Interventions for investigating and identifying the causes of stillbirth (Protocol)

# Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Header</td>
<td>1</td>
</tr>
<tr>
<td>Abstract</td>
<td>1</td>
</tr>
<tr>
<td>Background</td>
<td>1</td>
</tr>
<tr>
<td>Objectives</td>
<td>3</td>
</tr>
<tr>
<td>Methods</td>
<td>3</td>
</tr>
<tr>
<td>Acknowledgements</td>
<td>8</td>
</tr>
<tr>
<td>References</td>
<td>8</td>
</tr>
<tr>
<td>Appendices</td>
<td>10</td>
</tr>
<tr>
<td>Contributions of Authors</td>
<td>10</td>
</tr>
<tr>
<td>Declarations of Interest</td>
<td>10</td>
</tr>
<tr>
<td>Sources of Support</td>
<td>11</td>
</tr>
</tbody>
</table>

Interventions for investigating and identifying the causes of stillbirth (Protocol)
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Interventions for investigating and identifying the causes of stillbirth

Aleena M Wojcieszek1, Emily Shepherd2, Philippa Middleton3, Glenn Gardener4, David A Ellwood5, Elizabeth M McClure6, Katherine J Gold7, Teck Yee Khong8, Robert M Silver9, Jan Jaap HM Erwich10, Vicki Flenady1

1Stillbirth Research Team, Mater Research Institute - The University of Queensland (MRI-UQ), Brisbane, Australia. 2ARCH: Australian Research Centre for Health of Women and Babies, Robinson Research Institute, Discipline of Obstetrics and Gynaecology, The University of Adelaide, Adelaide, Australia. 3Healthy Mothers, Babies and Children, South Australian Health and Medical Research Institute, Adelaide, Australia. 4Department of Maternal Fetal Medicine, Mater Mothers’ Hospital, Brisbane, Australia. 5School of Medicine, Griffith University, Gold Coast, Australia. 6Department of Maternal and Child Health, Research Triangle Institute, Research Triangle Park, NC, USA. 7Department of Family Medicine; Department of Obstetrics and Gynecology, University of Michigan, Ann Arbor, Michigan, USA. 8SA Pathology, Women’s and Children’s Hospital, Adelaide, Australia. 9Division of Maternal-Fetal Medicine, Health Services Center, University of Utah, Salt Lake City, Utah, USA. 10Department of Obstetrics and Gynecology, Rijks Universiteit Groningen, Groningen, Netherlands

Contact address: Aleena M Wojcieszek, Stillbirth Research Team, Mater Research Institute - The University of Queensland (MRI-UQ), Level 2 Aubigny Place, Mater Health Services, Brisbane, Queensland, 4101, Australia. aleena.wojcieszek@mater.uq.edu.au.

Editorial group: Cochrane Pregnancy and Childbirth Group.


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ABSTRACT

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

To assess the effect of different tests, protocols or guidelines for investigating and identifying the causes of stillbirth on outcomes for parents, including psychosocial outcomes, on rates of diagnosis of the causes of stillbirth, and on costs.

BACKGROUND

Description of the condition

Stillbirth is associated with profound and long-lasting adverse psychosocial outcomes for families and care providers, along with wider economic impacts on health systems and society (Heazell 2016). The global burden of stillbirth is high, with an estimated 2.6 million stillbirths (at 28 weeks’ gestation or greater) occurring every year. Although many of these deaths are preventable, global reduction in stillbirth rates remains slow and has not matched declines in maternal or child mortality (Lawn 2016). Accurate data on causes of stillbirth are limited, partly due to the difficulty in assigning causation owing to the often multifactorial circumstances (Silver 2007; Whitfield 1986). The use of various, disparate classification systems for assigning cause of death also hampers understanding of causes at the global level (Flenady 2015; Leisher 2016; Wojcieszek 2016). A recent systematic review
(Flenady 2016), showed wide variation in the reported contribution of different causes of stillbirth. For example, the proportion of stillbirths related to infection ranged from 5% to 22%, and the proportion of stillbirths related to congenital abnormalities ranged from 6% to 27%. “Unexplained” deaths were reported for up to 76% of cases, and showed particularly wide variation. Difficulties ascertaining causes of death are often compounded by limited availability of clinical information. In some low- and middle-income countries (LMICs), minimal or no diagnostic investigations are available (Flenady 2010). Despite these limitations, it is clear that over half of stillbirths globally are related to intrapartum complications, and that increased access to skilled birth attendants and emergency obstetric care could eliminate the majority of these deaths (Lawn 2016). Infection (such as malaria and syphilis) and placental conditions (such as fetal growth restriction (FGR), placental abruption, and pre-eclampsia) are other commonly reported causes of stillbirth. Pre-existing hypertension and diabetes are also important and common risk factors for stillbirth. These risk factors are often associated with obesity and advanced maternal age, which are independent risk factors for stillbirth that are increasingly common throughout the developed world (Flenady 2011). Other major risk factors for stillbirth include smoking, multiple pregnancy, previous stillbirth, primiparity (Flenady 2011), and post-term pregnancy (Flenady 2011; Lawn 2016). Although the burden of stillbirth lies predominantly in LMICs, thousands of potentially preventable stillbirths also occur in high-income countries (HICs) (Flenady 2016). In these settings, the majority of stillbirths occur in the antenatal period, and are associated with placental dysfunction (Flenady 2016). Disparities in stillbirth rates are clearly evident, with the risk of stillbirth among disadvantaged women roughly double that among more advantaged women (Flenady 2016).

**Description of the intervention**

To enable focused strategies to reduce stillbirth rates, accurate determination of causes and contributing factors is needed. To identify causes of death, collection of data related to the stillbirth, such as demographic data, maternal risk factors and labour and birth information is required (Barfield 2011; Flenady 2009). A range of diagnostic investigations, as described in further detail below, may also be recommended.

This review focuses on interventions for investigating and identifying the causes of stillbirth. Such interventions are likely to be diverse, but may include, for example:

- review of maternal and family history, and current pregnancy history;
- clinical history of present illness;
- maternal investigations (such as ultrasound, amniocentesis, antibody screening, blood grouping, etc);
- examination of the stillborn baby (including full-autopsy, partial autopsy or non-invasive components, such as magnetic resonance imaging (MRI), computerised tomography (CT) scanning, and radiography);
- umbilical cord examination;
- placental examination (including histopathology); and
- verbal autopsy (interviews with care providers and support people to ascertain causes without examination of the baby).

Among the investigations listed, autopsy is considered the ‘gold standard’ in determining causes of death (Alderliesten 2003; Lyon 2004; Rose 2006). Autopsy can identify a wide range of causes of stillbirth, including infection, anaemia, and morphologic and metabolic abnormalities (Silver 2007). However, there is variation in the reported yield of the procedure following a stillbirth (Gordijn 2002). Further, many factors influence parents’ decision regarding whether to consent to or decline autopsy (Breeze 2012), and some parents may decline the examination to avoid subjecting their baby to invasive examination (Lyon 2004). Cultural and religious practices, such as the requirement of prompt burial and/or for the baby’s body to be left undisturbed, may also influence decision-making (Gordijn 2007). While some parents later regret having or not having an autopsy of their baby (Heazell 2012; Rankin 2002), there are currently no interventions to support parents’ decision-making around this procedure (Horey 2013). Medical personnel are often reluctant to approach parents about autopsy for various reasons, including emotional burden (Khong 2010; Rose 2006) and/or because they do not believe the investigation will yield any new information (Lyon 2004; Rose 2006). Therefore, when full autopsy is not possible, alternative investigations such as fetal CT scan, fetal radiography (Lim 2005), and fetal MRI (Alderliesten 2003; Arthurs 2015) may be performed.

Alongside autopsy, examination of the placenta and testing for chromosomal abnormalities have shown high value in ascertaining causes of death (Bukowski 2011; Korteweg 2008; Korteweg 2012). Other investigations that may be included in the routine evaluation of stillbirth include (but are not limited to) maternal thyroid, liver and kidney function tests, testing for gestational diabetes (Flenady 2009), toxicology screening (to detect maternal drug use), and tests for various infections and viruses (Silver 2007). Investigations to identify maternal antibodies and blood clotting disorders (thrombophilias) may be valuable in some situations. As stated above, the ability to undertake certain investigations may be extremely limited in LMICs due to a lack of resources (Flenady 2010). In these settings, verbal autopsy (involving interviews with care providers and support people as stated above, without examination of the baby) may be relied upon as an indirect method of ascertaining cause of death (Nausheen 2013). Therefore, it is also important to identify which tests are feasible in a setting where cost and access to equipment are barriers.

**How the intervention might work**
A high-quality investigation into the causes of stillbirth will ideally place minimal emotional and financial burden on parents, staff, and health services, while maintaining high diagnostic yield (Corabian 2005; Lim 2005; Silver 2007). A number of formal protocols are currently in use to standardise investigations following stillbirth, but there is large variation in the recommended investigations (Corabian 2005). A specific comprehensive investigation protocol has previously been shown to be cost-effective when incorporated into routine stillbirth evaluation (Michalski 2002). Comprehensive investigations protocols may be advantageous where there are multiple, interacting causes which may not otherwise be detected (Silver 2007). Another approach to the workup of stillbirth is selective testing, where investigations are undertaken based on clinical features and presumed diagnosis (Flenady 2010; Lim 2005). A selective approach to investigations may reduce costs (Lim 2005), while also minimising the chance of producing positive test results that cause anxiety among parents and are unhelpful in ascertaining a cause of death (Korteweg 2012; Silver 2007). Sequential testing, where tests are undertaken based on the results of other tests, has been proposed as another alternative (Flenady 2010; Korteweg 2012). This approach suggests a platform of basic tests with follow-up investigations undertaken as indicated (Korteweg 2012). For example, while routine thrombophilia testing is not commonly recommended, it may be considered in cases where there is evidence of placental complications, such as FGR (Korteweg 2010; Silver 2007).

High-quality tests, protocols or guidelines for investigating and identifying the causes of stillbirth have substantial potential to reduce the number of unexplained deaths and misdiagnosed causes of death. Investigations may also have value in confirming clinical diagnoses, providing additional information that may not have been expected clinically (Gordijn 2002; Horn 2004), and/or excluding specific causes of death (Horn 2004; Korteweg 2012). Relying solely on death certificates to identify causes of death is problematic, as death certificates are not required for stillbirths in many LMICs (Flenady 2015). Even in developed settings, the causes of death documented on death certificates are frequently inaccurate (Cockerill 2012; Headley 2009; Measey 2007). Retrospective cohort studies have shown that the proportion of deaths initially classified as unexplained can be reduced by up to 65% following investigation and clarification (Headley 2009; Measey 2007).

Accurate identification of causes of stillbirth not only aids parents’ emotional closure, it provides a platform for clinical management in subsequent pregnancies (Flenady 2009; Michalski 2002; Silver 2007). Indeed, the need for information for planning of future pregnancies is one of the most important factors that influences parents’ decision regarding whether to have an autopsy of their baby (Breeze 2012). The identification of a known recurrent cause of death, or a death unexplained despite thorough investigation, may prompt additional testing and surveillance in subsequent pregnancies (Mistry 2013). In contrast, the identification of a known non-recurrent cause may reassure parents and spare them from unnecessary testing and intervention in subsequent pregnancies (Silver 2007). A recent UK study showed pregnancies subsequent to stillbirths that were unexplained or had known recurrent causes were £500 more costly than pregnancies subsequent to stillbirths due to known non-recurrent causes (Mistry 2013). The study suggested that while a comprehensive workup of stillbirth may bring a higher initial cost to health systems, the costs of care in subsequent pregnancies may be reduced if investigations can exclude recurrent causes and reduce unexplained deaths (Mistry 2013). Importantly, the quality of the postmortem investigation and report, regardless of the investigations performed, will impact on the likelihood of yielding clinically meaningful information (Cartlidge 1995; Corabian 2005).

Why it is important to do this review

At the heart of the prevention of stillbirth is understanding of its causes. Diagnostic investigations aim to meet this need, but there is currently no consensus on the optimal approach to the investigation of stillbirth (Korteweg 2012; Lim 2005). Accurate identification of the causes of stillbirth is of paramount importance, given that additional knowledge may allow informed counselling for parents about recurrence risks, and assist in the management of subsequent pregnancies. A wide variety of investigations are potentially available for the investigation of stillbirth. However, given their economic cost, and their potential to add further emotional burden to parents, there is a need to systematically assess the effect of these interventions on outcomes for parents, including psychosocial outcomes, and on rates of diagnosis of the causes of stillbirth.

OBJECTIVES

To assess the effect of different tests, protocols or guidelines for investigating and identifying the causes of stillbirth on outcomes for parents, including psychosocial outcomes, on rates of diagnosis of the causes of stillbirth, and on costs.

METHODS

Criteria for considering studies for this review

Types of studies

We plan to include randomised controlled trials, quasi-randomised controlled trials and cluster-randomised trials. We plan to exclude
cross-over trials. We plan to include studies published as abstract only, provided there is sufficient information to allow us to assess study eligibility.

**Types of participants**
The participants will be parents (including mothers, fathers, and partners) who have experienced a stillbirth of 20 weeks’ gestation or greater.

**Types of interventions**
We will include trials assessing any test, protocol or guideline (or combinations of tests/protocols/guidelines) for investigating the causes of stillbirth, compared with the absence of a test, protocol or guideline, or usual care (see above Description of the intervention for further details as to the types of tests or investigations that might be included in such protocols/guidelines).

We will also include trials comparing any test, protocol or guideline (or combinations of tests/protocols/guidelines) for investigating the causes of stillbirth with another (for example, the use of a limited investigation protocol compared with a comprehensive investigation protocol).

**Types of outcome measures**
No core outcomes were identified for this review topic. We therefore selected a range of important outcomes with respect to the effects of investigations.

**Primary outcomes**
- Change in the final cause(s) of death from the presumed or clinical a priori cause of death
- Final cause(s) of death unknown
- Additional parental counselling or subsequent pregnancy care information (e.g. determination of or change in recurrence risk; exclusion of suspected causes of death; exclusion of recurrent causes of death; or combination of these)
- Parental satisfaction with the process and outcomes of investigations

**Secondary outcomes**

**In postpartum period**
- Confirmation of clinical diagnosis
- Attainment of unexpected findings
- Exclusion of suspected causes of death
- Exclusion of recurrent causes of death
- Compliance with test/protocol/guideline
- Parental understanding of the cause(s) of death
- Parental regret about the investigations performed
- Parental attitudes towards process and outcomes of investigations
- Parental psychosocial outcomes including anxiety and quality of life
- Parental satisfaction with care around the time of death and at follow-up
- Care provider satisfaction with the process and outcomes of investigations
- Frequency of investigations performed, e.g. maternal and family history; maternal investigations prior to delivery; stillborn examination; umbilical cord examination; placental examination
- Costs of investigations

**In subsequent pregnancy**
- Stillbirth
- Neonatal death
- Preterm birth
- Induction of labour
- Caesarean birth
- Low birthweight
- Parental anxiety
- Costs of the subsequent pregnancy

**Search methods for identification of studies**
The following methods section of this protocol is based on a standard template used by Cochrane Pregnancy and Childbirth.

**Electronic searches**
We will search Cochrane Pregnancy and Childbirth’s Trials Register by contacting their Information Specialist. The Register is a database containing over 22,000 reports of controlled trials in the field of pregnancy and childbirth. For full search methods used to populate Pregnancy and Childbirth’s Trials Register including the detailed search strategies for CENTRAL, MEDLINE, Embase and CINAHL; the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service, please follow this link to the editorial information about Cochrane Pregnancy and Childbirth in the Cochrane Library and select the ‘Specialized Register’ section from the options on the left side of the screen.

Briefly, the Cochrane Pregnancy and Childbirth’s Trials Register is maintained by their Information Specialist and contains trials identified from:
1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE (Ovid);
3. weekly searches of Embase (Ovid);
4. monthly searches of CINAHL (EBSCO);
5. handsearches of 30 journals and the proceedings of major conferences; and
6. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Search results are screened by two people and the full text of all relevant trial reports identified through the searching activities described above is reviewed. Based on the intervention described, each trial report is assigned a number that corresponds to a specific Pregnancy and Childbirth review topic (or topics), and is then added to the Register. The Information Specialist searches the Register for each review using this topic number rather than keywords. This results in a more specific search set that will be fully accounted for in the relevant review sections (Included, Excluded, Awaiting Classification or Ongoing).

In addition, we will search ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) for unpublished, planned and ongoing trial reports using the terms given in Appendix 1.

Searching other resources
We will search the reference lists of retrieved studies for further eligible studies. We will not apply any date or language restrictions.

Data collection and analysis
The following methods will be used for assessing studies identified by the search.

Selection of studies
Two review authors will independently assess for inclusion all the potential studies we identify as a result of the search strategy. We will resolve any disagreement through discussion or, if required, we will consult a third review author.

We will create a Study flow diagram to map out the number of records identified, included and excluded.

Data extraction and management
We will design a form to extract data. For eligible studies, two review authors will extract the data using the agreed form. We will resolve discrepancies through discussion or, if required, we will consult a third review author. We will enter data into Review Manager software (RevMan 2014) and check for accuracy. When information regarding any of the above is unclear, we will attempt to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies
Two review authors 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 disagreement by discussion or by involving a third assessor.

(1) Random sequence generation (checking for possible selection bias)
We will describe for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We will assess the method as:
- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)
We will describe for each included study the method used to conceal allocation to interventions prior to assignment and will assess whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We will assess the methods as:
- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)
We will describe for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We will consider that studies are at low risk of bias if they were blinded, or if we judge that the lack of blinding would be unlikely to affect results. We will assess blinding separately for different outcomes or classes of outcomes.

We will assess the methods as:
- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)
We will describe for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We will assess blinding separately for different outcomes or classes of outcomes.

We will assess methods used to blind outcome assessment as:
- low, high or unclear risk of bias.
(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We will describe for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We will state whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information is reported, or can be supplied by the trial authors, we will re-include missing data in the analyses which we undertake.

We will assess methods as:
- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We will describe for each included study how we investigated the possibility of selective outcome reporting bias and what we found. We will assess the methods as:
- low risk of bias (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

We will describe for each included study any important concerns we have about other possible sources of bias. We will assess whether each study was free of other problems that could put it at risk of bias:
- low risk of other bias;
- high risk of other bias;
- unclear whether there is risk of other bias.

Assessing the quality of the evidence using the GRADE approach

We will use the GRADE approach as outlined in the GRADE handbook in order to assess the quality of the body of evidence relating to the following outcomes for the main comparisons:
- change in the final cause(s) of death from the presumed or clinical a priori cause of death;
- final cause(s) of death unknown;
- additional parental counselling or subsequent pregnancy care information (e.g. determination of or change in recurrence risk; exclusion of suspected causes of death; exclusion of recurrent causes of death; or combination of these);
- parental satisfaction with the process and outcomes of investigations;
- compliance with test/protocol/guideline;
- costs of investigations; and
- stillbirth (in the subsequent pregnancy).

We will use the GRADEpro Guideline Development Tool to import data from Review Manager 5.3 (RevMan 2014) in order to create 'Summary of findings' tables. A summary of the intervention effect and a measure of quality for each of the above outcomes will be produced using the GRADE approach. The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. The evidence can be downgraded from 'high quality' by one level for serious (or by two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias.

Measures of treatment effect

Dichotomous data

For dichotomous data, we will present results as summary risk ratio with 95% confidence intervals.

Continuous data

For continuous data, we will use the mean difference if outcomes are measured in the same way between trials. We will use the standardised mean difference to combine trials that measure the same outcome, but use different methods.

Unit of analysis issues

Cluster-randomised trials

We will include cluster-randomised trials in the analyses along with individually-randomised trials. We will adjust their sample sizes using the methods described in the Handbook using an estimate of the intracluster correlation co-efficient (ICC) derived from the
trial (if possible), from a similar trial or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely.

We will also acknowledge heterogeneity in the randomisation unit and perform a sensitivity analysis to investigate the effects of the randomisation unit.

We plan to include multi-armed trials, ensuring analyses are independent. If multi-armed trials are included, we will split the ‘shared’ group into two or more groups with smaller sample size, and include two or more (reasonably independent) comparisons. Alternatively, we will combine groups to create a single pair-wise comparison.

**Cross-over trials**

We will exclude cross-over designs as these are unlikely to be a valid study design for Pregnancy and Childbirth reviews.

**Dealing with missing data**

For included studies, we will note levels of attrition. We will explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis. For all outcomes, we will carry out analyses, as far as possible, on an intention-to-treat basis, i.e. we will attempt to include all participants randomised to each group in the analyses, and all participants will be analysed in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial will be the number randomised minus any participants whose outcomes are known to be missing.

**Assessment of heterogeneity**

We will assess statistical heterogeneity in each meta-analysis using the $\tau^2$, $I^2$ and $\chi^2$ statistics. We will regard heterogeneity as substantial if an $I^2$ is greater than 30% and either the $\tau^2$ is greater than zero, or there is a low $P$ value (less than 0.10) in the $\chi^2$ test for heterogeneity.

**Assessment of reporting biases**

If there are 10 or more studies in the meta-analysis, we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually. If asymmetry is suggested by a visual assessment, we will perform exploratory analyses to investigate it.

**Data synthesis**

We will carry out our statistical analysis using the Review Manager software (RevMan 2014). We will use fixed-effect meta-analysis for combining data where it is reasonable to assume that studies are estimating the same underlying treatment effect: i.e. where trials are examining the same intervention, and the trials’ populations and methods are judged sufficiently similar. If there is clinical heterogeneity sufficient to expect that the underlying treatment effects differ between trials, or if substantial statistical heterogeneity is detected, we will use random-effects meta-analysis to produce an overall summary, if an average treatment effect across trials is considered clinically meaningful. The random-effects summary will be treated as the average of the range of possible treatment effects and we will discuss the clinical implications of treatment effects differing between trials. If the average treatment effect is not clinically meaningful, we will not combine trials. If we use random-effects analyses, the results will be presented as the average treatment effect with 95% confidence intervals, and the estimates of $\tau^2$ and $I^2$.

We plan to consider separately those trials assessing any test/protocol or guideline (or combinations of tests/protocols/guidelines) compared with no test/protocol/guideline or usual care, and those comparing different tests/protocols/guidelines.

**Subgroup analysis and investigation of heterogeneity**

If we identify substantial heterogeneity, we will investigate it using subgroup analyses and sensitivity analyses. We will consider whether an overall summary is meaningful, and if it is, use random-effects analysis to produce it. We plan to carry out the following subgroup analyses across the primary outcomes:

- number and type of investigations included in the protocol/guideline (e.g. single/limited investigation(s) recommended versus multiple/comprehensive investigations recommended);
- quality of the autopsy/postmortem report (e.g. low quality versus high quality, or not meeting a minimum standard versus meeting a minimum standard);
- presumed cause(s) of death prior to investigations: unexplained stillbirth at time of death versus stillbirth with known/presumed cause(s);
- gestational age at death: death at less than 28 weeks' gestation versus at 28 weeks' gestation or greater;
- setting: LMICs versus HICs; and
- classification systems used.

We will assess subgroup differences by interaction tests available within RevMan (RevMan 2014). We will report the results of...
subgroup analyses quoting the Chi² statistic and P value, and the interaction test I² value.

Sensitivity analysis

Sensitivity analyses will be conducted to explore the effects of trial quality and trial design on the outcomes. We will explore the effects of trial quality assessed by allocation concealment and random sequence generation (considering selection bias), by omitting studies rated as ‘high risk of bias’ (including quasi-randomised trials) or ‘unclear risk of bias’ for these components. We will investigate the effects of the randomisation unit (individual versus cluster) on the outcomes, and the impact of including studies with high levels of missing data. We will explore the effects of fixed-effect or random-effects analyses for outcomes with statistical heterogeneity, and the effects of any assumptions made such as the value of the ICC used for cluster-randomised trials. We will use primary outcomes in sensitivity analyses.

ACKNOWLEDGEMENTS

We thank the Cochrane Pregnancy and Childbirth Group for support with title registration and protocol development.

As part of the pre-publication editorial process, this protocol has been commented on by three peers (an editor and two referees who are external to the editorial team), members of the Pregnancy and Childbirth Group’s international panel of consumers and the Group’s Statistical Adviser.

This project was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to Cochrane Pregnancy and Childbirth. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

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Corabian 2005

Flenady 2009

Flenady 2010

Flenady 2011

Flenady 2015
Interventions for investigating and identifying the causes of stillbirth (Protocol)

Flenady 2016

Gordijn 2002

Gordijn 2007

Headley 2009

Heazell 2012

Heazell 2016

Higgins 2011

Horney 2013

Horn 2004

Khong 2010

Korteweg 2008

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Korteweg 2012

Lawn 2016

Leisher 2016

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Measey 2007

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Mistry 2013

Nausheen 2013

Rankin 2002

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Rose C, Evans M, Tooley J. Falling rates of perinatal postmortem examination: are we to blame?. *Archives of Disease in Childhood Fetal and Neonatal Edition* 2006;91(6):F465.

**Silver 2007**

**Whitfield 1986**

**Wojcieszek 2016**

* Indicates the major publication for the study

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**APPENDICES**

**Appendix 1. Search terms for ICTRP and ClinicalTrials.gov**

We will run each line separately and deduplicate manually:
stillbirth AND cause
stillbirth AND causes

**CONTRIBUTIONS OF AUTHORS**

Vicki Flenady, Philippa Middleton, and Aleena M Wojcieszek designed the review with contribution from all authors. Aleena Wojcieszek led the drafting of the protocol with contributions from all authors.

**DECLARATIONS OF INTEREST**

Aleena M Wojcieszek: is an associate investigator for a National Health and Medical Research Council (NHMRC) Centre of Research Excellence in stillbirth, and member of the International Stillbirth Alliance Scientific Advisory Committee executive.

Emily Shepherd: none known.

Philippa Middleton: is a chief investigator for an NHMRC Centre of Research Excellence in stillbirth.

Glenn Gardener: is an associate investigator for an NHMRC Centre of Research Excellence in stillbirth.

David A Ellwood: has received sitting fees from the Australian Medical Council but this work is not related to this Cochrane review; has received payment for providing expert witness reviews for medico-legal cases unrelated to the topic under review; is a chief investigator for an NHMRC Centre for Research Excellence in stillbirth.

Elizabeth M McClure: none known.

Katherine J Gold: serves as an unpaid board member for the International Stillbirth Alliance.

Teck Yee Khong: has received fees for expert testimony for plaintiffs and defence in obstetrics cases; royalties from book publication; expenses for attending scientific meetings of paediatric pathology societies; and holds shares in one health insurance provider listed in the Australian Stock Exchange.

Robert M Silver: is conducting NIH sponsored research investigating pregnancy as a window to future maternal health, human placental function and clinical obstetric trials. None of these directly address the work for this report; is a member of the International Stillbirth Alliance Scientific Advisory Committee executive.
Jan Jaap H.M. Erwich: is chair of a foundation for the organisation of conferences on stillbirth and perinatal death, without a fee; received funding across 2002-2006 to investigate the causes of stillbirth.

Vicki Flenady: is the lead investigator of a NHMRC Centre of Research Excellence in Stillbirth in Australia.

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