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[Intervention Protocol]

Drug-eluting stents versus bare-metal stents for acute coronary syndrome

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ABSTRACT

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

To assess the benefits and harms of drug-eluting stents versus bare-metal stents in participants with acute coronary syndrome.

BACKGROUND

Description of the condition

Cardiovascular disease, in which ischaemic heart disease is the largest component, is considered to be the number one cause of death globally (Lloyd-Jones 2010; Nichols 2014; Rosamond 2008). Ischaemic heart disease is generally divided into acute coronary syndrome and stable ischaemic heart disease (Roffi 2016). The disease remains prevalent, with more than seven million people worldwide expected to develop acute coronary syndrome each year (White 2008). According to the World Health Organization (WHO), 7.4 million people died from ischaemic heart disease in 2012, representing 15% of all global deaths, with acute coronary syndrome accounting for approximately half of the deaths (Turpie 2006; WHO 2015). The in-hospital mortality rates across different countries range from 5% to 10% (Gupta 2003). Ischaemic heart disease remains increasingly prevalent and costly to treat due to an increase in life expectancy and a decrease in death rates (Cooper 2000; Schmidt 2012).

Acute coronary syndrome is a collective term for the following:

1. unstable angina pectoris (myocardial ischaemia at rest or minimal exertion in the absence of cardiomyocyte necrosis (Roffi 2016));
2. non-ST-segment elevation myocardial infarction (NSTEMI); and
3. ST-segment elevation myocardial infarction (STEMI) (Amsterdam 2014). Myocardial infarction may be recognised by clinical features, including electrocardiographic (ECG) findings, elevated values of biochemical markers (biomarkers) of

myocardial necrosis, or imaging, or pathology might define it (Thygesen 2012). The diagnosis of myocardial infarction is dependent on an elevation of the serum levels of cardiac-specific troponin I, troponin T, or the myocardial band isoenzyme of creatine kinase (CK-MB), among others (Roffi 2016). Cardiac troponin levels will usually be positive within one hour in patients with myocardial infarction when using high-sensitivity assays (Roffi 2016). If the initial test is negative, a repeat test is advisable after three hours to rule out a myocardial infarction, since in some cases, there is a delay in the elevation of the cardiac enzymes (Roffi 2016). The changes in the ST-segment reflected in an ECG provide the basis for the distinction between NSTEMI and STEMI (Roffi 2016). Compared to NSTEMI and STEMI, unstable angina pectoris presents without the characteristic rise in cardiac-specific biomarkers (Roffi 2016).
For research purposes, the causes of myocardial infarction are generally divided into five main classes (Thygesen 2012).

- Type 1: spontaneous myocardial infarction related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries often caused by coronary artery disease.
- Type 2: myocardial infarction secondary to an ischaemic imbalance, such as coronary artery spasm, coronary embolism, anaemia, arrhythmias, hypertension, or hypotension.
- Type 3: myocardial infarction with symptoms suggestive of myocardial ischaemia and resulting in sudden unexpected cardiac death when biomarker values are unavailable or unobtainable before death.
- Type 4a: myocardial infarction associated with percutaneous coronary intervention.
- Type 4b: myocardial infarction associated with stent thrombosis, as documented by angiography or at autopsy.
- Type 5: myocardial infarction associated with coronary artery bypass graft.

Major complications associated with myocardial infarction

- Life-threatening ventricular arrhythmias caused by changes in the electrophysiologic characteristics of the myocyte, electrolyte imbalance, continuous ischaemia, and variations in heart rate, which are all due to obstruction and hence reduced flow to the myocardium and myocardial necrosis (Brieger 2009; Stevenson 1989).
- Mechanical complications caused by necrosis of the myocardium, such as ventricular wall rupture, septum rupture, and papillary muscle rupture (Brieger 2009; Pohjola-Sintonen 1989; Stevenson 1989).
- Cardiogenic shock caused by failure of the ventricle to pump an adequate amount of blood leading to systemic hypotension (Brieger 2009; Stevenson 1989).
- Acute decompensated heart failure caused by impairment in systolic and diastolic function due to myocardial ischaemia (Brieger 2009).
- Depression (Thombs 2006).

A narrowing of a coronary vessel causes unstable angina due to one of five reasons:

1. non-occlusive thrombus on pre-existing plaques;
2. dynamic obstruction, i.e. coronary vasoconstriction;
3. progressive mechanical obstruction, such as restenosis after percutaneous coronary intervention;
4. inflammation or infection; and
5. secondary unstable angina due to conditions increasing the oxygen demand, such as hypertension, thyrotoxicosis, and tachycardia (Braunwald 1998; Roffi 2016). Unstable angina is associated with lower mortality compared to myocardial infarction but similar rates of re-hospitalisations; however, it may have worse quality of life (Dudas 2013; Maddox 2007; Roffi 2016). Patients with unstable angina are also at risk of cardiogenic shock (Ruiz-Bailén 2008).

Historically, the degree of luminal stenosis and the number of coronary arteries involved (single-vessel disease, double-vessel disease, or triple-vessel disease) have defined the severity of ischaemic heart disease (Ringqvist 1983). Researchers have since developed more comprehensive scorings systems (Gensini 1983; Seizer 1982). Coronary angiography score and two additional scores, i.e. vascular scoring and stenosis scoring, determine the Gensini score (Gensini 1983). The results of the coronary angiography determines the SYNTAX score and takes into account lesion complexity, lesion location, and the number of lesions (Sianos 2005). The SYNTAX score II is used to improve the decision-making in choosing between percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) for a long-term, individualised risk assessment in patients with complex ischaemic heart disease. The SYNTAX score II combines the anatomical-based SYNTAX score (Sianos 2005), as well as seven clinical variables (creatinine clearance, peripheral vascular disease, unprotected left main coronary disease, gender, chronic obstructive pulmonary disease, age, and left ventricular ejection fraction) (Farooq 2013; Sianos 2005). A glossary for medical terms is available in Appendix 1.

Description of the intervention

Percutaneous coronary intervention (PCI) is performed by inserting an access sheath into a peripheral artery (most often the femoral artery or the radial artery); a catheter is advanced, under X-ray screening, through the blood vessels to the aortic root, at the origin of the coronary arteries. Other tools such as balloons and stents can then be advanced down the artery, over a guide wire, to the location of the narrowing or blockage (Cantor 2005; Hamon 2009). Andreas Roland Grüntzig performed the first PCI in 1977 (Grüntzig 1978). PCI has since then evolved to become one of the cornerstones in the treatment of ischaemic heart disease.

PCI in patients with acute coronary syndrome can be performed both as primary and secondary (subacute and elective) PCI (Meyer 1981; Meyer 1982; Meyer 1982a; Meyer 1983). Primary PCI may be performed in the acute phase of myocardial infarction if patients present with STEMI. Patients presenting with NSTEMI or unstable angina pectoris that is characterised as high-risk acute coronary syndrome may also benefit from undergoing angiography and PCI either immediately or as part of an early (within 24 hours) invasive strategy (Hoenig 2010; Roffi 2016). The high-risk factors include haemodynamic instability, severe left ventricular dysfunction, recurrent or persistent rest angina, mechanical complications, sustained ventricular tachycardia, and dynamic ST-T wave electrocardiographic changes (Hoenig 2010).

Secondary PCI includes both subacute PCI and elective PCI. Subacute PCI is generally performed within the first 72 hours after symptom debut in patients with unstable angina pectoris or NSTEMI who are not candidates for primary PCI because of being haemodynamically stable with medical therapy and not at high risk (Breall 2016; Roffi 2016). Elective PCI is performed in patients where coronary artery bypass grafting is not indicated, as well as in patients who are dissatisfied with their quality of life because of symptoms related to ischaemic heart disease or with adverse events due to their medical treatment (Levin 2016).

The first PCI was performed by inflating a balloon at the blockage of the coronary artery to dilate the artery ('balloon angioplasty') (Grüntzig 1978; Grüntzig 1979). The healing properties of the treatment seem to be related to the PCI expanding the outer diameter of the blocked coronary artery and not by decompression of the arterial plaque (Düber 1986). Balloon angioplasty however generally did not seem to achieve a long-lasting result, with restenosis occurring over time (Dangas 2002; Puel 1988). In an attempt to keep the lumen open for longer, the next development was a small metallic scaffold called a "stent". These tubular devices are expanded over a balloon and press against the walls of the artery to keep it open (Puel 1988). These first devices were subsequently termed "bare-metal stents" (after the later introduction of "drug-eluting stents") and improved outcomes over balloon angioplasty, but still had high rates of restenosis over time (Cutlip 2002; Erbel 1998; Fischman 1994; Macaya 1996; Puel 1988; Serruys 1994; Serruys 1998).

The next stents were drug-eluting stents consisting of three main components:

1. a metal mesh;
2. an antiproliferative drug (e.g. sirolimus, paclitaxel, zotarolimus, and everolimus); and
3. a polymer used to coat the metal mesh. An antiproliferative drug to limit the excessive growth of neointima using cytotoxic or cytostatic agents, as well as a polymer to control the release of the antiproliferative drug, supplemented the metal mesh (Degertekin 2002; Fajadet 2006; Holmes 2004; Lee 2005; Morice 2002; Moses 2003; Stone 2004; Stone 2004a).

Newer drug-eluting stents have decreased strut thickness and are meant to have improved flexibility/deliverability, enhanced polymer biocompatibility/drug-eluting profiles, and superior re-endothelialisation kinetics (Serruys 2010; Stone 2010). They typically use everolimus or zotarolimus as their antiproliferative drug (Serruys 2010; Stone 2010).

The polymer-coating of the drug-eluting stents has been linked with adverse events, such as stent thrombosis (Chen 2015). Therefore, both drug-eluting stents with a biodegradable polymer as well as polymer-free drug-eluting stents have been developed. Polymer-free drug-eluting stents use the same antiproliferative drugs (such as paclitaxel or sirolimus) as the polymer drug-eluting stents (Abizaid 2010; Chen 2015).

In an attempt to further reduce the risk of restenosis, bioresorbable (also called biodegradable) stents were developed. The principal components of the bioresorbable stent are the same as the drug-eluting stents; however, in most cases, a polylactic acid mesh replaces the metal mesh (Haude 2013; Puricel 2015). The polylactic acid mesh is broken down and removed over time (Tamai 2000). The same types of drugs (everolimus, paclitaxel, sirolimus) used in drug-eluting stents along with biolimus are used in bioresorbable stents (Haude 2013; Haude 2016; Puricel 2015).

Bare-metal stents, drug-eluting stents, and bioresorbable stents are used in modern PCIs, with drug-eluting stents generally being the first choice (Windecker 2014). Guidelines recommend that acute coronary syndrome patients receive 12 months of antiplatelet therapy (aspirin and a P2Y12 receptor blocker) regardless of whether PCI is performed (Windecker 2014). The minimum length of duration for the implant of the bare-metal stents and drug-eluting stents is recommended to be one month and six months, respectively (Windecker 2014).

Adverse events associated with PCI include death, coronary artery complications (such as perforation of the artery, distal embolisation (passage of an intravascular mass, which is capable of clogging capillaries), or stent thrombosis), myocardial infarction (type four myocardial infarction) (Thygesen 2012), vascular complications (such as bleeding or infection at the access site, retroperitoneal bleeding, or atheroembolism), stroke, and acute kidney failure (Baim 1996; Cantor 1998; Stankovic 2004).

How the intervention might work

PCI aims to decrease the stenosis of the coronary artery resulting in increased blood flow to the myocardium of the heart, which is thought to limit ischaemia and potentially reinfarction. Drug-eluting stents may be more beneficial than bare-metal stents because they release antiproliferative drugs, which cause less neointimal growth (Degertekin 2002; Fajadet 2006; Holmes 2004; Lee 2005; Morice 2002; Moses 2003; Stone 2004; Stone 2004a). The new bioresorbable stents as well as the polymer-free drug-eluting stents may be even more beneficial since they remove material that has been associated with adverse events (Abizaid 2010; Chen 2015; Haude 2013; Puricel 2015).

Why it is important to do this review

The prevalence of ischaemic heart disease is considerable and causes one third of all deaths in patients over the age of 35 years (Lloyd-Jones 2010; Nichols 2014; Rosamond 2008). Beneficial treatments can therefore alleviate a considerable disease burden and healthcare cost.

Former evidence on drug-eluting stents versus bare-metal stents for acute coronary syndrome

A 2010 Cochrane Review compared drug-eluting stents with bare-metal stents in participants with both acute coronary syndrome and stable ischaemic heart disease (Greenhalgh 2010). It found no significant difference on mortality, incidence of acute myocardial infarction, or thrombosis. However, the review showed indications of beneficial effects of drug-eluting stents on target lesion revascularisation, target vessel revascularisation, and a composite outcome of cardiac events compared with bare-metal stents.

Six non-Cochrane Reviews compared drug-eluting stents with bare-metal stents in participants with ischaemic heart disease (De Luca 2012; Kastrati 2007; Roukoz 2009; Stettler 2007; Suh 2011; Zheng 2014). Three reviews included only STEMI patients (De Luca 2012; Suh 2011; Zheng 2014). Two of the reviews did not find any difference in either intervention on all-cause mortality and stent thrombosis, but they had a beneficial effect on target vessel revascularisation (De Luca 2012; Suh 2011). Suh 2011 observed improvement of recurrent myocardial infarction with drug-eluting stents, while De Luca 2012 found no effect. Zheng 2014, which included four trials, compared the effects of bare-metal stents with drug-eluting stents in STEMI participants at five-year follow-up. The review found that there was no difference in the interventions with regard to all-cause mortality and acute myocardial infarction, as well as no effect on thrombosis, except for its occurrence later than one year after PCI. Three reviews assessed the effects of drug-eluting stents versus bare-metal stents in participants with ischaemic heart disease (including STEMI, NSTEMI, unstable angina pectoris, and stable angina pectoris) (Kastrati 2007; Roukoz 2009; Stettler 2007). Of the three reviews, two compared sirolimus stents and paclitaxel stents with bare-metal stents (Roukoz 2009; Stettler 2007), while one compared only sirolimus stents with bare-metal stents (Kastrati 2007). All reviews found no statistically significant difference between drug-eluting stents compared with bare-metal stents on mortality. While Stettler 2007 found a beneficial effect in favour of the drug-eluting stents using sirolimus on myocardial infarction, they found no effect for drug-eluting stents using paclitaxel. Kastrati 2007 and Roukoz 2009 found no difference between drug-eluting stents versus bare-metal stents on myocardial infarction. All three reviews found a beneficial effect favouring drug-eluting stents on target vessel revascularisation (Kastrati 2007; Roukoz 2009; Stettler 2007).

Current guidelines on drug-eluting stents versus bare-metal stents for acute coronary syndrome

The 2011 American College of Cardiology Foundation/American Heart Association/Society for Cardiovascular Angiography and Interventions guideline recommends drug-eluting stents as a useful alternative to bare-metal stents to prevent restenosis in cases where there is an increased risk of restenosis, and the patient is likely to be able to tolerate and comply with prolonged dual antiplatelet therapy (evidence A for STEMI, evidence C for NSTEMI/unstable angina pectoris, evidence levels are explained in the Glossary, Appendix 1) (Levine 2011). The clinical situations associated with increased risk of restenosis are left main disease, small vessels, in-stent restenosis, bifurcations, diabetes, long lesions, multiple lesions, and saphenous vein grafts (Levine 2011; Levine 2016). The guideline also states that bare-metal stents should be used in patients with a high risk of bleeding; inability to comply with one year of dual antiplatelet therapy; or anticipated invasive or surgical procedures in the next year, which the 2013 American College of Cardiology Foundation/American Heart Association Guideline for the Management of ST-Elevation Myocardial Infarction also recommends (ACEP 2013; Levine 2011).

The National Institute for Health and Care Excellence (NICE) has assessed the effects of drug-eluting stents (NICE 2008). NICE recommends drug-eluting stents in cases where the target artery for treatment has less than a 3 mm calibre or the lesion is longer than 15 mm, and the price difference between drug-eluting stents and bare-metal stents is no more than £300 (GBP).

Problems with major adverse cardiac events (MACE) as an outcome

In recent years, two major reports have described and analysed several issues regarding the cardiac composite outcome MACE (Cutlip 2007; Kip 2008). The main issues regarding MACE concern the variability and lack of consistency in which outcomes are included in the composite outcome (Cutlip 2007; Kip 2008), which may lead to misleading conclusions. The main issue with MACE in this particular review is the problem with using target vessel revascularisation or target lesion revascularisation as components of MACE. There are several reasons that this is problematic. First, it is important to remember that the decision of whether or not target vessel revascularisation will be performed is based on a subjective opinion. Since both treatment providers and participants will presumably not be blinded to treatment allocation in the included trials, target vessel revascularisation and target lesion revascularisation may introduce bias. Secondly, using a composite outcome consisting of safety endpoints (death and myocardial infarction) and outcomes presumed to be a measure of procedural effectiveness (target vessel revascularisation and target lesion revascularisation) could lead to erroneous conclusions (Kip 2008). Therefore, we have decided not to use MACE as a composite out-

come. Instead, we will use a composite cardiovascular outcome consisting of cardiovascular mortality and myocardial infarction. This review is an update of a 2010 Cochrane Review that has now been divided into a review including acute coronary syndrome participants and a review including stable ischaemic heart disease participants (Greenhalgh 2010). The present review will do the following:

1. take full account of the risk of systematic errors ('bias'), design errors, and risks of random errors ('play of chance') (Higgins 2011; Jakobsen 2014; Keus 2010; Thorlund 2011; Wetterslev 2008);
2. include trials irrespective of outcome, follow-up duration, and number of participants;
3. assess outcomes at several time points and take into account the variability of the follow-up period; and
4. include all types of drug-eluting stents, including polymer-free stents and bioresorbable stents.

OBJECTIVES

To assess the benefits and harms of drug-eluting stents versus bare-metal stents in participants with acute coronary syndrome.

METHODS

Criteria for considering studies for this review

Types of studies

We will search for randomised clinical trials (both individual and cluster-randomised trials) irrespective of publication type, publication status, publication date, and language. We will either handle non-English studies internally (i.e. by the authors of this review) or enlist external experts skilled in the given language. We will report any external source of data extraction in the review.

Types of participants

We will include participants of any age with a diagnosis of acute coronary syndrome (according to the definition of the trialists).

Types of interventions

We will include any type of drug-eluting stents, including bioresorbable stents and polymer-free drug-eluting stents.
We will accept any type of medical therapy as a co-intervention to percutaneous coronary intervention (PCI).
We will include any type of bare-metal stent as a control intervention.

Types of outcome measures

Primary outcomes

1. All-cause mortality.
2. Serious adverse events defined as any untoward medical occurrence that resulted in death, was life-threatening, was persistent, or led to significant disability; prolonged hospitalisation; or any medical event that had jeopardised the participant or required intervention to prevent it (ICH-GCP 1997).
3. Major cardiovascular event defined as a composite outcome consisting of cardiovascular mortality and myocardial infarction.
4. Quality of life measured on any valid scale, such as the Seattle Angina Questionnaire or 36-Item Short Form Survey (SF-36) (Ware 1992; Wyrwich 2004).

Secondary outcomes

1. Cardiovascular mortality (defined by the trialists).
2. Myocardial infarction (defined by the trialists).
3. Angina on a continuous scale, such as 'angina stability' and 'angina frequency' used in the Seattle Angina Questionnaire (Wyrwich 2004).

Exploratory outcomes

1. Stent thrombosis.
2. Target vessel revascularisation (defined by the trialists). In general, target vessel revascularisation is any repeat percutaneous intervention or surgical bypass of any segment of the target vessel (Hicks 2010).

We will narratively report adverse events, presenting them in a table.
We will conduct meta-analyses when possible of all dichotomous and continuous outcomes at the following two time points:

- outcomes assessed at maximal follow-up (this will be the time point of primary interest); and
- outcomes assessed at three months or earlier.

Search methods for identification of studies

Electronic searches

We will identify trials through systematic searches of the following bibliographic databases:

- the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library;
- MEDLINE Ovid;
- Embase Ovid;
- LILACS (Latin American and Caribbean Health Science Information Database) (BIREME);
- Science Citation Index Expanded (Thomson Reuters Web of Science);
- BIOSIS Citation Index (Thomson Reuters Web of Science).

The preliminary search strategy for MEDLINE Ovid will be adapted for use in the other databases (Appendix 2). The Cochrane sensitivity-maximising RCT filter, Lefebvre 2011, will be applied to MEDLINE Ovid, and adaptations of it will be applied to the other databases, except CENTRAL.

We will also conduct a search of the US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization International Clinical Trials Registry Platform (ICTRP) (www.apps.who.int/trialsearch). We will also search Google Scholar manually for trials not found in the preliminary search (Lefebvre 2011).

We will search all databases from their inception to the present, and we will impose no restriction on language of publication.

Searching other resources

We will identify additional trials from the reference lists of review articles and identified trials.

Data collection and analysis

We will perform the review following the recommendations of the*Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will perform the analyses using Review Manager 5 (RevMan 2014), Stata 14 (Stata 2015), and trial sequential analysis (CTU 2011).

Selection of studies

Two review authors (JF and EEN) will independently screen titles and abstracts of all of the potentially eligible trials for inclusion. We will code all of these studies as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. If there are any disagreements, we will ask a third author to arbitrate (JCJ). We will retrieve the full-text trial reports/publications, and two review authors (JF and EEN) will independently screen the full texts and identify trials for inclusion. We will report reasons for exclusion of the ineligible studies. We will resolve any disagreement through discussion, or if required, we will consult a third person (JCJ). We will identify and exclude duplicates and collate multiple reports of the same trial so that each trial, rather than each report, is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' tables.

Data extraction and management

We will use a data collection form, which we have piloted on at least one trial in the review, to collect trial characteristics and outcome data. Two review authors (JF and EEN) will extract trial characteristics from included trials. We will extract the following trial characteristics.

1. Methods: duration of the trial, details of any 'run-in' period, and date of publication.
2. Participants: number randomised, number analysed, number lost to follow up/withdrawn, mean age, sex, inclusion criteria, and exclusion criteria.
3. Interventions: intervention, comparison, concomitant medications, and excluded medications.
4. Outcomes: primary and secondary outcomes specified and collected and time points reported.
5. Notes: trial funding and notable conflicts of interest of the trial authors.

Two review authors (JF and EEN) will independently extract outcome data from included studies. We will resolve disagreements by consensus or by involving a third person (JCJ). One review author (EEN) will transfer data into the Review Manager 5 file (RevMan 2014). We will double-check that data are entered correctly by comparing the data presented in the systematic review with the study reports. A second review author will spot-check study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

Two review authors (JF and EEN) will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will resolve any disagreements by discussion or by involving another author (JCJ). We will assess the risk of bias according to the random sequence generation; allocation sequence concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective outcome reporting; and other bias sources. This is done because these components enable classification of randomised trials with a bias assessment of low, high, or unclear. Trials at high risk of bias overestimate benefits and underestimate harms (Gluud 2006; Kjaergard 2001; Lundh 2012; Moher 1998; Savović 2012; Savović 2012a; Schulz 1995; Wood 2008). For additional details on how we will assess risk of bias, see Appendix 3. We will assess risk of bias on both trial level and outcome level.

Assessment of bias in conducting the systematic review

We will conduct the review according to this published protocol and report any deviations from it in the 'Differences between protocol and review' section of the review.

Measures of treatment effect

Dichotomous outcomes

We will calculate risk ratios (RR) with 95% confidence intervals (CIs) for dichotomous outcomes.

Continuous outcomes

We will include both end scores and change scores in our analyses. We will use end scores in the analyses if both are reported. We will calculate the mean differences (MD) and the standardised mean differences (SMDs) with 95% CIs for continuous outcomes. We will use the standardised mean difference when the trials all assess the same outcome but measure it in a variety of ways, e.g. with different scales (Higgins 2011).

Dealing with missing data

We will contact investigators or study sponsors to obtain any missing data.

Dichotomous outcomes

We will not impute missing values for any outcomes in our primary analysis. In two of our sensitivity analyses, we will impute data (see Sensitivity analysis).

Continuous outcomes

We will not impute missing values for any outcomes in our primary analysis. In our sensitivity analysis for dichotomous and continuous outcomes, we will impute data (see Sensitivity analysis). If studies do not report standard deviations (SD), we will calculate them using data from the trial if possible.

Assessment of heterogeneity

We will primarily investigate forest plots to visually assess any sign of heterogeneity. We will secondly assess the presence of statistical heterogeneity by Chi^2 test (threshold $P < 0.10$) and measure the quantities of heterogeneity by the I^2 statistic (Higgins 2002; Higgins 2003). We will follow the recommendations for thresholds in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011):

- 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%: may represent considerable heterogeneity.

We will investigate possible heterogeneity through subgroup analyses. Ultimately, we may decide that we should avoid a meta-analysis (Higgins 2011).

Assessment of reporting biases

We will assess publication bias and other reporting biases by visual inspection of funnel plots for primary outcomes if we include at least 10 trials (Higgins 2011). Using the asymmetry of the funnel plot, we will assess the risk of bias.
For dichotomous outcomes, we will test asymmetry with the Harbord test, Harbord 2006, if τ^2 is less than 0.1 and with the Rücker test, Rücker 2008, if τ^2 is more than 0.1.
For continuous outcomes, we will use the regression asymmetry test (Egger 1997).

Data synthesis

Meta-analysis

We will undertake this systematic review according to the recommendations stated in the*Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), according to Keus 2010, and according to the eight-step assessment suggested by Jakobsen 2014.
We will use the statistical software Review Manager 5, provided by Cochrane, to meta-analyse data (RevMan 2014).
We will use Stata, Stata 2015, in case of zero-event trials where Review Manager 5's zero-event handling (replacing zero with a constant of 0.5) is not sufficient, e.g. in cases with a skewed number of participants between groups, which we will handle with reciprocal zero-event handling according to Sweeting 2004, and in case we need to undertake meta-regression (posthoc).
We will use trial sequential analysis (TSA) to assess and control the risk of random error. If the review does not reach the required information size, we will present TSA-adjusted confidence intervals to account for the lack of information.
If the included studies report both end scores and change-from-baseline scores, meta-analysing continuous outcomes, we will use end scores. If they report only change, we will analyse the results together with end scores (Higgins 2011a).
We will include all studies in our initial analyses and conduct a sensitivity analysis of studies at low risk of bias. If the results are similar, we will base our primary conclusions on the overall analysis. If they differ, we will base our primary conclusions on studies at low risk of bias.

Trial sequential analysis

Cumulative meta-analyses are at risk of producing random errors due to sparse data and multiple testing of accumulating data (Brok

2008; Brok 2009; Higgins 2011a; Pogue 1997; Thorlund 2009; Wetterslev 2008); therefore, TSA can be applied to control this risk (CTU 2011; www.ctu.dk/tsa;Thorlund 2011). The required information size (that is, the number of participants needed in a meta-analysis to detect or reject a certain intervention effect) can be calculated in order to minimise random errors (Wetterslev 2008; Wetterslev 2009). The required information size takes into account the event proportion in the control group, the assumption of a plausible relative risk reduction, and the heterogeneity of the meta-analysis (Wetterslev 2008; Wetterslev 2009; Turner 2013). TSA enables testing for significance each time a meta-analysis includes a new trial. On the basis of the required information size, trial sequential monitoring boundaries can be constructed. This enables one to determine the statistical inference concerning cumulative meta-analysis that has not yet reached the required information size (Wetterslev 2008).

Firm evidence for benefit or harms may be established if the trial sequential monitoring boundary is crossed before reaching the required information size, in which case further trials may turn out to be superfluous. In contrast, if the boundaries for benefit or harm are not surpassed, one may conclude that it is necessary to continue with further trials before a certain intervention effect can be detected or rejected. Firm evidence for lack of the postulated intervention effect can also be assessed with TSA. This occurs when the cumulative Z-score crosses the trial sequential monitoring boundaries for futility.

To control the risks of random error, we have used relatively conservative estimations of the anticipated intervention effect estimates (Jakobsen 2014). Large anticipated intervention effects lead to small required information sizes, and the thresholds for significance will be less strict after the information size has been reached (Jakobsen 2014).

We will analyse all primary and secondary outcomes with TSA. We will use the following assumptions.

Primary outcomes

We will estimate the diversity-adjusted required information size based on the proportion of participants with an outcome in the control group (Wetterslev 2009). We will use an alpha of 2% (Jakobsen 2014), a beta of 20%, and the diversity suggested by the trials in the meta-analysis (Jakobsen 2014).

As anticipated intervention effects for the primary outcomes in the trial sequential analysis, we will use the following relative risk reductions or increases because they seem to be the maximum realistic intervention effect estimates based on former studies, trials, and meta-analyses.

- All-cause mortality: relative risk reduction or increase of 10% (De Luca 2012; Suh 2011).
- Serious adverse events: relative risk reduction or increase of 10%.
- Major cardiovascular event defined as a composite outcome consisting of cardiovascular mortality and myocardial infarction: relative risk reduction or increase of 10% (De Luca 2012; Suh 2011).
- Quality of life measured on any valid scale, such as the Seattle Angina Questionnaire or SF-36: we will use the observed SD, a clinically relevant mean difference equal to SD/2.

Secondary outcomes

We will estimate the diversity-adjusted required information size based on the proportion of participants with an outcome in the control group (Wetterslev 2009). We will use an alpha of 2.5% (Jakobsen 2014), a beta of 10%, and the diversity suggested by the trials in the meta-analysis (Jakobsen 2014).

As anticipated intervention effects for the secondary outcomes in the trial sequential analysis, we will use the following relative risk reductions or increases because they seem to be realistic intervention effect estimates based on former studies, trials, and meta-analyses as cited below.

- Angina (continuous outcome): we will use the observed SD, a clinically relevant mean difference equal to SD/2.

Exploratory outcomes

- Stent thrombosis: relative risk reduction or increase of 10% (De Luca 2012; Suh 2011).
- Target vessel revascularisation: relative risk reduction or increase of 30% (De Luca 2012; Suh 2011).

As a supplementary trial sequential analysis, we will use the limit of the confidence interval closest to zero effect as the anticipated intervention effect for all trial sequential analyses (Jakobsen 2014).

Assessment of significance

We will assess our intervention effects with both random-effects meta-analyses, DerSimonian 1986, and fixed-effect meta-analyses, Demets 1987, and we will use the more conservative point estimate of the two (Jakobsen 2014). The more conservative point estimate is the estimate closest to zero effect. If the two estimates are equal, we will use the estimate with the widest confidence interval. We have four primary outcomes and will therefore consider a P value less than 2% as significant (Jakobsen 2014). We will use the eight-step procedure to assess if the thresholds for significance are crossed or not (Jakobsen 2014).

We will present a table describing the types of serious adverse events in each trial.

'Summary of findings' tables

We will use the GRADE system to assess the quality of the body of evidence associated with each of the primary outcomes (all-cause mortality, serious adverse events, major cardiovascular events, and quality of life) and secondary outcomes (cardiovascular mortality, myocardial infarction, and angina) in our review (Guyatt

2008), constructing 'Summary of findings' ('SoF') tables using the GRADEpro software (www.gradepro.org). The GRADE approach appraises the quality of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. The quality measure of a body of evidence considers within-study risk of bias, the directness of the evidence, heterogeneity of the data, precision of effect estimates, and risk of publication bias (Guyatt 2008). We will assess the precision of the effect estimates according to Jakobsen and colleagues (Jakobsen 2014). We will include all studies in our analyses and conduct a sensitivity analysis with studies at low risk of bias. If we include no studies at low risk of bias, we will conduct the sensitivity analysis with studies that have low risk of bias in all domains other than 'blinding of participants and personnel'. If the results are similar, we will base our primary 'SoF' tables and primary conclusions on the overall analysis. If they differ, we will base our primary 'SoF' and primary conclusions on studies with low risk of bias or alternatively, studies with low risk of bias in all 'Risk of bias' domains except 'blinding of participants and personnel' (Gluud 2006; Kjaergard 2001; Lundh 2012; Moher 1998; Savović 2012; Schulz 1995; Wood 2008).

Subgroup analysis and investigation of heterogeneity

We plan to carry out the following subgroup analyses.
A) Type of drug-eluting stents used:

- paclitaxel-eluting stents;
- sirolimus-eluting stents;
- zotarolimus-eluting stents;
- everolimus-eluting stents;
- bioresorbable stents;
- polymer-free drug-eluting stents; and
- mixed drug-eluting stents.

B) Unstable angina pectoris/non-ST-segment elevation myocardial infarction participants compared with ST-segment elevation myocardial infarction participants.
C) Length of maximum follow up:

- less than or equal to six months;
- between six months and 12 months;
- between one year and three years; and
- more than or equal to three years.

D) Participants with diabetes compared with participants without diabetes.
E) Participants with high risk of bleeding (as defined by trialists) compared with participants without high risk of bleeding.
F) Age of participants:

- age 0 to 18;
- age 19 to 75; and
- age 76 or above.

G) Comparison of the effect of drug-eluting stents versus bare-metal stents between trials with different clinical trial registration status:

- preregistration;
- postregistration; and
- no registration.

We will only use the primary outcomes in our subgroup analyses. We will use the formal test for subgroup differences in Review Manager 5 (RevMan 2014).

Sensitivity analysis

To assess the potential impact of bias, we will perform a sensitivity analysis where we exclude trials with an overall high risk of bias. As a secondary sensitivity analysis, we will only include trials with low risk of bias in all domains except 'blinding of participants and personnel', as we do not expect to find any trials at low risk of bias in this domain. We will thoroughly discuss the limitations of this sensitivity analysis in the discussion section (Hróbjartsson 2014; Pocock 2015).
To assess the potential impact of the missing data for dichotomous outcomes, we will perform the two following analyses.

1. 'Best-worst-case' scenario: we will assume that all participants lost to follow up in the experimental group survived, had no serious adverse event, had no major cardiovascular event, had no stent thrombosis, and had no target vessel revascularisation. We will assume that they also had a beneficial event with regard to quality of life and angina, defined as the group mean plus both one and two standard deviations of the group mean (Jakobsen 2014). We will assume that all of those with missing outcomes in the control group died, had a serious adverse event/s, had a major cardiovascular event, had stent thrombosis, and had target vessel revascularisation. We will assume that they also had a harmful event with regard to quality of life and angina, defined as the group mean plus both one and two standard deviations of the group mean (Jakobsen 2014).
2. 'Worst-best-case' scenario: we will assume that all participants lost to follow up in the experimental group died, had a serious adverse event, had a major cardiovascular event, had stent thrombosis, and had target vessel revascularisation. We will assume that they also had a harmful event with regard to quality of life and angina, defined as the group mean plus both one and two standard deviations of the group mean (Jakobsen 2014). We will assume that all of those with missing outcomes in the control group survived, had no serious adverse event, had no major cardiovascular event, had no stent thrombosis, and had no target vessel revascularisation. We will assume that they also had a beneficial event with regard to quality of life and angina, defined as the group mean plus both one and two standard deviations of the group mean (Jakobsen 2014).

We will present results from both scenarios.

To assess the potential impact of missing SDs for continuous outcomes, we will perform the following sensitivity analyses.

- Where SDs are missing and not possible to calculate, we will impute SDs from trials with similar populations and low risk of bias.
- If we find no such trials, we will impute SDs from trials with a similar population. As the final option, we will impute SDs from all trials.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Glossary

Ischaemic: reduced blood supply to an organ.
ST: ST is short for the ST-segment, which is a specific segment of the printout when recording an electrocardiogram. It is used to differentiate between ST and non-ST myocardial infarction.
Angina pectoris: medical term for chest pain or discomfort due to ischaemic heart disease.
Myocardial ischaemia: reduced blood supply to the heart.
Cardiomyocyte necrosis: undesirable death of the cells of the heart.
Non-ST-elevation myocardial infarction: a kind of heart attack which does not show ST-segment elevation on an electrocardiogram.
ST-elevation myocardial infarction: a kind of heart attack which shows ST-segment elevation on an electrocardiogram.
Troponin I: a cardiac protein which is released during a heart attack
Troponin T: a cardiac protein which is released during a heart attack
Myocardial band isoenzyme of creatine kinase (CK-MB): a specific type of the enzyme creatine kinase, which is highly specific for the heart.
Atherosclerosis: arterial wall-thickening due to build up of plaque.
Intraluminal thrombus: formation of a clot inside a vessel.
Arrhythmias: deviation from the normal heart rhythm.
Hypertension: increased pressure typically inside the arteries.
Hypotension: decreased pressure typically inside the arteries.
Percutaneous: through the skin.
Stent thrombosis: blockage of the stent by a blood clot.
Angiography: visualisation of the blood vessels typically by injection of contrast and using x-ray.
Ventricular arrhythmias: deviation from the normal heart rhythm involving the ventricles of the heart.
Myocyte: a heart muscle cell.
Continuous ischaemia: prolonged reduced blood supply (to the heart).
Myocardium: the muscle tissue of the heart.
Myocardial necrosis: death of the muscle tissue of the heart.

Acute decompensated heart failure: heart failure where the heart is unable to overcome the pressure in the blood vessels and results in symptoms such as difficulty breathing, edema, and fatigue.
Systolic: the time period in which the ventricles of the heart contract.
Diastolic: the time period in which the ventricles of the heart relax.
Nonocclusive thrombus: the blood clot does not completely prevent blood flow through the vessel.
Coronary vasoconstriction: narrowing due to muscle contraction of the blood vessels of the heart.
Restenosis: narrowing of a previously narrowed blood vessel due to a blood clot.
Thyrotoxicosis: excessive levels of the hormone produced by the thyroid gland resulting in unwanted symptoms.
Tachycardia: a faster than normal heart beat typically above 100 beats per minute.
Biolimus: the trade name of the drug Umirolimus. The mechanism of action is believed to be anti proliferation of smooth muscle cells.
Atheroembolism: embolism originating from an atherosclerotic plaque.
Retroperitoneal bleeding: bleeding behind the peritoneum, a membrane lining the abdominal cavity.
Stenosis: narrowing of a vessel.
Neointimal: scar tissue formed in a vessel after an injury.
Revascularisation: removing the cause of the stenosed blood vessel, allowing blood flow to resume.
Sirolimus stent: a stent using the sirolimus drug, a drug used in stents with the aim of reducing restenosis.
Paclitaxcel stent: a stent using the paclitaxel drug, a drug used in stents with the aim of reducing restenosis.
Bifurcation: when a blood vessel splits into two different blood vessels.
Saphenous vein grafts: when performing bypass surgery, one may use the saphenous vein (located in the leg) to bypass the occluded vessel, ultimately reestablishing heart flow.
Bioresorbable stents: stents that are absorbed after initial placement with the intent of reducing restenosis.
Percutaneous coronary intervention: an intervention where a balloon is guided up to the heart through an access sheath penetrating the skin to reduce a narrowing of a blood vessel.
Balloon angioplasty: using a balloon to open a narrowed vessel.
Re-endothelialisation: regrowth of endothelium after injury.
Everolimus: a drug used in stents with the aim of reducing restenosis.
Zotarolimus: a drug used in stents with the aim of reducing restenosis
Paclitaxel: a drug used in stents with the aim of reducing restenosis
Sirolimus: a drug used in stents with the aim of reducing restenosis
Level of evidence A: data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B: data derived from a single randomized clinical trial or large non-randomized studies.
Level of evidence C: consensus of opinion of the experts and/ or small studies, retrospective studies, registries.

Appendix 2. Preliminary MEDLINE Ovid search strategy

1. Stents/
2. stent*.tw.
3. 1 or 2
4. drug elut*.tw.
5. Sirolimus/
6. sirolimus.tw.
7. rapamycin.tw.
8. paclitaxel.tw.
9. taxol.tw.
10. exp Immunosuppressive Agents/
11. coat* stent*.tw.
12. exp Taxoids/
13. taxane*.tw.
14. qp2.tw.
15. hexanoyltaxol.tw.
16. everolimus.tw.
17. abt-578.tw.

18. Tacrolimus/
19. Dactinomycin/
20. actinomycin.tw.
21. batimastat.tw.
22. exp Dexamethasone/
23. dexamethasone.tw.
24. exp Estradiol/
25. estradiol.tw.
26. praxel.tw.
27. paxene.tw.
28. onxol.tw.
29. anzatax.tw.
30. immunosuppress*.tw.
31. prograf*.tw.
32. meractinomycin.tw.
33. cosmegen.tw.
34. dactinomycin.tw.
35. millicorten.tw.
36. maxidex.tw.
37. decaspray.tw
38. dexpak.tw.
39. dexasone.tw.
40. oradexon.tw.
41. hexadecadrol.tw.
42. decaject.tw.
43. hexadrol.tw.
44. decameth.tw.
45. methylfluorprednisolone.tw.
46. vivelle.tw.
47. oestradiol.tw.
48. estrace.tw.
49. aerodiol.tw.
50. estraderm.tw.
51. ovocyclin.tw.
52. estramustin*.tw.
53. estracyt.tw.
54. emcyt.tw.
55. tacrolimus.tw.
56. taxoids.tw.
57. zotarolimus.tw.
58. umirolimus.tw.
59. biolimus.tw.
60. pimecrolimus.tw.
61. elidel.tw.
62. or/4-61
63. 3 and 62
64. eluting stent*.tw.
65. 63 or 64
66. exp Angioplasty, Balloon, Coronary/ or exp Percutaneous Coronary Intervention/
67. balloon angioplast*.tw.
68. (percutaneous adj6 coronary intervention*).tw.
69. PCI.tw.
70. (intervention* adj6 percutaneous coronary).tw.

71. (revascularization* adj6 percutaneous coronary).tw.
72. (angioplast* adj6 coronary).tw.
73. percutaneous coronary.tw.
74. ((transluminal or trans-luminal) adj6 coronary).tw.
75. or/66-74
76. exp Myocardial Ischemia/
77. ((myocardial or myocardium or subendocardial or transmural or cardiac or cardial or coronary or heart) adj2 (infarct* or postinfarct* or hypoxi* or anoxi* or failure* or decompensation or insufficien*)).tw.
78. (heart disease* or coronary disease* or IHD or CIHD or CHD).tw.
79. (myocardial dysfunction or angina or stenocardia).tw.
80. ((ischemi* or ischaemi*) adj2 (myocardium or myocardial or heart or coronary or cardiac or cardial or subendocardial or cardiomyopath*)).tw.
81. ((artery occlusion* or artery disease* or arterioscleros* or atheroscleros*) adj2 coronary).tw.
82. or/76-81
83. Acute Coronary Syndrome/
84. exp Myocardial Infarction/
85. exp Coronary Thrombosis/
86. coronary thrombosis.tw.
87. acute coronary.tw.
88. exp Angina, Unstable/
89. myocardial infarct*. tw.
90. heart infarct*.tw.
91. acs.tw.
92. ami.tw.
93. (coronary adj3 syndrome*).tw.
94. acute angina.tw.
95. (unstable adj3 angina).tw.
96. unstable coronary.tw.
97. or/83-96
98. randomized controlled trial.pt.
99. controlled clinical trial.pt.
100. randomized.ab.
101. placebo.ab.
102. drug therapy.fs.
103. randomly.ab.
104. trial.ab.
105. groups.ab.
106. or/98-105
107. exp animals/ not humans.sh.
108. 106 not 107
109. 65 or 75
110. 82 or 97
111. 108 and 109 and 110

Appendix 3. Details on assessment of risk of bias

We will classify each trial according to the domains below for each outcome result.

Random sequence generation

- Low risk: if sequence generation is achieved using a computer random number generator or a random numbers table. We will also consider drawing lots, tossing a coin, shuffling cards, and throwing dice as adequate if an independent adjudicator performs these methods.
- Unclear risk: if there is insufficient information to permit judgement of 'low risk' or 'high risk'.
- High risk: if the allocation sequence is not randomised or only quasi-randomised.

Allocation sequence concealment

- Low risk: if the allocation of participants results from a central independent unit, on-site locked computer, identical-looking numbered sealed opaque envelopes, drug bottles or containers prepared by an independent investigator.
- Unclear risk: if there is insufficient information to permit judgement of 'low risk' or 'high risk'.
- High risk: if the allocation sequence is known to the investigators who assigned participants.

Blinding of participants and personnel

- Low risk: if the participants and the personnel are blinded to treatment allocation and this is described.
- Unclear risk: if there is insufficient information to permit judgement of 'low risk' or 'high risk'.
- High risk: if blinding of participants and personnel is not performed.

Blinding of outcome assessment

- Low risk: if the trial investigators performing the outcome assessments, analyses, and calculations are blinded to the intervention.
- Unclear risk: if there is insufficient information to permit judgement of 'low risk' or 'high risk'.
- High risk: if blinding of outcome assessment is not performed.

Incomplete outcome data

- Low risk: (1) there are no dropouts or withdrawals for all outcomes, or (2) the numbers and reasons for the withdrawals and dropouts for all outcomes are clearly stated, can be described as being similar in both groups, and the trial handles missing data appropriately in intention-to-treat analysis using proper methodology, e.g. multiple imputations*. As a general rule, we will judge the trial as at low risk of bias due to incomplete outcome data if the number of dropouts is less than five per cent. However, the five per cent cut off is not definitive.
- Unclear risk: if there is insufficient information to permit judgement of 'low risk' or 'high risk'.
- High risk: the pattern of dropouts can be described as being different in the two intervention groups or the trial uses improper methodology in dealing with the missing data, e.g. last observation carried forward.

*Multiple imputation is a general approach to the problem of missing data. It aims to allow for the uncertainty about the missing data by creating several different plausible imputed data sets and appropriately combining results obtained from each of them. The first stage is to create multiple copies of the dataset, with the missing values replaced by imputed values. These are sampled from their predictive distribution based on the observed data; thus, multiple imputation is based on a bayesian approach. The imputation procedure must fully account for all uncertainty in predicting the missing values by injecting appropriate variability into the multiple imputed values. The second stage is to use standard statistical methods to fit the model of interest to each of the imputed datasets. The estimated associations from the imputed datasets will differ and are only useful when averaged together to give overall estimated associations. Valid inferences are obtained because we are averaging over the distribution of the missing data given the observed data (Sterne 2009).

Selective outcome reporting

- Low risk: a protocol is published before or at the time the trial begins and the outcomes called for in the protocol are reported on. If there is no protocol or the protocol is published after the trial begins, reporting of the primary outcomes will grant the trial a grade of low risk of bias.
- Unclear risk: if there is no protocol and the primary outcomes are not reported on.
- High risk: if the outcomes that are called on in a protocol are not reported on.

Other bias risk

- Low risk of bias: the trial appears to be free of other components (for example, academic bias or for-profit bias) that could put it at risk of bias.
- Unclear risk of bias: the trial may or may not be free of other components that could put it at risk of bias.
- High risk of bias: there are other factors in the trial that could put it at risk of bias (for example, authors have conducted trials on the same topic, for-profit bias, etc).

Overall risk of bias

- Low risk of bias: we will classify the outcome result as overall 'low' risk of bias only if we classify all of the bias domains described in the aforementioned text as low risk of bias. Due to the nature of the PCI procedure, we do not expect to find any trials at low risk of bias. We provide a description of how we will deal with this scenario in Data synthesis.
- High risk of bias: we will classify the outcome result as 'high' risk of bias if we classify any of the bias risk domains in the aforementioned text as 'unclear' or 'high' risk of bias.

We will grade each potential source of bias as high, low, or unclear and provide a quote from the study report together with a justification for our judgment in the 'Risk of bias' table. We will summarise the 'Risk of bias' judgements across different studies for each of the domains listed. Where information on risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the 'Risk of bias' table.
When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome.

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Joshua Feinberg (JF) conceived and revised the protocol.

Emil E Nielsen (EEN) conceived and revised the protocol.

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Christian Gluud (CG) provided advice and revised the protocol.

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All authors agreed on the final protocol version.

DECLARATIONS OF INTEREST

The performance of this review is free of any real or perceived bias introduced by receipt of any benefit in cash or kind, on any subsidy derived from any source that may have or be perceived to have an interest in the outcomes of the review.

Joshua Feinberg (JF): no conflict of interest.

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