensive database of relevant published and unpublished articles will be constructed using the Reference Manager software package. The searches carried out will include:

i) General health and biomedical databases including MEDLINE, EMBASE. Science Citation Index, BIOSIS

ii) Specialist electronic databases: DARE, the Cochrane library.
iii) Grey literature and conference proceedings.
iv) Contact with individual experts and those with an interest in the field.
v) Checking of reference lists
vi) Research in progress: National Research Register (historical), UKCRN, Current Controlled Trials (CCT), Clinical trials.gov

All databases will be searched from their inception to the current date (see appendix 1 for an example of draft search strategy). In the first instance searches will be conducted in all languages with non-English language articles set to one side in a separate foreign language reference database. Thereafter an assessment of the volume of non-English language literature will be made and, translation and time restrictions permitting, these will be included in the review. Letters will be sent to experts to ask if they know of any relevant published or unpublished studies that we have not identified.

Study inclusion
Studies will be selected for inclusion in the review in a two stage process using the predefined and explicit selection criteria outlined in Section 2.5 below. The full literature search results will be screened independently by two reviewers to identify all citations that may meet the inclusion criteria. Full manuscripts of all selected citations will be retrieved and assessed by two independent reviewers against the inclusion criteria. These criteria will be piloted on a sample of papers. Any disagreements over study inclusion will be resolved by consensus or if necessary by arbitration involving a third reviewer.

4.4.2 Planned inclusion/exclusion criteria

The planned inclusion/exclusion criteria for the systematic review are shown in Table 1.

Table 1 Inclusion criteria for systematic reviews

Interventions	• All methods of ear wax removal or softening, including: o Drops ▪ Almond oil ▪ Olive oil ▪ Sodium bicarbonate drops ▪ Cerumol ▪ Exterol ▪ Molcer ▪ Otex ▪ Waxsol o Irrigation (e.g. syringing, electronic irrigators) o Mechanical removal other than syringing (e.g. suction, probes and forceps) o Other methods o Combinations of above methods (Note: Interventions specify methods of removal and softening. Although it does not outline methods of visualisation (e.g. microscope, endoscope and head light loop) these will be identified in data extraction as they will be important elements of removal).
Population	• Adults and children presenting with build up of ear wax requiring removal.
Outcomes	• Measures of hearing • Adequacy of clearance of wax (e.g. visualisation of tympanic membrane) • Quality of life • Time to recurrence or further treatment • Adverse events • Measures of costs and cost effectiveness (e.g. cost per QALY) (Note: Studies must report summary statistics or present sufficient raw data to allow these to be calculated.)
Study Design	• Randomised controlled trials • Controlled clinical trials • Cohort studies (adverse events)

	• Costing studies, cost-effectiveness evaluations (including modelling studies). (Note: Where there is evidence from different types of study design for a specific intervention, only those studies with the most rigorous designs will be included and data extracted.)

Data extraction
The extraction of studies' characteristics, methods and findings will be conducted by one reviewer and checked by a second reviewer using a pre-designed and piloted data extraction form to avoid any errors (see appendix 2). Any disagreements between reviewers will be resolved by consensus or if necessary by arbitration by a third reviewer.

Quality assessment
The methodological quality of all included studies will be appraised using a formal quality assessment criteria recommended by CRD,[17] (see appendix 3) and criteria for appraising economic evaluations.[19;20] Study quality will be assessed by one reviewer and checked by a second reviewer. Any disagreements between reviewers will be resolved by consensus or if necessary by arbitration involving a third reviewer.

Data synthesis
The results of included studies will be tabulated and summarised in a narrative review. The methods of data synthesis will be determined by the nature of the studies identified through searches and included in the review. Quantitative synthesis of results will be considered if there are several high quality studies of the same design, but specific details are not possible until the data has been obtained. Sources of heterogeneity will be investigated using appropriate methods.[21;22]

4.4.3 Economic evaluation

Cost-effectiveness will be assessed through a two stage process. First, a systematic review of cost-effectiveness studies (full economic evaluations) will be undertaken to address the question of the cost-effectiveness of different methods for ear wax removal in the different patient groups. The methods for the review will be analogous to those presented for the review of clinical effectiveness and results will be presented using a narrative synthesis. Quality assessment of cost-effectiveness studies will be conducted using a checklist adapted from those developed by Drummond and colleagues[19] and Philips and colleagues.[20]

Second, if no economic evaluation relevant to the UK setting is identified, construction of a de novo economic model will be considered where appropriate with the aim of establishing the relative cost-effectiveness of the different interventions for removing ear wax. The structure of the model will reflect current treatment pathways employed by clinicians and other health professionals for the removal of ear wax. Any proposed alternatives to current practice identified in the literature or through consultation with practicing clinicians and other health professionals will also be considered. The structural validity of the model will be checked through consultation with clinicians and other health professionals in the UK experienced in ear wax removal. The model will be either a decision-tree or a Markov process model, although its design will be determined, in part, by the data available to populate it. Health states will likely comprise: occlusion; complete clearance; and adverse events (e.g. perforation leading to long term hearing loss). It is expected that the model will be populated with the data from the systematic review of clinical and cost effectiveness and from other routinely collected data sources (e.g. unit costs from the Personal Social Services Research Unit). If data are not identified from these sources, we will consider performing additional targeted searches and/or consultation with experts on all model inputs to provide appropriate data. The model will be from the perspective of the NHS and will include, where possible, all costs and consequences related to the NHS perspective and all patient related benefits.

The base case model will aim to focus on adults who are eligible for the entire range of treatment alternatives for ear wax removal, although the model will aim to assess those interventions shown to be effective in the systematic review of clinical effectiveness. Subject to data availability, alternative versions of the model may be developed to examine sub-groups, who may respond differently to treatment. Possible sub-groups will be identified through consultation with clinical advisors and through the evidence from the systematic review. Each alternative treatment pathway is likely to be quantified in terms of the success of treatment, symptom recurrence, serious adverse events suffered, the resource cost of treatment, and impact on patients' quality of life. Costs will be presented in a base year and discounting of costs and benefits will

be performed. Incremental costs and benefits will then be measured for alternative treatments. If possible, the outcome measure from the economic evaluation will be cost per quality adjusted life year (QALY).

The model's underlying assumptions will be assessed through sensitivity analyses and threshold analysis for a range of parameters at which reasonable cost-effectiveness levels could be achieved. Probabilistic sensitivity analysis, whereby parameters are varied within reported ranges and distributions, will be undertaken to determine the impact of uncertainty upon the model.

Value of information analysis will be undertaken where possible to help identify future research priorities quantified by the value of reducing decision uncertainty (and its consequences in terms of the opportunity costs) which could be derived from additional research investment on earwax removal technologies.[23;24] It is intended this approach will systematically appraise which future research would be most valuable and also assist in identifying appropriate research designs.[25]

The model will be constructed in TreeAge Pro 2007 or MS Excel and will be made as transparent as possible in order that it can be readily updated when new data emerge. The modeling work will follow guidelines for good practice reported by Philips and colleagues.[20] Building a model is an iterative process and quality control checks will be included at several points during the process to ensure that appropriate structure and data are applied. This is necessary to ensure that the results can be relied upon to inform decision-makers regarding the cost-effectiveness of the intervention. There are several steps to this formal process:

- A comparison of the model results with those from any other relevant models identified from our systematic review. Any differences between the results will be explored and, if necessary, appropriate modifications made to the model.
- Model results will be analysed to ensure they accurately reflect the inputs used in the model. This ensures that the data used to populate the model are being applied at the correct times and locations. Extreme parameter values can be used to test whether the model behaves as expected.
- The model will be critically appraised by a second health economist/modeler. This will allow the approach to be validated and permits any areas of disagreement to be resolved prior to generation of model results.

These three steps help ensure that all aspects of potential error in the model – a lack of internal validity, a lack of external validity and any omissions or biases from an individual health economist – are addressed.

Types and Sources of Information for Economic Evaluation

Epidemiology
Information on the epidemiology of hearing impairment including the incidence, prevalence and prognosis of the condition will be identified from the literature and supplemented if necessary with clinical expertise.

Treatment efficacy and safety
Efficacy and safety data will be extracted from the clinical studies identified in our systematic review of clinical effectiveness. If there is a paucity of data on parameters, clinicians may need to be consulted in order to obtain estimates of, or variability around, the parameters included in the model. The outcomes are likely to be assessed in terms of symptom relief, adverse events suffered and symptom recurrence.

Quality of life
In order to calculate cost per QALY the estimates of utility decrements for patients who suffer symptoms of hearing impairment and adverse events typically associated with wax removal will be sought. Ideally utility weights for common adverse effects will be obtained from patient- (or potentially guardian- in the case of children) based estimates. These decrements may be reported in literature and preference will be given to the utility weights expressed in age- and sex-specific EQ-5D population norms for the UK.[26] Separate targeted searches will be undertaken to try and identify relevant data. If necessary, however, they will be obtained from alternative sources such as clinical opinion through contact with clinicians.

Cost and resource use measurement
The pattern of resource use and their associated costs may be identified from published or official sources. If necessary these data will be supplemented by contact with clinicians and NHS trust finance departments. Major resource components will include: treatment costs in terms of primary and/or secondary care visits (including staff costs, equipment and overheads), treatment of adverse events and follow-up visits. All drug

costs will be obtained from the British National Formulary (BNF) online. Inpatient days and outpatient visits costs will also be obtained from NHS reference costs. Unit costs for home visits by GPs or district nurses will be obtained from published data.[27].

4.4.4 Ethical arrangements

No specific ethical arrangements necessary.

4.4.5 Outputs of the review

In addition to the preparation of the HTA monograph, the findings of this project will be published through submission of papers to peer review journals and professional journals and through presentation at conferences.

5 Project management and milestones

Project management and milestones

Major Milestones	**Date**
Project Initiation	1 April 2008
Submission of progress report	1 October 2008
Submission and dissemination of report	31 March 2009

Competing Interests: No member of the team has registered any competing interests.

6 Advisory Group

Representatives and other potential users of the review from different professional backgrounds and opinions, including academics, clinicians, health economists, commissioners, patient groups, professional organizations, will be invited to provide expert advice to support the project. Experts will be asked to provide comments on a version of the protocol and of the final report, as well as advising on the identification of relevant evidence. All experts will be asked to register competing interests and to keep the details of the report confidential

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Appendix 1: Examples of draft search strategy for systematic review

(a) Clinical effectiveness draft search strategy

Databases	**Search strategy**
Medline	1 cerumen/ 2 cerum*.tw. 3 (ear* and wax*).tw. 4 earwax*.tw. 5 or/1-4 6 randomized controlled trial.pt. 7 controlled clinical trial.pt. 8 randomized.ab. 9 placebo.ab. 10 clinical trials as topic.sh. 11 randomly.ab. 12 trial.ti. 13 exp Cohort Studies/ 14 cohort.tw. 15 or/6-14 16 5 and 15 17 humans.sh. 18 16 and 17 19 from 18 keep 1-105

(b) Cost effectiveness draft search startegy

Databases	**Search strategy**
Medline	1 exp economics/ (389606) 2 exp economics hospital/ (15338) 3 exp economics pharmaceutical/ (1867) 4 exp economics nursing/ (3834) 5 exp economics dental/ (3693) 6 exp economics medical/ (11652) 7 exp "Costs and Cost Analysis"/ (135753) 8 Cost Benefit Analysis/ (42569) 9 value of life/ (4916) 10 exp models economic/ (5730) 11 exp fees/ and charges/ (7280) 12 exp budgets/ (9751) 13 (economic$ or price$ or pricing or financ$ or fee$ or pharmacoeconomic$ or pharma economic$).tw. (348701) 14 (cost$ or costly or costing$ or costed).tw. (205010) 15 (cost$ adj2 (benefit$ or utilit$ or minim$ or effective$)).tw. (52788) 16 (expenditure$ not energy).tw. (11184) 17 (value adj2 (money or monetary)).tw. (667) 18 budget$.tw. (11349) 19 (economic adj2 burden).tw. (1649) 20 "resource use".ti,ab. (2250) 21 or/1-20 (799377) 22 (news or letter or editorial or comment).pt. (986155) 23 21 not 22 (739582) 24 cerumen/ (584) 25 cerum*.tw. (541) 26 (ear* and wax*).tw. (586) 27 earwax.tw. (61) 28 or/24-27 (1300) 29 23 and 28 (47) 30 limit 29 to humans (34) 31 from 30 keep 1-34 (34) 32 from 30 keep 4-5,9,12,14,17,20,22-24,30-31 (12)

Appendix 2: Data extraction form

Reference and Design	**Intervention**	**Participants**	**Outcome measures**
Author: *Year*: *Country*: *Study design*: *Number of centres*: *Setting* *Funding*:	(including dose etc) 1. *Intervention*: 2. *Control*: *Duration of treatment:* *Other interventions used:*	*Number of Participants*: *Intervention*: *Control*: *Sample attrition/dropout*: *Inclusion criteria for study entry*: *Exclusion criteria for study entry*:	*Primary outcomes*: *Secondary outcomes*: *Method of assessing outcomes*: *Adverse symptoms*: *Length of follow-up*:

Baseline characteristics of participants:

	Treatment X (*specify)* (n=)	**Treatment Y (*specify)* (n=)**	**P Value**

Results:

Primary Outcomes	Intervention (*specify)* (n=)	Control (*specify)* (n=)	P Value

Comments:

Secondary outcomes	Intervention (*specify)* (n=)	Control (*specify)* (n=)	P value

Comments:

Note: If reviewer calculates a summary measure or confidence interval PLEASE INDICATE

Methodological comments

Allocation to treatment groups:
Blinding:
Comparability of treatment groups:
Method of data analysis:
Sample size/power calculation:
Attrition/drop-out:

General comments
Generalisability:
Outcome measures:
Inter-centre variability:
Conflict of interests:

Appendix 3: Quality assessment

a. Quality criteria for assessment of RCTs (NHS CRD)[17]

Item	Judgement*
1. Was the assignment to the treatment groups really random?	
2. Was the treatment allocation concealed?	
3. Were the groups similar at baseline in terms of prognostic factors?	
4. Were the eligibility criteria specified?	
5. Were outcome assessors blinded to the treatment allocation?	
6. Was the care provider blinded?	
7. Was the patient blinded?	
8. Were the point estimates and measure of variability presented for the primary outcome measure?	
9. Did the analyses include an intention to treat analysis?	
10. Were withdrawals and dropouts completely described?	

* adequate, inadequate, partial, not reported, unclear

b. Quality criteria for assessment of controlled clinical studies[17]

Item	Judgement*
Were the groups similar at baseline in terms of prognostic factors?	
Were the eligibility criteria specified?	
Were outcome assessors blinded to the treatment allocation?	
Were the point estimates and measure of variability presented for the primary outcome measure?	
Did the analyses include an intention to treat analysis?	
Were withdrawals and dropouts completely described?	
Were participants likely to be representative of the intended population?	

* adequate, inadequate, partial, not reported, unclear