

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Priorities for research in miscarriage: A priority setting partnership between people affected by miscarriage and professionals, following the James Lind Alliance methodology.
AUTHORS	Prior, Matthew; Bagness, Carmel; Brewin, Jane; Coomarasamy, Arri; Easthope, Lucy; Hepworth-Jones, Barbara; Hinshaw, Kim; O'Toole, Emily; Orford, Julie; Regan, Lesley; Raine-Fenning, Nick; Shakespeare, Judy; Small, Rachel; Thornton, Jim; Metcalf, Leanne

VERSION 1 - REVIEW

REVIEWER	Ole B. Christiansen, professor Fertility Clinic, Rigshospitalet Copenhagen University Hospital and Department of Obstetrics and Gynaecology Aalborg University Hospital Aalborg Denmark
REVIEW RETURNED	26-Mar-2017

GENERAL COMMENTS	<p>This is a very important study providing information about which questions should have highest priority in future miscarriage/recurrent miscarriage research primarily based on the opinion of the patients.</p> <p>It is not surprising that research into preventive treatment comes up with highest priority</p> <p>It is good that the authors chose to include patients with miscarriages defined by a positive pregnancy test in addition to clinical miscarriages happening until the possibility of survival. In too many studies biochemical pregnancies have been neglected.</p> <p>I need some points to be clarified before possible publication: It is indicated that participants were identified by patient organisations, newsletters, flyers in clinics and social media. However, from these sources it is unclear whether participants were included consecutively: in the order that they came into contact with the steering committee or were some kind of selection undertaken in a larger group of potential participants? Were patients equally distributed according geographical regions in the UK and social status (income and education)? If there is no information about this, it should be discussed as a limitation of the validity of the findings. Patients were included after only one miscarriage. It is likely that the priority for research questions would differ between patients with only one and those with several miscarriages. Is it possible to get any information about this? As a minimum, in the final workshop</p>
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	<p>including 11 patients, how many had recurrent miscarriage?</p> <p>It may be a problem that patients with threatened miscarriage (not ending in miscarriage) were included. Is it possible to get information about how many had "only" threatened miscarriage?</p> <p>The number of respondents vary from 1093 in the primary survey to 2122 in the interim survey. Was there any overlap between these two groups of respondents? For clarification, I need the number 2122 in the "interim box" in the figure.</p> <p>Minor point: sometimes the term "uncertainties" and sometimes the term "questions" are used e.g. in the abstract. Are there any differences in the meaning of the two terms? Otherwise, I would prefer that only one is used or that it is stressed that they are synonyms.</p>
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REVIEWER	James R. Scott University of Iowa and University of Utah U.S.
REVIEW RETURNED	04-Jun-2017

GENERAL COMMENTS	<p>The purpose of this study was to identify and prioritise important research questions for miscarriage. The study utilized a priority setting partnership which brings together patients, carers and clinicians; it is similar to the Delphi consensus process used for establishing core outcomes sets for research studies. The paper is well written, and the methods utilized are suitably described for this innovative, thoughtful and transparent process. My comments and questions are as follows:</p> <ol style="list-style-type: none"> 1. The inclusion of patient input along with healthcare professionals to determine clinically important research priorities is a relatively recent concept. Since a similar format will undoubtedly be used for other clinical entities, it is important to critique this technique and develop standardized guidelines for investigators to use for future partnership studies. 1. Page 3, Line 44 - Who decided that ethical approval was not required and on what basis? 2. Page 3, Line 48 - Exactly how were key stakeholders identified and selected through "peer knowledge and consultation?" Were the patients identified by the organizations involved, and were informed consent forms used? How many of the healthcare providers surveyed were physicians and what were their specialties or subspecialties? What is the optimum number, mix and percentages for each category of participants? What should the criteria and guidelines be for selecting participants from representative regions and different countries? All involved in this study were apparently from the U.K., but patients and physicians from the U.S. or other countries might have other questions or different priorities that are important or unique to them. For example, they might feel that it is more important to clarify long-standing controversial treatments such as lymphocyte immunization or new treatments such as preimplantation genetic screening than this group did. All of these factors could affect the top 10 results. 3. Page 4, Line 11 - Please define or describe what information was obtained on the "declaration of interest form." 4. Page 4, Line 50 - Exactly how did the steering committee determine the validity of the questionnaire? 5. Page 7. Line 30 - Although prioritizing the top 10 unanswered research questions is useful, simply adding more studies that are poorly done in these areas would not advance the field. Nothing is
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	<p>mentioned about the quality of research needed nor avoiding wasteful research. Perhaps there should be more emphasis on high quality RCTs or at least a mention that the future research generated and its publication should follow EQUATOR guidelines.</p> <p>6. Page 7, Lines 51 & 55 - Can you provide more details about what you mean by "The response rate to both surveys was considerable"? The inability to assess the response rate is a significant weakness and makes it difficult to rule out non-response bias and assess the scientific validity of the survey results.</p> <p>7. Page 8, Line 40 - What is the evidence for the statement that "This area of care is often overlooked and most women do not receive any explanation for their miscarriage or any psychological or emotional support." Does this mean care in the U.K or everywhere?</p> <p>8. Page 8, Line 46 - Perhaps the NIHR funded PRISM and C-Stitch trials should be defined or explained for readers not familiar with them.</p> <p>9. Page 12, Table 1. There seems to be some overlap in the final top 10 uncertainties listed. Numbers 1 and 8 both list interventions, Numbers 3 and 9 mention investigations and numbers 3 and 8 describe preconception tests.</p> <p>10. Page 24, Appendix 5 - The numbers don't always line up with a new uncertainty.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name:

Ole B. Christiansen, professor Institution and Country:

Fertility Clinic, Rigshospitalet,

Copenhagen University Hospital and Department of Obstetrics and Gynaecology, Aalborg University Hospital,

Aalborg, Denmark Competing Interests: None declared

This is a very important study providing information about which questions should have highest priority in future

miscarriage/recurrent miscarriage research primarily based on the opinion of the patients.

It is not surprising that research into preventive treatment comes up with the highest priority

It is good that the authors chose to include patients with miscarriages defined by a positive pregnancy test in

addition to clinical miscarriages happening until the possibility of survival. In too many studies.biochemical

pregnancies have been neglected. need some points to be clarified before possible publication:

1. It is indicated that participants were identified by patient organisations, newsletters, flyers in clinics and social

media. However, from these sources it is unclear whether participants were included consecutively: in the

order that they came into contact with the steering committee or were some kind of selection undertaken in

a larger group of potential participants?

Rephrased this sentence to clarify that the survey was hosted on the psp website and potential participants invited to complete the survey instead of sending it out to participant.

2. Were patients equally distributed according geographical regions in the UK and social status (income and

education)? If there is no information about this, it should be discussed as a limitation of the validity of the

findings.

Geographical data are now presented in the results and social status, income and education included as limitations in the discussion

3. Patients were included after only one miscarriage. It is likely that the priority for research questions would

differ between patients with only one and those with several miscarriages. Is it possible to get any information

about this? As a minimum, in the final workshop including 11 patients, how many had recurrent miscarriage?

These data are now included in Appendix 3 and referred to in the manuscript

4. It may be a problem that patients with threatened miscarriage (not ending in miscarriage) were included. Is

it possible to get information about how many had “only” threatened miscarriage?

1% of survey respondents had only experienced threatened miscarriage.

Now included in the results

5. The number of respondents vary from 1093 in the primary survey to 2122 in the interim survey. Was there

any overlap between these two groups of respondents? For clarification, I need the number 2122 in the

“interim box” in the figure.

Included in the revised figure

6. Minor point: sometimes the term “uncertainties” and sometimes the term “questions” are used e.g. in the

abstract. Are there any differences in the meaning of the two terms? Otherwise, I would prefer that only

one is used or that it is stressed that they are synonyms.

Revision has changed the language from uncertainties to questions

Reviewer: 2

Reviewer Name: James R. Scott Institution and Country: University of Iowa and University of Utah, U.S.

Competing Interests: None Declared

The purpose of this study was to identify and prioritise important research questions for miscarriage.

The study

utilized a priority setting partnership which brings together patients, carers and clinicians; it is similar to the Delphi

consensus process used for establishing core outcomes sets for research studies. The paper is well written, and the

methods utilized are suitably described for this innovative, thoughtful and transparent process. My comments and

questions are as follows:

1. The inclusion of patient input along with healthcare professionals to determine clinically important research

priorities is a relatively recent concept. Since a similar format will undoubtedly be used for other clinical

entities, it is important to critique this technique and develop standardized guidelines for investigators to use

for future partnership studies.

We used the standardised James Lind Alliance methodology reference number 10. We have now added a sentence and reference to the methods section to highlight this. We also a published protocol linked in the first paragraph of the methods.

2. Page 3, Line 44 - Who decided that ethical approval was not required and on what basis?

We have clarified that priority setting partnerships are considered a service evaluation and that ethical approval is not required.

3. Page 3, Line 48 - Exactly how were key stakeholders identified and selected through "peer knowledge and consultation?" Were the patients identified by the organizations involved, and were informed consent forms used?

We have tightened up the language to make clear that the proceeding paragraph explains this process

4. How many of the healthcare providers surveyed were physicians and what were their specialties or subspecialties?

Now included in Appendix 3

5. What is the optimum number, mix and percentages for each category of participants? What should the

criteria and guidelines be for selecting participants from representative regions and different countries? All

involved in this study were apparently from the U.K., but patients and physicians from the U.S. or other

countries might have other questions or different priorities that are important or unique to them. For example, they might feel that it is more important to clarify long-standing controversial treatments such as

lymphocyte immunization or new treatments such as preimplantation genetic screening than this group did.

All of these factors could affect the top 10 results.

Now in the discussion

6. Page 4, Line 11 - Please define or describe what information was obtained on the "declaration of interest form."

Included in the revised manuscript

7. Page 4, Line 50 - Exactly how did the steering committee determine the validity of the questionnaire?

Revised in the manuscript

8. Page 7. Line 30 - Although prioritizing the top 10 unanswered research questions is useful, simply adding

more studies that are poorly done in these areas would not advance the field. Nothing is mentioned about

the quality of research needed nor avoiding wasteful research. Perhaps there should be more emphasis on

high quality RCTs or at least a mention that the future research generated and its publication should follow

EQUATOR guidelines.

Thank you for this suggestion, we have now raised this issue in the discussion

9. Page 7, Lines 51 and 55 - Can you provide more details about what you mean by "The response rate to both

surveys was considerable"? The inability to assess the response rate is a significant weakness and makes it

difficult to rule out non-response bias and assess the scientific validity of the survey results.

We agree this is an assestion and have amended the text to remove the word considerable. The Appendix compares responses with other PSPs

10. Page 8, Line 40 - What is the evidence for the statement that "This area of care is often overlooked and most

women do not receive any explanation for their miscarriage or any psychological or emotional support." Does

this mean care in the U.K or everywhere?

We have referenced NICE Guideline for miscarriage and ectopic pregnancy.

11. Page 8, Line 46 - Perhaps the NIHR funded PRISM and C-Stitch trials should be defined or explained for readers not familiar with them.

We have explained these in more detail

12. Page 12, Table 1. There seems to be some overlap in the final top 10 uncertainties listed. Numbers 1 and 8

both list interventions, Numbers 3 and 9 mention investigations and numbers 3 and 8 describe preconception tests.

We have now mentioned this limitation in the discussion

13. Page 24, Appendix 5 - The numbers don't always line up with a new uncertainty.

Aligned in the revision

VERSION 2 – REVIEW

REVIEWER	James R. Scott, MD University of Iowa and University of Utah, U.S.
REVIEW RETURNED	21-Jun-2017

GENERAL COMMENTS	<p>The manuscript is now ready for publication. The authors have satisfactorily addressed the questions I raised, but two answers are still somewhat unclear to me:</p> <p>1. I asked who decided that ethical approval was not required and on what basis. The authors have only one sentence about this: "Priority setting partnerships are considered service evaluations and therefore approval from an NHS ethics committee is not required." I am not sure what "service evaluation" is nor exactly who decides that ethics committee approval is not required. Is this decided by the investigators or the James Lind Alliance? I notice that other consensus outcomes publications have similar statements, but they usually state that the Ethics committee has declared this.</p> <p>2. I requested evidence for the general statement that women do not receive any explanation for their miscarriage or emotional support. The authors referenced the NICE guidelines. I read the guidelines, but I did not see any evidence for the statement. Perhaps this is true in the U.K., but I think these women get extensive counselling, support and explanation in most miscarriage clinics in the U.S.</p>
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VERSION 2 – AUTHOR RESPONSE

Reviewer: 2

Reviewer Name: James R. Scott, MD

Institution and Country: University of Iowa and University of Utah, U.S.

Competing Interests: None declared

The manuscript is now ready for publication. The authors have satisfactorily addressed the questions I raised, but two answers are still somewhat unclear to me:

1. I asked who decided that ethical approval was not required and on what basis. The authors have only one sentence about this: "Priority setting partnerships are considered service evaluations and therefore approval from an NHS ethics committee is not required." I am not sure what "service evaluation" is nor exactly who decides that ethics committee approval is not required. Is this decided by the investigators or the James Lind Alliance? I notice that other consensus outcomes publications

have similar statements, but they usually state that the Ethics committee has declared this.

Response:

We have added a statement and three further references, including manuscripts published by BMJ Open to satisfy this concern regarding ethical approval. JLA has a well established methodology that has been operational since 2004, and there is no evidence that the JLA methodology has resulted in any harm.

"Previous James Lind Alliance priority setting partnerships have been reviewed by research ethics committees and judged as service evaluations, and therefore as not requiring research ethics committee review. In view of this, in the present case, we followed the practice of many recent priority setting partnerships [14,16,17,18] and made this decision ourselves without formally asking the research ethics committee."

2. I requested evidence for the general statement that women do not receive any explanation for their miscarriage or emotional support. The authors referenced the NICE guidelines. I read the guidelines, but I did not see any evidence for the statement. Perhaps this is true in the U.K., but I think these women get extensive counselling, support and explanation in most miscarriage clinics in the U.S.

Response: The statement has been updated to accurately reflect the NICE guidelines. It now states: "There has been very little good quality research on improving physical and emotional health for couples with pregnancy loss".