## PEER REVIEW HISTORY



## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | Development of a Core Outcome Sets for IMmunomodulation in PREGnancy (COSIMPREG): a protocol for a systematic review and Delphi study |
| **AUTHORS** | Prins, Jelmer; Holvast, Floor; Van 't Hooft, Janneke; Bos, Arend; Ganzevoort, Jan; Scherjon, Sicco; Robertson, Sarah; Gordijn, Sanne |

## VERSION 1 – REVIEW

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| **REVIEWER** | James R. Scott, MD<br>Department of Obstetrics and Gynecology, University of Iowa Carver College of Medicine, Iowa City, Iowa, U. S. |
| **REVIEW RETURNED** | 18-Jan-2018 |

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| **GENERAL COMMENTS** | This is an important and needed protocol to standardize outcomes and advance the field of reproductive immunology. The methods and planned Delphi process are excellent and well described. I have a few comments for the authors to consider:<br>1. Much of the Introduction and background information is very optimistic and is opinion rather than fact. For example, perhaps you can provide a reference for the statements "Immune-modulating therapeutic options are projected to improve (by whom?), will become more tailored, and will be more common(ly) used in the next few years....." Is aspirin really an immune modulating agent?<br>2. How can human and animal studies be combined? I have some concerns about including animal studies because they usually cannot be interpolated to the human situation. Also, I am not sure how patients on the panel could evaluate these studies.<br>3. Line 140 - I am not clear on the reason for not assessing bias but including funding sources. Will the quality of the studies selected for the systematic review be graded?<br>4. Lines 162-175 Exactly how will the panel members for the Delphi procedure be identified and selected, how many, and what proportion from each group? What is meant by "at least 10 experts per "subpanel"?<br>I hope these comments are helpful. Best wishes |

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| **REVIEWER** | Jens Langhoff-Roos, MD PhD<br>Dept Obstetrics, Rigshospitalet, University of Copenhagen, Denmark |
| **REVIEW RETURNED** | 21-Jan-2018 |

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| **GENERAL COMMENTS** | An interesting project on the democratic approach to sound reporting of scientific research.<br>Does the search term "immune modulation" include sufficient number of relevant publications on severe pregnancy complication (prophylaxis and treatment)? |

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| | How do you select relevant experts (friends, neighbours, etc)? :-)<br>How do you avoid a Dutch dominance? Do you think that a final meeting in Paris (SRI 2019) will improve the likelihood that the international perspective is covered?<br>This is a very subjective study, lots of potential bias.<br>Did you consider a controlled study, having two parallel Delphi studies one in mid Europe (The Netherlands) and another in North America?<br>Why not? |

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| **REVIEWER** | Paul Smith<br>The University of Birmingham |
| **REVIEW RETURNED** | 22-Jan-2018 |

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| **GENERAL COMMENTS** | This paper is well written and the general methodology for this work is good. I have some doubts regarding the subject of the core outcome set. Core outcome sets are usually done for a particular condition rather than a treatment type. For instance, a core outcome set for preeclampsia trials would seem better than trying to encompass multiple conditions using a term like immunotherapy. For example, immunotherapy for rheumatology conditions in pregnancy is likely to need very different outcomes than a trial for aspirin and preeclampsia. A core outcome set encompassing varied conditions such as recurrent miscarriage, preeclampsia etc would essentially be a core outcome set for trials in pregnant women.<br><br>How they are defining immunomodulation is not completely clear and the search terms used need to be more explicit. I would expect many trials looking at immunomodulation not to use that actual term or synonyms. |

**VERSION 1 – AUTHOR RESPONSE**

Reviewer(s)' Comments to Author:

Reviewer: 1
Reviewer Name: James R. Scott, MD
Institution and Country: Department of Obstetrics and Gynecology, University of Iowa Carver College of Medicine, Iowa City, Iowa, U. S.
Please state any competing interests or state ‘None declared’: None

Please leave your comments for the authors below This is an important and needed protocol to standardize outcomes and advance the field of reproductive immunology. The methods and planned Delphi process are excellent and well described.

Thank you.

I have a few comments for the authors to consider:

1. Much of the Introduction and background information is very optimistic and is opinion rather than fact. For example, perhaps you can provide a reference for the statements "Immune-modulating therapeutic options are projected to improve (by whom?), will become more tailored, and will be more common(ly) used in the next few years....."

We thank the reviewer for this useful comment. We agree that some of the introduction is overly optimistic, and indeed there are many challenges to developing save and effective immune modulating therapies, and selecting appropriate patient groups. We also agree that part of this is opinion. However, interest and effort in developing immune-modulating therapies is growing, and many (pre-)clinical studies have been initiated to evaluate the effect of immune modulating agents in pregnancy. Therefore we believe it is reasonable to expect that in time, effective therapies will emerge, and that development of therapies will be assisted by a consensus core outcome set. We have adjusted the relevant sentences in the introduction to read:

'There is a reasonable prospect that given advances in other disease conditions such as oncology and autoimmune disease, more targeted and effective immune-modulating therapeutic options will emerge for reproduction medicine. Although several pre-clinical / animal studies show promising results, these options must now be tailored to achieve targeted, safe immunotherapy both as prevention and therapy for pregnancy complications. Moreover, since a range of immune factors are implicated in pregnancy complications selection of the right patients will be essential for the success of therapy.'

Is aspirin really an immune modulating agent?

Aspirin does not solely target the immune system and has effects on many different biological processes, including effects on platelets, pain perception, and inflammation. We have adjusted this sentence to read:

'These approaches include drugs which have effects on the immune system, but also on other pathways. For example, a commonly used therapy is acetylsalicylic acid (aspirin), which is widely used to prevent preeclampsia.'

2. How can human and animal studies be combined? I have some concerns about including animal studies because they usually cannot be interpolated to the human situation. Also, I am not sure how patients on the panel could evaluate these studies.

This is a valid question. Indeed, human and animal studies cannot fully be combined and animal studies cannot be directly extrapolated to the human situation. However, the field of reproductive immunology is relatively small, and many researchers perform both human and animal studies. Moreover, to identify possible human therapies, preclinical data from animal studies evaluating similar outcomes and parameters are necessary. Therefore, we aim to define a separate core outcome set for both human and animal studies.

We have clarified this in the manuscript to read: "We aim to develop COSs for studies both in humans and animals, that will be reported separately."

Regarding patients and animal studies, indeed patients cannot evaluate animal outcomes. Moreover, some other panels can also not evaluate animal outcomes. Therefore not all panels will evaluate all outcomes.

We have clarified this in the manuscript to read: "As not all different panels will include experts in animal studies, and since we aim to develop two separate COS documents for animal and human studies, only the reproductive science and immunology panels will be able to contribute to assembling the animal COS."

3. Line 140 - I am not clear on the reason for not assessing bias but including funding sources. Will the quality of the studies selected for the systematic review be graded?

The reviewer is right, it does not make sense to include funding sources but not to assess bias. As the aim of the systematic review is to identify all outcomes that have been used within studies using immune modulation in pregnancy we will include all studies reporting on this. We have deleted the sentence about assessing bias from the manuscript.

The quality of the studies will not be graded in this systematic review, since the aim is only to identify all outcomes already in use, regardless of study quality. We will count how often a specific outcome is used.

We have clarified this in the manuscript to read: “Since we aim to include all relevant outcomes and parameters reported to date and we will not discriminate on efficacy of intervention, the included studies will not be assessed regarding their risk of bias, nor will they be graded.”. And also into: “Overlapping outcomes will be collated and reported under a covering term. For each reported outcome the number of times it is reported (absolute and relative) in studies will be shown. This scoring will also be done in the categories mentioned earlier.”

4. Lines 162-175 Exactly how will the panel members for the Delphi procedure be identified and selected, how many, and what proportion from each group? What is meant by "at least 10 experts per "subpanel"?

We appreciate this question. Experts should have at least 5 years experience within their expert field, and / or should have recent relevant publications related to immune modulation in pregnancy, or have a well-known status in a relevant field. To ensure that all panels have equal geographical distribution and to prevent bias, panel members for the Delphi procedure will be identified and selected through different processes.
Firstly, we will identify potential experts involved in immune modulating studies through the systematic review. This will identify potential experts with >5 years of work in this field, and also experts with relevant recent publications. Secondly, we will ask potential panel members to provide us with the names of other relevant experts who meet the inclusion criteria, and should be invited to participate in order for this procedure to be optimally executed. We will underline the need for experts in all regions and ask the experts specifically to mention experts in South America, Africa, and Asia-Oceania as these are the regions that have been relatively under-represented in previous Delphi procedures with Obstetric focus (Gordijn 2016, Khalil 2018). Professor Robertson and Professor Scherjon, both internationally renowned experts on reproductive immunology, will be responsible for creating diverse expert panels.

Additionally we felt that we had overlooked including a neonatologist on the core outcome team. Therefore we have now consulted a neonatologist, who is renowned internationally for neonatal care. He has approved the manuscript and will help us assemble a neonatologist panel.

Regarding the patient / consumer selection the procedure is slightly different. We will ask patient / consumer organizations to be involved and to provide us with contact details of patients who are willing to help. To fully guarantee diversity in the Delphi procedure we will include at least 10 experts in every panel (as in at least 10 pediatricians, at least 10 patients, etcetera), to a total of not less than 100 experts.

We have clarified this in the manuscript.

I hope these comments are helpful. Best wishes

They certainly are, thank you.

Reviewer: 2
Reviewer Name: Jens Langhoff-Roos, MD PhD Institution and Country: Dept Obstetrics, Rigshospitalet, University of Copenhagen, Denmark Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below An interesting project on the democratic approach to sound reporting of scientific research.
Does the search term "immune modulation" include sufficient number of relevant publications on severe pregnancy complication (prophylaxis and treatment)?

We understand the concern of the reviewer, and indeed the term 'immune modulation' will not capture a sufficient number of relevant publications. This term was used in a preliminary search strategy, and we are now finalizing the search strategy terms with the assistance of a search expert. To be sure that we include all relevant publications we will use a refined search approach, we have adjusted this in the manuscript, and added the preliminary search strategy as a table.

How do you select relevant experts (friends, neighbours, etc)? :-) How do you avoid a Dutch dominance? Do you think that a final meeting in Paris (SRI 2019) will improve the likelihood that the international perspective is covered?

This is a very valid question, we agree with the reviewer that Dutch / European dominance must be prevented, if world wide buy-in and uptake is to be achieved. As also explained to reviewer 1, to ensure that panels have appropriate geographical distribution and to prevent bias, panel members for the Delphi procedure will be identified and selected through different processes. In short potential experts should have worked at least 5 years within their expert field, and / or should have recent relevant publications related to immune modulation in pregnancy, or have a well-known status in a relevant field. Firstly, we will identify potential experts involved in immune modulating studies through the systematic review. This will identify potential experts with >5 years of work in this field, and also experts with relevant recent publications. Secondly, we will ask potential panel members to provide us with the names of other relevant experts who meet the inclusion criteria, and should be invited to participate in order for this procedure to be optimally executed. We will underline the need for experts in all regions and ask the experts specifically to mention experts in South America, Africa, and Asia-Oceania as these are the regions that have been under relatively under-represented in previous Delphi procedures with Obstetric focus (Gordijn 2016, Khalil 2018). Professor Robertson and Professor Scherjon, both internationally renowned experts on reproductive immunology, will be responsible for creating diverse expert panels.

We believe that the Society of Reproductive Investigation meeting is a suitable meeting for finalizing the core outcome set, as the SRI has a very broad and international membership. However, we also understand the concern of the reviewer. To optimize geographical diversity we will enquire on the availability of the experts to attend different meetings, presumably the following meetings: Society of Reproductive Investigation, annual meeting of American Society of Reproductive Immunology, or International Society for Immunology of Reproduction, all in 2019. We will also investigate the possibility of teleconferencing from one or more international sites. We have adjusted this in the manuscript.

This is a very subjective study, lots of potential bias. Did you consider a controlled study, having two parallel Delphi studies one in mid Europe (The Netherlands) and another in North America? Why not?

We agree with the reviewer that such a study has potential biases. We believe that by using a systematic review to include all outcomes already in use, will prevent bias in selecting relevant outcomes. Identifying potential experts via the systematic review, will also limit selection bias. Moreover, we will limit the chance of geographical bias by furthermore ensuring contribution of diverse experts on each panel and at the consensus meeting. We believe these steps will minimized potential bias.
Although we can see the merit of two parallel Delphi studies, this would not address geographical bias against regions including Asia, Africa, and Southern America that would not be represented. Moreover, discussion between different experts will be limited, thereby not resulting in a worldwide consensus COS.

Reviewer: 3
Reviewer Name: Paul Smith
Institution and Country: The University of Birmingham Please state any competing interests or state 'None declared': None

Please leave your comments for the authors below

This paper is well written and the general methodology for this work is good.

Thank you.

I have some doubts regarding the subject of the core outcome set. Core outcome sets are usually done for a particular condition rather than a treatment type. For instance, a core outcome set for preeclampsia trials would seem better than trying to encompass multiple conditions using a term like immunotherapy. For example, immunotherapy for rheumatology conditions in pregnancy is likely to need very different outcomes than a trial for aspirin and preeclampsia. A core outcome set encompassing varied conditions such as recurrent miscarriage, preeclampsia etc would essentially be a core outcome set for trials in pregnant women.

We thank the reviewer for this valuable comment. We agree that core outcome sets are usually composed for a condition instead of a treatment type. However, we believe that there are immune outcomes / parameters that are of particular importance to include in trials evaluating immunotherapy in pregnancy, compared with (for example) anti-hypertensive drugs. Therefore, in cases where immune modulation is studied in a specific clinical condition, then outcomes from both the COS for the clinical condition of investigation and immune modulation would need to be collected, and most likely there will be overlap of some core outcomes. Immune modulation is attracting more and more attention for many diseases and conditions, including pregnancy conditions. In future management of these conditions it will be important to align the outcomes for comparison, especially in 'hot topic' areas, where unregulated proliferation of studies without harmonized outcomes wastes money and creates confusion.

We would like to set out again that the aim of this core set of outcomes would be used in studies when the immunotherapy is used as a therapy or preventive for immune-mediated complications of pregnancy, not for 'regular' (non-immune) therapies in pregnant women.

We have clarified this in the manuscript.

How they are defining immunomodulation is not completely clear and the search terms used need to be more explicit. I would expect many trials looking at immunomodulation not to use that actual term or synonyms.

We understand the concern of the reviewer. As detailed in our response to reviewer 1 and 2, indeed the term ‘immune modulation’ is limiting. We are developing the search strategy in consultation with a literature search expert. We have adjusted this in the manuscript, and added the preliminary search strategy as a table.

## VERSION 2 – REVIEW

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| **REVIEWER** | James R. Scott, MD<br>Department of Obstetrics and Gynecology, University of Iowa Carver College of Medicine, Iowa City, Iowa, U.S. |
| **REVIEW RETURNED** | 15-Mar-2018 |

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| **GENERAL COMMENTS** | The authors have adequately addressed my original comments. The development of standardized, clinically important outcomes such as live birth rate, and not just surrogate markers, is important and the Methods to achieve this objective are excellent . Having said that, not all experts are as convinced as the authors that immunologic therapies in the future will solve the human pregnancy problems that they list (i.e. ....."holds enormous potential." - Line 62) For example, recurrent pregnancy loss is mentioned in the Introduction. It is the prototype of a clinical problem that has been investigated with hundreds of immunologic studies over 50 years, but nothing of significance has emerged. In fact, potential immunologic factors are becoming less convincing as evidenced by the following two references: 1. Hviid MM, Macklon N. Immune modulation treatments - where is the evidence? Fertil Steril 2017;107(6):1264-93. 2. Popescu F, Jaslow CR, Kutteh WH. Recurrent pregnancy loss evaluation combined with 24-chromosome microarray of miscarriage tissue provides a probable or definite cause of pregnancy loss in over 90% of patients. Hum Reprod 2018:1-9 doi:1093/humrep/dey021 (published ahead of print) This does not detract from the Delphi study, but promotion of immunologic therapeutic possibilities in my view should be presented in a realistic, objective and evidence-based manner. |

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| **REVIEWER** | Jens Langhoff-Roos, MD PhD<br>Dept Obstetrics, Rigshospitalet, University of Copenhagen, Denmark |
| **REVIEW RETURNED** | 31-Mar-2018 |

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| **GENERAL COMMENTS** | Do you still believe in your idea? Don't you think that your scope is too broad and "immune modulation" very difficult to define? Is the project worth while compared to other "urging" projects?<br>If you answer: "yes", "no", "yes" - I wish you luck! :-) |

## VERSION 2 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Reviewer Name: James R. Scott, MD

Institution and Country: Department of Obstetrics and Gynecology, University of Iowa Carver College of Medicine, Iowa City, Iowa, U.S.

Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below

The authors have adequately addressed my original comments. The development of standardized, clinically important outcomes such as live birth rate, and not just surrogate markers, is important and the Methods to achieve this objective are excellent.

Thank you.

Having said that, not all experts are as convinced as the authors that immunologic therapies in the future will solve the human pregnancy problems that they list (i.e. ....."holds enormous potential." - Line 62) For example, recurrent pregnancy loss is mentioned in the Introduction. It is the prototype of a clinical problem that has been investigated with hundreds of immunologic studies over 50 years, but nothing of significance has emerged. In fact, potential immunologic factors are becoming less convincing as evidenced by the following two references: 1. Hviid MM, Macklon N. Immune modulation treatments - where is the evidence? Fertil Steril 2017;107(6):1264-93. 2. Popescu F, Jaslow CR, Kutteh WH. Recurrent pregnancy loss evaluation combined with 24-chromosome microarray of miscarriage tissue provides a probable or definite cause of pregnancy loss in over 90% of patients. Hum Reprod 2018:1-9 doi:1093/humrep/dey021 (published ahead of print). This does not detract from the Delphi study, but promotion of immunologic therapeutic possibilities in my view should be presented in a realistic, objective and evidence-based manner.

We thank the reviewer for this useful comment. Indeed, there are many challenges to developing save and effective immune modulating therapies, and selecting appropriate patient groups.

Recurrent miscarriage is indeed a relevant example, underlining the difficulties in using immune modulation as a therapy. As the reviewer states recurrent miscarriage is a clinical problem in which most immune therapies have not been proven successful. Although there is a scientific rationale, only a few studies suggest possible beneficial effects of immune modulators as a therapy for recurrent miscarriage (Prins 2014 Eur J Obstet Gynecol Reprod Biol). We believe that this can be partially explained by its multifactorial pathogenesis and that developing a successful immune modulator depends on selecting appropriate patient groups. We also believe it is reasonable to expect that in time, effective therapies will emerge. We have made changes throughout the manuscript to emphasize the possibilities of immune therapies in a realistic and (more) objective manner.

Reviewer: 2

Reviewer Name: Jens Langhoff-Roos, MD PhD Institution and Country: Dept Obstetrics, Rigshospitalet, University of Copenhagen, Denmark Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below Do you still believe in your idea? Don't you think that your scope is too broad and "immune modulation" very difficult to define? Is the project worthwhile compared to other "urging" projects?

If you answer: "yes", "no", "yes" - I wish you luck! :-)

Thank you. Our answers to the questions are: yes, no, yes.

Regarding the first question: we still believe in our idea.

Regarding the second and third question: Indeed immune modulation is broad, we will underline in our questionnaires (during the Delphi procedure) that we need relevant outcomes for ALL these trials/studies, meaning we need restrictive voting by the panel members as many outcomes are interesting, but not relevant for all trials/studies. Since many (pre-)clinical studies have been initiated to evaluate the effect of immune modulating agents in pregnancy, we believe that the development of therapies is assisted by a consensus core outcome set, which will help comparing studies in future. More specific COS's can be developed when necessary. In our opinion this is not (yet) applicable for the many small COS's that need to be developed and therefore we chose to facilitate comparison on a more basic level regarding immune modulation in pregnancy.