

Interventions for the management of taste disturbances (Protocol)

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Interventions for the management of taste disturbances

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the effects of interventions for the management of patients with taste disturbances.

BACKGROUND

The sense of taste is important for health and quality of life, yet it is often taken for granted. Each year, more than 200,000 people visit a physician for chemosensory problems such as taste disorders. Many more taste disorders go unreported (NIDCD 2010). Approximately 240,000 people in Japan have an altered taste sensation and present to health professionals for evaluation (Ikeda 2005). Alterations in taste can lead to loss of appetite, resulting in malnutrition affecting both physical and psychological well-being (NIDCD 2009).

The basic tastes are salty, sour, bitter, sweet and umami (found in glutamates). It has been also suggested that fatty taste may be recognised as another basic taste quality (Mattes 2009). In humans, there are approximately 5000 taste buds in the oral cavity, situated on the superior surface of the tongue, on the palate, and on the

epiglottis (Miller 1995). Taste receptor signalling is not limited to taste buds but occurs in a variety of tissues like chemosensory cells of the alimentary tract, pancreas, brain and airway epithelium (Kinnamon 2012).

It is important to understand how our taste buds function, both as an organ and in conjunction with other factors, especially our sense of smell. Taste buds are onion-shaped aggregates of approximately 50 to 100 elongated cells, with a life span of 10 to 11 days (Porter 2010). Due to such a fast turnover rate, the taste cells used for breakfast may be different from those used for lunch (Spielman 1992). They extend from the basal lamina to the surface of the tongue, where their apical microvilli extend through an opening in the epithelium to contact sapid chemicals in the oral cavity. Salts and acids utilise apically located ion channels for transduction, while bitter, sweet and umami stimuli utilise G-protein-coupled receptors (GPCRs) and second-messenger signalling mechanisms

(Kinnamon 2012). These taste cells receive tastant from the apical pore and transduce the signal to gustatory nerves that innervate taste buds (Iwatsuki 2012). Taste related impulses are then transmitted via the facial, glossopharyngeal and vagus nerves to the nucleus of the solitary tract and thereafter to the thalamus and upwards to the post-central gyrus-facial area and olfactory area of the cortex (Porter 2010). However, there are super tasters who experience the sense of taste with far greater intensity than average due to an increased number of fungiform papillae and have extreme sensitivity to n-propylthiouracil (Bartoshuk 1994).

As important as taste is to food enjoyment, flavour is even more important. It is the distinctive quality of a particular food or drink. Flavour tells us whether we are eating a pear or an apple. In order to perceive flavour, the brain interprets not only taste stimuli, but also olfactory, thermal and tactile sensations. With spicy food, the brain will perceive pain as one aspect of flavour. When one cannot 'taste' food due to common cold, in reality it is the inability to smell that is affecting the 'flavour' of the food and not the basic tastes of the food. What is the mechanism by which taste and smell work together? When one chews food, aromas are released that enter the nose through a retro nasal passage connecting the roof of the mouth with the nose. Nerve endings in the olfactory bulb in the nose send these smell stimuli to the brain. It is the aroma, when combined with the stimuli of taste, temperature and texture that give the food a 'flavour'. It is the integration of these stimuli by the brain that distinguishes between, for example, eating an apple rather than a pear.

With the growing population of elderly people globally, and with the effects of drugs and other treatment forms of modern medicine at any age, peoples' senses of taste and smell will continue to be adversely affected. The sense of smell is more impaired by aging compared with the sense of taste (Winkler 1999). Both anatomical investigations and human taste threshold studies indicate that age-related differences in the gustatory system are not as substantial as investigators have suggested in the past (Mistretta 1984).

Taste and smell protect against malnutrition, depression and their concomitant diseases. The taste or smell of rancid food telling us to avoid it, or perhaps the odour of gas alerting us to danger, are lost or diminished without these senses. Simple pleasures like delicious foods and their aroma enable an individual to enjoy quality of life.

People who suffer from dysgeusia are also forced to manage the impact that the disorder has on their quality of life. An altered taste has effects on food choice and intake and can lead to weight loss, malnutrition, impaired immunity, and a decline in health (Bromley 2000). Patients diagnosed with dysgeusia must use caution when adding sugar and salt to food and must be sure not to over-compensate for their lack of taste with excess amounts. Since the elderly are often on multiple medications, they are at risk for taste disturbances increasing the chances of developing depression, loss of appetite, and extreme weight loss. This is cause

for an evaluation and management of their dysgeusia. In patients undergoing chemotherapy, taste distortions can often be severe and make compliance with cancer treatment difficult. Other problems that may arise include anorexia and behavioural changes that can be misinterpreted as psychiatric delusions regarding food. Symptoms including paranoia, amnesia, cerebellar malfunction and lethargy can also manifest when undergoing histidine treatment. This makes it critical that these patient's dysgeusia is either treated or managed in order to improve their quality of life (Padala 2006).

Description of the condition

The symptoms of taste impairment may vary depending on the cause. Patients may experience a reduced ability to taste (hypogeusia), the distortion of taste (dysgeusia) and/or the total lack of taste (ageusia). Anything that negatively affects either the physical make-up of the taste buds or their cells, saliva production, the nerve pathway, or brain can cause a taste disorder. Therefore, in addition to the normal aging process, a host of other factors such as smoking, infection, nerve diseases, tumours, radiation treatment, drugs, chemicals, head injury, zinc deficiency, dry mouth and poor oral hygiene can also affect the ability to taste.

Taste impairment may be caused not only by an altered threshold of taste and sensory pathway but also by various mental and physical disorders, including depression, taste bud or mucosal lesions, gum disease, dry mouth, gastrointestinal diseases, zinc deficiency, and medication. Therefore the symptoms of taste impairment may vary depending on the cause. Subnormal taste often induces appetite loss, which results in malnutrition and impairs the quality of life (Kashihara 2011).

Any disturbance in taste perception can hamper the quality of life in such patients by influencing their appetite, body weight and psychological well-being (Heckmann 2005).

The sense of taste is very much essential to enjoy food, which in turn provides nutrition to an individual. Taste disorders are classified based on two principles: type and site of the lesion. Based on the type of lesion, taste disorders are grouped as quantitative dysgeusias (ageusia, hypogeusia and hypergeusia) and qualitative dysgeusias (parageusia, pseudogeusia, phantogeusia and agnogeusia). Based on the site of the lesion, taste disorders are classified as epithelial, neural and central dysgeusias (Fikentscher 1987). Systemic disorders like renal disorders (Mahajan 1980), alcoholic cirrhosis (Russell 1980), regional enteritis (Solomons 1974), and iatrogenic causes like post radiation therapy (Silverman 1983), or chemotherapy (Wickham 1999), can lead to taste disorders.

Description of the intervention

Various treatment modalities have been used to improve taste disorders. These include the use of zinc (Heckmann 2005; Sakai

2002), transcranial magnetic stimulation (Henkin 2011a), alpha lipoic acid (Femiano 2002), ginkgo biloba (Mattes 2004), and pilocarpine (Aframian 2007). The ability to manage taste disorders varied with each intervention.

Diminished taste acuity resulting in malnutrition in haemodialysis patients was studied (Mahajan 1980). The subjects were tested for taste acuity related to plasma zinc concentration. This double-blinded study was instituted using a zinc supplement (zinc acetate) and a placebo. The same authors have studied the effect of zinc supplements on patients undergoing regular haemodialysis (Mahajan 1982). Treatment of taste abnormalities with zinc sulphate was tried in patients receiving external beam radiation therapy (ERT) for head and neck cancers (Halyard 2007; Ripamonti 1998). In a double-blind, placebo controlled trial, efficacy of zinc picolinate and zinc gluconate were studied in idiopathic zinc deficiency taste disorders (Sakai 2002). Zinc gluconate was tested in patients with drug induced taste disorders (Yoshida 1991). Zinc supplements were also tried in taste disorders due to head trauma and malignant tumours of head and neck (Henkin 1976).

Dosage of the zinc varied drastically in different trials: capsules containing 22.6 mg of zinc (Barrie 1987); 29 mg of zinc three times a day for 3 months (Sakai 2002); 45 mg of zinc sulphate three times a day (Ripamonti 1998); and 50 mg of elementary zinc (as zinc acetate) per day (Mahajan 1980).

In an open cross-over trial on idiopathic dysgeusia patients, considering idiopathic dysgeusia as a neuropathy similar to burning mouth syndrome, an alpha lipoic acid intervention was studied (Femiano 2002).

Ginkgo biloba extracts were tried to enhance cognitive, taste and smell functions in dementia patients (Mattes 2004).

Repetitive transcranial magnetic stimulation (rTMS) was used in patients having smell and taste disorders (Henkin 2011a).

Other than these interventional studies, many individual case reports on management of taste disorders like high dose biotin (Greenway 2011), application of glutamate (Sasano 2010), branched-chain amino acid-enriched supplementation (Aminofeel) (Nagao 2010), and transient cooling of the mouth by using ice cubes (Fujiyama 2010), are found in the literature.

How the intervention might work

Zinc is an important element in both the maintenance and repair of taste buds. Zinc influences the synthesis of the protein gustin, which is linked to the production of taste buds. Decrease in the salivary gustin/carbonic anhydrase VI is associated with taste and smell disorders and can be effectively treated with zinc supplementation (Henkin 1999). It has also been shown to increase calcium concentration in saliva. Taste buds rely on calcium receptors to work properly (Heckmann 2005). Finally, zinc is an important cofactor for alkaline phosphatase, the most important enzyme in taste bud membranes (Bicknell 1988). Zinc supplementation has

shown to be effective in treating taste disorders. It can also be found in natural foods such as meat, cereals, beans and oysters.

Alpha lipoic acid (ALA) is an antioxidant that is produced naturally in human cells. Among its functions, it has an important role in the Krebs cycle assisting in the production of nerve growth factor. Research in animals has shown that ALA can improve nerve induction velocity. However, there are contradictory opinions about the efficacy of ALA in treating burning mouth syndrome and dysgeusia (de Moraes 2012; Femiano 2002).

Ginkgo biloba, an herbal extract, may have three effects on the human body: improvement in blood flow to most tissues and organs, protection against oxidative cell damage from free radicals and blockage of many of platelet-activating factors (aggregation and blood clotting). These anti-clotting characteristics may be of help with circulatory problems attributed to aging. It is being used to treat ADD and memory loss and the impact to the brain and circulation may make it helpful in treating taste disorders (Mattes 2004). However, there is no evidence for its clinically significant benefits in dementia patients (Birks 2009).

Transcranial magnetic stimulation (TMS) uses electromagnetic induction to induce weak electric currents stimulating activity in specific parts of the brain with minimal discomfort. A variant of TMS, called repetitive TMS, was used to treat various neurological and psychiatric disorders including migraines, Parkinson's disease, tinnitus, stroke, depression (Henkin 2011a), and phantogeusia (unpleasant taste sensation in the absence of food or drink) (Henkin 2011b).

Research has found that saliva contains specific proteins that are growth factors (nerve growth factor, epidermal growth factor) that make taste buds develop and mature. Without these growth factors, taste buds degenerate (Gardiner 2008). Pilocarpine, by increasing saliva production, gives taste buds greater access to food molecules and may be responsible for maintenance of taste buds. Studies have shown that treatment with pilocarpine enhances taste (Aframian 2007; Leek 2002).

Why it is important to do this review

Taste disturbances are not uncommon, have a range of causes, and result in considerable loss of quality of life. A systematic review is necessary to summarise the evidence of the effects of the many interventions available to treat taste disturbances and to provide evidence to guide decision making.

OBJECTIVES

To assess the effects of interventions for the management of patients with taste disturbances.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs) with either a pharmacological or non-pharmacological intervention in this review. We will include cross-over trials if this is an appropriate design for the intervention. We will exclude quasi-RCTs.

Types of participants

We will include patients with taste disorders diagnosed clinically as dysgeusia or parageusia or ageusia or hypogeusia regardless of their age, sex, race, profession or residential location. It is a well established fact that many treatment procedures like surgery, radiation therapy and chemotherapy can cause taste perception problems, and once the effect of these treatment procedures reduces, the taste perception reverts back to normal slowly. Considering these variations, we have agreed upon the following exclusion criteria. The following types of patients are deemed inappropriate for this trial.

- Demolitive surgery of tongue, palate or oropharynx.
- Presence of oral lesions such as ulcers, stomatitis, candidiasis and necrosis.
- Cerebral lesions or surgical damage to the nervous system.
- Endocrinal and neurological disorders known to affect taste and/or smell sensitivity.
- Patients undergoing treatment with drugs known to affect taste perception e.g. chemotherapy.

Types of interventions

- Any pharmacological agent (inclusive of alternative medicine) should be the experimental intervention and the control intervention should be either a placebo or no treatment.
- Any non-pharmacological method should be the experimental intervention with a control intervention (placebo or no treatment).
- Any direct comparisons between two active interventions, e.g. Drug A versus Drug B, or between two doses of the same drug e.g. Drug A dose X versus Drug A dose Y.
- All routes of drug administration or modes of application will be included.

Types of outcome measures

Improvement in the taste acuity to at least one quality of taste by subjective/objective assessment scales will be considered as the most important outcome. It can be any one of the following.

- Sip and spit method (traditional method): In this method, a solution of a known concentration of a sweet, salty, bitter, or sour substance is gargled and slobbered in the mouth and then discarded. The patient is asked to identify the taste substance, and the concentration can be varied to determine threshold sensitivity. It is an easy test to administer but assumes severe taste loss. Regional damage (e.g. on the front or tip of the tongue) would be masked by stimulation of the remaining taste cells elsewhere in the mouth.

- Filter-paper disc method (Tomita 1986): In this test, filter paper or a dissolvable strip is impregnated with a known concentration of a sweet, salty, bitter, or sour substance, and the filter paper or strip is placed on a specific part of the tongue or palate. The patient is asked to identify the taste substance. The concentration can be varied to determine threshold sensitivity. This test is also easy to administer. The goal is to activate major regions of taste cells to determine whether the individual has partial taste deficit or damage.

- Electrogustometry (Tomita 1986): Electrogustometry is the measurement of taste threshold by passing controlled anodal current through the tongue. When current passes through the tongue a unique and distinct metallic taste is perceived.

- Three stimulus drop technique (Mossman 1978): Testing involves a three stimuli forced choice drop technique given in a type of staircase technique. The subject is given three drops of liquid which are placed successively onto the lingual surface. Out of three, two drops are water and one drop is water with a solute, either NaCl (salt), sucrose (sweet), HCl (sour) or urea (bitter).

- Edible taste strips: Edible strips are prepared from pullulan-hydroxypropyl methylcellulose solutions that are dried to a thin film. The maximal amount of a tastant that could be incorporated in a 2.54 × 2.54 cm taste strip is 5% for each class of tastant (sweet, sour, salty, bitter, and umami) during strip formation (Smutzer 2008).

- Visual analogue scale (traditional method).
- Self reporting questionnaire method (Soter 2008).
- Spatial taste test (Gondivkar 2009).
- Clinical bitterness masking test for phantogeusia (Ishimaru 2001).

If there are any other/newer methods for assessment which are deemed to be scientifically appropriate, we will include such studies in the review.

Primary outcomes

- Improvement in the taste acuity to at least one quality of taste by subjective/objective assessment scales will be considered as the most important outcome.
- Improvement in taste discrimination.

Secondary outcomes

- Adverse effects related to drugs.
- Health-related quality of life.

Search methods for identification of studies

For the identification of studies included or considered for this review, detailed search strategies will be developed for each database searched. These will be based on the search strategy developed for MEDLINE (Appendix 1), but revised appropriately for each database to take account of differences in controlled vocabulary and syntax rules.

The search strategy will combine the subject search with the Cochrane Highly Sensitive Search Strategy for identifying reports of randomised controlled trials (2008 revision), as published in Box 6.4.c in the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011] (Higgins 2011). The subject search will use a combination of controlled vocabulary and free text terms.

Electronic searches

The following databases will be searched.

- The Cochrane Oral Health Group Trials Register (whole database).
- The Cochrane Ear, Nose and Throat Disorders Group Trials Register (whole database).
- The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, current issue).
 - MEDLINE via OVID (1946 to date).
 - EMBASE via OVID (1980 to date).
 - CINAHL via EBSCO (1980 to date).
 - AMED via OVID (1985 to date).

There will be no restrictions on language or date of publication. Non-English papers will be translated.

Searching other resources

Reference lists of included studies will be checked to identify any further additional studies. Authors of the included studies will be contacted for relevant unpublished material. Abstracts from scientific meetings and conferences will be searched for appropriate studies using the following websites.

- [International Association of Dental Research/American Association of Dental Research Conference Proceedings](#)
- [Association for Research in Otolaryngology Conference Proceedings](#)

The following databases will be searched for ongoing trials.

- The National Institutes of Health (NIH) database (<http://www.clinicaltrials.gov>).
- The *meta*Register of Controlled Trials (*mRCT*) (<http://www.controlled-trials.com/mrct/>).

- The World Health Organization's International Clinical Trials Registry Platform (WHO ICTRP) (<http://apps.who.int/trialsearch/>).

- International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) Clinical Trials Portal (http://clinicaltrials.ifpma.org/clinicaltrials/no_cache/en/myportal/index.htm).

Handsearching for this review will be limited to those journals searched as part of the Cochrane Worldwide Handsearching Programme (see the [Cochrane Masterlist](#) for details of journals searched to date).

Data collection and analysis

Selection of studies

Two review authors will screen the titles and abstracts of all the obtained reports for eligibility, independently and in duplicate. Full papers of relevant RCT's (based on the inclusion and exclusion criteria) will be obtained and screened independently by two review authors, and any disagreement on eligibility will be resolved by discussion. When resolution is not possible, we will consult an arbiter. We will record studies excluded at this point in the 'Characteristics of excluded studies' table along with reasons for exclusion.

Data extraction and management

Two review authors will extract the data independently and in duplicate, using a data extraction form specifically designed for this review. Any disagreements will be resolved by consulting a third review author. We will enter study details in the 'Characteristics of included studies' table in Revman (RevMan 2012).

The following details will be recorded for each study.

- Publication details like year of publication, language.
- Demographic details of the report.
- Inclusion and exclusion criteria.
- Sample size, method of randomisation, allocation concealment, blinding, type of trial, method of assessing the outcome, and drop-outs if any.
 - Type of intervention.
 - Details of the outcome reported.
 - Duration of follow-up.
 - Results of the intervention.
 - Funding details.

We will write, e-mail, or telephone the author/s of included studies where clarification of any details is required and, if necessary, to obtain any additional data.

Assessment of risk of bias in included studies

We will assess the risk of bias of included studies using The Cochrane Collaboration's risk of bias tool as described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will complete a 'Risk of bias' table for each included study. Within each table, we will assess the following domains of risk of bias: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other potential sources of bias. For each domain, we

will describe what was reported to have happened, using quotes from the study, followed by a judgement of 'Low risk', 'High risk' or 'Unclear risk' of bias. We will contact the study authors for clarification where necessary, quoting their responses in the risk of bias table. Any disagreements on risk of bias will be resolved by consulting a third review author.

Summarising risk of bias for a study

Studies will be grouped into the following categories.

Risk of bias	Interpretation	Within a study	Across studies
Low risk of bias	Plausible bias unlikely to seriously alter the results	Low risk of bias for all key domains	Most information is from studies at low risk of bias
Unclear risk of bias	Plausible bias that raises some doubt about the results	Unclear risk of bias for one or more key domains	Most information is from studies at low or unclear risk of bias
High risk of bias	Plausible bias that seriously weakens confidence in the results	High risk of bias for one or more key domains	The proportion of information from studies at high risk of bias is sufficient to affect the interpretation of results

Risk of bias will be summarised graphically using the plots available in RevMan (RevMan 2012).

Measures of treatment effect

For dichotomous data, we will express the estimates of effect of an intervention as risk ratios together with 95% confidence intervals. For continuous outcomes, we will use mean differences (between the two groups at the end of the study) and 95% confidence intervals to summarise the data for each group where the mean difference and standard deviations are calculable from the data presented. We will use standardised mean difference if studies use different scales to measure the same primary outcome (e.g. improvement in the taste acuity). However, we will also explore the possibility of converting the continuous outcomes to dichotomous outcomes.

Unit of analysis issues

We will analyse cross-over studies according to the methods in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Dealing with missing data

We will contact study authors to obtain missing data. We will use methods in section 7.7.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* to estimate missing standard deviations (Higgins 2011).

Assessment of heterogeneity

If we are able to undertake meta-analyses, we will assess heterogeneity of the studies by examining the forest plots, with poor overlap of the confidence intervals indicating the presence of heterogeneity. We will also use the Chi² test to assess whether heterogeneity is present and we will quantify it using the I² statistic. We will use the guidance given in the *Cochrane Handbook for Systematic Reviews of Interventions* to interpret the I² statistic: 0% to 40% might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; and 75% to 100% indicates considerable heterogeneity (Higgins 2011).

Assessment of reporting biases

If there are more than 10 studies in any meta-analysis, we will assess reporting bias using the test for asymmetry described by Egger et al (Egger 1997).

Data synthesis

We will analyse the data using RevMan software (RevMan 2012). If the data available from the studies have similar comparisons and outcomes, we will undertake meta-analysis. Random-effects models will be used when there are more than three studies in a meta-analysis, and fixed-effect models otherwise. We will combine data from cross-over studies with data from parallel group trials using the method outlined by Elbourne et al (Elbourne 2002), using the generic inverse variance method in RevMan. The techniques described by Follmann et al will be used to estimate the standard error (SE) of the difference for cross-over studies where the appropriate data were not presented and could not be obtained (Follmann 1992).

Subgroup analysis and investigation of heterogeneity

If there are at least two studies available, we will consider subgroup analysis for studies based on the different groups of patients.

Sensitivity analysis

Providing there are sufficient included studies, we will undertake sensitivity analysis based on risk of bias, including only studies at low risk of bias.

Summarising and interpreting results

We will use the GRADE approach to interpret findings. We will use the GRADE Profiler software (version 3.6), and import the data from RevMan to create 'Summary of findings' tables for each comparison included in this review. These tables will provide information concerning the overall quality of the evidence from the trials, the magnitude of effect of the interventions examined, and the sum of available data on the primary outcome and secondary outcomes. The outcomes selected for inclusion in these tables will be improvement in the taste acuity and adverse effects.

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* Indicates the major publication for the study

APPENDICES

Appendix I. MEDLINE via OVID search strategy

1. exp Taste disorders/
2. Taste perception/
3. (ageusia\$ or hypogeusia\$ or dysgeusia\$ or parageusia\$).mp.
4. (taste adj3 (distort\$ or dysfunction\$ or disorder\$ or alter\$ or change\$ or abnormal\$ or blind\$)).mp.
5. (gustatory adj3 (perception\$ or sensitive\$ or distort\$)).mp.
6. or/1-5

The above subject search will be linked to the Cochrane Highly Sensitive Search Strategy (CHSSS) for identifying randomised trials in MEDLINE: sensitivity maximising version (2008 revision) as referenced in Chapter 6.4.11.1 and detailed in box 6.4.c of the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011] ([Higgins 2011](#)).

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. drug therapy.fs.
6. randomly.ab.
7. trial.ab.
8. groups.ab.
9. or/1-8
10. exp animals/ not humans.sh.
11. 9 not 10

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- Sumanth Kumbargere Nagraj: Protocol, select trials, analysis, final review and update review.
- Naresh Yedthare Shetty: Obtain copies of trials, select trials, extract data.
- Srinivas Kandula: Develop search strategy, search for trials, extract data from trials, enter data into Revman.
- Ashish Shreshtha: Carry out analysis and interpret analysis.
- Renjith George: Search for trials, extract data from trials, enter data into Revman, draft the final review.
- David Levenson: Protocol, draft the final review and update review.
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