Protocol template (Protocol)

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TABLE OF CONTENTS

[Intervention Protocol]

Protocol template

N N[1]

[1]Not specified

Contact address: N N, Not specified.

ABSTRACT

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

To assess the effects of ...

BACKGROUND

Description of the condition

Diabetes mellitus is a metabolic disorder resulting from a defect in insulin secretion, insulin action, or both. A consequence of this is chronic hyperglycaemia (that is elevated levels of plasma glucose) with disturbances of carbohydrate, fat and protein metabolism. Long-term complications of diabetes mellitus include retinopathy, nephropathy and neuropathy, and an increased risk of cardiovascular disease.

Description of the intervention

...

Adverse effects of the intervention

...

How the intervention might work

...

Why it is important to do this review

...

OBJECTIVES

To assess the effects of ...

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled clinical trials (RCTc).

Types of participants

Diagnostic criteria (diabetes mellitus)

To be consistent with changes in classification and diagnostic criteria of diabetes mellitus over the years, the diagnosis should be established using the standard criteria valid at the time of the trial commencing (for example ADA 1999; ADA 2008; WHO 1998). Ideally, diagnostic criteria should have been described. If necessary, we will use the study authors' definition of diabetes mellitus. We plan to subject diagnostic criteria to a sensitivity analysis.

Diagnostic criteria (...)

...

Types of interventions

We plan to investigate the following comparisons of intervention versus control/comparator where the same letters indicate direct comparisons.

Intervention

(a) Intervention
(b) Intervention + other therapy

Comparator

(a1) Placebo
(a2) Usual care
(b1) Placebo + other therapy
(b2) Usual care + other therapy
Concomitant therapies will have to be the same in the intervention and comparator groups.

Types of outcome measures

Primary outcomes

- Adverse events.

Secondary outcomes

Method and timing of outcome measurement
Summary of findings' table

We will present a 'Summary of findings table' reporting the following outcomes listed according to priority.

Search methods for identification of studies

Electronic searches

We will search the following sources from inception to the present.
- *The Cochrane Library.*
- MEDLINE.
- EMBASE.
- *Other databases ...*

We will also search databases of ongoing trials including Clinical-Trials.gov (http://clinicaltrials.gov/), *meta*Register of Controlled Trials (http://www.controlled-trials.com/mrct/), the EU Clinical Trials register (https://www.clinicaltrialsregister.eu/) and the World Health Organization (WHO) International Clinical Trials Registry Platform Search Portal (http://apps.who.int/trialsearch/). For detailed search strategies see Appendix 1. We will continuously apply PubMed's 'My NCBI' (National Center for Biotechnology Information) email alert service to identify newly published studies using a basic search strategy (see Appendix 1). Four weeks before we submit the final review draft to the Cochrane Metabolic and Endocrine Disorders Group (CMED) for editorial approval, we will perform an updated search on all specified databases. If we identify new studies for inclusion we will evaluate these and incorporate findings in our review before submission of the final review draft (Beller 2013).

If we detect additional relevant key words during any of the electronic or other searches, we will modify the electronic search strategies to incorporate these terms and document the changes. We will place no restrictions on the language of publication when searching the electronic databases or reviewing reference lists in identified studies.

We will send results of electronic searches to the CMED for databases which are not available at the editorial office.

Searching other resources

We will try to identify other potentially eligible trials or ancillary publications by searching the reference lists of retrieved included trials, (systematic) reviews, meta-analyses and health technology assessment reports.
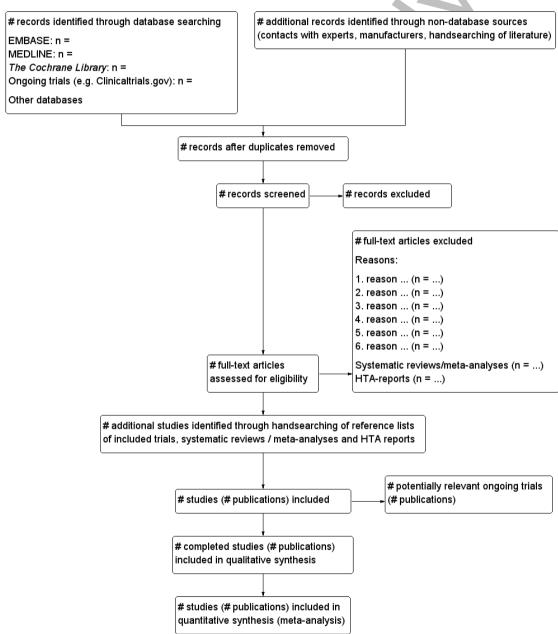
Data collection and analysis

Selection of studies

Two review authors (NN, NN) will independently scan the abstract, title, or both, of every record retrieved, to determine which studies should be assessed further. We will investigate all potentially-relevant articles as full text. We will resolve any discrepancies through consensus or recourse to a third review author (NN). If

resolving disagreement is not possible, the article will be added to those 'awaiting assessment' and we will contact study authors for clarification. We will present an adapted PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow-chart of study selection (Figure 1) (Liberati 2009).

Figure 1.   Study flow diagram.

Data extraction and management

For studies that fulfil inclusion criteria, two review authors (NN, NN) will independently abstract key participant and intervention characteristics and report data on efficacy outcomes and adverse events using standard data extraction templates, with any disagreements to be resolved by discussion, or if required by a third author (NN) (for details see Table 1; Appendix 2; Appendix 3; Appendix 4; Appendix 5; Appendix 6; Appendix 7; Appendix 8; Appendix 9; Appendix 10; Appendix 11; Appendix 12; Appendix 13; Appendix 14) .

We will provide information including trial identifier about potentially-relevant ongoing studies in the table 'Characteristics of ongoing studies' and in the appendix 'Matrix of study endpoints (trial documents)'. We will try to find the protocol of each included study, either in databases of ongoing trials or in publications of study designs, or both, and specify the data in the appendix 'Matrix of study endpoints (protocol/trial documents)'.

We will send an e-mail to all study authors of included studies to enquire whether they are willing to answer questions regarding their trials. We will present the results of this survey in Appendix 15. Thereafter, we will seek relevant missing information on the trial from the primary author(s) of the article, if required.

Dealing with duplicate and companion publications

In the event of duplicate publications, companion documents or multiple reports of a primary study, we will maximise yield of information by collating all available data and use the most complete dataset aggregated across all known publications. In case of doubt the publication reporting the longest follow-up associated with our primary or secondary outcomes will be given priority.

Assessment of risk of bias in included studies

Two review authors (NN, NN) will assess the risk of bias of each included study independently. We will resolve disagreements by consensus, or by consultation with a third author (NN).

We will assess risk of bias using the Cochrane Collaboration's tool for assessment of risk of bias (Higgins 2011a; Higgins 2011b). We will assess the following criteria in this assessment:

- Random sequence generation (selection bias).
- Allocation concealment (selection bias).
- Blinding (performance bias and detection bias), blinding of participants and personnel assessed separately from blinding of outcome assessment.
- Incomplete outcome data (attrition bias).
- Selective reporting (reporting bias).
- Other bias.

We will assess outcome reporting bias by integrating the results of 'Examination of outcome reporting bias' (Appendix 7), 'Matrix of study endpoints (protocol/trial documents)' (Appendix 6) and

section 'Outcomes (outcomes reported in abstract of publication)' of the 'Characteristics of included studies' section (Kirkham 2010). This analysis will form the basis for the judgement of selective reporting (reporting bias).

We will judge 'Risk of bias criteria' as 'low risk', 'high risk' or 'unclear risk' and evaluate individual bias items as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). We will present a 'Risk of bias' graph and a 'Risk of bias summary' figure.

We will assess the impact of individual bias domains on study results at the endpoint and study levels.

For blinding of participants and personnel (performance bias), detection bias (blinding of outcome assessors) and attrition bias (incomplete outcome data) we intend to evaluate risk of bias separately for subjective and objective outcomes (Hróbjartsson 2013). We will consider the implications of missing outcome data from individual participants.

We define the following endpoints as subjective outcomes.

We define the following outcomes as objective outcomes.

Measures of treatment effect

We will express dichotomous data as odds ratios (ORs) or risk ratios (RRs) with 95% confidence intervals (CIs). We will express continuous data as mean differences (MD) with 95% CIs.

Unit of analysis issues

We will take into account the level at which randomisation occurred, such as cross-over trials, cluster-randomised trials and multiple observations for the same outcome.

Dealing with missing data

We will obtain missing data from authors, if feasible, and carefully evaluate important numerical data such as screened, randomised participants as well as intention-to-treat (ITT), and as-treated and per-protocol populations. We will investigate attrition rates, e.g. drop-outs, losses to follow up and withdrawals, and critically appraise issues of missing data and imputation methods (e.g. last observation carried forward (LOCF)).

Where standard deviations for outcomes are not reported we will impute these values by assuming the standard deviation of the missing outcome to be the average of the standard deviations from those studies where this information was reported. We will investigate the impact of imputation on meta-analyses by means of sensitivity analysis.

Assessment of heterogeneity

In the event of substantial clinical, methodological or statistical heterogeneity, we will not report study results as the pooled effect estimate in a meta-analysis. We will identify heterogeneity by visual inspection of the forest plots and by using a standard Chi^2 test

with a significance level of $\alpha = 0.1$, in view of the low power of this test. We will examine heterogeneity using the I^2 statistic, which quantifies inconsistency across studies, to assess the impact of heterogeneity on the meta-analysis (Higgins 2002; Higgins 2003); an I^2 statistic of 75% or more indicates a considerable level of inconsistency (Higgins 2011a).

When we find heterogeneity, we will attempt to determine potential reasons for it by examining individual study and subgroup characteristics.

We expect the following characteristics to introduce clinical heterogeneity:

Assessment of reporting biases

If we include 10 studies or more that investigate a particular outcome, we will use funnel plots to assess small study effects. Owing to several possible explanations for funnel plot asymmetry, we will interpret results carefully (Sterne 2011).

Data synthesis

Unless there is good evidence for homogeneous effects across studies, we will summarise primarily low risk of bias data by means of a random-effects model (Wood 2008). We will interpret random-effects meta-analyses with due consideration of the whole distribution of effects, ideally by presenting a prediction interval (Higgins 2009). A prediction interval specifies a predicted range for the true treatment effect in an individual study (Riley 2011). In addition, we will perform statistical analyses according to the statistical guidelines contained in the latest version of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a).

Subgroup analysis and investigation of heterogeneity

We will carry out the following subgroup analyses and plan to investigate interaction.

Sensitivity analysis

We will perform sensitivity analyses in order to explore the influence of the following factors (when applicable) on effect sizes.

- Restricting the analysis to published studies.
- Restricting the analysis by taking into account risk of bias, as specified in the section Assessment of risk of bias in included studies.
- Restricting the analysis to very long or large studies to establish the extent to which they dominate the results.
- Restricting the analysis to studies using the following filters: diagnostic criteria, imputation, language of publication, source of funding (industry versus other), country.

We will also test the robustness of the results by repeating the analysis using different measures of effect size (RR, OR etc.) and different statistical models (fixed-effect and random-effects models).

R E F E R E N C E S

Additional references

ADA 1999

The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care* 1999;**22**(Suppl 1):S5–19.

ADA 2008

American Diabetes Association. Standards of medical care in diabetes - 2008. *Diabetes Care* 2008;**31**(Suppl 1): S12–54. [PUBMED: 18165335]

Beller 2013

Beller EM, Chen JK, Wang UL, Glasziou PP. Are systematic reviews up-to-date at the time of publication?. *Systematic Reviews* 2013;**2**(1):36. [2046–4053: (Electronic)]

Higgins 2002

Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine* 2002;**21**:1539–58.

Higgins 2003

Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analysis. *BMJ* 2003;**327**: 557–60.

Higgins 2009

Higgins JPT, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis. *Journal of the Royal Statistical Society: Series A (Statistics in Society)* 2009; **172**(1):137–59.

Higgins 2011a

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

Higgins 2011b

Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al.The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;**343**: d5928.

Hróbjartsson 2013

Hróbjartsson A, Thomsen AS, Emanuelsson F, Tendal B, Hilden J, Boutron I, et al.Observer bias in randomized clinical trials with measurement scale outcomes: a systematic review of trials with both blinded and nonblinded assessors. *Canadian Medical Association Journal* 2013;**185** (4):E201–11.

Kirkham 2010

Kirkham JJ, Dwan KM, Altman DG, Gamble C, Dodd S, Smyth R, et al.The impact of outcome reporting bias in randomised controlled trials on a cohort of systematic reviews. *BMJ* 2010;**340**:c365. [DOI: 10.1136/bmj.c365]

Liberati 2009

Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al.The PRISMA statement for reporting systematic and meta-analyses of studies that evaluate interventions: explanation and elaboration. *PLoS Medicine* 2009;**6**(7):1–28. [DOI: 10.1371/journal.pmed.1000100]

Riley 2011

Riley RD, Higgins JP, Deeks JJ. Interpretation of random effects meta-analyses. *BMJ* 2011;**342**:d549.

Sterne 2011

Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J, et al.Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ* 2011;**343**:d4002.

WHO 1998

Alberti KM, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part I: diagnosis and classification of diabetes mellitus. Provisional report of a WHO consultation. *Diabetic Medicine* 1998;**15**:539–53.

Wood 2008

Wood L, Egger M, Gluud LL, Schulz KF, Juni P, Altman DG, et al.Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. *BMJ* 2008;**336** (7644):601–5.

* *Indicates the major publication for the study*

ADDITIONAL TABLES

Table 1. Overview of study populations

Charac-teristic	Intervention(s) and comparator(s)	Sample size[a]	[N] Screened/ eligible	[N] Randomised	[N] Safety	[N] ITT	[N] Finishing study	[%] Randomised finishing study	Follow-up [b]
(1) Study ID	Intervention 1								
	Intervention 2								
	Comparator 1								
	Comparator 2								
		total:							
Grand total	*All interventions*			...			...		
	All comparators			...			...		
	All interventions and comparators			...			...		

[a]According to power calculation in study publication or report
[b]Duration of intervention or follow-up, or both, under randomised conditions until end of study
"-" denotes not reported
ITT: intention-to-treat; N/A: not applicable

A P P E N D I C E S

Appendix 1. Search strategies

Search terms and databases
Unless otherwise stated, search terms are free text terms. Abbreviations: '$': stands for any character; '?': substitutes one or no character; adj: adjacent (i.e. number of words within range of search term); exp: exploded MeSH; MeSH: medical subject heading (MEDLINE medical index term); pt: publication type; sh: MeSH; tw: text word
The Cochrane Library
MEDLINE (state platform/delete as appropriate: OvidSP/PubMed/other)
EMBASE (state platform/delete as appropriate: OvidSP/other)
'My NCBI' alert service (PubMed)
Other databases ... (state platform)

Appendix 2. Description of interventions

Characteristic	Intervention(s) [route, frequency, total dose/day]	Adequate[a] intervention [Yes / No]	Comparator (s) [route, frequency, total dose/day]	Adequate[a] comparator [Yes / No]
Study 1	Intervention 1		Comparator 1	
	Intervention 2		Comparator 2	

Footnotes
"-" denotes not reported
[a]The term 'adequate' refers to sufficient use of the intervention/comparator with regard to dose, dose escalation, dosing scheme, provision for contraindications and other features necessary to establish a fair contrast between intervention and comparator
N: no; Y: yes

Appendix 3. Baseline characteristics (I)

Characteristic	Intervention(s) and comparator (s)	Duration of intervention (duration of follow-up)	Participating population	Study period [year to year]	Country	Setting	Ethnic groups [%]	Duration of disease [mean/ range years (SD), or as reported]
Study 1	Intervention 1							
	Intervention 2							
	Comparator 1							
	Comparator 2							
						all:		

Footnotes
"-" denotes not reported
SD: standard deviation

Appendix 4. Baseline characteristics (II)

Characteristic	Intervention(s) and comparator(s)	Sex [female %]	Age [mean/ range years (SD), or as reported]	HbA1c [%]	BMI [mean kg/m^2 (SD)]	Co-medications / Co-interventions	Co-morbidities
Study 1	Intervention 1						
	Intervention 2						
	Comparator 1						
	Comparator 2						
	all:						

Footnotes
"-" denotes not reported
BMI: body mass index; C: comparator; HbA1c: glycosylated haemoglobin A1c; I: intervention; SD: standard deviation

Appendix 5. Matrix of study endpoints (publications)

Study ID	Characteristic	Endpoint reported in publication	Endpoint <u>not</u> reported in publication	Endpoint not measured	Time of measurement [a]
Example	**Review's primary outcomes**				
			x		N/A
		x			6, <u>12</u> mo
	Adverse events	x			<u>12</u> mo
	Review's secondary outcomes				
		x			<u>12</u> mo
		x			<u>6</u>, <u>12</u> mo
			x		N/A
	Other than review's primary/secondary outcomes reported in publication (classification: P/S/O)[b]				

FBG (S), HDL-cholesterol (O), insulin resistance (P), LDL-cholesterol (O), nocturnal hypoglycaemic episodes (O), PPG (S), patient satisfaction (S), safety parameters (O), socioeconomic outcomes (O), total cholesterol (O), triglycerides (O)	
Subgroups reported in publication	
Age < 65 years vs ≥ 65 years, cardiovascular risk factors vs no cardiovascular risk factors, type 1 diabetes vs type 2 diabetes	

Footnotes

[a] Underlined data denote times of measurement for primary and secondary review outcomes, if measured and reported in the results section of the publication (other times represent planned but not reported points in time)

[b] (P) Primary or (S) secondary endpoint(s) refer to verbatim statements in the publication, (O) other endpoints relate to outcomes which were not specified as 'primary' or 'secondary' outcomes in the publication

FBG: fasting blood glucose; HbA1c: glycosylated haemoglobin A1c; HDL: high-density lipoprotein; LDL: low-density lipoprotein; mo: months; N/A: not acknowledged; PPG (postprandial glucose)

Appendix 6. Matrix of study endpoints (trial documents)

Characteristic / Study ID (trial identifier)	Endpoint[a]	Review's primary outcome	Review's secondary outcome	Time of measurement	Source (FDA document / EMA document / manufacturer's website / design paper / trial protocol document)
Example	Cardiovascular mortality (P)		x	12 mo	
	HbA1c (O)	x		3, 6, 12 mo	
	Insulin sensitivity (O)	N/A	N/A	N/A	
	Myocardial infarction (S)		x	6, 12 mo	

Footnotes

"-" denotes not reported

[a] (P) Primary or (S) secondary endpoint(s) refer to verbatim statements in the publication, (O) other endpoints relate to outcomes which were not specified as 'primary' or 'secondary' outcomes in the report

HbA1c: glycosylated haemoglobin A1c; mo: months; N/A: not acknowledged

Appendix 7. Examination of outcome reporting bias

Characteristic	Clear that outcome was measured and analysed[a] [trial report states that outcome was analysed but only reports that result was not significant]	Clear that outcome was measured and analysed[b] [trial report states that outcome was analysed but no results reported]	Clear that outcome was measured[c] [clear that outcome was measured but not necessarily analysed (judgement says likely to have been analysed but not reported because of non-significant results)]	Unclear whether the outcome was measured[d] [not mentioned but clinical judgement says likely to have been measured and analysed but not reported on the basis of non-significant results]
Study 1				

Footnotes
'High risk of bias' categories for outcome reporting bias according to the Outcome Reporting Bias In Trials (ORBIT) study classification system for missing or incomplete outcome reporting in reports of randomised trials (Kirkham 2010).
[a]Classification 'A' (table 2, Kirkham 2010)
[b]Classification 'D' (table 2, Kirkham 2010)
[c]Classification 'E' (table 2, Kirkham 2010)
[d]Classification 'G' (table 2, Kirkham 2010)

Appendix 8. Definition of endpoint measurement (I)

Characteristic	Cardiovascular mortality	Sudden death	Composite macrovascular complications	Non-fatal myocardial infarction	Non-fatal stroke	Amputation of lower extremity	Peripheral revascularization
Study 1							

Footnotes
ND: not defined; N/I: not investigated

Appendix 9. Definition of endpoint measurement (II)

Characteristic	Coronary revascularization	Composite microvascular complications	End-stage renal disease	Nephropathy	Retinopathy	Retinal photocoagulation	Blindness
Study 1							

(Continued)

Appendix 10. Definition of endpoint measurement (III)

Characteristic Study ID	Cancer	Mild hypoglycaemia	Moderate hypo- glycaemia	Severe hypoglycaemia	Nocturnal hypo- glycaemia	Severe/serious adverse events
Study 1						

Appendix 11. Adverse events (I)

Character- istic	Interven- tion(s) and comparator (s)	Ran- domised / Safety [N]	Deaths [N]	Deaths [%]	All adverse events [N]	All adverse events [%]	Severe/seri- ous adverse events [N]	Severe/seri- ous adverse events [%]
Study 1	Intervention 1							
	Intervention 2							
	Comparator 1							
	Comparator 2							
	all:							

Appendix 12. Adverse events (II)

Character-istic	Interven-tion(s) and comparator (s)	Ran-domised / Safety [N]	Left study due to ad-verse events [N]	Left study due to ad-verse events [%]	Hospitali-sation [N]	Hospitali-sation [%]	Outpa-tient treat-ment [N]	Outpa-tient treat-ment [%]
Study 1	Intervention 1							
	Intervention 2							
	Comparator 1							
	Comparator 2							
	all:							

Footnotes
"-" denotes not reported

Appendix 13. Adverse events (III)

Character-istic	Interven-tion(s) and comparator (s)	Ran-domised / Safety [N]	All hypo-glycaemic episodes [N]	All hypo-glycaemic episodes [%]	Severe/se-rious hypo-glycaemic episodes [N]	Severe/se-rious hypo-glycaemic episodes [%]	Nocturnal hypogly-caemic episodes [N]	Nocturnal hypogly-caemic episodes [%]
Study 1	Intervention 1							
	Intervention 2							
	Comparator 1							
	Comparator 2							
	all:							

(*Continued*)

Appendix 14. Adverse events (IV)

Characteristic	Intervention(s) and comparator(s)	Randomised / Safety [N]	Specific adverse events [description]	Specific adverse events [N]	Specific adverse events [%]
Study 1	Intervention 1				
	Intervention 2				
	Comparator 1				
	Comparator 2				
	all:				

Appendix 15. Survey of authors providing information on included trials

Characteristic	Study author contacted	Study author replied	Study author asked for additional information	Study author provided data
Study 1	Y			

Appendix 16. Protocol submission form

- This two-part document is designed to help you complete your final Cochrane protocol draft before you submit it for editorial and peer review and will later on be deleted by the CMED (Cochrane Metabolic and Endocrine Disorders Group).
- All items here refer either to the CMED or the official Cochrane MECIR (Methodological Expectations of Cochrane Intervention Reviews) standards (standards for the conduct of Cochrane intervention reviews).
- There is a 'Notes' section at the end of the form to alert the editorial office to the reason for any incomplete checks.

Part I

Part I of the document is thought to ensure that review authors adequately adhere to some very basic guidance. Should any item of part I be missing the CMED will send the protocol draft back for correction to the contact person without further peer review. In case the next protocol draft does not completely resolve issues the title might be de-registered:

ESSENTIAL ITEM LIST TO PASS THE CMED'S THRESH-HOLD FOR ACCEPTING PROTOCOL DRAFT FOR PEER REFEREEING:	(For editorial office only)
1. <u>All</u> review authors have an <u>active</u> Archie account and have seen and approved the final protocol draft.	**1.** **2.**
2. Names and details (email addresses!) of all review authors and the contact person were checked and appear correctly.	**3.**
3. Validation report was run (<u>F</u>ile → <u>R</u>eports → Validation Report) and is free of errors and warnings (as far as possible).	**4.** **5.**
4. RevMan spell checker (all parts of protocol) used and errors corrected (Tools → Check Spelling).	**6.**
5. Subheadings provided in the protocol template not changed, unless agreed by the CMED.	**7.**
6. Tables/appendices provided in the protocol template not deleted (unless agreed by the CMED) and adapted to review topic, if necessary.	
7. References to studies according to Cochrane Style Guide (see below 'Studies and references').	

Part II

This part of the document is thought to establish a smooth peer review process. All items here are mandatory unless explicitly negotiated with the CMED. Review authors who do not integrate this guidance will receive avoidable lengthy comments and also risk downgrading of the allocated time slots for their protocol. Review authors who apply all items of part II will receive priority peer review:

General

- Text clearly written and all technical and medical terms explained for the non-expert reader.
- Avoided long sentences (aim at 20 to 30 words) and used <u>active voice</u> whenever possible.
- Methods section written in the future tense (for example "we will analyse").

Title and review information (see Cochrane Handbook Section 4.2)

- Title is the same as the registered title, unless a change has been agreed with the CMED.
- Authors are listed in the correct order and have agreed to the order in which they are listed.
- Completed the 'Date next stage expected' field, estimating when the Cochrane review will be completed.

Background (see Cochrane Handbook Section 4.5)

- Maximum number of words: 2000.
- Condition and intervention(s) as well as known or theoretical adverse effects clearly described.
- Explained why this review is being prepared (for example to resolve conflicting evidence, help people make practical decisions etc.)
- Description of already existing systematic reviews, meta-analyses or health-technology assessment reports about this topic (state if none was found!). Listing of potential shortcomings in comparison to the new review project.

- Searched for and cited other Cochrane reviews relevant to own research question.

Objectives (see Cochrane Handbook Section 4.5)

- Precise statement of the Cochrane review's primary objective (preferably in a single sentence: "To assess the effects of ….").

Methods (see Cochrane Handbook Section 4.5)
Criteria for considering studies for this review

Types of studies
- Included study designs that are consistent with the objectives of the Cochrane review, and the CMED has approved these designs (for non-RCTs/CCTs only).
- Match the search strategies.

Types of participants
- Explained populations and specified (if applicable) gender, age groups, <u>diagnostic criteria</u> etc.

Types of interventions
- Used subheadings 'Intervention' and 'Comparator' or provided matrix.

Types of outcome measures
(the following outcomes always have to be investigated: all-cause mortality, morbidity/complications, health-related quality of life, adverse events and socioeconomic costs; adverse effects have to be listed under primary outcomes)
- Primary outcomes: maximum three (no clustering of outcomes, if possible) including adverse effects
- Secondary outcomes: visible attempt to keep the number of secondary outcomes to a minimum (beware of future workload in updates if you specify many endpoints).
- Specified all outcomes and how these will be measured.
- Described appropriate time points for measurement of outcomes.
- Selected a maximum of seven important outcomes, including adverse effects, to be included in the 'Summary of findings table (s)' (see Cochrane Handbook Section 11.5.2).

Search methods for identification of studies

Electronic searches
- Minimum database set searched: *The Cochrane Library*, MEDLINE, EMBASE.
- Described <u>all</u> search strategies in the appendix 'search strategies'.
- Search strategies were signed off by the CMED's Trials Search Coordinator.
- Described databases of ongoing trials.

(Continued)

Searching other resources
- Named additional sources like reference lists of included trials and (systematic) reviews, meta-analyses and health-technology assessment reports.

Data collection and analysis

Selection of studies
- Stated that at least two authors will conduct selection of studies for inclusion in the Cochrane review, and described a strategy for resolving disagreements.

Data extraction and management
- Used the CMED appendices, additional table and 'characteristics of included studies' table and adapted these, if necessary.
- Added additional appendices, if necessary.

Assessment of risk of bias in included studies
- Stated that at least two authors will conduct the assessment of risk of bias, and described a strategy for resolving disagreements.
- Described subjective and objective outcomes for risk of bias evaluation at endpoint level.
- Methods are consistent with Chapter 8 of the Cochrane Handbook, and the CMED has approved any additional items.

Assessment of heterogeneity
- Described characteristics possibly leading to clinical heterogeneity

---

Data synthesis
- Described the methods that will be used for meta-analysis, and how results will be synthesised if meta analysis is not appropriate.

Subgroup analysis and investigation of heterogeneity
- Visible attempt to limit the number of subgroup analyses.

Sensitivity analysis
- Listed according to the CMED's template (minimum: risk of bias, statistical model, measures of effect size, published versus unpublished studies, commercially funded versus non-(commercially) funded).

Acknowledgements (see Cochrane Handbook Section 4.5)

- Acknowledged those people who contributed to the Cochrane protocol, but are not named as authors, and included the reasons for acknowledging each person (if applicable).
- Permission has been granted from all the people named to include them in this section.

Contributions of authors

- List and order of authors for citation: agreed and completed.
- Contribution of each author described (structure: First name second name colon (e.g. 'David Smith: '): contribution according to template).

Declarations of interest (see Cochrane Handbook Section 4.5)

- Completed for each author, noting present or past affiliations that may lead to a real or perceived conflict of interest, including whether authors are investigators on studies likely to be included in the review.
- If no potential conflicts are identified for a particular author, "None known" has been stated.

References

All sources of information in the Cochrane Protocol must be appropriately referenced to prevent plagiarism. Reference citation IDs and the reference list must be consistent with the Cochrane Style Guide and the CMED's Basic Style Guide. In particular, check the following items:

- References in the text: checked that a link has been created wherever a reference citation ID appears in the text of the Cochrane protocol using the 'Find and Mark Links' tool.
- References in text: grouped reference citation IDs and links in the text in alphabetical order, surrounded by round brackets and separated by semi-colons (e.g. Arosa 1991; Arosa 1996; Bartoldi 1980; Chiasson 2000).
- References to studies: none included in the Cochrane protocol.
- Additional references: reference citation IDs are in the correct format (first author or group abbreviation and year of publication, e.g. Smith 1983 or UKPDS 1990).
- Additional references: included each journal title in full, with no abbreviations (if in doubt, use right mouse-click in Journal/ Book/Source field → "Choose From List ..").
- Additional references: checked how each reference is displayed to remove unnecessary punctuation.
- Additional references: where applicable, listed the first six authors before using 'et al'.
- Additional references: written the page numbers correctly (e.g. 354-7).
- Additional references: included the date accessed in any references to web pages.
- Other published versions of this review: included references to any previous or derivative published versions of this Cochrane protocol.

Figures (see Cochrane Handbook Section 4.9 and the RevMan User Guide for specifications on size and resolution)

- Permission received to reproduce any figures included in the Cochrane protocol.
- Each figure has a brief caption describing the purpose of the figure, and acknowledging its source.
- All figures used are scaled so that a reader can see the complete picture within the RevMan window.
- All figures are of a sufficient resolution and quality for publication.

Sources of support (see Cochrane Handbook Section 4.10)

- Listed all sources of funding and in-kind support, including internal sources (e.g. the home institution of any author) and external sources (e.g. grant funding).

Appendices

The titles of any appendices are clear and informative.

All abbreviations explained and sorted in alphabetical order

Each appendix mentioned and linked in the Cochrane protocol text.

The CMED's templates used and adapted (if necessary) to your research question

Style (see Cochrane Style Guide**)**

- Proofread the Cochrane protocol carefully in accordance with the CMED's Basic Style Guide.
- If additional subheadings have been added, the appropriate heading style has been selected using the drop
· down box on the RevMan toolbar.
  - Used either UK or US English consistently throughout the review (e.g. either 'randomised' or 'randomized').
  - Explained all acronyms and abbreviations (e.g. World Health Organization (WHO)).
  - Written numbers up to and including nine as words, and numbers 10 or higher as numerals (excluding those at the start of a sentence and numbers appearing in tables or figures).
  - Included a space before and after each unit of measurement or mathematical symbol (e.g. 5 mL, P = 0.03)

Amended Cochrane Protocols (see Cochrane Handbook Chapter 3)
If you are submitting an amendment to an already published Cochrane protocol, please address these additional criteria:

- Added an event in the 'What's New' section to describe all relevant changes since the last published version of the Cochrane protocol.
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Queries or notes for the editorial office

List any technical editing queries or note any difficulties with any of the above checks.

Note: *will expand if you type in data*

CONTRIBUTIONS OF AUTHORS

A A: protocol draft, search strategy development, acquiring trial reports, trial selection, data extraction, data analysis, data interpretation, review draft and future review updates.

B B: protocol draft, search strategy development, acquiring trial reports, trial selection, data extraction, data analysis, data interpretation, review draft and future review updates.

C C: protocol draft, search strategy development, acquiring trial reports, trial selection, data extraction, data analysis, data interpretation, review draft and future review updates.

D D: protocol draft, search strategy development, acquiring trial reports, trial selection, data extraction, data analysis, data interpretation, review draft and future review updates.

E E: protocol draft, search strategy development, acquiring trial reports, trial selection, data extraction, data analysis, data interpretation, review draft and future review updates.

F F: protocol draft, search strategy development, acquiring trial reports, trial selection, data extraction, data analysis, data interpretation, review draft and future review updates.

G G: protocol draft, search strategy development, acquiring trial reports, trial selection, data extraction, data analysis, data interpretation, review draft and future review updates.

DECLARATIONS OF INTEREST

A.A.: None known.

B.B.: