Check for updates

STUDY PROTOCOL

## REVISED A protocol for a systematic review of clinical practice guidelines for recurrent miscarriage [version 3; peer review: 3 approved, 1 approved with reservations]

Marita Hennessy [1-3], Rebecca Dennehy[1-3], Sarah Meaney[1-4], Declan Devane [2,5,6], Keelin O'Donoghue[1-3]

[1]Pregnancy Loss Research Group, Department of Obstetrics and Gynaecology, University College Cork, Cork, Ireland
[2]The Irish Centre for Maternal and Child Health, University College Cork, Cork University Maternity Hospital, Cork, Ireland
[3]College of Medicine and Health, University College Cork, Cork, Ireland
[4]National Perinatal Epidemiology Centre, University College Cork, Cork University Maternity Hospital, Cork, Ireland
[5]School of Nursing and Midwifery, National University of Ireland, Galway, Galway, Ireland
[6]Evidence Synthesis Ireland, National University of Ireland, Galway, Galway, Ireland

## 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

## Open Peer Review

### Reviewer Status ✓ ✓ ✓ ?

| | Invited Reviewers | | | |
|---|---|---|---|---|
| | **1** | **2** | **3** | **4** |
| version 3 (revision) 02 Oct 2020 | | | ✓ report | |
| version 2 (revision) 23 Sep 2020 | | | | |
| version 1 01 Apr 2020 | ✓ report | ✓ report | ? report | ? report |

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 Rasmark Roepke**, Lund University, Lund, Sweden

4. **Matthew Coleman**, University of

synthesis will be conducted to appraise and compare CPGs and their 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

Southampton, Southampton, UK

**Sarah Bailey**, University of Southampton, Southampton, UK

Any reports and responses or comments on the article can be found at the end of the article.

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

**REVISED** **Amendments from Version 2**

We have noted in the introduction that the actual term used to describe the condition can also vary between countries and/or professional bodies.

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

## Abbreviations

AGREE, Appraisal of Guidelines for Research and Evaluation; CPG, Clinical Practice Guideline; ESHRE, European Society of Human Reproduction and Embryology; NCEC, National Clinical Effectiveness Committee; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROSPERO, International Prospective Register of Systematic Reviews; RM, Recurrent Miscarriage; SIGN, Scottish Intercollegiate Guidelines Network; WHO, World Health Organisation

## 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[1]. 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[2]. The actual term used to describe the condition can also vary between countries and/or professional bodies; for example, ESHRE uses the term 'recurrent pregnancy loss'[1], while the Royal College of Obstetricians and Gynaecologists uses the term RM[2]. 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[1,3]. 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[1,4].

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[5,6]. A previous live birth does not prevent a woman experiencing RM[5,6]. There are a few common established biological causes of miscarriage[2,7], along with some more recent proposed aetiologies[7,8], 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[9], and similar procedures are included in all international clinical practice guidelines (CPGs)[1,7]. While some evidence-based treatments have improved the outcomes for couples with RM, almost half of cases remain unexplained and are empirically treated[9]. While future pregnancy may be difficult, the likelihood of subsequent live birth is approximately 70–75%[5,10]. 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[11]. 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[12]. 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[13–15].

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"[16]. CPGs for the management, investigation, and/or follow-up of those who experience RM have been issued by professional societies such as ESHRE[1], the American College of Obstetricians and Gynaecologists[17], and the Royal College of Obstetricians and Gynaecologists[18]; however, the existence of guidelines in other high-income countries is unknown to the study team. While there are CPGs on miscarriage in Ireland[19,20], 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 this 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[21]; the completed checklist is available as Extended Data[22]. 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[23].

### Eligibility criteria

The "PICAR" framework was used to guide review inclusion and exclusion criteria (Table 1). For the purpose of this review, CPGs are defined as "systematically developed statements to assist practitioners about appropriate health care for specific

**Table 1. PICAR statement.**

| PICAR framework | Eligibility criteria |
|---|---|
| **P**opulation, clinical indication(s), and condition(s) | **Study population**<br>• Women/couples experiencing recurrent miscarriage (RM)<br>• Humans only<br>**Clinical indication**<br>• Investigation, management and/or follow-up of women/couples with RM – specifically first trimester RM<br>**Clinical condition**<br>• RM; defined by the review team as the loss of two or more consecutive pregnancies[1], 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 |
| **I**nterventions | • Any intervention focusing on the investigation, management and/or follow-up of RM |
| **C**omparator(s), Comparison(s), and (key) Content | • Any comparator or comparison<br>• No 'key' CPG content is of interest – unless CPGs are broader in scope; in such instances, content specific to RM is only of interest |
| **A**ttributes of eligible CPGs | **Language**<br>• Available in English<br>• CPGs where summaries are available in English, but full text is not, will be excluded<br>**Year of publication**<br>• 2000 onwards<br>• In Ireland, the National Clinical Effectiveness Committee (NCEC), requires a full guideline update within three years[24]; while The Scottish Intercollegiate Guidelines Network (SIGN) also specifies three years, it also includes those over three years old and revalidated[25]. The World Health Organisation does not have a defined period for guideline updates[26]. 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[17,27]. A good quality older guideline could be a good base on which to develop a new guideline[28]<br>**Developing/publishing organisation**<br>• Only CPGs issued or endorsed by national or international scientific societies, professional colleges, charitable organisations, and government organisations will be included<br>**Country of publication**<br>• High-income countries, as defined by the World Bank[29]; given the large discrepancies in pregnancy outcomes and care structures between high, and low and middle-income countries[30,31]<br>**Version**<br>• Latest version only<br>**Development process**<br>• Evidence and/or consensus-based<br>**System of rating evidence**<br>• 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<br>**Quality of evidence**<br>• The eligibility of CPGs will not be based on a specific minimum quality cut-off score based on the AGREE II criteria.<br>• 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[23]); this will however be taken into consideration when synthesising and interpreting the review findings<br>**Scope**<br>• Must have a primary/secondary focus on the investigation and treatment of RM<br>• Must be national/international in scope<br>• 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<br>• Must be clearly identified as a CPG<br>• Must be published. Unpublished CPGs, conference papers, discussion papers, drafts and opinions will be excluded<br>**Recommendations**<br>• 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)<br>• 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 |

clinical circumstances"; an adaptation of the definitions used by National Clinical Effectiveness Committee (NCEC)[24] and Scottish Intercollegiate Guidelines Network (SIGN)[32].

## 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[33]. 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 using the "OR" Boolean operators. The search strategy will be developed in Medline (see Extended Data for sample search

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

| Guideline repositories | Website |
|---|---|
| Canadian Agency for Drugs and Technology in Health (CADTH) | www.cadth.ca |
| Guidelines International Network (GIN) | http://www.g-i-n.net/library/international-guidelines-library |
| Institute for Clinical Systems Improvement (ICSI) | www.icsi.org/guidelines |
| Lenus: The Irish Health Repository | https://www.lenus.ie/hse/ |
| National Institute for Health and Care Excellence (NICE) | www.nice.org.uk |
| Scottish Intercollegiate Guidelines Network (SIGN) | http://www.sign.ac.uk/index.html |
| TRIP database | https://www.tripdatabase.com |
| World Health Organisation | https://www.who.int/publications/guidelines/en/ |

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

| Organisation | Country/Region |
|---|---|
| Royal College of Physicians of Ireland Institute of Obstetricians and Gynaecologists | Ireland |
| Royal College of Obstetricians and Gynaecologists (RCOG) | UK |
| European Society of Human Reproduction and Embryology (ESHRE) | Europe |
| The International Federation of Gynaecology and Obstetrics (FIGO) | International |
| The American College of Obstetricians and Gynaecologists (ACOG) | US |
| The Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) | Australia & New Zealand |
| American Society for Reproductive Medicine (ASRM) | US |
| Society for Maternal-Fetal Medicine (SMFM) | International |
| Society of Obstetricians and Gynaecologists of Canada (SOGC) | Canada |

**Table 4. Search terms.**

| Concept | Search terms |
|---|---|
| 1: Clinical guidelines | guideline* OR standard* OR best practice* OR guidance |
| 2: Recurrent miscarriage | Miscarriage* OR pregnancy loss* OR spontaneous abortion* OR recurrent fetal loss* OR recurrent foetal loss* |

strategy[22] 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 subsequently, and independently, screen the full text articles of records identified to identify studies to be included. Any disagreements 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 completeness 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[22]), 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[28]
- 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 agreement 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[34]. 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[35]. It has limitations, however; for example, it does not assess the implementation of the guideline[36].

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[36,37]: 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[38] 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

Open Science Framework: A systematic review of clinical practice guidelines for recurrent miscarriage, https://doi.org/10.17605/OSF.IO/X7Y4N[22].

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).

## References

1.  ESHRE Early Pregnancy Guideline Development Group: **Guideline on the Management of Recurrent Pregnancy Loss. Version 2.** Grimbergen, Belgium: European Society of Human Reproduction and Embryology. 2017.
    **Reference Source**

2.  Royal College of Obstetricians and Gynaecologists: **Green-top Guideline Number 17. The Investigation and Treatment of Couples with Recurrent First-trimester and Second-trimester Miscarriage.** London: Royal College of Obstetricians and Gynaecologists; 2011.
    **Reference Source**

3.  Roman E: **Fetal loss rates and their relation to pregnancy order.** *J Epidemiol*

*Community Health.* 1984; **38**(1): 29–35.
**PubMed Abstract** | **Publisher Full Text** | **Free Full Text**

4. Rai R, Regan L: **Recurrent miscarriage.** *Lancet.* 2006; **368**(9535): 601–11.
**PubMed Abstract** | **Publisher Full Text**

5. Clifford K, Rai R, Regan L: **Future pregnancy outcome in unexplained recurrent first trimester miscarriage.** *Hum Reprod.* 1997; **12**(2): 387–9.
**PubMed Abstract** | **Publisher Full Text**

6. Nybo Andersen AM, Wohlfahrt J, Christens P, *et al.*: **Maternal age and fetal loss: population based register linkage study.** *BMJ.* 2000; **320**(7251): 1708–12.
**PubMed Abstract** | **Publisher Full Text** | **Free Full Text**

7. El Hachem H, Crepaux V, May-Panloup P, *et al.*: **Recurrent pregnancy loss: current perspectives.** *Int J Womens Health.* 2017; **9**: 331–45.
**PubMed Abstract** | **Publisher Full Text** | **Free Full Text**

8. Matjila MJ, Hoffman A, van der Spuy ZM: **Medical conditions associated with recurrent miscarriage-Is BMI the tip of the iceberg?** *Eur J Obstet Gynecol Reprod Biol.* 2017; **214**: 91–6.
**PubMed Abstract** | **Publisher Full Text**

9. Clifford K, Rai R, Watson H, *et al.*: **An informative protocol for the investigation of recurrent miscarriage: preliminary experience of 500 consecutive cases.** *Hum Reprod.* 1994; **9**(7): 1328–32.
**PubMed Abstract** | **Publisher Full Text**

10. Brigham SA, Conlon C, Farquharson RG: **A longitudinal study of pregnancy outcome following idiopathic recurrent miscarriage.** *Hum Reprod.* 1999; **14**(11): 2868–71.
**PubMed Abstract** | **Publisher Full Text**

11. Lok IH, Neugebauer R: **Psychological morbidity following miscarriage.** *Best Pract Res Clin Obstet Gynaecol.* 2007; **21**(2): 229–47.
**PubMed Abstract** | **Publisher Full Text**

12. Klock SC, Chang G, Hiley A, *et al.*: **Psychological distress among women with recurrent spontaneous abortion.** *Psychosomatics.* 1997; **38**(5): 503–7.
**PubMed Abstract** | **Publisher Full Text**

13. Farren J, Mitchell-Jones N, Verbakel JY, *et al.*: **The psychological impact of early pregnancy loss.** *Hum Reprod Update.* 2018; **24**(6): 731–49.
**PubMed Abstract** | **Publisher Full Text**

14. Tavoli Z, Mohammadi M, Tavoli A, *et al.*: **Quality of life and psychological distress in women with recurrent miscarriage: a comparative study.** *Health Qual Life Outcomes.* 2018; **16**(1): 150.
**PubMed Abstract** | **Publisher Full Text** | **Free Full Text**

15. Kolte AM, Olsen LR, Mikkelsen EM, *et al.*: **Depression and emotional stress is highly prevalent among women with recurrent pregnancy loss.** *Hum Reprod.* 2015; **30**(4): 777–82.
**PubMed Abstract** | **Publisher Full Text** | **Free Full Text**

16. Institute of Medicine: **Clinical Practice Guidelines We Can Trust.** In: Graham RMM, Wolman DM, Greenfield S, Steinberg E, editor. Washington, DC: The National Academies Press; 2011.
**PubMed Abstract** | **Publisher Full Text**

17. American College of Obstetricians and Gynecologists: **ACOG practice bulletin. Management of recurrent pregnancy loss. Number 24, February 2001. (Replaces Technical Bulletin Number 212, September 1995). American College of Obstetricians and Gynecologists.** *Int J Gynaecol Obstet.* 2002; **78**(2): 179–90.
**PubMed Abstract** | **Publisher Full Text**

18. Royal College of Obstetricians and Gynaecologists: **Recurrent Miscarriage, Investigation and Treatment of Couples (Green-top Guideline No. 17).** London: Royal College of Obstetricians and Gynaecologists; 2011.
**Reference Source**

19. Institute of Obstetricians and Gynaecologists Royal College of Physicians of Ireland, Directorate of Strategy and Clinical Programmes Health Service Executive: **Clinical Practice Guideline: Management of Early Pregnancy Miscarriage, Version 1.0.** Dublin: Institute of Obstetricians and Gynaecologists Royal College of Physicians of Ireland; 2012.
**Reference Source**

20. Institute of Obstetricians and Gynaecologists Royal College of Physicians of Ireland, Directorate of Strategy and Clinical Programmes Health Service Executive: **Clinical Practice Guideline: The Management of Second Trimester Miscarriage, Version 1.0.** Dublin: Institute of Obstetricians and Gynaecologists Royal College of Physicians of Ireland; 2014.
**Reference Source**

21. Moher D, Shamseer L, Clarke M, *et al.*: **Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 Statement.** *Syst Rev.* 2015; **4**(1): 1.
**PubMed Abstract** | **Publisher Full Text** | **Free Full Text**

22. Hennessy M, Dennehy R, Meaney S, *et al.*: **A systematic review of clinical practice guidelines for recurrent miscarriage.** 2020.
**http://www.doi.org/10.17605/OSF.IO/X7Y4N**

23. Johnston A, Kelly SE, Hsieh SC, *et al.*: **Systematic Reviews of Clinical Practice Guidelines: A Methodological Guide.** *J Clin Epidemiol.* 2019; **108**: 64–76.
**PubMed Abstract** | **Publisher Full Text**

24. National Clinical Effectiveness Committee: **How to develop a National Clinical Guideline: A manual for guideline developers.** Dublin: Department of Health; 2019.
**Reference Source**

25. Scottish Intercollegiate Guidelines Network (SIGN): **A guideline developer's handbook.** Edinburgh: Scottish Intercollegiate Guidelines Network; 2019.
**Reference Source**

26. World Health Organisation: **WHO handbook for guideline development –2nd ed.** Geneva: World Health Organistaion; 2014.
**Reference Source**

27. Association of Early Pregnancy Units: **Guidelines.** London: Association of Early Pregnancy Units; 2007.
**Reference Source**

28. The ADAPTE Collaboration: **The ADAPTE Process: Resource Toolkit for Guideline Adaptation. Version 2.0.** Berlin: Guideline International Network; 2009.
**Reference Source**

29. World Bank: **World Bank Country and Lending Groups.** 2020.
**Reference Source**

30. Goldenberg RL, McClure EM, Saleem S: **Improving pregnancy outcomes in low- and middle-income countries.** *Reprod Health.* 2018; **15**(Suppl 1): 88.
**PubMed Abstract** | **Publisher Full Text** | **Free Full Text**

31. Gage AD, Carnes F, Blossom J, *et al.*: **In Low- And Middle-Income Countries, Is Delivery In High-Quality Obstetric Facilities Geographically Feasible?** *Health Aff (Millwood).* 2019; **38**(9): 1576–84.
**PubMed Abstract** | **Publisher Full Text**

32. SIGN: **What are guidelines?** Edinburgh: SIGN; 2020.
**Reference Source**

33. Methley AM, Campbell S, Chew-Graham C, *et al.*: **PICO, PICOS and SPIDER: a comparison study of specificity and sensitivity in three search tools for qualitative systematic reviews.** *BMC Health Serv Res.* 2014; **14**(1): 579.
**PubMed Abstract** | **Publisher Full Text** | **Free Full Text**

34. Brouwers MC, Kho ME, Browman GP, *et al.*: **AGREE II: advancing guideline development, reporting and evaluation in health care.** *CMAJ.* 2010; **182**(18): E839–42.
**PubMed Abstract** | **Publisher Full Text** | **Free Full Text**

35. Siering U, Eikermann M, Hausner E, *et al.*: **Appraisal tools for clinical practice guidelines: a systematic review.** *PLoS One.* 2013; **8**(12): e82915.
**PubMed Abstract** | **Publisher Full Text** | **Free Full Text**

36. Daley B, Hitman G, Fenton N, *et al.*: **Assessment of the methodological quality of local clinical practice guidelines on the identification and management of gestational diabetes.** *BMJ Open.* 2019; **9**(6): e027285.
**PubMed Abstract** | **Publisher Full Text** | **Free Full Text**

37. Eady EA, Layton AM, Sprakel J, *et al.*: **AGREE II assessments of recent acne treatment guidelines: how well do they reveal trustworthiness as defined by the U.S. Institute of Medicine criteria?** *Br J Dermatol.* 2017; **177**(6): 1716–25.
**PubMed Abstract** | **Publisher Full Text**

38. Moher D, Liberati A, Tetzlaff J, *et al.*: **Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement.** *PLoS Med.* 2009; **6**(7): e1000097.
**PubMed Abstract** | **Publisher Full Text** | **Free Full Text**

# Open Peer Review

## Current Peer Review Status: ✓ ✓ ✓ ?

---

**Version 3**

Reviewer Report 14 December 2020

https://doi.org/10.21956/hrbopenres.14282.r28055

✓ **Emma Rasmark Roepke**
Department of Obstetrics and Gynecology, Institute of Clinical Sciences Lund, Skåne University Hospital, Lund University, Lund, Sweden

I find that the revisions are appropriate and sufficient to be Approved for indexing.

*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.**

---

**Version 1**

Reviewer Report 21 September 2020

https://doi.org/10.21956/hrbopenres.14119.r27802

? **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 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.

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'[1], while the Royal College of Obstetricians and Gynaecologists uses the term RM[2]. "

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.

Reviewer Report 15 September 2020

https://doi.org/10.21956/hrbopenres.14119.r27846

? **Emma Rasmark Roepke**

Department of Obstetrics and Gynecology, Institute of Clinical Sciences Lund, Skåne University Hospital, Lund University, Lund, Sweden

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:
- The PICAR states that only published guidelines will be included though "grey litteature" will also be serached for. Can the authors explaine this further?

- Why is GRADE system not used instead of AGREE?

- How will "low quality" guidelines be compared with "high quality"? How will different quality be implented in the en result (a new guideline)?

- 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.

Reviewer Report 07 September 2020

✔ **Jennifer Kaiser** (iD)
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.

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

Reviewer Report 18 May 2020

https://doi.org/10.21956/hrbopenres.14119.r27360

✓ **Merel M. J. van den Berg**
Centre for Reproductive Medicine, Amsterdam University Medical Centres, University of Amsterdam, Amsterdam, The Netherlands

Summary
This systematic review identifies and describes published clinical practice guidelines for the management, diagnostics and/or follow-up of women with RM. This studies 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.