STUDY PROTOCOL

A protocol for a systematic review of clinical practice guidelines for recurrent miscarriage [version 2; peer review: 2 approved, 2 approved with reservations]

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Abstract

Recurrent miscarriage (RM) was recently re-defined by the European Society of Human Reproduction and Embryology (ESHRE) as the loss of two or more consecutive pregnancies. Before this, and indeed still in some countries, RM was defined as three or more consecutive pregnancy losses. While the incidence of RM depends on the definition employed and population studied, it is generally accepted to affect 1-6% of women of reproductive age. Clinical practice guidelines (CPGs) for RM have been published by some professional organisations. While there are CPGs on miscarriage in Ireland, there are none concerning RM specifically. The aim of this systematic review is to identify, appraise and describe published CPGs for the management, investigation and/or follow-up of RM within high-income countries. Electronic databases (MEDLINE (Ovid®; 1946), Embase® (Elsevier; 1980), CINAHL Complete (EBSCOhost; 1994), Web of Science™ (Thomson Reuters), Scopus (Elsevier; 2004), and Open Grey (INIST-CNRS; 2011)), selected guideline repositories, and the websites of professional societies will be searched to identify CPGs, published within the last 20 years, for potential inclusion. Two reviewers will review abstracts and full texts independently against the eligibility criteria. Characteristics and recommendations of included CPGs will be extracted by one reviewer and double-checked by another. Two reviewers will use the Appraisal of Guidelines for Research and Evaluation version 2 (AGREE II) instrument independently to assess the quality of the included CPGs. Narrative synthesis will be conducted to appraise and compare CPGs and their

Open Peer Review

Reviewer Status ✔ ✔ ? ?

Invited Reviewers

1. Merel M. J. van den Berg, University of Amsterdam, Amsterdam, The Netherlands
2. Jennifer Kaiser, University of Utah School of Medicine, Salt Lake City, USA
3. Emma Rasmak Roepke, Lund University, Lund, Sweden
4. Matthew Coleman, University of
recommendations or guidance therein. The identification, appraisal and description of published CPGs in other high-income countries will be a valuable first step in informing efforts to promote the optimisation and standardisation of RM care.

**Keywords**
recurrent miscarriage, miscarriage, early pregnancy loss, systematic review, clinical guidelines, antenatal, care quality

This article is included in the Maternal and Child Health collection.

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**Author roles:** Hennessy M: Conceptualization, Methodology, Writing – Original Draft Preparation, Writing – Review & Editing; Dennehy R: Writing – Review & Editing; Meaney S: Conceptualization, Funding Acquisition, Methodology, Supervision, Writing – Original Draft Preparation, Writing – Review & Editing; Devane D: Conceptualization, Funding Acquisition, Methodology, Writing – Review & Editing; O’Donoghue K: Conceptualization, Funding Acquisition, Methodology, Supervision, Writing – Original Draft Preparation, Writing – Review & Editing

**Competing interests:** No competing interests were disclosed.

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Revised Amendments from Version 1

We have removed reference to “unpublished” after “grey” literature to avoid confusion as to the consistency of the search strategy and eligibility criteria outlined in the PICAR statement in Table 1. Grey literature will be used to identify CPGs that may meet the eligibility criteria for this review. We have added clarification about sources and use of grey literature to the information sources section: “Searches of Web of Science, Scopus and Open Grey, as well as guideline repositories and the websites of professional bodies/organisations, will facilitate the identification of grey literature – such as conference proceedings and/or technical reports – which may contain information about potentially eligible CPGs.”

Any further responses from the reviewers can be found at the end of the article

Abstract

Purpose

To describe recommendations from the included CPGs and to appraise the quality of included CPGs using the Appraisal of Guidelines for Research and Evaluation version 2 (AGREE II) instrument.

Methods

We will conduct a systematic review of CPGs and include all CPGs of any type (for example, guidelines, protocols) and any language. CPGs will be identified through a search of grey literature, CPGs will be assessed for eligibility using the PICAR statement and will be included if they meet the eligibility criteria outlined in Table 1. CPGs will be appraised using the AGREE II instrument and will be synthesised thematically. The findings will be reported using the MOOSE checklist.

Eligibility criteria

We will include any CPGs that meet the eligibility criteria outlined in Table 1. The PICAR statement will be used to assess the eligibility of CPGs and will be included if they meet the eligibility criteria outlined in Table 1. CPGs will be appraised using the AGREE II instrument and will be synthesised thematically. The findings will be reported using the MOOSE checklist.

Introduction

Recurrent miscarriage (RM) was recently re-defined by the European Society of Human Reproduction and Embryology (ESHRE) as the loss of two or more consecutive pregnancies. Before this, it was defined as three or more consecutive pregnancy losses, and this definition is still in use in some countries, including the UK. While the incidence of RM depends on the definition employed and population studied, it is generally accepted to affect 1–6% of the reproductive age population. Given that 6% of women experience two or more consecutive miscarriages, more women will be accessing services for investigation and management as the new definition of RM is adopted internationally.

There is a need for consistent clinical care of RM that follows the best evidence-based practice. Previous reproductive history is an independent predictor of future pregnancy outcome. The risk of a further miscarriage increases after each successive pregnancy loss, reaching approximately 40% after three consecutive pregnancy losses, and the prognosis worsens with increasing maternal age. A live birth does not prevent a subsequent miscarriage. There are a few common established biological causes of miscarriage, along with some more recent proposed aetiologies, which are still controversial. However, a high proportion, even when recurrent, are classified as unexplained. Despite this, the standard investigations for RM continue to be important in evaluating potential factors responsible for pregnancy loss, and similar procedures are included in all international clinical practice guidelines (CPGs). While some evidence-based treatments have improved the outcomes for couples with RM, almost half of cases remain unexplained and are empirically treated. While future pregnancy may be difficult, the likelihood of subsequent live birth is approximately 70–75%.

The psychological impact of RM can be both severe and protracted, and studies indicate that it can negatively affect both men’s and women’s psychological well-being in the medium- to long-term. Studies have indicated that 32% of women with RM could be classified as depressed, against which having a living child was not a protective buffer. Thus, given its high frequency, RM can significantly contribute to the overall burden of psychopathology within a population, and recognition of this impact is important, so that affected individuals may be cared for appropriately.

CPGs are “statements that include recommendations intended to optimise patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options”. CPGs for the management, investigation, and/or follow-up of those who experience RM have been issued by professional societies such as ESHRE, the American College of Obstetricians and Gynaecologists, and the Royal College of Obstetricians and Gynaecologists; however, the existence of guidelines in other high-income countries is unknown to the study team. While there are CPGs on miscarriage in Ireland and the UK, there are none concerning RM specifically. The identification, appraisal and description of published CPGs in other high-income countries would be a valuable first step in informing efforts to promote the optimise and standardise RM care.

Aim of the review

The aim of this systematic review is to identify, appraise and describe published CPGs for the management, investigation and/or follow-up of RM within high-income countries.

Objectives

- To identify published CPGs for the management, investigation and/or follow-up of RM within high-income countries;
- To appraise the quality of included CPGs using the Appraisal of Guidelines for Research and Evaluation version 2 (AGREE II) instrument;
- To describe recommendations from the included CPGs concerning first trimester RM.

Protocol

Details of the review have been submitted for registration to the PROSPERO database (ID: 173881). Any protocol amendments will be noted on PROSPERO and in any publications arising from the study. This protocol follows the PRISMA-P guidelines for the reporting of systematic review protocols; the completed checklist is available as Extended Data. Methodological guidance on conducting systematic reviews of CPGs was also followed in the preparation of this protocol, as such reviews require tailored approaches to, and greater subjectivity in, design and execution compared with other systematic reviews.

Eligibility criteria

The “PICAR” framework was used to guide review inclusion and exclusion criteria (Table 1). For the purpose of this review,
<table>
<thead>
<tr>
<th>PICAR framework</th>
<th>Eligibility criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population, clinical indication(s), and condition(s)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Study population</strong></td>
<td>• Women/couples experiencing recurrent miscarriage (RM) • Humans only</td>
</tr>
<tr>
<td><strong>Clinical indication</strong></td>
<td>• Investigation, management and/or follow-up of women/couples with RM – specifically first trimester RM</td>
</tr>
<tr>
<td><strong>Clinical condition</strong></td>
<td>• RM; defined by the review team as the loss of two or more consecutive pregnancies; with a specific focus on first trimester RM. For the purposes of this review, all CPGs that focus on RM – regardless of the definition used – will be included. The definition applied by each included CPG will be extracted and considered when synthesising and interpreting the review findings</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>• Any intervention focusing on the investigation, management and/or follow-up of RM</td>
</tr>
<tr>
<td><strong>Comparator(s), Comparison(s), and (key) Content</strong></td>
<td>• Any comparator or comparison • No ‘key’ CPG content is of interest – unless CPGs are broader in scope; in such instances, content specific to RM is only of interest</td>
</tr>
<tr>
<td><strong>Attributes of eligible CPGs</strong></td>
<td><strong>Language</strong></td>
</tr>
<tr>
<td></td>
<td>• Available in English • CPGs where summaries are available in English, but full text is not, will be excluded</td>
</tr>
<tr>
<td><strong>Year of publication</strong></td>
<td>• 2000 onwards • In Ireland, the National Clinical Effectiveness Committee (NCEC), requires a full guideline update within three years; while The Scottish Intercollegiate Guidelines Network (SIGN) also specifies three years, it also includes those over three years old and revalidated. The World Health Organisation does not have a defined period for guideline updates. To be comprehensive, CPGs published within the last twenty years (January 2000 to date) will be eligible for inclusion given that international CPGs concerning RM can fall well outside the three-year period. A good quality older guideline could be a good base on which to develop a new guideline</td>
</tr>
<tr>
<td><strong>Developing/publishing organisation</strong></td>
<td>• Only CPGs issued or endorsed by national or international scientific societies, professional colleges, charitable organisations, and government organisations will be included</td>
</tr>
<tr>
<td><strong>Country of publication</strong></td>
<td>• High-income countries, as defined by the World Bank; given the large discrepancies in pregnancy outcomes and care structures between high, and low and middle-income countries</td>
</tr>
<tr>
<td><strong>Version</strong></td>
<td>• Latest version only</td>
</tr>
<tr>
<td><strong>Development process</strong></td>
<td>• Evidence and/or consensus-based</td>
</tr>
<tr>
<td><strong>System of rating evidence</strong></td>
<td>• Use of a system to rate the level of evidence within CPGs is not an eligibility criterion; however, such data will be extracted to inform synthesis and interpretation of findings</td>
</tr>
<tr>
<td><strong>Quality of evidence</strong></td>
<td>• The eligibility of CPGs will not be based on a specific minimum quality cut-off score based on the AGREE II criteria. • We are interested in all guidance generated regardless of quality (e.g. because CPGs determined to be of “high quality” may not necessarily report recommendations that are highly valid and implementable); this will however be taken into consideration when synthesising and interpreting the review findings</td>
</tr>
<tr>
<td><strong>Scope</strong></td>
<td>• Must have a primary/secondary focus on the investigation and treatment of RM • Must be national/international in scope • Covers any aspect of RM care and its organisation; including the provision of dedicated pregnancy loss clinics, treatment and management of RM, investigations performed following RM in order to inform prognosis of future pregnancy outcomes, and counselling of parents following RM</td>
</tr>
<tr>
<td><strong>Recommendations</strong></td>
<td>• Must be clearly identified as a CPG • Must be published. Unpublished CPGs, conference papers, discussion papers, drafts and opinions will be excluded</td>
</tr>
<tr>
<td></td>
<td>• Must have ‘recommendations’ concerning the identification, management and/or follow-up RM (either explicitly highlighted as such within the document, or noted within the body of the document, but not explicitly identified as a recommendation) • To be eligible, recommendations need not be accompanied by an explicit level of confidence (and quality assessment criteria system used specified); however, this data will be extracted (where available) and considered during the synthesis and interpretation of findings</td>
</tr>
</tbody>
</table>
CPGs are defined as “systematically developed statements to assist practitioners about appropriate health care for specific clinical circumstances”; an adaptation of the definitions used by National Clinical Effectiveness Committee (NCEC) and Scottish Intercollegiate Guidelines Network (SIGN).

Information sources
While many CPGs are published in journals and can be identified through systematic bibliographic database searching, others may only be published in non-commercial or proprietary formats and are accessible only through extensive searches of grey literature sources or posted by professional medical associations on their websites behind membership paywalls. We will therefore use a range of information sources to locate CPGs concerning RM.

A systematic literature search, covering CPGs published from 2000 to present, will be performed using the following databases: MEDLINE (Ovid; 1946), Embase® (Elsevier; 1980), CINAHL Complete (EBSCOhost; 1994), Web of Science™ (Thomson Reuters), Scopus (Elsevier; 2004), and Open Grey (INIST-CNRS; 2011). Guideline repositories (Table 2) and the websites of professional organisations/associations from around the world (Table 3) will also be searched. Searches of Web of Science, Scopus and Open Grey, as well as guideline repositories and the websites of professional bodies/organisations, will facilitate the identification of grey literature – such as conference proceedings and/or technical reports – which may contain information about potentially eligible CPGs.

Search strategy
This search strategy was developed with the assistance of a specialist librarian. Key word searches, using combinations of key words and Medical Subject Headings (or equivalent), will be used across two concepts using the AND Boolean operator: (1) clinical guidelines; (2) recurrent miscarriage (Table 4). Within each of the categories, keywords will be combined

### Table 2. Information sources: Guideline repositories.

<table>
<thead>
<tr>
<th>Guideline repositories</th>
<th>Website</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canadian Agency for Drugs and Technology in Health (CADTH)</td>
<td><a href="http://www.cadth.ca">www.cadth.ca</a></td>
</tr>
<tr>
<td>Guidelines International Network (GIN)</td>
<td><a href="http://www.g-i-n.net/library/international-guidelines-library">http://www.g-i-n.net/library/international-guidelines-library</a></td>
</tr>
<tr>
<td>Institute for Clinical Systems Improvement (ICSI)</td>
<td><a href="http://www.icsi.org/guidelines">www.icsi.org/guidelines</a></td>
</tr>
<tr>
<td>Lenus: The Irish Health Repository</td>
<td><a href="https://www.lenus.ie/hse/">https://www.lenus.ie/hse/</a></td>
</tr>
<tr>
<td>National Institute for Health and Care Excellence (NICE)</td>
<td><a href="http://www.nice.org.uk">www.nice.org.uk</a></td>
</tr>
<tr>
<td>Scottish Intercollegiate Guidelines Network (SIGN)</td>
<td><a href="http://www.sign.ac.uk/index.html">http://www.sign.ac.uk/index.html</a></td>
</tr>
<tr>
<td>TRIP database</td>
<td><a href="https://www.tripdatabase.com">https://www.tripdatabase.com</a></td>
</tr>
</tbody>
</table>

### Table 3. Information sources: Professional bodies/organisations.

<table>
<thead>
<tr>
<th>Organisation</th>
<th>Country/Region</th>
</tr>
</thead>
<tbody>
<tr>
<td>Royal College of Physicians of Ireland Institute of Obstetricians and Gynaecologists</td>
<td>Ireland</td>
</tr>
<tr>
<td>Royal College of Obstetricians and Gynaecologists (RCOG)</td>
<td>UK</td>
</tr>
<tr>
<td>European Society of Human Reproduction and Embryology (ESHRE)</td>
<td>Europe</td>
</tr>
<tr>
<td>The International Federation of Gynaecology and Obstetrics (FIGO)</td>
<td>International</td>
</tr>
<tr>
<td>The American College of Obstetricians and Gynaecologists (ACOG)</td>
<td>US</td>
</tr>
<tr>
<td>The Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG)</td>
<td>Australia &amp; New Zealand</td>
</tr>
<tr>
<td>American Society for Reproductive Medicine (ASRM)</td>
<td>US</td>
</tr>
<tr>
<td>Society for Maternal-Fetal Medicine (SMFM)</td>
<td>International</td>
</tr>
<tr>
<td>Society of Obstetricians and Gynaecologists of Canada (SOGC)</td>
<td>Canada</td>
</tr>
</tbody>
</table>
using the “OR” Boolean operators. The search strategy will be
developed in Medline (see Extended Data for sample search
strategy and tailored for use within the other databases, and
piloted, before final searches are run.

Study records

Data management. Records will be imported into EndNote
X9 and de-duplicated using the ‘remove duplicates’ function,
as well as manually screening results for accuracy.

Selection process. Two independent reviewers (MH and RD)
will screen titles and abstracts of retrieved records against the
inclusion criteria. Records not meeting the eligibility criteria
will be excluded. Two reviewers (MH and RD) will subse-
quently, and independently, screen the full text articles of records
identified to identify studies to be included. Any disagree-
ments in eligibility assessments will be discussed and resolved
via consensus. If consensus on eligibility cannot be agreed
between the two reviewers, a third reviewer (KOD) will review
the particular record(s) in order to determine its eligibility of
the CPG.

A Preferred Reporting Items for Systematic Review and
Meta-Analysis (PRISMA) flow diagram will show the overall
process of CPG selection and summarise the inclusion and
exclusion of records/CPGs at each stage of the review.

Data collection process. Once the final set of included CPGs
has been obtained, all documents related to the CPGs (cited
as supplemental documents, summaries of recommendations,
and others) will be retrieved by MH before data extraction or
quality assessment is undertaken. If links to these documents
are not provided in the included CPG, MH will conduct searches
to locate them. For CPGs published only in summary or where
important information is missing, we will try to find complete
information by contacting the authors. All documents collected
will be verified independently by RD to confirm complete-
ness and to ensure that companion documents are matched
appropriately. MH will also conduct searches to ensure that the
latest version of each included CPG has been included, and none is
present in duplicate.

Data items

Key features of CPGs and recommendations, for all included
CPGs, will be extracted using a structured data extraction form
in Microsoft Excel (Microsoft Corporation, Redmond, WA) (see
template in Extended Data), which will be piloted in advance.

Key features of CPGs to be extracted, include:

- Title
- Year of publication
- Language
- Developing/publishing organisation and/or authors
- Country/countries of publication
- How described by the authors (e.g. guideline / standard)
- Version
- Type of CPG (formulated, adapted, updated or revised)
- Topic addressed (i.e. RM or broader)
- Development process (evidence- and/or expert
  consensus-based)
- Composition of guideline development group
- Peer-review conducted, or not
- Target users
- Definition of RM employed – to include number of
  miscarriages, whether consecutive/not, number of
  weeks gestation
- System of rating evidence/Quality instrument used
during CPG development (GRADE, Oxford, not
mentioned, or other), if any – some developers do not
include levels of evidence with their recommendations
- All recommendations related to first trimester RM
  within the CPG.

Data will be extracted by one reviewer (MH) and independently
verified for accuracy and completeness by a second reviewer
(SM), with discrepancies resolved through consensus. If agree-
ment cannot be reached, a third reviewer (KOD) will review
and make a final decision. If a member of the review team has
been involved in the development of any of the CPGs eligible for
the review, an independent reviewer will extract the required data
from the study.

Outcomes and prioritisation

Not applicable.
Risk of bias in individual studies/quality assessment
The quality of included CPGs will be assessed using the Appraisal of Guidelines, Research and Evaluation version 2 (AGREE II) criteria. The criteria encompass 23 items, over six domains, rated on a 7-point Likert scale: (i) Scope and purpose of the guideline; (ii) Stakeholder involvement in the development of the guidelines; (iii) Rigour of development and formulation of the recommendations within the guideline; (iv) Clarity of presentation of the guideline; (v) Applicability of the guideline; (vi) editorial independence in the formulation of recommendations within the guideline. As part of the overall assessment, two global ratings are included: (i) a rating on the overall quality of the guideline, and (ii) whether the guideline would be recommended for use in practice. AGREE II is an accepted and validated tool for assessing the methodological quality of CPGs. It has limitations, however; for example, it does not assess the implementation of the guideline.

Two reviewers with methodological and clinical expertise (MH/SM and KOD) will conduct an independent quality assessment of the CPGs. Domain scores will be calculated by summing up all the scores of the individual items in a domain and by scaling the total as a percentage of the maximum possible score for that domain, as per the AGREE II User Manual. The six domains are independent, and the scores will be calculated as the sum of the individual items in each domain.

To make the scores more relevant to readers and enable fair comparison, our review will report the AGREE II outcomes categorically rather than statistically, using the 5-point Likert scale described by other reviews: excellent (>80%), good (>60%–80%), average (>40%–60%), fair (>20%–40%) and poor (≤20%).

Data synthesis
A narrative synthesis approach will be used to describe and appraise CPGs and their recommendations or guidance therein, taking account of quality appraisal (using the AGREE II tool), and recency of publication. The levels of evidence associated with the recommendations within each CPG will be reported, and quality assessment rating system used; we will not attempt to standardise evidence ratings across CPGs.

Dissemination
The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist will be used to report findings of the review, as there is currently no specific checklist for systematic reviews of CPGs. We will share the findings in a peer-reviewed journal, through communications with professional bodies and policymakers (through briefings), and participation in scientific meetings and national and international conferences.

Patient and public involvement (PPI)
This systematic review protocol was developed in conjunction with a Pregnancy Loss Patient Representative and through consultations with Specialist Bereavement and Loss Midwives. A PPI group is currently being established and will have input into discussions and decisions concerning the conduct, findings and outputs of this review.

Study status
Database searches have been completed.

Conclusions/discussion
CPGs for RM have been published by some professional organisations. In Ireland, there is currently no national standard for the management, investigation or follow-up of those who experience RM. The aim of this systematic review is to identify, appraise and describe published CPGs for the management, investigation and/or follow-up of RM within high-income countries. This will be a valuable first step in informing efforts to promote the optimisation and standardisation of the management, investigation and follow-up of RM.

Data availability
Underlying data
No data are associated with this article.

Extended data

This project contains the following extended data:
- Supplementary File 1. PRISMA-P checklist for the reporting of systematic review protocols
- Supplementary File 2. Sample search strategy
- Supplementary File 3. Data extraction form template

Data are available under the terms of the Creative Commons Zero “No rights reserved” data waiver (CC0 1.0 Public domain dedication).

Acknowledgments
We wish to thank Donna Ó Doibhlin, Medicine & Health Sciences Liaison Librarian at University College Cork for her assistance when developing the search strategy for this review.
References

Matthew Coleman
University Hospital Southampton, University of Southampton, Southampton, UK
Sarah Bailey
University Hospital Southampton, University of Southampton, Southampton, UK

This peer review report was updated on 22nd September 2020 to incorporate further comments from the reviewers.

Matthew Coleman:
Summary
A few comments to help guide the authors. The vision is laudable however I am uncertain about the process especially in this highly emotive area.

Whilst the overall methods quote and follow national and international recommended methodology, the original challenge is made extremely complex by any number of human factors and biases. Current evidence is largely opinion based and confounded by bias and human factors. And given the distress caused by the disease these have sometimes been exaggerated. For example, the reasons behind the recent change in Rm definition, which might include as many as 6% of women, is complex and multi factorial and makes evaluating possible interventions difficult for the majority of women for whom the outlook is already consistent with women who have not experienced to consecutive miscarriages.

Understanding the psychology and reasons behind the recommendations would provide much more useful background for developing future guidelines which are rational fair and achievable.

Scope There appears to be some conflict in the defined scope of this review;
Scope:
- Must have a primary/secondary focus on the investigation/treatment of RM.
- Must be national/international in scope.
Covers any aspect of RM care and its organisation.

- Must be clearly identified as a CPG.
- Must be published.

**Time span:** given the rapid evolution of recommended managements in this particular area including recent and distant past guideline recommendations (as far back as 2000) any review is likely to produce significant inconsistencies related to change over time. Amalgamating them together will require some complexity to control for these changes, which are also destabilised by the paucity of data, bias and frequent personal opinion.

**Sarah Bailey:**
The objective of this protocol for a systematic review of clinical practice guidelines (CPG) is to identify, appraise and describe published CPGs of the management, investigation and follow-up of recurrent miscarriage (RM) within high-income countries. The aim being to take the timely and important first step to promote consistent and evidence based care for couples with RM in Ireland.

The protocol is well-written and easy to follow and the proposed methodology is, overall, clearly described using recognised frameworks and tools to assist.

Please see below comments;

**Introduction:**
- In addition to highlighting that the definition of RM, with regards to number of miscarriages that constitute the term, varies from country to country, it would be useful to note at this point that actual term used to describe the condition can significantly vary between countries and CPGs – e.g. ESHRE uses term recurrent pregnancy loss (ESHRE 2017).

**Protocol:**
- The PICAR statement provides a useful and thorough framework to guide the review of inclusion and exclusion criteria, as clearly demonstrated in Table 1.
- Clarification is required of how the researchers plan to identify relevant ‘grey’ unpublished literature and I would advise the authors to make clear the exact range of information sources that will be utilised to locate CPGs concerning RM to allow a reproducible literature search. However, the PICAR statement in Table 1, also identifies that unpublished CPGs will be excluded. This is confusing given the plan to locate unpublished literature sources and this inconsistency should be addressed.
- I was pleased to see the protocol was developed in conjunction with a Pregnancy Loss Patient Representative and encourage the prompt establishment of a PPI group to support this research.

**Conclusion:**
I assume the overall aim of the systematic review is to develop a CPG on RM to promote consistent and standardized care for couples with RM in Ireland, but the actual planned outcome is not clearly articulated and it would be useful to have clarification of this.

**Is the rationale for, and objectives of, the study clearly described?**
Yes

Is the study design appropriate for the research question?
Partly

Are sufficient details of the methods provided to allow replication by others?
Yes

Are the datasets clearly presented in a useable and accessible format?
Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Obstetric medicine, haematology and pregnancy, diabetes pregnancy, hypertension pregnancy. Clinical Specialist in Recurrent Miscarriage.

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however we have significant reservations, as outlined above.

Author Response 02 Oct 2020

Marita Hennessy, University College Cork, Cork, Ireland

Matthew Coleman

Comment 1:
A few comments to help guide the authors. The vision is laudable however I am uncertain about the process especially in this highly emotive area. Whilst the overall methods quote and follow national and international recommended methodology, the original challenge is made extremely complex by any number of human factors and biases. Current evidence is largely opinion based and confounded by bias and human factors. And given the distress caused by the disease these have sometimes been exaggerated. For example, the reasons behind the recent change in Rm definition, which might include as many as 6% of women, is complex and multi factorial and makes evaluating possible interventions difficult for the majority of women for whom the outlook is already consistent with women who have not experienced to consecutive miscarriages. Understanding the psychology and reasons behind the recommendations would provide much more useful background for developing future guidelines which are rational fair and achievable.

Response:
Thank you for taking the time to review and provide considered feedback on our protocol paper. We acknowledge the challenges in this area. As noted in the protocol, this study is a first step in informing efforts to promote the optimisation and standardisation of RM care. This review is being conducted as part of a larger project titled “REcurrent miscarriage: Evaluating CURRENT services (RE:CURRENT)” which is looking at service provision in Ireland. The findings from the systematic review will be used by the RE:CURRENT Team to inform this evaluation; however, we did not detail this within the protocol as the findings of this
A national guideline is not a planned output of this project; however, evidence gathered during the project may aid future development of a national guideline.

Comment 2:
There appears to be some conflict in the defined scope of this review;

Scope:
- Must have a primary/secondary focus on the investigation/treatment of RM.
- Must be national/international in scope.
- Covers any aspect of RM care and its organisation.
- Must be clearly identified as a CPG.
- Must be published.

Time span; given the rapid evolution of recommended managements in this particular area including recent and distant past guideline recommendations (as far back as 2000) any review is likely to produce significant inconsistencies related to change over time. Amalgamating them together will require some complexity to control for these changes, which are also destabilised by the paucity of data, bias and frequent personal opinion.

Response:
Thank you for raising these important points. CPGs which focus specifically on RM, or address any aspect of RM care within a broader/different topic area (e.g. CPGs on pregnancy loss, or thrombophilia, which may have a section on RM), are eligible for inclusion.

While we are including CPGs published from 2000 onwards, we also state that CPGs must be ‘latest version only’ and note in the data collection process section that MH will conduct searches to ensure that the latest (i.e. current and valid) version of each included CPG has been included. We also state that when describing and appraising CPGs and recommendations therein in our narrative synthesis, we will take account of quality appraisal scores (as per the six domains within the AGREEII tool, including rigour of development and formulation of recommendations) and recency of publication. We will also extract systems of rating evidence used by CPGs and present these along with the recommendations.

Sarah Bailey

General comment
The objective of this protocol for a systematic review of clinical practice guidelines (CPG) is to identify, appraise and describe published CPGs of the management, investigation and follow-up of recurrent miscarriage (RM) within high-income countries. The aim being to take the timely and important first step to promote consistent and evidence based care for couples with RM in Ireland.

The protocol is well-written and easy to follow and the proposed methodology is, overall, clearly described using recognised frameworks and tools to assist. Please see below comments.

General response
Thank you for taking the time to review and provide considered feedback on our protocol paper.

Comment 1:
Introduction: In addition to highlighting that the definition of RM, with regards to number of miscarriages that constitute the term, varies from country to country, it would be useful to note at this point that actual term used to describe the condition can significantly vary between countries and CPGs – e.g. ESHRE uses term recurrent pregnancy loss (ESHRE 2017).
Response:
Thank you; we have added the following to the introduction: “The actual term used to describe the condition can also vary between countries and/or professional bodies; for example, ESHRE uses term ‘recurrent pregnancy loss’, while the Royal College of Obstetricians and Gynaecologists uses the term RM.”

Comment 2:
The PICAR statement provides a useful and thorough framework to guide the review of inclusion and exclusion criteria, as clearly demonstrated in Table 1.
Response:
Thank you; it was certainly helpful in thinking through the inclusion and exclusion criteria.

Comment 3:
Clarification is required of how the researchers plan to identify relevant ‘grey’ unpublished literature and I would advise the authors to make clear the exact range of information sources that will be utilised to locate CPGs concerning RM to allow a reproducible literature search. However, the PICAR statement in Table 1, also identifies that unpublished CPGs will be excluded. This is confusing given the plan to locate unpublished literature sources and this inconsistency should be addressed.
Response:
We have removed reference to “unpublished” after “grey” literature to avoid confusion between the search strategy and the PICAR statement. Grey literature will be used to identify CPGs that may be eligible for inclusion. We will use bibliographic databases (Web of Science, Scopus and Open Grey), as well as guideline repositories (detailed in Table 2) and the websites of professional bodies/organisations (detailed in Table 3), to identify grey literature including conference proceedings and/or technical reports. These, along with the other databases mentioned, comprise the full range of information sources used to locate CPGs. While search terms are presented in Table 4, the full search strategy will be published alongside the paper outlining the findings of this systematic review.
We have added the following sentence to the “information sources” section to clarify what we mean by grey literature: “Searches of Web of Science, Scopus and Open Grey, as well as guideline repositories and the websites of professional bodies/organisations, will facilitate the identification of grey literature – such as conference proceedings and/or technical reports – which may contain information about potentially eligible CPGs.”

Comment 4:
I was pleased to see the protocol was developed in conjunction with a Pregnancy Loss Patient Representative and encourage the prompt establishment of a PPI group to support this research.
Response:
Thank you; this aspect of the work is incredibly important to us. We have since established our PPI group.

Comment 5:
Conclusion: I assume the overall aim of the systematic review is to develop a CPG on RM to promote consistent and standardized care for couples with RM in Ireland, but the actual planned outcome is not clearly articulated and it would be useful to have clarification of this.

Response:
As noted in the protocol, this study is a first step in informing efforts to promote the optimisation and standardisation of RM care. This review is being conducted as part of a larger project titled “REcurrent miscarriage: Evaluating CURRENT services (RE:CURRENT)” which is looking at service provision in Ireland. The findings from the systematic review will be used by the RE:CURRENT Team to inform this evaluation; however, we did not detail this within the protocol as the findings of this systematic review will have relevance to the field in general, not just the RE:CURRENT Team. A national guideline is not a planned output of this project; however, evidence gathered during the project may aid future development of a national guideline.

Competing Interests: No competing interests were disclosed.
o Why is GRADE system not used instead of AGREE?

o How will "low quality" guidelines be compared with “high quality”? How will different quality be implemented in the end result (a new guideline)?

o What will the end results be from this expansive research? Is it a national guideline in Ireland?

Is the rationale for, and objectives of, the study clearly described?
Yes

Is the study design appropriate for the research question?
Partly

Are sufficient details of the methods provided to allow replication by others?
Yes

Are the datasets clearly presented in a useable and accessible format?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Recurrent pregnancy loss

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 02 Oct 2020

Marita Hennessy, University College Cork, Cork, Ireland

General comment:
The aim of this systematic review protocol is to identify and describe published clinical practice guidelines for management, diagnostics and/or follow-up of women with RM. The authors will use an electronic database search to identify published guidelines in English within the last 20 years in high-income countries. This study aims to assess a standardisation of RM care. Overall, the protocol is well described with an appropriate study design. There are some concerns.

Response:
Thank you for taking the time to review and provide considered feedback on our protocol paper.

Comment 1:
The PICAR states that only published guidelines will be included though "grey literature" will also be searched for. Can the authors explain this further?

Response:
We have removed reference to “unpublished” after “grey” literature to avoid confusion between the search strategy and the PICAR statement. Grey literature will be used to identify CPGs that may be eligible for inclusion. We will use bibliographic databases (Web of Science, Scopus and Open Grey), as well as guideline repositories (detailed in Table 2) and the websites of professional bodies/organisations (detailed in Table 3), to identify grey literature including conference proceedings and/or technical reports. These, along with the other databases mentioned, comprise the full range of information sources used to locate CPGs. While search terms are presented in Table 4, the full search strategy will be published alongside the paper outlining the findings of this systematic review.

We have added the following sentence to the “information sources” section to clarify what we mean by grey literature: “Searches of Web of Science, Scopus and Open Grey, as well as guideline repositories and the websites of professional bodies/organisations, will facilitate the identification of grey literature – such as conference proceedings and/or technical reports – which may contain information about potentially eligible CPGs.”

Comment 2:
Why is GRADE system not used instead of AGREE?

Response:
We are using AGREEII to assess the quality of included CPGs, across the six AGREEII domains. We are not using the GRADE system as we are not assessing the evidence behind the recommendations within each guideline. We are, however, extracting and noting the system of rating evidence used by each CPG. We note within the protocol that “The levels of evidence associated with the recommendations within each CPG will be reported, and quality assessment rating system used; we will not attempt to standardise evidence ratings across CPGs.”

Comment 3:
How will "low quality" guidelines be compared with "high quality"? How will different quality be implemented in the end result (a new guideline)?

Response:
We will report the AGREEII scores, by domain, for each CPG. In the narrative synthesis, we will describe CPGs, and recommendations therein, taking account of this quality appraisal. The aim of the review is to identify and appraise CPGs, and describe recommendations therein. We do not aim to develop a CPG from this work (see response 4 for further information).

Comment 4:
What will the end results be from this expansive research? Is it a national guideline in Ireland?

Response:
As noted in the protocol, this study is a first step in informing efforts to promote the optimisation and standardisation of RM care. This review is being conducted as part of a larger project titled “REcurrent miscarriage: Evaluating CURRENT services (RE:CURRENT)” which is looking at service provision in Ireland. The findings from the systematic review will be used by the RE:CURRENT Team to inform this evaluation; however, we did not detail this within the protocol as the findings of this systematic review will have relevance to the field in general, not just the RE:CURRENT Team. A national guideline is not a planned output of
this project; however, evidence gathered during the project may aid future development of a national guideline.

**Competing Interests:** No competing interests were disclosed.

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**Reviewer Report 07 September 2020**

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Jennifer Kaiser

Department of Obstetrics and Gynecology, University of Utah School of Medicine, Salt Lake City, UT, USA

This protocol outlines a systematic review of English language, high-income country CPGs for recurrent pregnancy loss in the first trimester. The intention is to identify and describe published CPGs in order to move towards standardization of management, investigation, and follow-up of RM. The strengths of this protocol include its registration with PROSPERO, utilization of a specialist librarian, and adherence to the PRISMA-P guidelines.

- The "grey" literature is denoted as being "unpublished" in the protocol. However, in the PICAR statement, it states that unpublished material will be excluded. Please clarify this seeming inconsistency. Further detail on the "range of information sources" used to locate CPGs would improve reproducibility.

- A lingering question is what the final product of this protocol will be. The aim is to identify, appraise, and describe CPGs with the intent of promoting standardization, but ultimately will this information be use to create a national CPG for Ireland? Or some other consensus statement? A clearer statement on its final uses would strengthen the rationale for this review further.

**Is the rationale for, and objectives of, the study clearly described?**

Yes

**Is the study design appropriate for the research question?**

Yes

**Are sufficient details of the methods provided to allow replication by others?**

Yes

**Are the datasets clearly presented in a useable and accessible format?**

Not applicable
**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Early pregnancy loss, miscarriage management

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 23 Sep 2020

**Marita Hennessy, University College Cork, Cork, Ireland**

Thank you for taking the time to review and provide feedback on our protocol paper.

**Comment 1:**
The "grey" literature is denoted as being "unpublished" in the protocol. However, in the PICAR statement, it states that unpublished material will be excluded. Please clarify this seeming inconsistency. Further detail on the "range of information sources" used to locate CPGs would improve reproducibility.

**Response:**
We have removed reference to “unpublished” after “grey” literature to avoid confusion between the search strategy and the PICAR statement. Grey literature will be used to identify CPGs that may be eligible for inclusion. We will use bibliographic databases (Web of Science, Scopus and Open Grey), as well as guideline repositories (detailed in Table 2) and the websites of professional bodies/organisations (detailed in Table 3), to identify grey literature including conference proceedings and/or technical reports. These, along with the other databases mentioned, comprise the full range of information sources used to locate CPGs. While search terms are presented in Table 4, the full search strategy will be published alongside the paper outlining the findings of this systematic review.
We have added the following sentence to the “information sources” section to clarify what we mean by grey literature: “Searches of Web of Science, Scopus and Open Grey, as well as guideline repositories and the websites of professional bodies/organisations, will facilitate the identification of grey literature – such as conference proceedings and/or technical reports – which may contain information about potentially eligible CPGs.”

**Comment 2:**
A lingering question is what the final product of this protocol will be. The aim is to identify, appraise, and describe CPGs with the intent of promoting standardisation, but ultimately will this information be use to create a national CPG for Ireland? Or some other consensus statement? A clearer statement on its final uses would strengthen the rationale for this review further.

**Response:**
As noted in the protocol, this study is a first step in informing efforts to promote the optimisation and standardisation of RM care. This review is being conducted as part of a larger project titled “REcurrent miscarriage: Evaluating CURRENT services (RE:CURRENT)” which is looking at service provision in Ireland. The findings from the systematic review will be used by the RE:CURRENT Team to inform this evaluation; however, we did not detail this within the protocol as the findings of this systematic review will have relevance to the field in general, not just the RE:CURRENT Team.
This systematic review identifies and describes published clinical practice guidelines for the management, diagnostics and/or follow-up of women with RM. This study focuses on high-income countries. Electronic databases, selected guideline repositories and the websites of professional societies will be searched to identify guidelines within the last 20 years.

This study is the first step for the optimisation and standardisation of RM care.

Overall, the protocol is clearly described. The aim of the study is clear with an appropriate study design.

The only thing what is unclear for me is how the researchers will search for the so-called grey literature. They state that ‘We will therefore use a range of information sources to locate CPGs concerning RM.’ What do they mean by that? How will they do that? This needs more clarification.

Is the rationale for, and objectives of, the study clearly described?  
Yes

Is the study design appropriate for the research question?  
Yes

Are sufficient details of the methods provided to allow replication by others?  
Partly

Are the datasets clearly presented in a useable and accessible format?  
Yes

Competing Interests: No competing interests were disclosed.
Reviewer Expertise: Early pregnancy.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 23 Sep 2020

Marita Hennessy, University College Cork, Cork, Ireland

Thank you for taking the time to review and provide feedback on our protocol paper.

Comment 1:
The only thing what is unclear for me is how the researchers will search for the so-called grey literature. They state that 'We will therefore use a range of information sources to locate CPGs concerning RM.' What do they mean by that? How will they do that? This needs more clarification.

Response:
Grey literature will be used to identify CPGs that may be eligible for inclusion. We will use academic databases (Web of Science, Scopus and Open Grey), as well as guideline repositories (detailed in Table 2) and the websites of professional bodies/organisations (detailed in Table 3), to identify grey literature including conference proceedings and/or technical reports. These, along with the other databases mentioned, comprise the full range of information sources used to locate CPGs. While search terms are presented in Table 4, the full search strategy will be published alongside the paper outlining the findings of this systematic review.

We have added the following sentence to the “information sources” section to clarify what we mean by grey literature: “Searches of Web of Science, Scopus and Open Grey, as well as guideline repositories and the websites of professional bodies/organisations, will facilitate the identification of grey literature – such as conference proceedings and/or technical reports – which may contain information about potentially eligible CPGs.”

Competing Interests: No competing interests were disclosed.