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# BMJ Open

## Development of a Core Outcome Sets for IMmunomodulation in PREGnancy (COSIMPREG): a protocol for a systematic review and Delphi study

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Manuscripts

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3 1 Development of a Core Outcome Sets for IMmunomodulation in PREGnancy  
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6 2 (COSIMPREG): a protocol for a systematic review and Delphi study  
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## 26 **Abstract**

27 **Introduction:** To establish pregnancy the maternal immune system must adapt to tolerate the semi-  
28 allogenic fetus. Less than optimal adaptation of the maternal immune system during (early) pregnancy is  
29 implicated in several complications of pregnancy. The development of effective immune modulation  
30 interventions as preventive or therapeutic strategies holds promise, and several studies sought to  
31 evaluate the safety and effectiveness of various approaches. However, a limitation is the high variability  
32 in clinical and immune outcomes that are reported. We therefore aim to develop a core outcome set for  
33 application to studies of immune modulation in pregnancy (COSIMPREG).

34 **Methods and analysis:** We will use a step-wise approach to develop a COS for immune modulation in  
35 pregnancy. First, we will perform a systematic review to identify reported outcomes. For this review  
36 PRISMA guidelines will be followed. Second, we will use the Delphi method to develop a preliminary  
37 COSIMPREG. In three rounds the outcomes of the systematic review will be scored. A panel comprising  
38 experts from relevant disciplines and diverse geographical locations will be assembled until a sufficient  
39 quality of the panel is reached. We will use predefined decision rules for outcomes. After each round  
40 outcomes, including scores, will be returned to the panel for further refinement. The outcomes not  
41 excluded after the third round will be taken to a consensus meeting. In this meeting experts from all  
42 relevant disciplines will discuss and finalize the COSIMPREG.

43 **Ethics and dissemination:** For this study no ethical approval is required. The systematic review will be  
44 published in an appropriate open access reproductive immunology journal. Once the COSIMPREG is  
45 finalised it will be published in an open access reproductive immunology journal, and disseminated at  
46 appropriate international meetings, as well as through relevant research and scientific societies. Experts  
47 involved in the Delphi study will be asked to give informed consent.

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**Key words: immune modulation, therapy, prevention, pregnancy, core outcome set, COS**

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For peer review only

## 51 **Strengths and limitations of this study**

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- 53 • The Delphi procedure involves experts from all relevant stakeholder groups including patients.
- 54 • The Delphi procedure allows unbiased contributions, and is anonymous.
- 55 • The systematic review and input of topic experts will assemble and synthesise evidence from a
- 56 broad, inclusive base.
- 57 • This protocol covers a topic which holds enormous potential for future reproductive medicine.
- 58 • The intention is to publish the results in open access journals to optimize dissemination.

## 59 Introduction

60 The maternal immune response is instrumental in pregnancy health <sup>1</sup>. Failure of the immune response  
61 to adapt and respond correctly to conception and embryo implantation is associated with, and likely  
62 plays a causal role in, most complications of pregnancy <sup>2</sup>. During early pregnancy the maternal immune  
63 system must adapt to tolerate the fetus and placenta, that both express maternal as well as paternal  
64 (foreign) antigens. Maladaptation of the maternal immune system has been associated with common  
65 complications of pregnancy including preterm birth, preeclampsia, fetal growth restriction, and  
66 recurrent miscarriages <sup>2-4</sup>. Various approaches to immunomodulation have been used for several  
67 indications to improve pregnancy outcome <sup>5</sup>. For example, a commonly used immune modulating  
68 therapy is acetylsalicylic acid (aspirin), which is widely used to prevent preeclampsia <sup>6</sup>. In other  
69 reproductive disorders, such as recurrent miscarriage, several approaches like paternal leukocyte  
70 immunization, progesterone, and steroids have been used with most of them no beneficial effect <sup>5</sup>.  
71 Immune-modulating therapeutic options are projected to improve, will become more tailored, and will  
72 be more common used in the next few years, with the development of several initiatives to achieve  
73 targeted, safe immunotherapy both as prevention and therapy for pregnancy complications.

74 In current literature, there is high variability in the different reported clinical outcomes and immunologic  
75 parameters. This variability hampers proper comparison across studies and harmonisation of data sets.  
76 Therefore, the objective of this study is to develop a core outcome set (COS) for studies investigating  
77 immunomodulation in pregnancy <sup>7,8</sup>. Although immunologic studies in pregnancy are usually condition  
78 based with associated condition specific outcomes, the COS developed in the current study will  
79 comprise the fundamental outcomes which are considered essential for reporting in all reproductive  
80 immunology studies. For multiple various clinical conditions, specific COS have been developed <sup>9</sup>. In  
81 cases where immune modulation is studied in a specific clinical condition, then outcomes from both the

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3 82 COS for the clinical condition of investigation and immune modulation need to be collected, and most  
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5 83 likely there will be overlap of core outcomes.  
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8 84 **Aim:** The aim of this study is to develop a core outcome set (COS) for studies of immune modulation in  
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10 85 pregnancy. We will obtain this COS through consensus in a group of relevant experts using a Delphi  
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12 86 procedure with the outcomes generated by a systematic review as input.  
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## 87 **Methods and analysis**

### 88 **Overview**

89 To develop a core outcome set (COS) for studies of immune modulation in pregnancy (COSIMPREG) we  
90 will use a step-wise approach<sup>10</sup>:

- 91 1. Perform a systematic review to identify reported outcomes for immune modulation already  
92 in use
- 93 2. Use a Delphi procedure to develop a preliminary COS with input from the systematic review  
94 and experts
- 95 3. Organise a consensus meeting to discuss and finalize the COSIMPREG
- 96 4. Disseminate, and promote application of the final COSIMPREG

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98 This study will be conducted from December 2017 onwards, and we aim to have the COS finalised in  
99 March 2019. This study is registered at the Comet Initiative: [http://www.comet-](http://www.comet-initiative.org/studies/details/1004?result=true)  
100 [initiative.org/studies/details/1004?result=true](http://www.comet-initiative.org/studies/details/1004?result=true).

#### 102 **1. Perform a systematic review to identify reported outcomes for immune modulation already in use.**

103 The aim of the systematic review is to identify all outcomes that have been used in studies reporting on  
104 immune modulation in pregnancy. The review will be conducted according to PRISMA guidelines<sup>11</sup> and  
105 published separately. Within this review we will include all studies, human as well as animal,  
106 investigating immune modulation to improve pregnancy outcomes either as therapy or prevention. A  
107 comprehensive search will be conducted using the databases of PubMed, Embase, and Cochrane Central

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3 108 Register of Controlled Trials. We will use the following search terms: (immune modulation OR synonyms)  
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5 109 AND (adverse pregnancy outcome OR synonym) AND (therapy OR prevention). We will use free text  
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7 110 words and index terms (MeSH for Pubmed, and Emtree for Embase). We aim to start this review in  
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9 111 January 2017. If the selection process takes longer than 6 months, we will update the search. No  
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11 112 language or date restriction will be applied.  
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15 113 In order to identify all reported outcomes, we will not restrict data collection to RCTs only. We aim to  
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17 114 include: a) randomized clinical trials, open label clinical trials, and cohort studies reporting on b) immune  
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19 115 therapy or interventions targeting the immune response, in c) pregnant human or animal subjects  
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21 116 studying d) the preventive or therapeutic effect on (adverse) reproductive outcome.  
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25 117 Studies will not be included, when they do not meet the criteria, for example: a) reported pregnancy  
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27 118 outcome as secondary outcome; b) case-reports, reviews, and expert opinions.  
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30 119 Two reviewers (JRP and FH) will independently screen titles and abstracts of all citations in order to  
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32 120 exclude all overtly irrelevant papers. One of the members of the review team (FH) is not involved in  
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34 121 obstetric research, and will therefore be unaware of authors and journals credentials. Consensus on  
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36 122 inclusion is reached when: a) both reviewers included a study, b) based on discussion in case of  
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38 123 difference opinions, or c) after consultation of the third reviewer (SJG) in case of persistent  
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40 124 disagreement. Of potentially relevant papers full text will be retrieved and studied in detail, to  
41  
42 125 determine whether the inclusion criteria are met. In case of disagreement, consensus between the  
43  
44 126 reviewers will be reached upon discussion, and if necessary through consultation of a third reviewer  
45  
46 127 (SJG). To search for additional studies, reference lists of all included studies and of relevant reviews will  
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48 128 be checked, conference abstracts will be screened, and published protocols without published follow-up  
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50 129 data will be identified. If necessary, authors will be contacted.  
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3 130 Two authors (JRP and FH) will independently extract data from the included studies. Data will be  
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5 131 extracted on the year of study, study design, study size, study population, human / animal study,  
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7 132 disclosures, and reported outcome. The reported outcomes in the included studies will first be  
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10 133 summarized into four categories, namely: maternal clinical outcomes, fetal clinical outcomes, maternal  
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12 134 immune outcomes, and fetal immune outcomes. Furthermore, the above categories will be displayed  
13  
14 135 for both preventive and therapeutic immune modulation therapies. The study outcome will have no  
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16 136 influence on the extraction of the reported outcomes. For each reported outcome the number of times  
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18 137 it is reported in studies will be shown. This scoring will also be done in the four categories mentioned  
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21 138 earlier. Data will be collected, entered in a predefined fact sheet, and analysed using Microsoft Excel.  
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24 139 Since we aim to include all outcomes reported to date and we do not focus on study outcome, included  
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26 140 studies will not be assessed regarding their risk of bias. However, information on funding sources of  
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28 141 individual studies (disclosure, see above) will be collected.  
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31 142 The protocol for the systematic review is currently under review at Prospero. The review will be started  
32  
33 143 early 2018. JRP will be the guarantor of this review. JRP and FH are responsible for selection of studies  
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35 144 for inclusion and for data-extraction. SJG will be consulted in case of disagreement. For the study there  
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38 145 are no sources of financial support.  
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41 146 The findings of this systematic review will serve two purposes. First, in order to disseminate the results,  
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43 147 it will be published in an open access peer reviewed journal according to PRISMA (Preferred Reporting  
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45 148 Items for Systematic Reviews and Meta-analyses) guidelines<sup>11</sup>. Second, these results will be used for the  
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48 149 Delphi procedure in order to develop a COS for studies focussing on immune modulation in pregnancy.  
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3 151 **2. Use a Delphi procedure to develop a preliminary COS with input from the systematic review and**  
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5 152 **experts.**  
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8 153 To develop a preliminary COS for immune modulation studies in pregnancy we will use Delphi  
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10 154 methodology. In general, the aim of the Delphi method is to obtain consensus upon a subject and to  
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12 155 develop new knowledge, for example a COS<sup>7 12</sup>. Within a Delphi process structured statements are  
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14 156 scored by experts on relevance, then these statements are returned to the experts with scores at  
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16 157 individual and discipline group level, and this process is repeated until consensus is reached. It has been  
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18 158 reported that a Delphi procedure in general has an average of three rounds<sup>12</sup>. As we do not aim to  
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20 159 reach final consensus through the Delphi procedure, but instead through a consensus meeting, our  
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22 160 Delphi procedure is anticipated to consist of three rounds. Thereafter the not excluded outcomes will be  
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24 161 taken into the consensus meeting.  
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29 162 In the Delphi procedure we will include several groups of experts from different disciplines (panels)  
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31 163 based on professional background, together with patients. To be included within the professional expert  
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33 164 panel, experts should have worked at least 5 years within their expert field, and / or should have recent  
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35 165 relevant publications related to immune modulation in pregnancy, or have a well-known status in a  
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37 166 relevant field, and should have adequate English language skills. Experts having a professional  
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39 167 background as obstetrician, paediatrician, immunologist, reproductive scientist, or midwife will be  
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41 168 included in the expert panels. As the use of medication during pregnancy is dependent on the  
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43 169 motivation and understanding of pregnant women, we will also include healthy pregnant women within  
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45 170 our panels, and women who have experienced adverse outcomes that might reasonably have been  
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47 171 qualified for prevention or treatment with immunomodulation (lay experts). Women with a history of  
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49 172 recurrent miscarriage, and women with a history of preterm birth, fetal growth restriction and  
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51 173 preeclampsia, all complications of pregnancy for which immune modulation is considered as promising  
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3 174 will be considered as eligible. To be included within the patient subpanel, women should have adequate  
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5 175 English language skills.  
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8 176 Possible participants will be invited to participate in the Delphi procedure by email in which we will  
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10 177 explain the background and goals of the study. Patients will be included through patient organisations  
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12 178 (as for example the Dutch preeclampsia / help foundation) and invitational posters at the participating  
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14 179 centers.  
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18 180 In the explanatory email we will use written text supported by a video explaining the need for a set of  
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20 181 core outcomes in reproductive immunology. We will also provide information on the time schedule for  
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22 182 every Delphi round. This email will also contain a link to accept the invitation, to provide informed  
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24 183 consent, and to register in the DelphiManager software system. We will furthermore ask the nominated  
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26 184 experts to provide us with the names of any other relevant experts who meet the inclusion criteria, and  
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28 185 should be invited to participate in order for this procedure to be optimally executed. We will ask all  
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30 186 participants to not personally contact any other potential experts, and to not discuss the Delphi  
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32 187 procedure. Furthermore, during the rest of the Delphi procedure all answers will be semi-anonymised,  
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34 188 participants are aware of their fellow panel members but not of their individual responses. Results  
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36 189 returned will include individual expert responses as well as responses on panel group level. We aim to  
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38 190 include at least 10 experts per subpanel to ensure optimal representation of all relevant disciplines and  
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40 191 to minimize attrition.  
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46 192 We will use an anticipated 3 round Delphi procedure to reach consensus about the potential list of core  
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48 193 outcomes. The aim of the Delphi procedure is to eliminate all outcomes that are not fundamental or  
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50 194 essential. Experts can only be part of a next round if they have completed the former one. In each round  
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52 195 the participants will receive an email with a summary of the response rates and results so far and a link  
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3 196 to the next questionnaire. Each round will take approximately 3 weeks. Reminders will be send to the  
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5 197 respondents who have not yet responded, and 2 days before the deadline a final reminder will be send.  
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11 199 *First Delphi round*  
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14 200 In the first round a first voting of the relevance of possible outcomes, derived from the systematic  
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16 201 review, will be made on a Likert-scale. Panel members will be asked to score the importance of  
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18 202 outcomes on a Likert-scale, following the COMET advice<sup>10</sup>. Panel members will be scoring on a 9-point  
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20 203 Likert scale (see below). The items that have a median of at least 7 when a Likert of 9 is used. To ensure  
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22 204 a complete set of outcomes using the input of topic experts and (recently) pregnant women,  
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24 205 participants will be asked to add any outcome they miss within the list of outcomes and which they  
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26 206 consider as a core outcome.  
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31 207 *Second round*  
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34 208 In the second round the response rates for each panel and the total response rate will be reported. All  
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36 209 outcomes from round one will be presented again for weighting the importance, and in addition all  
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38 210 outcomes suggested by at least two participants. For each outcome the scoring of round one will be  
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40 211 presented at three levels: a) at the participants' individual level; b) at the level of the subpanel the  
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42 212 expert is participating in; and c) at the level of the other expert panels. These results will be presented  
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44 213 graphically in the form of a histogram (as generated by Delphimanager). Panel members own individual  
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46 214 responses can then be compared against the score of their respective subpanel, and against the score of  
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48 215 other subpanels. Participants will be asked to rate the importance of all outcomes again, but now with  
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50 216 the knowledge of the scores in round one. We will again underline in the explanatory text the aim of the  
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52 217 study, namely to identify fundamental / essential outcomes to be reported as a minimum set in each  
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3 218 study. Therefore, we will underline the importance to not be excessively inclusive, in order that a  
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5 219 manageable COS is delivered. We will emphasise that for every future reproductive immunology study  
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7 220 this will be a minimum outcome set, and that other outcomes relevant to individual studies can be  
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9 221 added. Furthermore, in this round we poll the panel members for availability to join the consensus  
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11 222 meeting as a satellite meeting of another event, probably Society of Reproductive Investigation (SRI)  
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14 223 2019.

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17 224 *Third round*

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20 225 In round three outcomes will not be taken forward from the previous round if more than 70% of the  
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22 226 total panel judged the outcome as not important (score 1-3 on 9-point Likert scale) AND less than 15%  
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24 227 of experts regard this same outcome as important (score  $\geq 7$  on 9-point Likert scale). All the other  
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26 228 outcomes will be presented in round three.

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30 229 A preliminary list of outcomes for the consensus meeting will be assembled. To that end, the outcomes  
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32 230 retained after round two will be presented to the participants. The outcomes will be presented in similar  
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34 231 way as in round two.

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38 232 After the third round all outcomes having a score  $\geq 7$  on the 9-point Likert scale in at least 70% of the  
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40 233 participants will be taken forward into the consensus meeting as potential COS. Outcomes with more  
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42 234 than 70% of the participants judged as less important (score 1-3 on 9-point Likert scale) and less than 15%  
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44 235 as important (score  $\geq 7$  on 9-point Likert scale) will be excluded. Furthermore, the outcomes not  
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46 236 regarded as essential for the core outcome set and also not excluded will be presented at the consensus  
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48 237 meeting for further consensus voting.

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55 239 **3. Organise a consensus meeting to discuss and finalize the COS for immune modulation in pregnancy.**

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3 240 To finalize the COS for immune modulation in pregnancy, we will organize a consensus meeting as a  
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5 241 satellite event to an international conference, presumably the SRI 2019 (March 2019). The Delphi  
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7 242 process is expected to take 12 months with final outcomes in early 2019. Within this consensus meeting,  
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9 243 we aim to have members of each stakeholder group present in person. A full day meeting, with an open  
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11 244 and collaborative character is proposed with an objective facilitator who will actively encourage equal  
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13 245 input of all participants and will prevent effect of strong voice or dominance by using nominal group  
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15 246 techniques. All outcomes still present after round three (of either Likert, so added) will be presented at  
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17 247 the consensus meeting.  
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#### 25 249 **4. To implement the COS for immune modulation in pregnancy.**

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28 250 After the COS for immune modulation in pregnancy is finalised, application in studies reporting on  
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30 251 immune modulation in pregnancy is stimulated by publication of the COS in an open access peer  
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32 252 reviewed reproductive immunology journal. Further, dissemination will also be through presentations at  
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34 253 appropriate international meetings, through relevant research and scientific societies, and through  
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36 254 relevant journals.  
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## 255 **Ethics and dissemination**

256 For this study ethics approval is not required. Participants will be asked to provide informed consent. For  
257 the dissemination of the COS we will use different strategies. We will disseminate all possible outcome  
258 measures as a systematic review, and publish this in a peer reviewed reproductive immunology or  
259 methodology journal. After we have finalised the COS for immune modulation in pregnancy, we will  
260 disseminate it through different channels. First, we will publish the COS in a reproductive immunology  
261 journal. Second, we will disseminate the COS at appropriate international meetings, such as  
262 reproductive immunology and reproductive sciences meetings. We will furthermore discuss it with  
263 patient organisations on how to inform pregnant women. We will also disseminate the COS through  
264 research and scientific societies.

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3 **295 Authors' contributions**  
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7 296 J.R.P., S.J.G. and S.A.R initiated this study and designed the protocol. J.R.P., F.H., and S.J.G. wrote the  
8 297 first draft of this manuscript. All authors critically revised the protocol and the manuscript. J.R.P. and  
9 298 F.H. will be responsible for selection of studies for inclusion and for data-extraction for the systematic  
10 299 review. J.R.P., J.W.G., J.H., and S.J.G. will be responsible for the Delphi procedure. S.A.S and S.A.R. will  
11 300 select and invite the experts.  
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304 **Competing interests statement**

305 The authors have no competing interests other than being involved in reproductive immunology  
306 research.

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# BMJ Open

## Development of a Core Outcome Sets for IMmunomodulation in PREGnancy (COSIMPREG): a protocol for a systematic review and Delphi study

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Keywords:	immune modulation, therapy, prevention, pregnancy, core outcome set, COS

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Manuscripts

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6 2 (COSIMPREG): a protocol for a systematic review and Delphi study  
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**Abstract**

**Introduction:** To establish pregnancy the maternal immune system must adapt to tolerate the semi-allogenic fetus. Less than optimal adaptation of the maternal immune system during (early) pregnancy is implicated in several complications of pregnancy. The development of effective immune modulation interventions as preventive or therapeutic strategies for pregnancy complications holds promise. Several studies sought to evaluate the safety and effectiveness of various approaches. However, a limitation is the high variability in clinical and immune outcomes that are reported. We therefore aim to develop a core outcome set for application to studies of immune modulation in pregnancy (COSIMPREG).

**Methods and analysis:** We will use a step-wise approach to develop a COS for immune modulation in pregnancy. First, we will perform a systematic review to identify reported outcomes. For this review PRISMA guidelines will be followed. Second, we will use the Delphi method to develop a preliminary COSIMPREG. In three rounds the outcomes of the systematic review will be scored. A panel comprising experts from relevant disciplines and diverse geographical locations will be assembled until a sufficient quality of the panel is reached. We will use predefined decision rules for outcomes. After each round outcomes, including scores, will be returned to the panel for further refinement. The outcomes not excluded after the third round will be taken to a consensus meeting. In this meeting experts from all relevant disciplines will discuss and finalize the COSIMPREG.

**Ethics and dissemination:** For this study ethical approval is not required. The systematic review will be published in an appropriate open access reproductive immunology journal. Once the COSIMPREG is finalised it will be published in an open access reproductive immunology journal, and disseminated at appropriate international meetings, as well as through relevant research and scientific societies. Experts involved in the Delphi study will be asked to give informed consent.

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**Key words: immune modulation, therapy, prevention, pregnancy, core outcome set, COS**

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3 56 **Strengths and limitations of this study**  
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- The Delphi procedure involves experts from all relevant stakeholder groups including patients.
  - The Delphi procedure allows unbiased contributions, and is anonymous.
  - The systematic review and input of topic experts will assemble and synthesise evidence from a broad, inclusive base.
  - This protocol covers a topic which holds enormous potential for future reproductive medicine.
  - The intention is to publish the results in open access journals to optimize dissemination.
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## 65 Introduction

66 The maternal immune response is instrumental in pregnancy health <sup>1</sup>. Failure of the immune response  
67 to adapt and respond correctly to conception and embryo implantation is associated with, and likely  
68 plays a causal role in, many complications of pregnancy <sup>2</sup>. During early pregnancy the maternal immune  
69 system must adapt to tolerate the fetus and placenta, both of which express paternal (foreign) as well as  
70 maternal histocompatibility antigens. Maladaptation of the maternal immune system is associated with  
71 common complications of pregnancy including preterm birth, preeclampsia, fetal growth restriction, and  
72 recurrent miscarriages <sup>2-4</sup>. Various approaches to immune modulation have been used for several  
73 indications in attempts to improve pregnancy outcome <sup>5</sup>. These approaches include drugs which have  
74 effects on the immune system, but also on other pathways. For example, a commonly used therapy is  
75 acetylsalicylic acid (aspirin), which is widely used to prevent preeclampsia <sup>6</sup>. In other reproductive  
76 disorders, such as recurrent miscarriage, interventions including paternal leukocyte immunization,  
77 progesterone, and steroids have been used, mostly with no demonstrable benefit <sup>5</sup>. There is a  
78 reasonable prospect that given advances in other disease conditions such as oncology <sup>7</sup> and  
79 autoimmune disease <sup>8-9</sup>, more targeted and effective immune-modulating therapeutic options will  
80 emerge for reproduction medicine. Although several pre-clinical / animal studies show promising results  
81 <sup>10-13</sup>, these options must now be tailored to achieve targeted, safe immunotherapy both as prevention  
82 and therapy for pregnancy complications. Moreover, since a range of immune factors are implicated in  
83 pregnancy complications <sup>14</sup> selection of the right patients will be essential for the success of therapy <sup>5,15</sup>.

84 In the current literature, there is high variability in the reported clinical outcomes and immunologic  
85 parameters measured. This variability hampers proper comparison across studies and harmonisation of  
86 data sets. Therefore, the objective of this study is to develop a core outcome set (COS) for studies  
87 investigating immune modulation in pregnancy <sup>16,17</sup>. Although immunologic studies in pregnancy are

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3 88 usually condition-based with associated condition-specific outcomes, the COS developed in the current  
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5 89 study will comprise the fundamental outcomes which are considered essential for reporting in all  
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7 90 reproductive immunology studies. Specific COS have now been developed for multiple clinical  
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9 91 conditions, with demonstrable benefit for advancing medical care <sup>18</sup>. In cases where immune  
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11 92 modulation is studied in a specific clinical condition, then both COS outcomes for the clinical condition  
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14 93 and the immune modulation will be collected, and most likely there will be overlap of core outcomes  
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16 94 across conditions.

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19 95 **Aim:** The aim of this study is to develop a core outcome set (COS) for studies of immune modulation in  
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21 96 pregnancy. We aim to develop COSs for studies both in humans and animals, that will be reported  
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23 97 separately. We will obtain these COSs by consensus amongst a group of relevant experts using a Delphi  
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26 98 procedure, using a systematic review as the initial input.  
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## 100 **Methods and analysis**

### 101 **Overview**

102 To develop a COS for studies of immune modulation in pregnancy (COSIMPREG) a step-wise approach  
103 will be utilised <sup>19</sup>:

- 104 1. Perform a systematic review to identify reported outcomes for immune modulation already  
105 in use
- 106 2. Use a Delphi procedure to develop a preliminary COS with input from the systematic review  
107 and experts
- 108 3. Organize a consensus meeting to discuss and finalize the COSIMPREG
- 109 4. Disseminate, and promote application of the final COSIMPREG

110

111 This study commenced in December 2017, with an expected completion date of December 2019. The  
112 study is registered at the Comet Initiative: [http://www.comet-](http://www.comet-initiative.org/studies/details/1004?result=true)  
113 [initiative.org/studies/details/1004?result=true](http://www.comet-initiative.org/studies/details/1004?result=true).

### 114 **Patient and Public Involvement**

115 Patient and Public were not involved in the development of this protocol. However, they will be involved  
116 and included within the Delphi procedure as expert group. And they will participate in the consensus  
117 meeting.

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3 **119 1. Perform a systematic review to identify reported outcomes for immune modulation already in use.**  
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6 120 The aim of the systematic review is to identify all outcomes that have been used to date in studies  
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8 121 reporting on immune modulation in pregnancy. A secondary aim of this review is to identify potential  
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10 122 experts for the Delphi panels. The review will be conducted according to PRISMA guidelines<sup>20</sup>, and will  
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13 123 be published separately. The review will include all studies, human as well as animal, investigating  
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15 124 immune modulation either as therapy or prevention, with the goal of improving pregnancy outcome. A  
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17 125 comprehensive search will be conducted using the databases of PubMed, Embase, and Cochrane Central  
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19 126 Register of Controlled Trials. The search strategy will be different for human and animal studies. We will  
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21 127 use free text words and index terms (MeSH for Pubmed, and Emtree for Embase). See Table 1 for the  
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23 128 preliminary Medline search strategies for human and animal studies. We will perform the literature  
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25 129 search early March 2018. If the selection process extends beyond 6 months, the search will be updated  
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28 130 to cover the interim period. No language or date restriction will be applied.

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31 131 In order to identify all reported outcomes, we aim to include: a) randomized clinical trials, open label  
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33 132 clinical trials, and cohort studies reporting on b) immune therapy or other interventions targeting the  
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35 133 immune response, in c) pregnant human or animal subjects studying d) the preventive or therapeutic  
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37 134 effect on an adverse reproductive outcome.

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41 135 Studies will not be included when they do not meet the inclusion criteria, for example: a) pregnancy  
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43 136 outcome reported as secondary outcome; b) case-reports, reviews, and expert opinions.

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46 137 Two reviewers (JRP and FH) will independently screen titles and abstracts of all citations in order to  
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48 138 exclude all overtly irrelevant papers. One of the members of the review team (FH) is not involved in  
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50 139 obstetric research, and will therefore be unaware of author and journal credentials. Consensus on  
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52 140 inclusion will be reached when: a) both reviewers include a study, b) agreement is reached after  
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54 141 discussion in the case of differing opinions, or c) a third reviewer (SJG) is consulted in the case of  
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142 persistent disagreement. For potentially relevant papers the full text will be retrieved and studied in  
 143 detail, to determine whether the inclusion criteria are met. In case of disagreement, consensus between  
 144 the reviewers will be reached upon discussion, and if necessary through consultation with a third  
 145 reviewer (SJG). To search for additional studies, reference lists of all included studies and relevant  
 146 reviews will be checked, conference abstracts will be screened, and published protocols without  
 147 published follow-up data will be identified. If necessary, authors will be contacted.

148 Table 1 Search strategy

#1	pre-eclampsia*[tiab] OR preeclampsia*[tiab] OR miscarriage*[tiab] OR pregnancy loss*[tiab] OR abort*[tiab] OR pre-term[tiab] OR preterm[tiab] OR growth restrict*[tiab] OR pregnancy fail*[tiab] OR fetal loss* [tiab] OR infertile* [tiab]	
#2	"immunoproteins"[Mesh] OR "cytokines"[Mesh] OR "immunology" [Subheading] OR immunomodulation[tiab] OR immune modulation[tiab] OR immunotherapy[tiab] OR "immunomodulation"[Mesh]	
#3	randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]))	
#4	animal*[tiab] OR mice[tiab] OR mouse[tiab] OR rat[tiab] OR rats[tiab] OR pig[tiab] OR pigs[tiab]OR sheep[tiab] OR goat*[tiab] OR lamb[tiab] OR lambs[tiab]	
#5	improve*[Title] OR outcome*[Title] OR loss*[Title] OR treatment*[Title] OR decreas*[Title] OR failure*[Title] OR promot*[Title] OR impair*[Title] OR prevent*[Title] OR induc*[Title] OR restor*[Title] OR rebalanc*[Title]	
#6	#1 AND #2 AND #3 NOT #4	Human studies
#7	#1 AND #2 AND #4 AND #5	Animal studies
#8	#6 OR #7	Preliminary search



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3 149 Two authors (JRP and FH) will independently extract data from the included studies. Data will be  
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5 150 extracted on the year of study, study design, study size, study population, human / animal study,  
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7 151 reported outcome(s), and authors. The reported outcomes in the included studies will first be  
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9 152 summarized into human and animal studies, and thereafter into four categories, namely: maternal  
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11 153 clinical outcomes, fetal clinical outcomes, maternal immune parameters, and fetal immune parameters.  
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14 154 Furthermore, the above categories will be displayed for both preventive and therapeutic immune  
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16 155 modulation interventions. The study outcome will have no influence on the extraction of the reported  
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18 156 outcomes and parameters. Overlapping outcomes will be collated and reported under a covering term.  
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21 157 For each reported outcome the number of times it is reported (absolute and relative) in studies will be  
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23 158 shown. This scoring will also be done in the categories mentioned earlier. References will be organized  
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25 159 using RefWorks. Data will be collected, entered in a predefined fact sheet, and analysed using Microsoft  
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27 160 Excel.

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31 161 Since we aim to include all relevant outcomes and parameters reported to date and we will not  
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33 162 discriminate on efficacy of intervention, the included studies will not be assessed regarding their risk of  
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35 163 bias, nor will they be graded.

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38 164 The protocol for the systematic review is not eligible for registration at Prospero as it has no direct  
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40 165 health-related outcomes. JRP will be the guarantor of this review. JRP and FH are responsible for  
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42 166 selection of studies for inclusion and for data-extraction. SJG will be consulted in case of disagreement.  
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45 167 For the systematic review there are no sources of financial support.

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48 168 The findings of this systematic review will serve three purposes. Firstly, in order to disseminate the  
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50 169 results, it will be published in an open access peer-reviewed journal according to PRISMA (Preferred  
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52 170 Reporting Items for Systematic Reviews and Meta-analyses) guidelines<sup>20</sup>. Secondly, the results will be  
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55 171 used for the Delphi procedure in order to develop a COS for studies focusing on immune modulation in  
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3 172 pregnancy. Third, the extracted data regarding authors will help to identify potential experts for the  
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5 173 Delphi procedure.  
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11 175 **2. Use a Delphi procedure to develop a preliminary COS with input from the systematic review and**  
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14 176 **experts.**  
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17 177 To develop a preliminary COS for immune modulation studies in pregnancy we will use Delphi  
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19 178 methodology. In general, the aim of the Delphi method is to obtain consensus upon a subject and to  
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21 179 develop new knowledge, and this has been applied previously to COS development<sup>16,21</sup>. In the Delphi  
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23 180 process, structured statements are scored by experts on relevance, then these statements are returned  
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25 181 to the experts with scores at individual and discipline group level, and this process is repeated until  
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27 182 consensus is reached. On average, Delphi procedures are reported to require three iterative rounds<sup>21</sup>.  
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29 183 Since we plan to reach final consensus by adding a consensus meeting at the completion of the Delphi  
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31 184 procedure, three rounds of Delphi procedure are expected to be sufficient. All outcomes not excluded  
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33 185 through the three Delphi rounds will be taken into the consensus meeting for final approval.  
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38 186 For the Delphi procedure we will take an inclusive approach and cast a wide net to assemble several  
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40 187 panels comprising experts from different professional disciplines, together with a patient / consumer  
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42 188 group. To be included on a professional expert panel, members should have worked at least 5 years  
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44 189 within their field, and / or should have recent publications related to immune modulation in pregnancy,  
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46 190 or have a well-known status in a relevant field, and should have adequate English language skills.  
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48 191 Experts in obstetrics, paediatrics, laboratory-based and clinical immunology, reproduction science, and  
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50 192 midwifery will be included on the expert panels. To ensure that all panels have sufficient geographic  
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52 193 distribution and to prevent bias, experts will be identified and selected through a range of processes,  
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54 194 with a goal to include at least 100 relevant participants. Firstly, potential experts involved in immune  
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3 195 modulating studies will be identified through the systematic review. This will identify potential experts  
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5 196 with >5 years of work in this field, and with relevant recent publications. Secondly, we will ask potential  
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7 197 panel members to identify other experts, and to provide names of other relevant experts (see below).  
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10 198 We will ask experts specifically to nominate potential experts in South America, Africa, and Asia-Oceania  
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12 199 as these are regions that have been under-represented in previous Delphi procedures with an obstetric  
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14 200 focus<sup>22 23</sup>.

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17 201 Regarding the patient / consumer group selection the procedure is slightly different. We will invite  
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19 202 patient and consumer organizations from a range of countries as above to become involved and to  
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21 203 nominate appropriate individuals. To ensure geographical diversity in the Delphi procedure we will  
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23 204 include at least 10 experts on each panel (at least 10 pediatricians, at least 10 patients, and etcetera).

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27 205 As the use of medication or other interventions during pregnancy is dependent on the motivation and  
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29 206 understanding of pregnant women, panels will include both healthy pregnant women and women who  
30  
31 207 have experienced adverse outcomes that might reasonably have qualified for prevention or treatment  
32  
33 208 with immune modulation. Women with a history of recurrent miscarriage, preterm birth, fetal growth  
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35 209 restriction and/or preeclampsia, all complications of pregnancy for which immune modulation is  
36  
37 210 considered as holding promise, will be eligible. To be included within a patient/consumer subpanel,  
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39 211 women must have adequate English language skills.

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43 212 Candidate expert and lay participants will be invited to participate in the Delphi procedure by email in  
44  
45 213 which we will explain the background and goals of the study. Lay participants will be accessed through  
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47 214 patient and consumer organizations (for example the Dutch preeclampsia / Hellp foundation / March of  
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49 215 Dimes / Perinatal Society of Australia New Zealand) and invitational posters at participating centres  
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51 216 distributed around the world.  
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3 217 In the explanatory email we will use written text supported by a video explaining the need for a set of  
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5 218 core outcomes in reproductive immunology, and information on the time commitment and schedule for  
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7 219 each Delphi round. The email will also contain a link to accept the invitation, to provide informed  
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9 220 consent, and to register in the software. Nominated experts will be invited to provide the names of  
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11 221 other relevant experts who meet the inclusion criteria, and reasonably should be invited to participate  
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13 222 to achieve optimal inclusion. Participants will be asked to not personally contact other potential experts,  
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15 223 and to not discuss the Delphi procedure, to ensure unbiased input. Responses to the Delphi procedure  
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17 224 will be semi-anonymised, such that participants are aware of their fellow panel members but not of  
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19 225 their individual responses. Results returned will include individual expert responses as well as responses  
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21 226 on a panel group level.

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26 227 As not all different panels will include experts in animal studies, and since we aim to develop two  
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28 228 separate COS documents for animal and human studies, only the reproductive science and immunology  
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30 229 panels will be able to contribute to assembling the animal COS.

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34 230 We anticipate a three round Delphi procedure to reach consensus on the shortlist of core outcomes. The  
35  
36 231 aim of the Delphi procedure is to eliminate all outcomes that are not fundamental or essential. Experts  
37  
38 232 can only be part of a subsequent round if they complete the former one. In each round the participants  
39  
40 233 will receive an email with a summary of the response rates and results to date and a link to the next  
41  
42 234 questionnaire. Each round will take approximately 3 weeks. Reminders will be send to the respondents  
43  
44 235 who have not yet responded, and 2 days before the deadline a final reminder will be send.

#### 45 46 47 48 236 *First Delphi round*

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51 237 In the first round an initial assessment of the relevance of possible outcomes, derived from the  
52  
53 238 systematic review, will be made. Panel members will be asked to score the importance of outcomes on a  
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55 239 9-point Likert-scale, following the COMET advice<sup>19</sup>. Items will be ranked and those with a median of at

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3 240 least 7 when a Likert of 9 is used will progress to the next round. To ensure a complete set of outcomes  
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5 241 using the input of topic experts and patients / consumers, participants will be asked to 'rescue' any  
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7 242 outcome missed by the panel's ranked list of outcomes and which they consider as a core outcome.  
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11 243 *Second round*  
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14 244 In the second round the response rate for each panel and the overall response rate will be reported. All  
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16 245 outcomes reaching the cut-off threshold from round one will be presented again plus outcomes put  
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18 246 forward for rescue by at least two participants. For each outcome the scoring of round one will be  
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20 247 presented at three levels: a) at the participants' individual level; b) at the level of the expert subpanel;  
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22 248 and c) at the level of the other expert panels. These results will be presented graphically in the form of a  
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24 249 histogram (as generated by Delphimanager). Panel members' own individual responses can then be  
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26 250 compared against the score of their respective subpanel, and against the score of other subpanels.  
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28 251 Participants will be asked to rate the importance of all outcomes again, but now with the knowledge of  
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30 252 the scores in round one. We will again underline in the explanatory text the aim of the study, namely to  
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32 253 identify fundamental / essential outcomes to be reported as a minimum set in each study. It will be  
33  
34 254 essential to not be excessively inclusive, in order that a manageable COS is delivered. We will emphasise  
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36 255 that for every future reproductive immunology study this will be a minimum outcome set, and that  
37  
38 256 additional outcomes relevant to individual studies can always be added. Furthermore, in this round we  
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40 257 poll the panel members for availability to join the consensus meeting as a satellite meeting of another  
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42 258 event (see below).  
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48 259 *Third round*  
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51 260 In round three outcomes will not be taken forward from the previous round if more than 70% of the  
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53 261 total panel judged the outcome as not essential (score 1-3 on 9-point Likert scale) AND less than 15% of  
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3 262 experts regard this same outcome as important (score  $\geq 7$  on 9-point Likert scale). All the other  
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5 263 outcomes will be presented in round three.  
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8 264 A preliminary list of outcomes for the consensus meeting will be assembled. To that end, the outcomes  
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10 265 retained after round two will be presented to the participants. The outcomes will be presented in similar  
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13 266 way as in round two. The reproductive scientists and immunologists will also receive a preliminary list of  
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15 267 animal studies core outcomes.  
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18 268 After the third round all outcomes having a score  $\geq 7$  on the 9-point Likert scale in at least 70% of the  
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20 269 participants will be taken forward into the consensus meeting as potential COS. Outcomes with more  
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22 270 than 70% of the participants judged as less important (score 1-3 on 9-point Likert scale) and less than  
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24 271 15% as important (score  $\geq 7$  on 9-point Likert scale) will be excluded. Furthermore, the outcomes not  
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26 272 regarded as essential for the core outcome set and also not excluded will be presented at the consensus  
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28 273 meeting for further consensus voting.  
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35 275 **3. Organise a consensus meeting to discuss and finalize the COS for immune modulation in pregnancy.**  
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38 276 To finalize the COS for immune modulation in pregnancy, we will organize a consensus meeting as a  
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40 277 satellite event to an international conference in 2019, most likely to one of the following meetings:  
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42 278 Society of Reproductive Investigation, annual meeting of American Society of Reproductive  
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44 279 Immunology, or International Society for Immunology of Reproduction. This consensus meeting will be  
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46 280 divided into a clinical consensus meeting (involving all experts in the human COS), and an animal  
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48 281 consensus meeting (involving the reproductive scientists and immunologists only). The Delphi process is  
49  
50 282 expected to take 12 months with final outcome disseminated in 2019. Within this consensus meeting,  
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52 283 we aim to have members of each stakeholder group present in person. A full day meeting, with an open  
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3 284 and collaborative character is proposed with an objective facilitator who will actively encourage equal  
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5 285 input of all participants and will prevent skewing by strong voices or dominance using nominal group  
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7 286 techniques. All outcomes still present after round three (of either Likert, so added by rescue) will be  
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10 287 presented at the consensus meeting.  
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16 289 **4. To implement the COS for immune modulation in pregnancy.**  
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19 290 After the COS for immune modulation in pregnancy is finalised, their uptake and application in studies  
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21 291 reporting on immune modulation in pregnancy will be stimulated by publication of both the human and  
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23 292 animal COS in an open access, peer-reviewed reproductive immunology journal. Further, dissemination  
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26 293 will also be through presentations at appropriate international meetings, through relevant research and  
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28 294 scientific societies, and through relevant journals and electronic media channels.  
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56 296 **Ethics and dissemination**  
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10 297 For this study ethics approval is not required. Participants will be asked to provide informed consent. For  
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12 298 the dissemination of the COS we will use a range of different strategies to maximise awareness and  
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14 299 encourage uptake. We will disseminate all possible outcome measures as a systematic review, and  
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16 300 publish this in a peer-reviewed reproductive immunology or methodology journal. Then after finalising  
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18 301 the COS for immune modulation in pregnancy, we will disseminate it through different channels. First,  
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20 302 we will publish the COS in a peer-reviewed reproductive immunology journal. Second, we will  
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22 303 disseminate the COS at appropriate international meetings, such as reproductive immunology and  
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24 304 reproductive sciences meetings. We will furthermore discuss it with patient / consumer organisations  
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26 305 with an emphasis on relevance to pregnant women. We will also disseminate the COS through scientific  
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28 306 societies, and appropriate electronic media.  
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9 369 first draft of this manuscript. All authors critically revised the protocol and the manuscript. J.R.P. and  
10 370 F.H. will be responsible for selection of studies for inclusion and for data-extraction for the systematic  
11  
12 371 review. J.R.P., J.W.G., J.H., and S.J.G. will be responsible for the Delphi procedure. S.A.S, A.F.B., and  
13 372 S.A.R. will select and invite the experts.  
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9 383 research.  
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# BMJ Open

## Development of a Core Outcome Sets for IMmunomodulation in PREGnancy (COSIMPREG): a protocol for a systematic review and Delphi study

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-021619.R2
Article Type:	Protocol
Date Submitted by the Author:	13-Jun-2018
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<b>Primary Subject Heading</b>:	Obstetrics and gynaecology
Secondary Subject Heading:	Immunology (including allergy), Paediatrics, Reproductive medicine
Keywords:	immune modulation, therapy, prevention, pregnancy, core outcome set, COS

SCHOLARONE™  
Manuscripts

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3 1 Development of a Core Outcome Sets for IMmunomodulation in PREGnancy  
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6 2 (COSIMPREG): a protocol for a systematic review and Delphi study  
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For peer review only

## 31 Abstract

32 **Introduction:** To establish pregnancy the maternal immune system must adapt to tolerate the semi-  
33 allogenic fetus. Less than optimal adaptation of the maternal immune system during (early) pregnancy is  
34 implicated in several complications of pregnancy. The development of effective immune modulation  
35 interventions as preventive or therapeutic strategies for pregnancy complications holds promise. Several  
36 studies sought to evaluate the safety and effectiveness of various approaches. However, a limitation is  
37 the high variability in clinical and immune outcomes that are reported. We therefore aim to develop a  
38 core outcome set for application to studies of immune modulation in pregnancy (COSIMPREG).

39 **Methods and analysis:** We will use a step-wise approach to develop a COS for immune modulation in  
40 pregnancy. First, we will perform a systematic review to identify reported outcomes. For this review  
41 PRISMA guidelines will be followed. Second, we will use the Delphi method to develop a preliminary  
42 COSIMPREG. In three rounds the outcomes of the systematic review will be scored. A panel comprising  
43 experts from relevant disciplines and diverse geographical locations will be assembled until a sufficient  
44 quality of the panel is reached. We will use predefined decision rules for outcomes. After each round  
45 outcomes, including scores, will be returned to the panel for further refinement. The outcomes not  
46 excluded after the third round will be taken to a consensus meeting. In this meeting experts from all  
47 relevant disciplines will discuss and finalize the COSIMPREG.

48 **Ethics and dissemination:** For this study ethical approval is not required. The systematic review will be  
49 published in an appropriate open access reproductive immunology journal. Once the COSIMPREG is  
50 finalised it will be published in an open access reproductive immunology journal, and disseminated at  
51 appropriate international meetings, as well as through relevant research and scientific societies. Experts  
52 involved in the Delphi study will be asked to give informed consent.

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3 54 **Key words: immune modulation, therapy, prevention, pregnancy, core outcome set, COS**  
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3 56 **Strengths and limitations of this study**  
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- The Delphi procedure involves experts from all relevant stakeholder groups including patients.
  - The Delphi procedure allows unbiased contributions, and is anonymous.
  - The systematic review and input of topic experts will assemble and synthesise evidence from a broad, inclusive base.
  - This protocol covers a topic which holds enormous potential for future reproductive medicine.
  - The intention is to publish the results in open access journals to optimize dissemination.
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## 64 Introduction

65 The maternal immune response is instrumental in pregnancy health <sup>1</sup>. Failure of the immune response  
66 to adapt and respond correctly to conception and embryo implantation is associated with, and likely  
67 plays a causal role in, many complications of pregnancy <sup>2</sup>. During early pregnancy the maternal immune  
68 system must adapt to tolerate the fetus and placenta, both of which express paternal (foreign) as well as  
69 maternal histocompatibility antigens. Maladaptation of the maternal immune system is associated with  
70 common complications of pregnancy including preterm birth, preeclampsia, fetal growth restriction, and  
71 recurrent miscarriages <sup>2-4</sup>. Various approaches to immune modulation have been used for several  
72 indications in attempts to improve pregnancy outcome <sup>5</sup>. These approaches include drugs which have  
73 effects on the immune system, but also on other pathways. For example, a commonly used therapy is  
74 acetylsalicylic acid (aspirin), which is widely used to prevent preeclampsia <sup>6</sup>. In other reproductive  
75 disorders, such as recurrent miscarriage, interventions including paternal leukocyte immunization,  
76 progesterone, and steroids have been used, mostly with no demonstrable benefit <sup>5</sup>. This could be  
77 explained by the fact that reproductive disorders, such as recurrent miscarriage, have a multifactorial  
78 pathogenesis, and that developing a successful immune modulator depends on selecting appropriate  
79 patient groups.

80 There is a reasonable prospect that given advances in other disease conditions such as oncology <sup>7</sup> and  
81 autoimmune disease <sup>8 9</sup>, more targeted and effective immune-modulating therapeutic options will  
82 emerge for reproduction medicine. Although several pre-clinical / animal studies show promising results  
83 <sup>10-13</sup>, these options must now be tailored to achieve targeted, safe immunotherapy both as prevention  
84 and therapy for pregnancy complications. Moreover, since a range of factors including non-immune  
85 related, are implicated in pregnancy complications <sup>14</sup> selection of the right patients will be essential for  
86 the success of therapy <sup>5 15</sup>.

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3 87 In the current literature, there is high variability in the reported clinical outcomes and immunologic  
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5 88 parameters measured <sup>15</sup>. This variability hampers proper comparison across studies and harmonisation  
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8 89 of data sets. Therefore, the objective of this study is to develop a core outcome set (COS) for studies  
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10 90 investigating immune modulation in pregnancy <sup>16 17</sup>. Although immunologic studies in pregnancy are  
11  
12 91 usually condition-based with associated condition-specific outcomes, the COS developed in the current  
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14 92 study will comprise the fundamental outcomes which are considered essential for reporting in all  
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16 93 reproductive immunology studies. Specific COS have now been developed for multiple clinical  
17  
18 94 conditions, with demonstrable benefit for advancing medical care <sup>18</sup>. In cases where immune  
19  
20 95 modulation is studied in a specific clinical condition, then both COS outcomes for the clinical condition  
21  
22 96 and the immune modulation will be collected, and most likely there will be overlap of core outcomes  
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25 97 across conditions.  
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29 98 **Aim:** The aim of this study is to develop a core outcome set (COS) for studies of immune modulation in  
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31 99 pregnancy. We aim to develop COSs for studies both in humans and animals, that will be reported  
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33 100 separately. We will obtain these COSs by consensus amongst a group of relevant experts using a Delphi  
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35 101 procedure, using a systematic review as the initial input.  
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## 103 **Methods and analysis**

### 104 **Overview**

105 To develop a COS for studies of immune modulation in pregnancy (COSIMPREG) a step-wise approach  
106 will be utilised <sup>19</sup>:

- 107 1. Perform a systematic review to identify reported outcomes for immune modulation already  
108 in use
- 109 2. Use a Delphi procedure to develop a preliminary COS with input from the systematic review  
110 and experts
- 111 3. Organize a consensus meeting to discuss and finalize the COSIMPREG
- 112 4. Disseminate, and promote application of the final COSIMPREG

113  
114 This study commenced in December 2017, with an expected completion date of December 2019. The  
115 study is registered at the Comet Initiative: [http://www.comet-](http://www.comet-initiative.org/studies/details/1004?result=true)  
116 [initiative.org/studies/details/1004?result=true](http://www.comet-initiative.org/studies/details/1004?result=true).

### 118 **Patient and Public Involvement**

119 Patient and Public were not involved in the development of this protocol. However, they will be involved  
120 and included within the Delphi procedure as expert group. And they will participate in the consensus  
121 meeting.

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3 123 **1. Perform a systematic review to identify reported outcomes for immune modulation already in use.**  
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6 124 The aim of the systematic review is to identify all outcomes that have been used to date in studies  
7  
8 125 reporting on immune modulation in pregnancy. A secondary aim of this review is to identify potential  
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10 126 experts for the Delphi panels. The review will be conducted according to PRISMA guidelines<sup>20</sup>, and will  
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12  
13 127 be published separately. The review will include all studies, human as well as animal, investigating  
14  
15 128 immune modulation either as therapy or prevention, with the goal of improving pregnancy outcome. A  
16  
17 129 comprehensive search will be conducted using the databases of PubMed, Embase, and Cochrane Central  
18  
19 130 Register of Controlled Trials. The search strategy will be different for human and animal studies. We will  
20  
21 131 use free text words and index terms (MeSH for Pubmed, and Emtree for Embase). See Table 1 for the  
22  
23 132 preliminary Medline search strategies for human and animal studies. We will perform the literature  
24  
25 133 search early March 2018. If the selection process extends beyond 6 months, the search will be updated  
26  
27 134 to cover the interim period. No language or date restriction will be applied.  
28  
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31 135 In order to identify all reported outcomes, we aim to include: a) randomized clinical trials, open label  
32  
33 136 clinical trials, and cohort studies reporting on b) immune therapy or other interventions targeting the  
34  
35 137 immune response, in c) pregnant human or animal subjects studying d) the preventive or therapeutic  
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37 138 effect on an adverse reproductive outcome.  
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41 139 Studies will not be included when they do not meet the inclusion criteria, for example: a) pregnancy  
42  
43 140 outcome reported as secondary outcome; b) case-reports, reviews, and expert opinions.  
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46 141 Two reviewers (JRP and FH) will independently screen titles and abstracts of all citations in order to  
47  
48 142 exclude all overtly irrelevant papers. One of the members of the review team (FH) is not involved in  
49  
50 143 obstetric research, and will therefore be unaware of author and journal credentials. Consensus on  
51  
52 144 inclusion will be reached when: a) both reviewers include a study, b) agreement is reached after  
53  
54 145 discussion in the case of differing opinions, or c) a third reviewer (SJG) is consulted in the case of  
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146 persistent disagreement. For potentially relevant papers the full text will be retrieved and studied in  
 147 detail, to determine whether the inclusion criteria are met. In case of disagreement, consensus between  
 148 the reviewers will be reached upon discussion, and if necessary through consultation with a third  
 149 reviewer (SJG). To search for additional studies, reference lists of all included studies and relevant  
 150 reviews will be checked, conference abstracts will be screened, and published protocols without  
 151 published follow-up data will be identified. If necessary, authors will be contacted.

152 Table 1 Search strategy

#1	pre-eclampsia*[tiab] OR preeclampsia*[tiab] OR miscarriage*[tiab] OR pregnancy loss*[tiab] OR abort*[tiab] OR pre-term[tiab] OR preterm[tiab] OR growth restrict*[tiab] OR pregnancy fail*[tiab] OR fetal loss* [tiab] OR infertile* [tiab]	
#2	"immunoproteins"[Mesh] OR "cytokines"[Mesh] OR "immunology" [Subheading] OR immunomodulation[tiab] OR immune modulation[tiab] OR immunotherapy[tiab] OR "immunomodulation"[Mesh]	
#3	randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]))	
#4	animal*[tiab] OR mice[tiab] OR mouse[tiab] OR rat[tiab] OR rats[tiab] OR pig[tiab] OR pigs[tiab]OR sheep[tiab] OR goat*[tiab] OR lamb[tiab] OR lambs[tiab]	
#5	improve*[Title] OR outcome*[Title] OR loss*[Title] OR treatment*[Title] OR decreas*[Title] OR failure*[Title] OR promot*[Title] OR impair*[Title] OR prevent*[Title] OR induc*[Title] OR restor*[Title] OR rebalanc*[Title]	
#6	#1 AND #2 AND #3 NOT #4	Human studies
#7	#1 AND #2 AND #4 AND #5	Animal studies
#8	#6 OR #7	Preliminary search

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3 153 Two authors (JRP and FH) will independently extract data from the included studies. Data will be  
4  
5 154 extracted on the year of study, study design, study size, study population, human / animal study,  
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7 155 reported outcome(s), and authors. The reported outcomes in the included studies will first be  
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9  
10 156 summarized into human and animal studies, and thereafter into four categories, namely: maternal  
11  
12 157 clinical outcomes, fetal clinical outcomes, maternal immune parameters, and fetal immune parameters.  
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14 158 Furthermore, the above categories will be displayed for both preventive and therapeutic immune  
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16 159 modulation interventions. The study outcome will have no influence on the extraction of the reported  
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19 160 outcomes and parameters. Overlapping outcomes will be collated and reported under a covering term.  
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21 161 For each reported outcome the number of times it is reported (absolute and relative) in studies will be  
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23 162 shown. This scoring will also be done in the categories mentioned earlier. References will be organized  
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25 163 using RefWorks. Data will be collected, entered in a predefined fact sheet, and analysed using Microsoft  
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28 164 Excel.

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31 165 Since we aim to include all relevant outcomes and parameters reported to date and we will not  
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33 166 discriminate on efficacy of intervention, the included studies will not be assessed regarding their risk of  
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35 167 bias, nor will they be graded.

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38 168 The protocol for the systematic review is not eligible for registration at Prospero as it has no direct  
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40 169 health-related outcomes. JRP will be the guarantor of this review. JRP and FH are responsible for  
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43 170 selection of studies for inclusion and for data-extraction. SJG will be consulted in case of disagreement.  
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45 171 For the systematic review there are no sources of financial support.

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48 172 The findings of this systematic review will serve three purposes. Firstly, in order to disseminate the  
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50 173 results, it will be published in an open access peer-reviewed journal according to PRISMA (Preferred  
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52 174 Reporting Items for Systematic Reviews and Meta-analyses) guidelines<sup>20</sup>. Secondly, the results will be  
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55 175 used for the Delphi procedure in order to develop a COS for studies focusing on immune modulation in  
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3 176 pregnancy. Third, the extracted data regarding authors will help to identify potential experts for the  
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5 177 Delphi procedure.  
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11 179 **2. Use a Delphi procedure to develop a preliminary COS with input from the systematic review and**  
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14 180 **experts.**  
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17 181 To develop a preliminary COS for immune modulation studies in pregnancy we will use Delphi  
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19 182 methodology. In general, the aim of the Delphi method is to obtain consensus upon a subject and to  
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21 183 develop new knowledge, and this has been applied previously to COS development<sup>16,21</sup>. In the Delphi  
22  
23 184 process, structured statements are scored by experts on relevance, then these statements are returned  
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25 185 to the experts with scores at individual and discipline group level, and this process is repeated until  
26  
27 186 consensus is reached. On average, Delphi procedures are reported to require three iterative rounds<sup>21</sup>.  
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29 187 Since we plan to reach final consensus by adding a consensus meeting at the completion of the Delphi  
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31 188 procedure, three rounds of Delphi procedure are expected to be sufficient. All outcomes not excluded  
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33 189 through the three Delphi rounds will be taken into the consensus meeting for final approval.  
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38 190 For the Delphi procedure we will take an inclusive approach and cast a wide net to assemble several  
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40 191 panels comprising experts from different professional disciplines, together with a patient / consumer  
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42 192 group. To be included on a professional expert panel, members should have worked at least 5 years  
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44 193 within their field, and / or should have recent publications related to immune modulation in pregnancy,  
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46 194 or have a well-known status in a relevant field, and should have adequate English language skills.  
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48 195 Experts in obstetrics, paediatrics, laboratory-based and clinical immunology, reproduction science, and  
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50 196 midwifery will be included on the expert panels. To ensure that all panels have sufficient geographic  
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52 197 distribution and to prevent bias, experts will be identified and selected through a range of processes,  
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54 198 with a goal to include at least 100 relevant participants. Firstly, potential experts involved in immune  
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3 199 modulating studies will be identified through the systematic review. This will identify potential experts  
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5 200 with >5 years of work in this field, and with relevant recent publications. Secondly, we will ask potential  
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7 201 panel members to identify other experts, and to provide names of other relevant experts (see below).  
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10 202 We will ask experts specifically to nominate potential experts in South America, Africa, and Asia-Oceania  
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12 203 as these are regions that have been under-represented in previous Delphi procedures with an obstetric  
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14 204 focus<sup>22 23</sup>.

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17 205 Regarding the patient / consumer group selection the procedure is slightly different. We will invite  
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19 206 patient and consumer organizations from a range of countries as above to become involved and to  
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21 207 nominate appropriate individuals. To ensure geographical diversity in the Delphi procedure we will  
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23 208 include at least 10 experts on each panel (at least 10 pediatricians, at least 10 patients, and etcetera).

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27 209 As the use of medication or other interventions during pregnancy is dependent on the motivation and  
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29 210 understanding of pregnant women, panels will include both healthy pregnant women and women who  
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31 211 have experienced adverse outcomes that might reasonably have qualified for prevention or treatment  
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33 212 with immune modulation. Women with a history of recurrent miscarriage, preterm birth, fetal growth  
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35 213 restriction and/or preeclampsia, all complications of pregnancy for which immune modulation is  
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37 214 considered as holding promise, will be eligible. To be included within a patient/consumer subpanel,  
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39 215 women must have adequate English language skills.

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43 216 Candidate expert and lay participants will be invited to participate in the Delphi procedure by email in  
44  
45 217 which we will explain the background and goals of the study. Lay participants will be accessed through  
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47 218 patient and consumer organizations (for example the Dutch preeclampsia / Hellp foundation / March of  
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49 219 Dimes / Perinatal Society of Australia New Zealand) and invitational posters at participating centres  
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51 220 distributed around the world.  
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3 221 In the explanatory email we will use written text supported by a video explaining the need for a set of  
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5 222 core outcomes in reproductive immunology, and information on the time commitment and schedule for  
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7 223 each Delphi round. The email will also contain a link to accept the invitation, to provide informed  
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9 224 consent, and to register in the software. Nominated experts will be invited to provide the names of  
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11 225 other relevant experts who meet the inclusion criteria, and reasonably should be invited to participate  
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13 226 to achieve optimal inclusion. Participants will be asked to not personally contact other potential experts,  
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15 227 and to not discuss the Delphi procedure, to ensure unbiased input. Responses to the Delphi procedure  
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17 228 will be semi-anonymised, such that participants are aware of their fellow panel members but not of  
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19 229 their individual responses. Results returned will include individual expert responses as well as responses  
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21 230 on a panel group level.  
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26 231 As not all different panels will include experts in animal studies, and since we aim to develop two  
27  
28 232 separate COS documents for animal and human studies, only the reproductive science and immunology  
29  
30 233 panels will be able to contribute to assembling the animal COS.  
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34 234 We anticipate a three round Delphi procedure to reach consensus on the shortlist of core outcomes. The  
35  
36 235 aim of the Delphi procedure is to eliminate all outcomes that are not fundamental or essential. Experts  
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38 236 can only be part of a subsequent round if they complete the former one. In each round the participants  
39  
40 237 will receive an email with a summary of the response rates and results to date and a link to the next  
41  
42 238 questionnaire. Each round will take approximately 3 weeks. Reminders will be send to the respondents  
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44 239 who have not yet responded, and 2 days before the deadline a final reminder will be send.  
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#### 48 240 *First Delphi round*

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51 241 In the first round an initial assessment of the relevance of possible outcomes, derived from the  
52  
53 242 systematic review, will be made. Panel members will be asked to score the importance of outcomes on a  
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55 243 9-point Likert-scale, following the COMET advice<sup>19</sup>. Items will be ranked and those with a median of at  
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3 244 least 7 when a Likert of 9 is used will progress to the next round. To ensure a complete set of outcomes  
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5 245 using the input of topic experts and patients / consumers, participants will be asked to 'rescue' any  
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7 246 outcome missed by the panel's ranked list of outcomes and which they consider as a core outcome.  
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11 247 *Second round*  
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14 248 In the second round the response rate for each panel and the overall response rate will be reported. All  
15  
16 249 outcomes reaching the cut-off threshold from round one will be presented again plus outcomes put  
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18 250 forward for rescue by at least two participants. For each outcome the scoring of round one will be  
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20 251 presented at three levels: a) at the participants' individual level; b) at the level of the expert subpanel;  
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22 252 and c) at the level of the other expert panels. These results will be presented graphically in the form of a  
23  
24 253 histogram (as generated by Delphimanager). Panel members' own individual responses can then be  
25  
26 254 compared against the score of their respective subpanel, and against the score of other subpanels.  
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28 255 Participants will be asked to rate the importance of all outcomes again, but now with the knowledge of  
29  
30 256 the scores in round one. We will again underline in the explanatory text the aim of the study, namely to  
31  
32 257 identify fundamental / essential outcomes to be reported as a minimum set in each study. It will be  
33  
34 258 essential to not be excessively inclusive, in order that a manageable COS is delivered. We will emphasise  
35  
36 259 that for every future reproductive immunology study this will be a minimum outcome set, and that  
37  
38 260 additional outcomes relevant to individual studies can always be added. Furthermore, in this round we  
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40 261 poll the panel members for availability to join the consensus meeting as a satellite meeting of another  
41  
42 262 event (see below).  
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48 263 *Third round*  
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51 264 In round three outcomes will not be taken forward from the previous round if more than 70% of the  
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53 265 total panel judged the outcome as not essential (score 1-3 on 9-point Likert scale) AND less than 15% of  
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3 266 experts regard this same outcome as important (score  $\geq 7$  on 9-point Likert scale). All the other  
4  
5 267 outcomes will be presented in round three.  
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8 268 A preliminary list of outcomes for the consensus meeting will be assembled. To that end, the outcomes  
9  
10 269 retained after round two will be presented to the participants. The outcomes will be presented in similar  
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12  
13 270 way as in round two. The reproductive scientists and immunologists will also receive a preliminary list of  
14  
15 271 animal studies core outcomes.  
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18 272 After the third round all outcomes having a score  $\geq 7$  on the 9-point Likert scale in at least 70% of the  
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20 273 participants will be taken forward into the consensus meeting as potential COS. Outcomes with more  
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22 274 than 70% of the participants judged as less important (score 1-3 on 9-point Likert scale) and less than  
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24 275 15% as important (score  $\geq 7$  on 9-point Likert scale) will be excluded. Furthermore, the outcomes not  
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26 276 regarded as essential for the core outcome set and also not excluded will be presented at the consensus  
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28 277 meeting for further consensus voting.  
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36 279 **3. Organise a consensus meeting to discuss and finalize the COS for immune modulation in pregnancy.**  
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39 280 To finalize the COS for immune modulation in pregnancy, we will organize a consensus meeting as a  
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41 281 satellite event to an international conference in 2019, most likely to one of the following meetings:  
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43 282 Society of Reproductive Investigation, annual meeting of American Society of Reproductive  
44  
45 283 Immunology, or International Society for Immunology of Reproduction. This consensus meeting will be  
46  
47 284 divided into a clinical consensus meeting (involving all experts in the human COS), and an animal  
48  
49 285 consensus meeting (involving the reproductive scientists and immunologists only). The Delphi process is  
50  
51 286 expected to take 12 months with final outcome disseminated in 2019. Within this consensus meeting,  
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54 287 we aim to have members of each stakeholder group present in person. A full day meeting, with an open  
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3 288 and collaborative character is proposed with an objective facilitator who will actively encourage equal  
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5 289 input of all participants and will prevent skewing by strong voices or dominance using nominal group  
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7 290 techniques. All outcomes still present after round three (of either Likert, so added by rescue) will be  
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10 291 presented at the consensus meeting.  
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16 293 **4. To implement the COS for immune modulation in pregnancy.**  
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19 294 After the COS for immune modulation in pregnancy is finalised, their uptake and application in studies  
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21 295 reporting on immune modulation in pregnancy will be stimulated by publication of both the human and  
22  
23 296 animal COS in an open access, peer-reviewed reproductive immunology journal. Further, dissemination  
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26 297 will also be through presentations at appropriate international meetings, through relevant research and  
27  
28 298 scientific societies, and through relevant journals and electronic media channels.  
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## 299 **Ethics and dissemination**

300 For this study ethics approval is not required. Participants will be asked to provide informed consent. For  
301 the dissemination of the COS we will use a range of different strategies to maximise awareness and  
302 encourage uptake. We will disseminate all possible outcome measures as a systematic review, and  
303 publish this in a peer-reviewed reproductive immunology or methodology journal. Then after finalising  
304 the COS for immune modulation in pregnancy, we will disseminate it through different channels. First,  
305 we will publish the COS in a peer-reviewed reproductive immunology journal. Second, we will  
306 disseminate the COS at appropriate international meetings, such as reproductive immunology and  
307 reproductive sciences meetings. We will furthermore discuss it with patient / consumer organisations  
308 with an emphasis on relevance to pregnant women. We will also disseminate the COS through scientific  
309 societies, and appropriate electronic media.

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3 **369 Authors' contributions**

4 370 J.R.P., S.J.G. and S.A.R initiated this study and designed the protocol. J.R.P., F.H., and S.J.G. wrote the  
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6 371 first draft of this manuscript. All authors critically revised the protocol and the manuscript. J.R.P. and  
7  
8 372 F.H. will be responsible for selection of studies for inclusion and for data-extraction for the systematic  
9  
10 373 review. J.R.P., J.W.G., J.H., and S.J.G. will be responsible for the Delphi procedure. S.A.S, A.F.B., and  
11  
12 374 S.A.R. will select and invite the experts.  
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