

The SPEAC Meta-DSMB: The Rationale and Experience with oversight of single sponsor DSMBs

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DSMB Approaches

DSMB Construct	Example	Advantages	Disadvantages
Single Sponsor DSMB only	many	Logistically easiest	1. Lack of coordination of multiple sponsor trials. 2. Inability to compare results in real time. 3. Lack of harmonization
Single DSMB for Multiple trials	1. Oxford COVID DSMB for 9 trials in multiple countries 2. NIH COVID DSMB	1. Can look across trials for the same vaccine in multiple countries if a rare event occurs. 2. Ability to harmonize across trials	1. DSMB meetings can be quite long. 2. Scope limited to one disease target. 3. Requires sponsor cooperation.
Meta DSMB	CEPI Meta DSMB	1. Can look across platforms as well as disease targets	1. Requires sponsor cooperation.

Genesis of the Meta DSMB

The setting:

CEPI is in an unusual position in that it is supporting multiple developers for the same disease target and also multiple developers using the same vaccine platform.

Risk:

- Each trial sponsor has their own approach
- Safety signal may be missed in a single trial especially in early phase one and two studies.

Opportunity:

- Assess information across trials to better assess safety
 - For the same platform
 - For the same disease target

Functions of Meta-DSMB

- Support CEPI by providing oversight of CEPI awardee vaccines with similar constructs/platforms or target disease via liaison members to sponsor study DSMBs
- Support CEPI-funded trials by providing expertise regarding assessment of vaccine safety
- Support sponsors/awardees conducting clinical trials

How is the Meta-DSMB different than a DSMB for an individual study?

- The study sponsor constitutes the individual DSMBs and the study DSMB has direct responsibility for oversight of the trial and reports to the sponsor.
- The goal of the Meta-DSMB is to provide overall oversight for all CEPI-funded vaccine clinical trials by identifying potential safety concerns:
 - Across trials using the same platform
 - Across platforms for the same disease target
 - To encourage harmonization regarding how safety data are collected and reported to facilitate data comparisons
- Meta-DSMB members are highly experienced **non-voting liaison members** to the individual study DSMBs; they are funded by SPEAC.
- The Meta-DSMB reports to SPEAC and through SPEAC to CEPI; its role is advisory and supportive.

Meta-DSMB: Information requested from sponsors

- Study protocols and CRFs should be shared with the liaison Meta-DSMB members so they understand the study and data collection (Note: Meta-DSMB members will not approve protocols but can provide input upon request)
- Names of study DSMB members so that Meta-DSMB liaison can establish communication
- The Meta-DSMB liaison member should have access to the same safety data as the sponsor DSMB Members
- For a blinded study, this is usually aggregate blinded data and DSMB minutes. Safety would normally be stratified by “group A” versus “group B” by outcome.

Meta-DSMB: Key Roles and Responsibilities

Members acts as **non-voting observers** for CEPI sponsored study DSMBs

The roles of the Meta-DSMB are:

- To monitor the safety profile of candidate vaccines across CEPI-funded clinical trials by looking at patterns related to vaccines, pathogens, platforms across trials.
- To review reasons to stop/pause enrollment of individual studies based on safety data with DSMB members and assess impact for similar vaccines/platforms
- To review safety data of individual studies and look for patterns across pathogens and platforms.
- To provide expertise when requested by individual study DSMBs

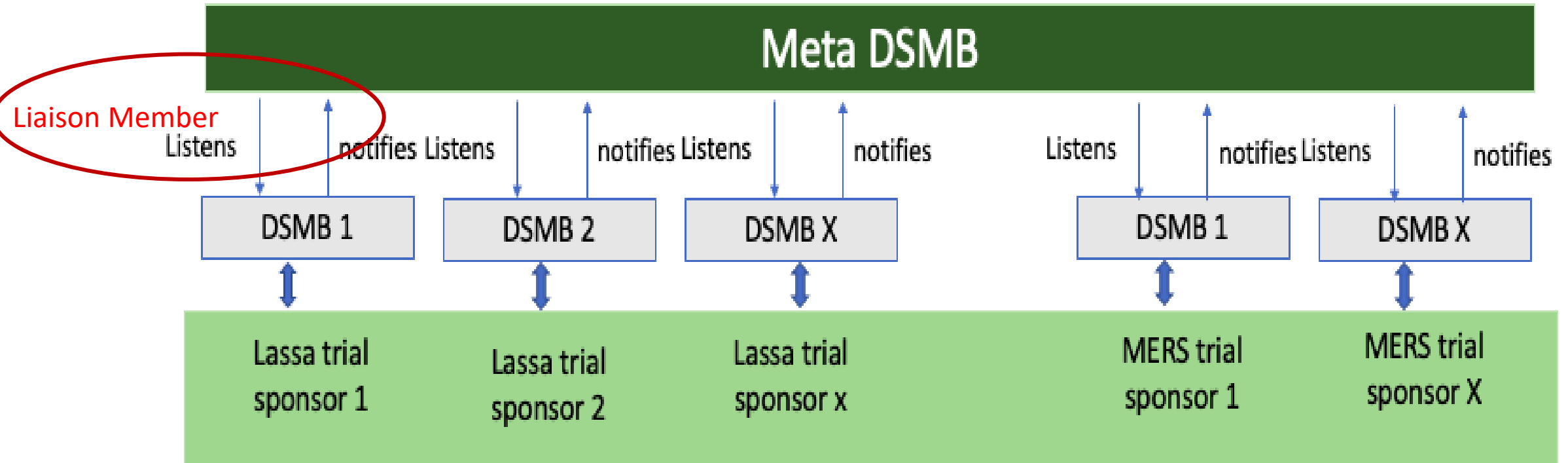
Meta-DSMB: Conflicts of Interest

- Meta-DSMB members complete a Conflict of Interest (COI) form which is reviewed and approved by both SPEAC Executive Board, CEPI and the sponsor. COI are updated at each Meta-DSMB meeting.
- If a Meta-DSMB member has a COI with one or more of the products under development or with the sponsor, that person will not be allowed to vote on those issues on the Meta-DSMB.
- A Meta-DSMB member is not allowed to be both an official DSMB member and a SPEAC liaison for the same study or sponsor.

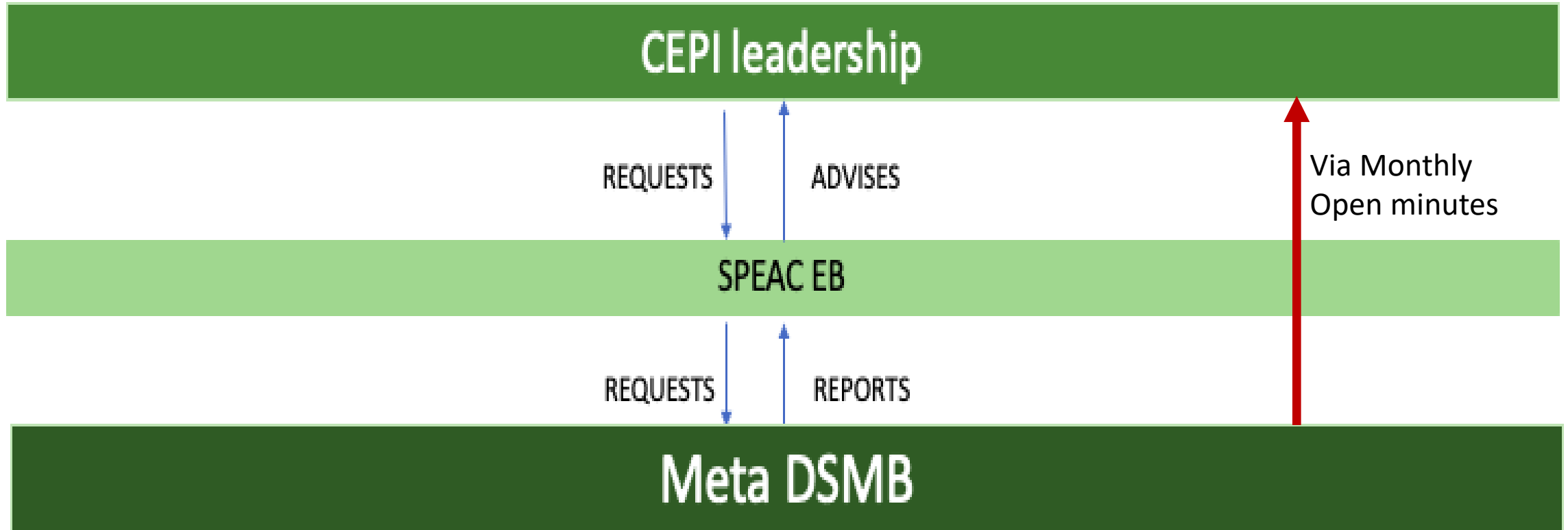
How does all of this work?

- A SPEAC Meta-DSMB liaison is assigned to **each developer**
- The liaison member attends each developer's DSMB meetings
 - As an observing non-voting member
 - Non-disclosure agreements are in place for each liaison member
 - Liaisons complete a brief reporting form for each meeting attended
 - This is kept in a secure file accessible to Meta-DSMB members.
- At a monthly Meta-DSMB meeting
 - All members disclose any new COI
 - Verbal reports with blinded slides from the DSMB meeting are given on the status of trials and any potential safety concerns
 - Minutes of the open session are generated and shared with key CEPI personnel
 - If there is a closed session, minutes are kept in a private Meta-DSMB folder.
- Of note: During early COVID vaccine development, we established an agreement with the NIH DSMB to share safety concerns as they arose.

Communication between the META DSMB, Study DSMBs and Sponsors



Communication between the Meta-DSMB, CEPI and SPEAC



Meta-DSMB: Two possible scenarios

- **Scenario 1:** In case a signal across the platforms/vaccines is discovered by the Meta-DSMB, the SPEAC Meta-DSMB will inform SPEAC Executive Board, CEPI and the sponsors as soon as possible but within two working days at most.
 - Contact with sponsor DSMBs would be through the Meta-DSMB liaisons.
 - Meta-DSMB would describe the concern and if appropriate make recommendations for any required actions
 - Following this, the relevant study DSMBs would also be informed by their liaisons.
- **Scenario 2:** In case of a signal in one trial: CEPI can request an opinion/review from Meta-DSMB which can query other related clinical trial sponsor DSMBs regarding any information they may have related to this particular issue.
 - This request could also come from a sponsor or sponsor DSMB.
 - The Meta-DSMB would offer an opinion but any decision to stop or continue a study would be at the discretion of the sponsor DSMB.

Current Status: The Meta-DSMB

SPEAC Meta-DSMB

- SPEAC is providing liaison observer members for each CEPI-funded vaccine trial.
- Have served as a consulting resource for study DSMBs and sponsors.
- Aim: to support sponsors and their studies and to provide safety oversight of CEPI-funded studies.

CURRENT MEMBERS

- Kathy Edwards (chair), Neal Halsey, Alex Dodoo, Ulrich Heininger, Cyndy Whitney, Walt Orenstein, Juhani Eskola, Mathu Santosham, Najwa Khuri, Jim Buttery, Marco Safadi, Narendra Arora, Youngmee Jee, Stephen Obaro, Punnee Pitisuttithum, Fred Zepp and consulting statistician Stephen Evans



Experience thus far

- The Meta DSMB members have participated in study DSMB meetings as observers and have been accepted as such.
- Liaisons have provided advice to sponsors when requested.
- Significant safety and other concerns have been discussed and recommendations made back to CEPI and developers in this regard.
- Confidentiality of information and discussions has been universally maintained.
- Excessive unblinding in clinical trials has been identified as a potential issue that could compromise trial integrity and a manuscript has been developed on this topic and submitted for publication.

In summary

- The SPEAC Meta DSMB is functioning well to provide oversight of CEPI clinical trials
- The Meta-DSMB model could be applicable for other settings to provide oversight where multiple trials by different sponsors are taking place concurrently.

Thank you

