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Guidance for the collection of case report form variables to assess safety in clinical trials of vaccines in pregnancy ☆

Christine E. Jones [a,*], Flor M. Munoz [b], Sonali Kochhar [c], Stefania Vergnano [a,d], Clare L. Cutland [e,f], Mark Steinhoff [g], Steven Black [h], Ulrich Heininger [i], Jan Bonhoeffer [i], Paul T. Heath [a]

[a] Paediatric Infectious Diseases Research Group, Institute of Infection and Immunity, St George's, University of London, UK
[b] Baylor College of Medicine, Houston, TX, USA
[c] Global Healthcare Consulting, India
[d] School of Clinical Sciences, University of Bristol, UK
[e] Medical Research Council: Respiratory and Meningeal Pathogens Research Unit, South Africa
[f] Department of Science and Technology National Research Foundation, Vaccine Preventable Diseases, Faculty of Health Sciences, University of the Witwatersrand, South Africa
[g] Cincinnati Children's Hospital Medical Center, USA
[h] Center for Global Health, Cincinnati Children's Hospital, USA
[i] University of Basel Children's Hospital, Basel, Switzerland

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ABSTRACT

Vaccination in pregnancy is an effective strategy to prevent serious infections in mothers and their infants. Safety of this strategy is of principal importance to all stakeholders. As the number of studies assessing safety of vaccines in pregnancy increases, the need to ensure consistent collection and reporting of critical data to allow comparisons and data pooling becomes more important. The Global Alignment of Immunization Safety Assessment in Pregnancy (GAIA) project aims to improve data collection and create a shared understanding of maternal, fetal and neonatal outcomes in order to progress the global agenda for vaccination in pregnancy.

The guidance in this document has been developed to harmonize the data collected in case report forms used for safety monitoring in clinical trials of vaccination in pregnant women. Data to be collected is prioritized to allow applicability in diverse research settings, including low and middle-income countries. Standardized data will enable the research community to have a common base upon which to conduct meta-analyses, strengthening the applicability of outcomes to different settings.

1. Preamble

1.1. Background and need for this guidance

Vaccination in pregnancy is an effective strategy to prevent serious infections in mothers and their infants [1–5]. Recommendations exist for use of tetanus and influenza vaccines in many countries and the number of countries recommending pertussis vaccination continues to increase. Other vaccines are recommended in pregnant women where there is perceived benefit, such as hepatitis A, hepatitis B and meningococcal (serogroups A,C,W,Y). Novel vaccines targeting group B streptococcus (GBS) and respiratory syncytial virus (RSV) are in various stages of development [6,7].

Safety of vaccination in pregnancy is a key consideration for pregnant women, healthcare providers, vaccine manufacturers, regulators, sponsors and ethics committees. The number of studies assessing safety of vaccination in pregnancy continues to increase; however, inter-study variability makes comparisons and pooling of data challenging [8]. The failure to collect and consistently report critical data and the absence of guidance for data collection were identified at two international conferences, which concluded that data collection and presentation should be harmonized across different studies and settings [9,10].

The Global Alignment of Immunization Safety Assessment in Pregnancy (GAIA) project (http://gaia-consortium.net), coordinated by the Brighton Collaboration Foundation (https://brighton-collaboration.org), aims to improve data collection and create a shared understanding of maternal, fetal and neonatal outcomes

☆ Brighton Collaboration homepage: http://www.brightoncollaboration.org.

* Corresponding author at: Paediatric Infectious Diseases Research Group, Institute of Infection & Immunity, St. Georges, University of London, Jenner Wing, Level 2, Room 2.215D, London SW17 0RE, UK.
E-mail address: contact@brightoncollaboration.org (C.E. Jones).

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in order to progress the global agenda for vaccination in pregnancy. The guidance proposed in this document have therefore been developed to harmonize the data collected in case report forms (CRFs) used for safety monitoring in clinical trials of vaccination in pregnant women. Guidance on the prioritization of the data to be collected is also provided to promote collection of at least a minimal set of high priority parameters in various settings, including low and middle-income countries (LMIC).

1.2. Use of this guidance

The aim of this guidance is to provide a standard for the collection of data in CRFs in clinical vaccine trials involving pregnant women where safety is an outcome. The guidance is presented as a series of tables and is referred to henceforth as a data collection matrix. It is intended as a tool to optimize data collection and to do so in a standardized manner in order to improve accuracy and comparability between clinical trials of vaccines in pregnancy. A standardized set of data will enable the research community to have a common base upon which to conduct meta-analyses, strengthening the applicability of outcomes to different settings. This data collection matrix is intended to be useful in all phases of clinical trials, from Phase I to Phase IV, from initial planning to implementation and evaluation. It is aimed at all stakeholders, from investigators, research networks, ethics committees and sponsors. It is also intended to be applicable in all resource settings; however, it is acknowledged that there are particular challenges to implementation in low and middle income countries (LMIC).

In consideration of this wide remit, data variables are prioritized into Priority 1 and Priority 2 data as follows:

Priority 1: Essential: data considered essential for the understanding of the trial results and/or required by national and/or international regulatory authorities
Priority 2: Complementary: data considered complementary, but not essential.

This data collection matrix is intended as a tool to assist all stakeholders; it is not regulatory or mandatory in nature. It is not intended to guide or establish criteria for clinical management. It is also not all-encompassing; it should be considered as a minimal data set in clinical trials where safety is an outcome. It is also expected that it may be adapted according to the specific aims and objectives of the individual clinical trial and that additional variables and data may also be collected.

It is intended that this guidance will be used alongside other existing guidelines from the Brighton Collaboration and the GAIA project. In particular, it is complementary to the "Guideline for collection, analysis and presentation of safety data in clinical trials of vaccines in pregnant women" [14]. The existing case definitions of key neonatal and maternal outcomes for clinical trials of vaccines in pregnancy, produced as part of GAIA should be referred to [14] as relevant and as new case definitions are developed these should also be used for safety assessments in future clinical trials. They will become available at www.brightoncollaboration.org.

1.3. Development process of data collection matrix

This data collection matrix was constructed using an iterative process. Six CRFs from investigator initiated and industry sponsored clinical trials carried out in diverse geographical settings, including Africa, Asia, Europe and North America, and assessing different vaccines were collected and all variables were extracted into Microsoft Excel (see acknowledgments section for contributors of the CRFs used). Each variable was then coded according to whether or not it was collected in each study. This enabled a visual representation of the variables in each study to be displayed. Each member of the Data Collection Matrix Working Group (CEJ, MS, PTH, SB, UH), then independently assessed each variable as essential, important or non-essential in clinical trials assessing safety of vaccination in pregnancy. Any other variables considered essential but missing from this master list were added at this stage. Each variable was then scored according to the number of individuals who considered it as essential or important. The list of variables for inclusion or exclusion was then reviewed and agreed by all members of the working group during a series of telephone conferences. Included variables were further refined during a process of review by the Executive Committee of the GAIA consortium by telephone calls and face to face meetings. Variables were grouped into tables and harmonized with the Guideline for collection, analysis and presentation of safety data in clinical trials of vaccines in pregnant women (referred to forthwith as the Guidelines document) [14]. The data collection matrix was then refined following structured peer-review by the broad global Brighton Collaboration Reference Group and review by subject matter experts attending the Harmonized Safety Monitoring of Immunization in Pregnancy International Consensus Conference and Investigators Workshop, 28–30th March 2016, National Institutes of Health, Bethesda, USA [11,12]. This guidance should be considered as a 'living document', which will be reviewed periodically and updated to take account of emerging data and feedback from investigators implementing this guidance, these will be available at www.brightoncollaboration.org.

1.3.1. Rationale for overall structure of the data collection matrix

The data collection matrix is presented as a series of tables of variables to be collected in case report forms. Each table relates to a different time-point or section of the case report forms.

1.4. Relationship of the data collection matrix to the "Guideline for collection, analysis and presentation of safety data in clinical trials of vaccines in pregnant women"

The data collection matrix and the Guidelines document are discrete documents, which are highly inter-related. It is expected that both documents will be used in parallel. The Guidelines document provides higher level information whereas the data collection matrix provides greater granularity. For example, the Guidelines document advises that safety follow-up should include a symptom diary to record solicited and unsolicited local and systemic adverse events following immunization (AEFI). The data collection matrix provides the detail of what variables should be collected in this symptom diary and suggests how signs and symptoms should be measured or graded. Each table in the data collection matrix relates to a section in the Guidelines document. Therefore, whilst distinct documents, they are harmonized and should be used together.

2. Guidance for the collection of case report form variables

The tables define data that should be collected prior to vaccination (Table 1), at the time of vaccination (Table 3) and in the follow-up period (Table 4). Early phase clinical trials may select pregnant women at low risk of obstetric complications, whereas in other studies, particularly late phase clinical trials, it may be preferable to enroll pregnant women regardless of their obstetric risk. In recognition of this, an example of variables that may be collected to assess obstetric risk is provided (Table 2).

In order to assess safety of vaccination in pregnancy, it is recommended that the minimum follow-up period for women is