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Prophylactic corticosteroids for paediatric heart surgery with cardiopulmonary bypass (Protocol)

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[Intervention Protocol]

Prophylactic corticosteroids for paediatric heart surgery with cardiopulmonary bypass

Ben Gibbison¹, José Carlos Villalobos Lizardi², Karla Isis Avilés Martínez², Daniel P Fudulu³, Miguel Angel Medina Andrade⁴, Giordano Pérez-Gaxiola⁵, Alvin WL Schadenberg⁶, Serban C Stoica⁷, Stafford L Lightman⁸, Gianni D Angelini³, Barnaby C Reeves⁹

¹Department of Cardiac Anaesthesia and Intensive Care, Bristol Heart Institute/University Hospitals Bristol NHS FT, Bristol, UK. ²Emergency Pediatric Department, Hospital Civil de Guadalajara “Fray Antonio Alcalde”, Guadalajara, Mexico. ³Department of Cardiac Surgery, University Hospital Bristol NHS Trust, Bristol, UK. ⁴Thoracic and Cardiovascular Department, Hospital Civil Fray Antonio Alcalde de Guadalajara, Guadalajara, Mexico. ⁵Evidence-Based Medicine Department, Hospital Pediátrico de Sinaloa, Culiacán, Mexico. ⁶Department of Paediatric Intensive Care, University Hospital Bristol NHS Trust, Bristol, UK. ⁷Department of Paediatric Cardiac Surgery, University Hospital Bristol NHS Trust, Bristol, UK. ⁸Henry Wellcome Laboratories for Integrative Metabolism and Neuroscience, University of Bristol, Bristol, UK. ⁹School of Clinical Sciences, University of Bristol, Bristol, UK

Contact address: Ben Gibbison, Department of Cardiac Anaesthesia and Intensive Care, Bristol Heart Institute/University Hospitals Bristol NHS FT, 7th Floor Queens Building, Bristol Royal Infirmary, Bristol, BS2 8HW, UK. ben.gibbison@bristol.ac.uk.

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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 prophylactic corticosteroids in children between birth and 18 years of age undergoing cardiac surgery with cardiopulmonary bypass.

BACKGROUND

Description of the condition

Paediatric heart surgery outcomes have improved markedly over time as a result of marginal gains in training, technology and safety systems (Brown 2015; Hoashi 2015; Jacobs 2016; NICOR 2016). This improvement has been particularly notable in the last 20 years: the publication of heart surgery outcomes after the Kennedy Inquiry in the UK has been associated with a large increase in survival for risk-adjusted surgery (Kennedy 2001; Grant 2013).

This has been mirrored worldwide (Brown 2015; Hoashi 2015; Jacobs 2016). One area where there is still controversy is corticosteroid use. Paediatric heart surgery with the use of cardiopulmonary bypass results in a systemic inflammatory response; corticosteroids have been widely used to mitigate the potential deleterious effects of this response. The surgical intervention for which corticosteroids are used includes a variety of surgeries performed on the heart and great vessels. In most cases this procedure aims to correct congenital heart diseases (i.e. heart malformations that the child is born with). In most cases (78% in the UK) (NICOR 2016), surgery will take place with the use Cardio-Pulmonary By-

pass (CPB), also known as the 'heart-lung machine'. Cannulae are placed in the child's major blood vessels and blood is channeled out of the body, oxygen is added, carbon dioxide is removed and the blood is then pumped back to the child's body. This allows the heart to be stopped and emptied of blood, thus allowing the surgeon to operate in a bloodless field on a non-beating heart (Barry 2015). As a result, there is activation of white blood cells and platelets, as well as coagulation cascades (Tarnok 2001), with the end signalling due to cytokines. Endothelial permeability increases and parenchymal damage by free radicals occurs (Fudulu 2016; Pesonen 2016). Fluid leaks out of the circulation and into the tissues, blood vessels vasodilate, hypovolaemia occurs and thus poor blood pressure results. Many of the complications of cardiac surgery, including multi-organ failure and death, result from these mechanisms (Huffmyer 2015). Nevertheless, the impact of prophylactic corticosteroids on clinical outcomes following heart surgery on children remains unclear (Pasquali 2010; Keski-Nisula 2013).

Description of the intervention

Corticosteroids are hormones produced by the adrenal glands of all mammals. In humans, the naturally-occurring corticosteroid is called cortisol (hydrocortisone) (Gibbison 2013). Corticosteroids, at a molecular level, are composed of a steroid backbone plus various modifications to side-chains which can change the activity of the molecule. These modified side-chains are exploited by drug manufacturers to modify the different properties of corticosteroids. Corticosteroids are fat soluble and therefore can pass freely through cell walls to bind to their receptors, which are found inside the target cells. Once they bind to their receptor, they travel into the cell nucleus and act as a transcription factor, changing the expression of cellular proteins (Gibbison 2013). Synthetic and naturally-occurring corticosteroids can be given either before, during or after cardiac surgery to elicit the beneficial effects described in the next section (Toledo-Pereyra 1980; Pasquali 2010; Keski-Nisula 2015). In this context, they are usually given as intravenous drugs and may be given as a bolus dose or by infusion. A variety of different steroid drugs are given. Frequently given drugs include dexamethasone (Lerzo 2011), methylprednisolone (Pasquali 2012), and hydrocortisone (Robert 2015). The dose given in this context is often equivalent to 10 to 20 times the total daily amount produced by adrenal glands in normal health.

How the intervention might work

Corticosteroids have several properties that make them attractive to give during the cardiac surgical peri-operative period. In this context, their anti-inflammatory potential represents their most desired feature. Cardiac surgery, with or without the use of CPB, causes systemic inflammation by the earlier-described mech-

anisms. This leads to poor perfusion which, coupled with the effects of inflammatory mediators that occur directly to organs, can lead to organ dysfunction and potentially death (Medzhitov 2008). To the clinician the most obvious organ dysfunction is altered haemodynamics, which translates into the need to use support with inotropes and vasopressors postoperatively. The lungs are also frequently affected: the fluid that leaks out of the vessels and into the lung tissue and alveoli (air spaces) can have a negative impact on ventilation and oxygenation, thus increasing the need for mechanical ventilatory support. Many studies have shown that corticosteroids reduce the concentrations and activity of inflammatory mediators after cardiac surgery and increase the concentrations of anti-inflammatory mediators, both locally in the heart and systemically in the circulating plasma (Keski-Nisula 2013; Graham 2014; Dreher 2015; Amanullah 2016). Inducing a shift of the inflammatory balance toward the anti-inflammatory reaction is thought to, by extrapolation, reduce capillary leak, vasodilatation and organ dysfunction. Corticosteroids act directly to vasoconstrict arterioles, as well as increasing salt and water retention in the kidney. These properties therefore improve blood pressure and, potentially, organ perfusion in the short- and medium-term. They also increase blood glucose levels by breaking down fats, proteins and carbohydrates into their constituent building blocks, which can be used for cellular energy.

Why it is important to do this review

Many corticosteroid studies are powered for and assess surrogate outcomes, such as inflammatory mediator levels, rather than objective clinical outcomes. Corticosteroids have several deleterious effects, which are traded off against the potentially beneficial effects outlined earlier. The increase in blood glucose is associated with less favourable outcomes after cardiac surgery (Pasquali 2010). In the critically ill, they impair wound healing and cause immunosuppression, which may allow secondary infections to develop (Pasquali 2012). Several studies also suggest that giving high-dose corticosteroids to a child may impair long-term cognitive development (Gibson 1993; Shinwell 2000; Yeh 2004). The neonatal population represents a group of particular interest, as the evidence for corticosteroid use remains inconclusive. Despite the lack of certainty over its risks and benefits, its use is still common practice in many centres. There is no consensus about whether to give corticosteroids or not (Fudulu 2018), or about the type of corticosteroids, dose regimen or when they may be beneficial, e.g. pre-operatively versus intraoperatively versus postoperatively. There are no national or international guidelines pertaining to corticosteroid use in the paediatric cardiac surgical perioperative period. Practice varies both between and within institutions; patients in one hospital may or may not receive corticosteroids depending on the treating surgeon/anaesthetist/intensivist.

OBJECTIVES

To assess the benefits and harms of prophylactic corticosteroids in children between birth and 18 years of age undergoing cardiac surgery with cardiopulmonary bypass.

METHODS

Criteria for considering studies for this review

Types of studies

We will include individually randomised controlled trials (RCTs), including trials with more than two groups (e.g. multi-drug or dose comparisons with a control group) but not 'head-to-head' trials without a placebo or no corticosteroids group. If we find any cross-over randomised studies, we will only include the initial period in our analyses. This Cochrane Review will examine the effect of prophylactic corticosteroids in the perioperative period and therefore it would be extremely difficult/impossible to design a crossover study reporting clinical outcomes examining this intervention. We will exclude any cluster-randomised studies we find; they would be subject to significant bias in this context because the perioperative protocols and workloads will differ widely between centres. Patients may therefore appear to be well-matched between groups with regard to demographics, but not to many other areas. We will include studies irrespective of their publication status.

We considered using large, published registry studies, but there is likely to be a critical risk of confounding in these study groups because the factors that cause clinicians to prescribe steroids prophylactically are not captured due to the difficulty in defining and documenting those reasons. Also, publications arising from registries have reported the same outcomes as reported in RCTs (e.g. mortality and hospital length of stay, so duplication of outcome domain but with lower confidence in the effect estimate); there would be more justification in including such studies if they reported rare or long-term outcomes such as cognitive function, which would complement outcomes reported in RCTs in an important way (Reeves 2013).

Types of participants

We will include children, from birth up to 18 years of age, including preterm infants undergoing cardiac surgery with the use of cardiopulmonary bypass. We will exclude studies that have included participants with any of the following co-morbidities/characteristics. If patient level data is available, we will only exclude patients with the following criteria.

- Undergoing heart or lung transplantation, or both
- On pre-existing corticosteroids

- With abnormalities of the hypothalamic-pituitary-adrenal (HPA) axis
- Given steroids at the time of cardiac surgery for indications other than cardiac-surgery (e.g. allergy, bronchoconstriction)

If any study includes only a subset of eligible patients, we will attempt to contact the study authors and obtain patient level data or aggregated data for the eligible subgroup. If this is not possible, then we will include a study if 80% or more of the participants satisfy our eligibility criteria. We have set this threshold on the assumption that up to 20% of ineligible participants would not markedly bias the average estimate. We recognise that this rule represents an uncertain compromise; the number of potential studies (and therefore participants) is likely to be small and this approach trades off the risk of a slightly biased answer against an answer that is too imprecise to be useful.

Types of interventions

Corticosteroids must be administered prophylactically, i.e. in anticipation of adverse effects of cardiac surgery. The corticosteroids can be administered at any point in the preoperative, intraoperative or postoperative period, but the time-point and regimen must be prespecified and given to all eligible participants randomised to the intervention arm (apart from protocol deviations). We will include studies that include single and multiple doses and all types of corticosteroids administered via any route. Corticosteroids drugs include: hydrocortisone, dexamethasone, prednisolone, prednisone and methylprednisolone or any other existing drugs/those to be developed.

We will exclude studies that evaluate the effectiveness of 'rescue' corticosteroids (i.e. given in response to a clinical deterioration). We will include studies that evaluate prophylactic corticosteroids which allow for 'rescue' corticosteroids to be given to treat patients who deteriorate.

We will include trials that compare any corticosteroids with placebo or usual care without the use of corticosteroids. We will also include multi-group studies comparing multiple doses, drugs or regimen of corticosteroids against a placebo/no corticosteroids control.

Types of outcome measures

Primary outcomes

- In-hospital, postoperative mortality
- Duration of postoperative mechanical ventilation (days)

An initial scoping search identified relatively few RCTs with relatively small numbers of participants. There may not be sufficient power when the data are pooled to detect a difference in postoperative mortality due to the low baseline mortality rate. Therefore, we have included a second, continuous primary outcome which, if

reported for a similar number of participants, should have greater power. Postoperative mechanical ventilation is an important outcome due to the risk of complications both directly attributable to the process itself and because, by definition, the patient must be treated on an intensive care unit (a proxy marker for critical illness) whilst receiving it.

Secondary outcomes

- Length of postoperative intensive care unit stay
- Length of postoperative hospital stay
- All-cause mortality at longest follow up
- Cardiovascular mortality at longest follow up
- Duration of postoperative inotropes/vasopressors
- Failure to separate from cardiopulmonary bypass
- Adverse events.

There is little consistency about the adverse events attributed to steroid use that clinicians regard as important in terms of both type of adverse event and the definitions and thresholds for reporting. Therefore, the adverse events that are reported by clinical trials are not consistent. They include outcomes such as infection, hyperglycaemia and poor wound healing. Such outcomes have never been universally defined. We anticipate that it may not be possible to fully provide adverse event data across the RCTs. We will however, collect all available data and review this. Where appropriate (similar definitions across studies) we will pool this and report it in the meta-analysis.

Reporting one or more of the outcomes listed here in the trial is not an inclusion criterion for the review. We will decide study eligibility according to the eligibility of the population studied and the intervention evaluated.

Search methods for identification of studies

Electronic searches

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

- Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library
- MEDLINE (Ovid)
- Embase (Ovid)
- Web of Science CPCI-S (Conference Proceedings citation index-science).

We will adapt the preliminary search strategy for MEDLINE (Ovid) ([Appendix 1](#)) for use in the other databases. We will apply the Cochrane sensitivity-maximising RCT filter to MEDLINE (Ovid) ([Lefebvre 2011](#)), and adaptations of it to the other databases, except CENTRAL.

We will also conduct a search of ClinicalTrials.gov (www.ClinicalTrials.gov) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) Search Portal (<http://apps.who.int/trialsearch/>), ISRCTN Registry (www.isrctn.com) and the European Union Clinical Trials Register (www.clinicaltrialsregister.eu) for ongoing or unpublished trials.

We will search all databases from 2000 to the present and will impose no restriction on language of publication or publication status. Thirty-day mortality has reduced remarkably in paediatric cardiac surgery (by around one-quarter to one-half in the UK, the USA and Japan) ([Brown 2015](#); [Hoashi 2015](#); [Jacobs 2016](#); [NICOR 2016](#)). Studies before 2000 would be weighted disproportionately because of the higher death rates. Changes in clinical practice also make older studies less relevant to current practice. See also [Sensitivity analysis](#).

We will not perform a separate search for adverse effects of corticosteroid use in paediatric cardiac surgery. The search strategy should capture studies reporting beneficial or detrimental outcomes with equal likelihood.

Searching other resources

We will check the reference lists of all included studies and any relevant systematic reviews identified for additional references to RCTs and will include them if eligible. We will also examine any relevant retraction statements and errata that apply to otherwise included studies. We will make every attempt to contact study authors for any missing data.

Data collection and analysis

Selection of studies

Two review authors (AWLSS, KIAM) will independently screen titles and abstracts retrieved by the literature searches to identify potentially eligible studies, and will code them as either 'obtain full text' (eligible or potentially eligible/unclear) or 'do not obtain full text'. If there are any disagreements, we will ask a third review author to arbitrate (BCR). We will retrieve the full-text study reports/publication and three review authors (BG, JCVS, KIAM) will screen batches of full-text articles in teams of two review authors to identify studies for inclusion. We will list all studies excluded after full-text assessment and their reasons for exclusion. We will resolve any disagreement through discussion or, if required, we will consult a fourth review author (GPG). We will identify duplicate reports of studies and collate multiple reports of the same study so that each study, 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 a 'Characteristics of excluded studies' table.

Data extraction and management

We will use a data collection form piloted on at least one study included in the review to record study characteristics and outcome data. Two review authors (DPF, JCVL) will independently extract study characteristics from included studies. We will resolve any differences in data extraction by discussion with a third review author (BG). The original extraction files will be retained and a third consensus file produced with discrepancies resolved. We will extract the following study characteristics.

- Methods: total duration of study, number of study centres and location, study setting, withdrawals and date of study.
- Participants: number randomised, number lost to follow-up/withdrawn, number analysed, mean age, age range, sex, inclusion criteria and exclusion criteria. Where reported we will attempt to extract the underlying cardiac pathology.
- Interventions: intervention(s), comparator, concomitant medications (by group).
- Outcomes: the primary and secondary outcomes specified and collected, and time points at which they were reported.
- Notes: funding for trial and notable conflicts of interest of authors of included studies.

One review author (BG) will transfer data into the Review Manager 5 (RevMan 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 (GPG) will spot-check study characteristics for accuracy against the reports of included studies.

Assessment of risk of bias in included studies

Two review authors (BCR, MAMA) will independently assess the risk of bias for each included study using the 'Risk of bias' tool Version 2.0 as described in *Cochrane methods for individually RCTs* ([Higgins 2016](#); see [Types of studies](#)). This is an updated version of the tool contained in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2017](#)). We will resolve any disagreements by discussion or by involving another review author (KA). We will assess the risk of bias according to the following domains.

- Bias arising from the randomisation process.
- Bias due to deviations from intended interventions.
- Bias due to missing outcome data.
- Bias in measurement of the outcome.
- Bias in selection of the reported result.

We intend to assess risk of bias in the effect of assignment to intervention (i.e. following an intention-to-treat approach). For each outcome, review authors' answers to signalling questions (supported by quotes from the study where possible) will classify the risk of bias in each domain as high, low or some concerns. The assessment tool will also assign an overall risk of bias (across domains) for the outcome. We will summarise the risk of bias judgements across different studies for each of the domains, and overall,

for the outcomes assessed. We will enter review authors' responses to signalling questions and 'Risk of bias' judgements into the Excel implementation of the tool, including free-text explanations for these responses. 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 (see below: [Sensitivity analysis](#)).

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

We will analyse dichotomous data as odds ratios (OR) or risk ratios (RR) with 95% confidence intervals (CIs) and continuous data as mean difference (MD) or standardised mean difference (SMD) values with 95% CIs. RRs would be broadly preferred; we can calculate these from reported numerators and denominators. However, we may want to analyse adjusted effects (e.g. for baseline imbalances, which may arise in small trials). In this case, then we will use the reported effect sizes and standard errors rather than the reported numerators and denominators. The primary analysis will estimate RRs using numerators and denominators. A secondary analysis may report ORs if researchers report adjusted analyses using ORs. We will use MD values when studies report an outcome in consistent units. We will use SMD when studies report an outcome in varying scales.

We will enter data presented as a scale with a consistent direction of effect.

In the event of skewed data, we will attempt to transform data from all studies and perform meta-analysis on the transformed data. Where transformation of all data is not available, we will narratively describe skewed data, preferably as medians and interquartile ranges.

Unit of analysis issues

If any multi-arm studies meet the inclusion criteria of this review, then we will merge studies where the patient has received the intervention of prophylactic corticosteroids, regardless of specific corticosteroid or dose. We will merge multiple follow-up times.

Dealing with missing data

We will apply standard statistical formulae to calculate missing parameter estimates, wherever possible (e.g. using the RevMan 5 calculator to compute the standard deviation of an estimate from

other report information such as the CI or exact P values). We will try to contact investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data (e.g. when a study is identified only as an abstract, or when a publication states clearly that a review outcome was measured but is not reported). Where this is not possible, and the missing data are thought to introduce serious bias, we will explore the impact of including such studies in the overall assessment of results by a [Sensitivity analysis](#) (see below).

Assessment of heterogeneity

We will use the I^2 statistic to describe heterogeneity among the treatment effects included in each analysis. We will follow the guidance outlined in Section 9.5.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017)

- 0% to 40%: might not be important
- 30% to 60%: may represent moderate heterogeneity*
- 50% to 90%: may represent substantial heterogeneity*
- 75% to 100%: considerable heterogeneity*

*The importance of the observed value of the I^2 statistic depends on (i) magnitude and direction of effects and (ii) strength of evidence for heterogeneity (e.g. P value from the Chi^2 test, or a CI for the I^2 statistic). If our I^2 statistic value indicates that heterogeneity is a possibility and either the Tau^2 is greater than zero or the P value is low (less than 0.10), heterogeneity may be due to a factor other than chance.

We will also assess forest plots visually for signs of heterogeneity (i.e. by comparing CIs and directions of effect).

If we identify substantial heterogeneity (see notes on interpreting the I^2 statistic value above), we will report it and explore possible causes by prespecified subgroup analyses (see [Subgroup analysis and investigation of heterogeneity](#)).

If we identify major methodological or statistical heterogeneity (I^2 statistic > 75% which is not reduced after exploration), we will not pool results into a meta-analysis. Instead, we will display a forest plot without a pooled estimate and group trials with similar populations and interventions together to attempt to identify reasons for heterogeneity, acknowledging that important aspects of these elements of the research question may co-vary.

Assessment of reporting biases

For all analyses in which treatment effects from 10 or more RCTs are synthesised, we will create and examine a funnel plot to explore possible small study biases for the primary outcomes.

Data synthesis

We will undertake meta-analyses only where this is meaningful i.e. if the treatments, participants and the underlying clinical question

are similar enough for pooling to make sense. If there is unexplained heterogeneity, we will display the forest plot and I^2 statistic, but without a pooled estimate.

We will use a random-effects model. We are evaluating a drug treatment which should be, in principle, homogeneous and thus a fixed-effect model could be used. In this case, however, there will be differences in the specific drug used and the timing and dose, plausibly introducing heterogeneity between reported treatment effects. A random-effects model will tend to make a pooled estimate more uncertain.

'Summary of findings' table

We will create a 'Summary of findings' table (see [Table 1](#)) using the following outcomes.

- In-hospital, post-operative mortality
- Duration of post-operative mechanical ventilation
- Length of post-operative intensive care unit stay
- Length of post-operative hospital stay

The above list does not include an explicit primary harm outcome for the reasons described above (see [Types of outcome measures](#)). Nevertheless, important harms might be expected to be reflected in the outcomes that steroids are hypothesised to benefit.

We will use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence as it relates to the studies that contribute data to the meta-analyses for the pre-specified outcomes. We will use methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017) using GRADEpro software (GRADEpro 2015). There is only one comparison (corticosteroids vs placebo) for which we will generate 'Summary of findings' table. We will justify all decisions to downgrade the quality of the evidence using footnotes and we will make comments to aid reader's understanding of the review where necessary.

Two review authors (JCVL, AWLS) will independently assess the quality of the evidence. We will resolve any disagreements by discussion or involving a third review author (GPG). Judgements will be justified, documented and incorporated into reporting of results for each outcome.

We plan to extract study data, format our comparisons in data tables and prepare a 'Summary of findings' table before writing the results and conclusions of our review. A template Summary of findings table is in the Additional tables section.

Subgroup analysis and investigation of heterogeneity

If there is sufficient data, then we will perform the following subgroup analysis.

- Age: from birth to \leq 30 days/from 30 days to 18 years
- Route of administration (intravenous or oral)

- Timing of administration (preoperative, intraoperative or postoperative)

Sensitivity analysis

We will use sensitivity analysis to assess the robustness of the results and for situations where it might affect the interpretation of significant results. The sensitivity analysis will allow us to evaluate the impact of including studies at risk of bias or missing data such as impact of borderline decisions. We plan to carry out the following sensitivity analyses.

- Only including studies with a low risk of bias. We will only consider the following bias domains when classifying studies as being at low risk of bias, or not: bias due to confounding; bias arising from the randomisation process; bias due to deviations from the intended interventions; bias due to missing outcome data; bias in measurement of the outcome; bias in selection of the reported result. With respect to bias due to deviations from the intended interventions and bias in measurement of the outcome, we will consider all studies to be at low risk for mortality.
- If we believe that there is large amount of missing data that will lead to serious bias, then we will explore the impact of including such studies by a sensitivity analysis ([Dealing with missing data](#)).

We will assess the overall risk of bias using the ‘Risk of bias’ Version 2.0 tool ([Higgins 2016](#)). Low risk of bias is defined as ‘low risk of bias’ in all domains for this outcome.

As described above, the improvement in cardiac surgery mortality over the last two decades may lead to a decrease in mortality for the control during the period specified by our search strategy (2000 to present, noting that surgery may have been considerably earlier in a study published in 2000). If we observe this relationship,

a further sensitivity analysis will consider the impact of down-weighting older studies (e.g. 2000 to 2005 versus 2006 to present) according to the mortality in the control group. To ensure that this sensitivity analysis has reasonable power, we will need to consider the distribution over time of participants in included RCTs as well as changes in mortality since 2000 to set a cut-off for down-weighting some studies. We envisage that “2000 to 2005” and “2006 to present” may represent a reasonable split. We will use STATA for this analysis since it allows for variable weighting of observations in meta-analyses (“metan” command; the “iweights” option will be used, specifying differential iweights for earlier (0.X) and more recent (1.0) studies; X will be chosen as the inverse of the ratio of the risks of the aggregate primary outcome frequencies in early and recent studies).

Reaching conclusions

We will base our conclusions only on findings from the quantitative analyses of included studies. We will avoid making recommendations for practice. Similarly, implications for future research that we report will suggest priorities based on the findings or absence of findings in relation to perceived clinical priorities. They will also outline what the remaining uncertainties are in the area.

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* Indicates the major publication for the study

ADDITIONAL TABLES

Table 1. Draft ‘Summary of findings’ table

Prophylactic corticosteroids compared with placebo/care without the use corticosteroids for paediatric cardiac surgery							
Patient or population: children (aged 0 to 18 years) having cardiac surgery with cardiopulmonary bypass Setting: hospital Intervention: prophylactic corticosteroids Comparison: placebo/care without the use of corticosteroids							
Outcomes	Anticipated absolute effects*		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments	
	Risk with placebo/care without the use of corticosteroids	Risk with prophylactic corticosteroids					
In-hospital post-operative mortality	0 per 1000	0 per 1000 (0 to 0)		N in (n RCTs)			
Duration of mechanical ventilation Hours until hos-	Mean duration was [value]	The mean duration was [value] higher/lower [95% CI [value]		N in (n RCTs)			

Table 1. Draft 'Summary of findings' table (Continued)

pital discharge		to [value]]				
Length of post-operative intensive care unit stay. Days until hospital discharge	Mean duration was [value]	The mean duration was [value] higher/lower [95% CI [value] to [value]]		N in (n RCTs)		
Length of post-operative hospital stay. Days until hospital discharge.	Mean duration was [value]	The mean duration was [value] higher/lower [95% CI [value] to [value]]		N in (n RCTs)		

***The risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

Abbreviations: **CI:** confidence interval; **RR:** risk ratio; **OR:** odds ratio.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: we are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect

Very low certainty: we have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect

APPENDICES

Appendix I. Preliminary MEDLINE (Ovid) search strategy

1. exp Adrenal Cortex Hormones/
2. (corticosteroid* or steroid*).tw.
3. corticoid*.tw.
4. exp Mineralocorticoids/
5. Mineralocorticoid*.tw.
6. Glucocorticoids/
7. Glucocorticoid*.tw.
8. Hydrocortisone/
9. Hydrocortisone*.tw.
10. Dexamethasone/
11. Dexamethasone*.tw.
12. Methylprednisolone/

13. Methylprednisolone*.tw.
14. Prednisolone/
15. Prednisolone*.tw.
16. Prednisone/
17. Prednisone*.tw.
18. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19. Thoracic surgery/
20. exp Cardiovascular Surgical Procedures/
21. exp cardiac surgical procedures/
22. ((cardiac or cardiol* or heart) adj2 (surgery or surgeries or surgical or procedure* or operat*)).tw.
23. Cardiopulmonary Bypass/
24. cardiopulmonary bypass.tw.
25. cpb.tw.
26. (heart adj3 bypass).tw.
27. (cardiac adj3 bypass).tw.
28. Heart Defects, Congenital/
29. 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
30. 18 and 29
31. randomized controlled trial.pt.
32. controlled clinical trial.pt.
33. randomized.ab.
34. placebo.ab.
35. drug therapy.fs.
36. randomly.ab.
37. trial.ab.
38. groups.ab.
39. 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38
40. exp animals/ not humans.sh.
41. 39 not 40
42. 30 and 41
43. limit 42 to ed=20000101-20180814

CONTRIBUTIONS OF AUTHORS

BG, JCVL, DPF, KIAM, BCR and AWLS wrote and edited the protocol.

BG, JCVL, DPF, AWLS, and BCR assessed manuscripts for primary and secondary outcomes.

GPG, MAMA, SCS, GDA and SLL provided advice on outcomes.

DECLARATIONS OF INTEREST

BG: Dr Gibbison's institution is in receipt of project grants from the UK National Institute of Health Research and the British Heart Foundation to carry out research surrounding the topics of cardiac surgery, peri-operative care and peri-operative hypothalamic-pituitary-adrenal function including corticosteroids.

JCVL: none known.

KIAM: none known.

DPF: none known.

MAMA: none known.

GPG: none known.

AWLS: none known.

SCS: none known.

SLL: none known.

GDA: none known.

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