Safety Platform for Emergency vACcines

Charter Meta-DSMB for CEPI Funded Vaccine Trials

Version 1.6 February 4, 2021
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1. Introduction

The Coalition for Epidemic Preparedness Innovations (CEPI) has funded the Brighton Collaboration to create the Safety Platform for Emergency vACcines (SPEAC) Project. SPEAC is supporting the safety assessment of all CEPI-sponsored vaccines, including the creation of a Meta-Data and Safety Monitoring Board (Meta-DSMB). This document is a charter and Standard Operating Procedure (SOP) to the Meta-DSMB.

1.1 CEPI

CEPI’s vision is to create a world in which epidemics are no longer a threat to humanity. CEPI is an innovative global partnership between public, private, philanthropic, and civil society organizations to develop vaccines to stop future epidemics. CEPI’s mission is to stimulate and accelerate the development of vaccines against emerging infectious diseases and enable access to these vaccines for people during outbreaks.

- CEPI will advance vaccines against known threats through proof-of-concept and safety testing in humans and will establish investigational vaccine stockpiles before epidemics begin—“just in case”.
- CEPI will fund new and innovative platform technologies with the potential to accelerate the development and manufacturing of vaccines against previously unknown pathogens (e.g.: within 16 weeks from identification of antigen to product release for clinical trials)—“just in time”.
- CEPI will support and coordinate activities to improve our collective response to epidemics, strengthen capacity for vaccine administration in countries at risk, and advance the regulatory science that governs product development.

1.2 SPEAC

SPEAC is focusing on supporting the safety assessment across CEPI funded vaccines by addressing the following needs:

a. Support and supplement safety expertise on data safety monitoring boards (DSMBs) for individual CEPI vaccine trials.

b. To form a Meta-DSMB advising the CEPI Vaccine R&D Committee and the developers on the safety profiles of constructs and target disease candidates in the portfolio.

c. Optimize the quality and utility of safety data by creating an online vaccine safety resource and literature repository of technical guidance, tools, information exchange and training modules for CEPI trial sponsors.

https://cepi.net
1.3 Meta-DSMB: Opportunity and Need

CEPI is in many ways in a unique situation. It is funding the evaluation of several vaccine candidates for each individual pathogen. In addition, it is supporting evaluation of the use of the same vaccine platform for several different pathogens. This approach has the advantage of selecting the best vaccine candidate for a given pathogen, but it also engenders unique responsibilities. Vaccines using the same platform might have common safety concerns.

Critically, individual studies against a vaccine target or using a common platform might be underpowered to detect rare safety concerns or patterns of adverse events that can only be identified through analyses of events that occur across individual studies that in aggregate would provide a larger number of subjects.

SPEAC is establishing a Meta-DSMB to facilitate these comparisons across individual studies to enhance and support safety assessment more comprehensively. The Meta-DSMB will therefore not replace the individual study DSMBs but rather support them by providing critical oversight of all the safety data. While the sponsor’s oversight is of their specific clinical trial, the Meta-DSMB is tasked with oversight of the entire CEPI vaccine clinical trial portfolio.

Furthermore, vaccines against the same pathogen need to be compared on their safety as well as effectiveness. SPEAC and the Meta-DSMB have the goal of advising CEPI and the sponsors on safety and assuring CEPI that vaccine candidates and platforms that are taken forward are safe. The Meta-DSMB will be independent of both the developer and the funder of the study.

1.4 Charter

This Charter is for the Meta- Data and Safety Monitoring Board - for Vaccine Studies funded by CEPI. Best practice and guidance on study DSMBs are described in FDA NIH and EMA guidance documents and have been the backbone of developing this charter.2,3,4 However, the Meta-DSMB is different from an individual study DSMB and is not intended to assume primary responsibility for ensuring the safety and wellbeing of study participants or of monitoring safety in individual clinical trials. These responsibilities remain with the sponsor and the individual sponsor DSMBs.

To our knowledge, this is the first time that a Meta-DSMB is being created. Therefore, this Charter is intended to be a living document. The Meta-DSMB members, study sponsors, CEPI and SPEAC will review it at regular intervals to determine whether any changes in procedures are needed.

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2 Guidance for Clinical Trial Sponsors Establishment and Operation of Clinical Trial Data Monitoring Committees. FDA 02-2019 accessed June 9, 2019
3 CHMP. Guideline on data monitoring committee 2005; Doc. Ref. EMEA/CHMP/EWP/5872/03 Corr
2. Roles and responsibilities of the Meta-DSMB

As stated in section 1.4 the role of the SPEAC Meta-DSMB (hereafter referred to as the “Meta-DSMB”) is distinct from the role of the individual study DSMBs, how they relate to each other is described in section 8.

Briefly, study specific DSMBs advise the sponsor regarding the continuing safety of trial subjects and those yet to be recruited to the trial, as well as the continuing validity and scientific merit of the trial. Study specific DSMBs are organized by the vaccine sponsors.

The goal of the SPEAC Meta-DSMB is to monitor the safety of the entire CEPI vaccine portfolio across all trials, pathogens and platforms by combining and accumulating experiences on safety of the vaccines across individual CEPI funded studies.

Specific responsibilities of the Meta-DSMB are:

1. To monitor the safety profile of candidate vaccines across CEPI-funded clinical trials by looking at patterns related to vaccines, pathogens, technology platforms across trials and at information from the SPEAC landscape analyses.

2. To review reasons to stop or pause enrollment and vaccine administration of individual studies or administration of second doses based on safety data with Meta-DSMB members and assess impact for similar vaccines and/or pathogens/technology platforms.

3. To review ongoing safety data (individual level and aggregate) of individual studies and look for patterns across pathogens and technology platforms. This would normally be of blinded safety data or safety data aggregated by an unblinded group designation such as group A or B. These data would normally be obtained by the liaison member as part of their participations in study DSMB meetings as the Meta-DSMB liaison member would have access to the same information as the study DSMB members in the study DSMB open sessions. Thus, if the study DSMB is only seeing blinded data, this is what the liaison member would see unless a concern was identified, and additional data requested through the study DSMB. However, where there was a specific safety concern, the Meta-DSMB could request that the study DSMB view an unblinded analysis for that outcome. A prototype reporting format from the study DSMB to the Meta-DSMB by the liaison member is provided in Appendix 2. After each meeting, a copy of this document will be provided to the sponsor to review for accuracy.

4. In addition to results of SPEAC conducted Landscape Analyses, the Meta-DSMB may review data from non-CEPI funded studies.

5. To provide expertise when requested by individual study DSMBs

6. To provide an opinion, when requested by CEPI or study sponsor, of the safety of study vaccines in individual studies. This opinion would be advisory and not binding.
7. Monitor the overall conduct of the individual studies upon specific request by CEPI or study sponsor, including means of improving clinical trial documents and procedures as related to safety data management.

8. Make suggestions for harmonization of safety data collection and analysis across studies to facilitate comparisons between studies.

9. Assess the completeness, quality, and interpretation of available safety data upon the request of CEPI or if potential issues arise.

10. The Meta-D fmap liaison member will liaise with individual study DSMBs and facilitate constructive communication.

11. Maintain confidentiality of treatment findings with regard to CEPI, sponsors and investigators. Maintenance of confidentiality is critical to the integrity of the clinical trials. (If it is deemed necessary to share a safety concern from a sponsor trial, the draft of this communication will be shared with the study sponsor for review prior to sharing with CEPI.)

12. Disclose all potential conflicts of interests (scientific, financial, other) among Meta-D fmap members to SPEAC, CEPI or sponsors, as applicable.

CEPI, the sponsor or the individual program DSMB may request advice from the Meta-D fmap about:

1. Recommendations for the evaluation of unanticipated events and abnormal findings with suggestions for referral if indicated.

2. Recommendations on study conduct including amendments to the study protocol and consent forms regarding safety data.

For all of these situations, the recommendations may be individual study specific, specific to a given vaccine, technology platform or pathogen.

As one task of SPEAC is to constitute a pool of qualified individuals from which study sponsors can select individuals as active members of their study DSMBs, the Meta-D fmap may be asked to review the qualifications of these candidate CEPI study DSMB members or be asked to make recommendations regarding individuals that might be included in this pool.

3. Members and Organization

The Meta-D fmap is a group of independent vaccine safety experts, (number depending on the number of ongoing CEPI funded trials), with experience of functioning in DSMBs, who will be employed and paid as consultants to The Taskforce for Global Health as part of the CEPI funded SPEAC grant on an annual basis.

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5 https://www.globalhealthfdn.org
Potential Meta-DSMB members will be required:
1. To provide a *curriculum vitae* (CV)
2. To complete a Conflict of Interest (COI) form
3. To be willing to serve as liaison member to specific study DSMBs and take part in the Meta-DSMB meetings under the conditions of the SPEAC contract including signing a confidentiality agreement.

The consulting statistician should have prior experience working on a DSMB and comply with requirements 1-2.

Eligibility and COI will be reviewed and approved prior to acceptance and the first Meta-DSMB/DSMB meeting by each of the following: the SPEAC Executive Board, and CEPI.

A Meta-DSMB member is not allowed to be both an official study DSMB member hired by the sponsor and a SPEAC Meta-DSMB liaison to a sponsor for the same study or pathogen.

However, they may be both a Meta-DSMB member and official study DSMB member, but not vote on any recommendations related to the sponsor for which they serve as a study DSMB member.

If a Meta-DSMB member has a COI with one or more of the products under development or with the sponsors that person will not be allowed to serve on the Meta-DSMB.

A Meta-DSMB member will serve as a liaison non-voting observer member on a specific CEPI funded study DSMB. In addition to the liaison Meta-DSMB member, CEPI may designate other individuals to attend some individual study DSMB meetings as observers as well.

Individual study sponsors or investigators will not routinely communicate with the Meta-DSMB. Requests to the Meta-DSMB should be made through the liaison member or the SPEAC contact (SPEAC work package one leader), except upon the request of the SPEAC consortium or following consultation with CEPI. Investigators will not communicate with Meta-DSMB members about the study directly except when responding to questions posed by the Meta-DSMB.

The Meta-DSMB is not assigned to any specific study or developer nor is it funded by them. The Meta-DSMB is funded by the SPEAC grant through The Task Force for Global Health.

The Meta-DSMB will have a Chair and Executive Secretary (ES) selected by the SPEAC EB.

1. The Chair should be eligible to be a Meta-DSMB member, and not have a COI regarding any of the products being evaluated and be willing to be available for the duration of the SPEAC project. The Chair will be (re)-appointed annually.
2. The ES will provide an unbiased SPEAC staff interface for the Meta-DSMB, especially during closed sessions. The ES is responsible for assuring the accuracy and timely transmission of the minutes of Meta-DSMB meetings and discussions and should not have any conflicts of interest.
absence of a permanent ES, the Meta-DSMB chair will designate a Meta-DSMB member to perform this function at the beginning of each meeting.

The Meta-DSMB will also include a consulting statistician. This person will serve as a consultant to the Meta-DSMB regarding statistical issues that may arise in their deliberations, will participate in both open and closed sessions, and will be a voting member of the Meta-DSMB.

4. Meta-DSMB Meetings

**Frequency:** Meetings of the Meta-DSMB, including in person and teleconference meetings, will be held at least twice a year, with additional meetings or conference calls scheduled as needed.

**Agenda:** For meetings and calls will be drafted by the SPEAC work package 1 leader in consultation with the Meta-DSMB chair, the Meta-DSMB members and CEPI. The agenda and meeting materials will be prepared by the SPEAC WP1 leader in consultation with the Meta-DSMB chair and should be distributed by at least two weeks before each meeting.

**Review of COI:** When they join the Meta-DSMB and before each meeting, when the agenda is sent out, the ES will ask all Meta-DSMB members to state in writing whether they have or have developed any new potential COI since the last meeting. If a new conflict is reported, the Chair and the SPEAC WP 1 leader will determine if this COI should limit or curtail their participation in the Meta-DSMB. This potential conflict and the discussion regarding its resolution will be recorded in the minutes of the meeting.

**Review of Charter:** At the first Meta-DSMB meeting, a draft of this charter was reviewed and discussed and the functioning of the Meta-DSMB reviewed, to provide an overview of activities, to discuss the format for reports and presentation of data, access to interim data, communication with individual study DSMB members, the process of review of conflicts of interest and review of any report.

**Regular Meta-DSMB meetings:** the Meta-DSMB will review:

1. AESI and SAEs in aggregate across disease areas and platforms.
2. Any SUSARs identified.
3. Reports from each Meta-DSMB liaison member regarding any potential issues or relevant discussions from individual study DSMB meetings that they attended. A template for this report is appended in Appendix 2.
4. Any questions or concerns identified in individual study DSMBs or referred to the Meta-DSMB for opinion
5. Follow up on any prior identified issues
6. New or potential safety aspects identified from the SPEAC landscape analyses as conducted by SPEAC WP-2 and from any other sources.
If a possible concern is identified, the Meta-DSMB may request additional information from the DSMB of a specific trial or across other trials with the same platform or disease target through the liaison member.

At intervals, as noted above, the Meta-DSMB will also review formal (interim and final) results of the primary (and possible secondary) end points as they become available for each study. The purpose of this review is not to duplicate or replace the role of the individual study DSMBs but rather to support DSMBs and sponsors by allowing identification of safety issues across trials for similar platforms or disease targets. All communication will be through the Meta-DSMB liaison and the study DSMB with the sponsor being copied on any written communication.

**Attendance:** It is expected that all Meta-DSMB members will attend every meeting. However, it is recognized that this may not always be possible. Quorum for voting is considered to be half the number of standing members plus one. The Board may wish to decide if particular expertise is needed within the quorum for the meeting to be valid. All standing Meta Data Safety Monitoring Board members are voting members of the Meta-DSMB unless they have a COI. Consultants to the Meta-DSMB do not have voting rights. (Such consultants with expertise in a specific safety topic would be contracted by the SPEAC project at the request of the Meta DSMB and with approval of SPEAC)

**Decision-making:** Voting on recommendations will follow Roberts’ Rules of Order<sup>6</sup> Each Meta-DSMB member and the Meta-DSMB statistician will each have one vote except in the case of Meta-DSMB members recusing themselves because of a potential conflict of interest as discussed above.

## 5. Meetings of meta-DMSB liaison with individual study DSMB

The Meta-DSMB liaison member assigned to a given clinical trial shall make every effort to attend each of the sponsor DSMB meetings for that trial as observer. During these study meetings, liaison Meta-DSMB members will be non-voting observers.

As part of their Meta-DSMB role, however, they may suggest additional analyses, provide expertise or request that additional safety data be provided. Normally, if an additional analysis is suggested, it would be performed at the discretion of the study DSMB. For an actual or potential safety concern where this would be more urgent, the Meta-DSMB would notify the SPEAC Meta DSMB work package leader and he/she would contact the sponsor to discuss.

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6. Review of Study Protocols and Analysis Plans

The Meta-DIBM liaison member will review and be familiar with the study protocol and analysis plans for each study that falls under the auspices of the individual study DSMB to which they serve as a liaison member so as to be better able to support individual study DSMB activities.

7. Reporting of liaison to Meta-DIBM and confidential material

The liaison Meta-DIBM members to individual CEPI funded trials are responsible for giving an overview report of the safety data in the individual CEPI funded trials to the Meta-DIBM based upon their review of material presented at the sponsor DSMB meeting for each Meta-DIBM meeting. The template for this is appended in Appendix two.

For each Meta-DIBM meeting, the SPEAC WP1 lead, in consultation with the chair of the Meta-DIBM and the Meta-DIBM statistician, will prepare an agenda to facilitate the functioning of the Meta-DIBM.

The Meta-DIBM should discuss at the first or subsequent meetings what data they wish to review and how it should be presented.

Meta-DIBM meetings and calls will be organized into open, and closed sessions.

- During the open sessions, information will be presented to the Meta-DIBM by the liaison member with SPEAC and any CEPI staff that are in attendance contributing as appropriate, with time for discussion.

- During the closed sessions, the Meta-DIBM members, and the statistician will discuss any confidential data or issues from CEPI funded studies. The Meta-DIBM will decide whether to remain masked to the treatment assignments at each meeting. If a potential serious safety concern is identified, the Meta-DIBM can ask for unblinded information from the individual DSMB.

If the closed session occurs on a conference call or video connection, steps will be taken to ensure that only the members of the Meta-DIBM are on the call, and to invite others to leave and then to re-join the call only at the conclusion of the closed session.

At the conclusion of the closed sessions, the participants will be re-convened so that the Meta-DIBM Chair can provide a summary of the Meta-DIBM’s recommendations. This provides an opportunity for Meta-DIBM individuals to ask questions to clarify the recommendations. The meeting is then adjourned.

All material discussed at the Meta-DIBM meeting will be considered confidential. Reports and findings of the open sessions of the Meta-DIBM will be shared with SPEAC and CEPI via a secure SharePoint created for this purpose. Material provided by sponsors will be stored in a secure SharePoint created for each sponsor. If safety concerns are identified with a specific product, they will be shared with SPEAC and then with the sponsor and CEPI. Concerns that might apply to more than one sponsor’s
product will be discussed with CEPI and disseminated to sponsor DSMBs and sponsors in as close to real time as possible. Communication regarding issues arising from one sponsor will be shared with that sponsor prior to disseminating to other relevant sponsors and CEPI.

8. Reports of Meta-DSMB Deliberations

The ES is responsible for the Meta-DSMB minutes. These will be placed in the secure Meta-DSMB SharePoint created for this purpose. These minutes should be placed in the SharePoint within five working days of each meeting. Minutes of the open sessions will be shared with SPEAC and CEPI.

These minutes are prepared to summarize:

- Meeting attendees
- The key points of the discussion and debate,
- Requests for additional information,
- Response of the investigators /developer to previous recommendations,
- Recommendations from the current meeting.

If concerns are identified, the minutes will include:

- Type of concerns,
- Meta-DSMB discussion of the concerns,
- The basis for any recommendations that the Meta-DSMB has made in response to the concerns.

Draft versions of the minutes will be shared with the Meta-DSMB members for review in SharePoint. The Meta-DSMB Chair may sign the minutes or indicate approval electronically via email.

- If there are no concerns or major issues raised, signed minutes from the open session will be sent to SPEAC Executive Board for forwarding to CEPI. Minutes of the closed session will be kept in a secure SharePoint by the Meta DSMB secretary.
- If concerns or major issues are raised during the meeting:
  - Signed minutes will be sent to the SPEAC Executive Board and CEPI Program Office within 3 working days of the meeting.
  - Relevant Individual study DSMBs and sponsors (those that might be also impacted by the nature of the concern) will be notified as soon as possible but within 48 hours if safety issues are identified. If the issued was identified from a single sponsor study, this sponsor will have the opportunity to review the communication prior to its distribution. Every effort will be made to anonymize the identity of the sponsor to the extent possible without compromising the utility of the communication.
Minutes are included in the materials for the subsequent Meta-DSMB meeting to be approved by voice vote at that meeting. Once they have been voted and approved by the Board, they are considered final. Archived versions of initial, interim and final minutes will be appropriately identified and stored in the Meta-DSMB secure SharePoint.

Minutes of the closed sessions of the Meta-DSMB will be generated separately and stored in a SharePoint accessible only to Meta-DSMB members created for this purpose.

9. Relationship between Meta-DSMB, DSMB, CEPI

As stated above the role of the Meta-DSMB is distinct from the role of the individual study DSMBs. The Meta-DSMB is not assigned to any specific study or study sponsor nor is it funded by study sponsors. Its role is advisory to CEPI. Rather than have responsibility or providing direct oversight of a specific trial, the goal of the Meta-DSMB is to enhance and support safety monitoring by sponsors and individual study DSMBs and to have the capacity to assess safety across platforms and disease. This higher-level view of the safety data will enhance the assessment of safety because by looking across trials, the statistical power limitations due to the small numbers of patients in individual trials will be somewhat mitigated.

Given the different roles that are foreseen and the need to maintain the independence of the Meta-DSMB, following communication diagrams are meant to summarize communication channels:

1. Between the Meta-DSMB, CEPI, SPEAC and the vaccine developer (sponsor)
2. And between the Meta-DSMB, the individual study DSMBs and the sponsors*

* NOTE: in these two diagrams Lassa and MERS are used as examples. However, the same infrastructure and relationships would apply for all vaccines clinical trials funded by CEPI.

Two possible scenarios have been developed to illustrate this:

1. Scenario 1: In case of signal across the platforms/vaccines is discovered by the Meta-DSMB, the SPEAC EB will inform SPEAC, CEPI, concerned study DSMBs and sponsors as soon as possible but within 48 hours for the sponsor and two working days for CEPI.

2. Scenario 2: In case of a signal in one trial: CEPI can request an opinion/review from Meta-DSMB and the Meta-DSMB can query other related clinical trial sponsor DSMBs regarding any information they may have related to this particular issue. This communication will be shared with the affected sponsor prior to release.

Individual study DSMB members may query their Meta-DSMB liaison member as to whether event(s) have occurred in other CEPI studies. However, without specific advance permission, the Meta-DSMB member should not disclose the specific trial or sponsor for these other event(s).

10. Financial arrangements

The cost of operating the Meta-DSMB as well as the cost of attending any in person meetings will be covered by the SPEAC grant.
Appendix 1
Meta-DSMB members as of April 1, 2020

For the Meta-DSMB members and the Meta-DSMB statistician, their expertise, information on potential conflicts of interest will be maintained separately by SPEAC in the SPEAC SharePoint and updated frequently at a minimum prior to each Meta-DSMB meeting.

Dr. Seif Al-Abri
Seif Al-Abri is a senior consultant in internal medicine and infectious diseases at the Royal Hospital, Muscat, Sultanate of Oman. He received his B.Sc. in Health Sciences and his MD degree from Sultan Qaboos university (SQU), Oman, and an MSC. in Infectious Diseases from the University of London, UK. He has also received a Diploma of London School of Hygiene and Tropical Medicine. He is also Chairman of Board of Trustees, Oman Medical College, and an International advisor for the Royal College of Physicians of London, UK as well as an Honorary Lecturer in Infectious Diseases, Liverpool School of Tropical Medicine. He is a member of the IHR Commission for EMRO.

Prof. James Buttery
Jim Buttery is a paediatric infectious diseases physician and vaccinologist who trained in Melbourne, Australia and Oxford, UK. He has been involved in the development of multiple vaccine candidates, including meningococcal and pneumococcal glycol-conjugate vaccines, Japanese encephalitis vaccines, and is an investigator in the development program of the RV3 candidate rotavirus vaccine in trials in New Zealand and Indonesia. He has worked as a consultant for WHO in vaccine safety and is a member of the Strategic Priority Group for the Global Vaccine Safety Initiative and is an investigator in the Global Vaccine Safety Multi-Country Collaborative Project.
Jim is head of Infection and Immunity, and Director of Research at Monash Children’s Hospital and head of Monash Immunisation, Monash Health. He leads SAEFVIC, the Victorian immunisation safety service, and is an Associate Professor in the Department of Paediatrics, Monash University. He is the president of the World Society of Paediatric Infectious Diseases and serves as a member of the Science Board of the Brighton Collaboration, and the Australian Advisory Committee on the Safety of Vaccines. He has over 120 peer reviewed publications.

Prof. Alex Dodoo
Alexander Dodoo is an Associate Professor at the Centre for Tropical Clinical Pharmacology, School of Medicine and Dentistry, University of Ghana as well as the Director of the WHO Collaborating Centre for Advocacy and Training at the University of Ghana. He serves on several local and international advisory, training and safety committees, including Member, WHO Advisory Committee on the Safety
of Medicinal Products, Member, Access and Delivery Advisory Committee of the Medicines for Malaria Venture and Chairman of the Global Vaccine Safety Initiative. He is the recipient of the Senior Pharmacovigilance Fellowship Award from the WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden. Prof. Dodoo has participated in DSMBs and has developed and conducted a DSMB training course.

Prof. Dr. Kathryn Edwards

Dr. Kathryn M. Edwards MD served as the Director of Vanderbilt Vaccine Research Program at Monroe Carell Jr. Children's Hospital at Vanderbilt for several decades. Currently she is an advisor to the program. Dr. Edwards' clinical expertise is in pediatric Infectious Diseases, recurrent fever syndromes, and vaccines development and safety. Dr. Edwards has been a Member of National Advisory Allergy and Infectious Diseases Council at National Institute of Allergy and Infectious Disease, has served a Member of Clinical Advisory Board at NexBio, has served on the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention; the Vaccine and Related Biologic Products Advisory Committee of the Food and Drug Administration; and the Institute of Medicine Committee for the Evaluation of the Safety and Effectiveness of the Anthrax Vaccine. Dr. Edwards is Sarah H. Sell Endowed Professor in Pediatrics at Vanderbilt University School of Medicine. Dr. Edwards was the Principal Investigator of the placebo-controlled influenza efficacy trial comparing live, attenuated and inactivated influenza vaccines in more than 3,000 volunteers. She was also the Principal Investigator of the NIH-funded multicenter acellular pertussis vaccine trial that compared 13 acellular vaccines and two whole cell vaccines. She published many pivotal articles on vaccines and their impact on disease burden. She has extensive DSMB and vaccine development experience

Prof. Dr. Juhani Eskola

Juhani Eskola graduated as a M.D. from the University of Helsinki in 1975 and as a Ph.D. in 1983. He went on to specialize as a pediatrician in 1983. In 1989, Juhani Eskola was appointed Associate Professor in Infectious Diseases at the University of Helsinki. Early on in his career, Juhani Eskola gained hands-on medical experience as a PI for several vaccine clinical trials, mainly with conjugate vaccines. Between 1991 – 1999, held several top positions (Department Head, Research Professor) at the National Public Health Institute (KTL). During the latter part of this period, Juhani Eskola was also Visiting Professor at the Imperial College of Science, Technology and Medicine in London. He augmented his international experience between 2000 – 2003 at Aventis Pasteur as Senior Vice President being responsible for the clinical development and medical affairs globally. Most recently he was Director General of the Finnish National Institute for Health and Welfare (THL) until he retired at the end of 2018. He has been a member of the Scientific Board of the European Vaccine Initiative (EVI), Chairman of the Tuberculosis Vaccine Initiative (TBVI) and a member of the WHO SAGE
committee. Apart from the over 100 articles in international scientific journals, Juhani Eskola has also written seven books.

Prof. Dr. Neal Halsey

Dr. Neal A. Halsey, M.D. has been on the faculty of Johns Hopkins University for 34 years and is a Professor emeritus in the Departments of International Health at the Bloomberg School of Public Health and the Department of Pediatrics in the School of Medicine. Dr. Halsey previously was on the faculty of Tulane University Schools of Public Health and Medicine for 5 years and he served in the US Public Health System at CDC for 3 years and The Indian Health Service for 2 years. Dr. Halsey has authored more than 240 peer reviewed publications and 41 book chapters. He has focused his research on vaccines and vaccine preventable diseases and he participated in the development of more than 100 guidelines for the use of vaccines while serving on advisory groups for the WHO Expanded Program on Immunization, the Advisory Committee for Immunization Practices (ACIP) for CDC and the American Academy of Pediatrics Committee on Infectious Diseases (The Red Book Committee). Dr. Halsey is the Director Emeritus of the Institute for Vaccine Safety at the Bloomberg School of Public Health. Dr. Halsey has served on 17 DSMBs or Safety Review Committees for phase 1, 2, and 3 vaccine studies.

Prof. Dr. Ulrich Heininger

Ulrich Heininger has been in charge of the division of Pediatric Infectious Diseases and Vaccinology at the University Children's Hospital in Basel since 1998. He received his general pediatric and specialized pediatric infectious diseases training at the University of Erlangen, Germany, from 1988 to 1994, followed by a research fellowship in molecular microbiology in the field of Bordetella pathogenesis at the University of California Los Angeles in 1995 and 1996. He then led the pediatric infectious disease unit in Erlangen before he was appointed head of the Pediatric Infectious Disease at the University Children's Hospital in Basel. In 2000, Ulrich was a founding member of The Brighton Collaboration and has served for it in various functions over the last 2 decades. Ulrich Heininger has conducted several vaccine safety and efficacy studies as principal investigator in the recent past, he is a member of the German and Swiss NITAGs (National Immunization Technology Advisory Group) and of the WHO Global Advisory Committee for Vaccine Safety, GACVS. He has a special interest in vaccine safety and has served on several DSMBs.

Najwa Khuri-Bulos MD, CIC, FIDSA

Dr. Khuri-Bulos is a Distinguished Professor, Pediatrics and Infectious Disease at the University of Jordan, Amman, Jordan and an Adjunct Professor of Pediatric Infectious Diseases at Vanderbilt University, Nashville, USA. She did her residency training in pediatrics at the university of North Carolina at Chapel Hill and completed at Yale University Hospital in New Haven, Connecticut and is
Board certified in pediatrics. She did a fellowship in pediatric infectious diseases at the University of Colorado, Denver Colorado and is board certified in pediatric infectious diseases. She is Division Head Pediatric Infectious Disease, University of Jordan; Founder and Head of the residency training program Jordan University Hospital; Chairman of the research, drugs and therapeutics, infection control, residency training and internship committees at the University of Jordan and Jordan University Hospital; Chairman of the Department of Pediatrics, University of Jordan; Vice Dean, Medical School, University of Jordan and Dean of Research, University of Jordan. She is the founder of the Infectious Disease and Vaccine center, University of Jordan. She is currently Professor Emeritus, The University of Jordan.

She is currently a Member of the Regional Technical Advisory Group of Expert on Immunization (RTAG), WHO, EMRO) and has been a member of The Brighton Collaboration for ten years, WHO Immunization Practices Advisory Committee (IPAC) for five years, Decade of Vaccines (DoV) Committee with the Gates foundation and a member of many working groups of the Brighton Collaboration for vaccine adverse events

**Prof Dr. Shabir Madhi**

Professor Shabir Madhi is a Professor of Vaccinology and Director of the Medical Research Council Respiratory and Meningeal Pathogens Research Unit at the University of Witwatersrand (Wits). He is co-Director of the African Local Initiative for Vaccinology Expertise (ALIVE). He is also the immediate past-Director of the National Institute for Communicable Diseases (2011-2017) in South Africa and Current Chair of the National Advisory Group on Immunization in South Africa. Professor Madhi completed his undergraduate and postgraduate training at Wits, qualified as a pediatrician in 1996, obtained his PhD in 2003, and is certified in Infectious Diseases in South Africa. Since 2017, he is an elected member of the Royal Society of South Africa and The World Academy of Sciences (TWAS).

Professor Madhi has been involved in research on vaccine-preventable diseases, including in HIV-exposed children, since 1997. His research included undertaking pivotal studies on the efficacy of pneumococcal conjugate vaccines (PCVs) and rotavirus vaccines in Africa. These studies contributed to the WHO recommending the introduction of these life-saving vaccines into public immunization programs globally, and also prompted South Africa to be the first in Africa to introduce these vaccines in its national immunization programs. More recently, his research focus has expanded to the prevention of infectious diseases during early infancy, including studies on the role of maternal immunization in improving fetal outcomes and reducing early-infancy morbidity and mortality. He has served and currently serves on several DSMBs.

**Prof. Dr. Walt Orenstein**

Walter A. Orenstein, MD, DSc (Hon) is Associate Director of the Emory Vaccine Center and Professor of Medicine, Pediatrics, and Global Health at Emory University. Dr. Orenstein has had a long and
distinguished career at Centers for Disease Control and Prevention (CDC), Emory University, and the Bill & Melinda Gates Foundation (BMGF). Dr. Orenstein began his career in the Epidemic Intelligence Service (EIS) of the CDC, focusing on immunization, particularly on smallpox eradication and measles elimination. Between 1988 and 2004, he was Director of the United States Immunization Program rising to become an Assistant Surgeon General of the United States Public Health Service. During Dr. Orenstein’s tenure at the CDC, record high levels of immunization coverage among children were reached and indigenous transmission of measles and rubella was eliminated. Multiple new vaccines were introduced into the childhood immunization schedule. From 2004-2008, Dr. Orenstein was Associate Director of the Emory Vaccine Program with a major focus on policy issues related to influenza vaccination in the United States. In 2008, he left Emory University to become the Deputy Director for Immunization Programs at the BMGF, in charge of a large portfolio ranging from implementation of polio eradication activities to basic research on improved vaccines and diagnostics. Polio eradication was the number one priority of the BMGF. He has now returned to Emory. His DSMB experience includes serving on the South American trial of ten valent pneumococcal vaccine.

Marco Safadi, MD Ph.D.
Professor of Pediatrics and Infectious Disease and Head of the Department of Pediatrics Santa Casa de São Paulo School of Medical Sciences. He is also the Chair of the Department of Infectious Diseases for the Brazilian Society of Pediatrics and Chair of the Department of Immunization for the São Paulo Society of Pediatrics. He is a member of the WHO SAGE working group on meningococcal vaccines. He is also a member of the ACIP of the Brazilian Ministry of Health. Dr. Safadi is an experienced clinical trialist. His research has included work on immunization strategies during the COVID-19 pandemic, the spectrum of COVID-19 disease in children, immunization in pregnancy, pneumococcal conjugate vaccination, meningococcal vaccination, RSV infection, and Zika virus.

Mathuram Santosham, MD, MPH
Professor, Departments of Intl Health and Pediatrics - Johns Hopkins Medical Institutions Director Emeritus, Johns Hopkins Center for American Indian Health (CAIH)
Senior Advisor - International Vaccine Access Center (IVAC)

Dr. Mathuram Santosham was born in Vellore, India and obtained his MBBS degree from the Jawaharlal Institute of Post Graduate Medical Education and Research (JIPMER) in Pondicherry, India in 1970. He subsequently moved to the US and obtained Board Certification in Pediatrics and an MPH degree from the Johns Hopkins University. He also completed a Fellowship in Pediatric Infectious Diseases at Johns Hopkins Hospital. Dr. Santosham was the Founder and Director of the Johns Hopkins Center for American Indian Health f(CAIH) from April 1991 to April 2016. He is currently the Director Emeritus of CAIH. He is also the Senior Advisor for the International Vaccine Access Center (IVAC) at Johns Hopkins Bloomberg School of Public Health. He holds Professorships in the Department of International Health and the Department of Pediatrics at Johns Hopkins University. He directed the Division of Health Systems for the Johns Hopkins Bloomberg School of Public Health from 2000-2009. He conducted landmark vaccine efficacy trials, including rotavirus vaccine, H. influenza type b (Hib) conjugate vaccine, and pneumococcal conjugate vaccine. Dr. Santosham serves on numerous national and international committees to promote childhood health throughout the world. He consults for
numerous international agencies including WHO, USAID, UNICEF and the Gates Foundation on aspects of child survival in over 30 countries. He is the author of over 290 peer-reviewed journals and serves as a reviewer for several international medical journals.
Dr. Cynthia Whitney

Dr. Cynthia G. Whitney joined Emory University in 2019 in the Hubert Department of Global Health of the Rollins School of Public Health. Before that, she was Chief of the Respiratory Diseases Branch, Division of Bacterial Diseases at the National Center for Immunization and Respiratory Diseases at the U.S. Centers for Disease Control and Prevention (CDC). Dr. Whitney also directed the pneumococcal epidemiology research program for the Respiratory Diseases Branch and has published extensively on pneumococcal disease epidemiology, drug resistance and vaccines. She held leadership positions for CDC emergency responses that employed vaccines, including Deputy Director of the Vaccines Task Force for the H1N1 influenza pandemic and Incident Commander for the Ebola response in West Africa. Dr. Whitney obtained her medical degree at the University of Minnesota and has been boarded in both Internal Medicine and Preventive Medicine. She has been a leader or active participant in multiple international boards and committees related to vaccine safety and evaluation.
Appendix 2
Liaison Reporting Template to the Meta DSMB

(Will include blinded information only. Unblinded data not to be included in this reporting)

1. Meta DSMB Liaison name

2. Trial sponsor

3. Date of Study DSMB meeting

4. Date of this report if different than above

Trial name, study ID number, phase (1-3)

5. Current trial status (phase of trial - one two or three, active, inactive, stopped, etc.). Enrollment to date

NOTE: for items 6, 7, 8 and 9 below, appropriate blinded material from the DSMB open session minutes may be pasted into this document.

6. A descriptive summary of local and systemic reactogenicity data. (Moderate and Severe reactogenicity proportions and when observed) (From blinded data) (Okay to cut and paste from DSMB minutes)

7. List of any Adverse Events of Special Interest (AESI) identified in the trial (number of each type of event, nature of event, time from vaccination to onset, current status, severity)

8. List of any related or unrelated SAEs identified (plus who relatedness was assigned by, and if there was any disagreement)

9. List of any SUSARs identified (plus who relatedness was assigned by, and if there was any disagreement)

10. List of any safety concerns identified at the study DSMB meeting, their current status and disposition plan. This could include events from the trial or related trials or animal studies.

11. Update on any prior concerns.