

# **Guidance for Investigators presenting a Study for Preview by the Southeast Asia Infectious Disease Clinical Research Network Data and Safety Monitoring Board (SEAICRN DSMB)**

## **I. Introduction**

All studies for which the SEAICRN DSMB will provide data and safety monitoring should be previewed by the Board before the study is initiated.

This document provides some guidance to PIs who are presenting their study plans to the DSMB for the first time.

## **II. Purpose of Study Preview**

When presenting a protocol to the DSMB, an investigator must ensure that DSMB members achieve a fundamental understanding of

- the rationale for the design and population being studied
- why the study is important
- the study design
- the plan for monitoring participant safety and study progress
- an overview of the analysis plan (and details of any planned interim safety or efficacy analysis)
- the overall soundness and feasibility of the plans for reaching their objective.

Note that even though the DSMB preview of a study is not a primary scientific review, the DSMB members should be comfortable with the overall scientific merits of the proposed study. This initial meeting is their chance to raise any ethical, scientific, or practical concerns that could interfere with successful study completion or with the Board's ability to monitor the study as planned.

## **III. Essential Documents**

Each PI should ensure that the Administrative Assistant to the DSMB receives the necessary documents (detailed below) at least three weeks prior to the DSMB meeting. A study will not be previewed without the documents listed in this section, although item 3.3 in particular may be in draft form.

### **3.1 Study protocol**

The current, Network Steering Committee (NSC) approved version of the protocol of the study should be submitted. Generally, the protocol should also have been approved by the corresponding IRBs. However, on some occasions including presence of significant scheduling conflicts, the DSMB might agree to

preview a protocol that has not yet received IRB approval. [Note: submission of the protocol to the DSMB does not constitute a submission to the NSC. The operation of the DSMB is independent from the Network.]

### **3.2 Informed Consent forms**

Similarly, approved versions of the informed consent forms, including an evaluation of the translation from or into a language other than English, should be submitted to the DSMB along with the protocol.

### **3.3 Data and Safety Monitoring plan**

The data and safety monitoring (DSM) plan for the study describes the strategy for the monitoring of the study. A DSM plan should have been included in the protocol, but a detailed version including details for its implementation should be submitted to the DSMB for their review. A DSM plan should include a description of:

- a. The content of interim reports (key efficacy and safety outcomes of interest).
- b. The frequency of interim reports.
- c. The statistical methods, interim stopping rules, as appropriate, and rules that would trigger immediate DSMB review of safety outcomes.
- d. The procedures to ensure confidentiality of DSMB reports. Especially for studies that involve any kind of masking, it is important that the results in the interim reports are not divulged to the study team to ensure that the study conduct is not impacted by this knowledge. The SEA-ICRN DSMB recommends that the DSMB report be generated by an independent statistician whenever possible, so that no one from the study team has access to the report. A general way to accomplish this is as follows:
  - i. The study statistician will write and debug programs (and table shells) for the planned interim analyses using a dummy treatment code that he or she assigns to each participant.
  - ii. An independent statistician not otherwise associated with the study will re-run the programs after first merging in coded indicators for each participant's true treatment group (provided by the Randomization Manager<sup>1</sup> but coded to hide the actual identity of each group). The completed DSMB report should then be forwarded to the DSMB Administrative Assistant. (This means that the Independent statistician, who will be partially unblinded,

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<sup>1</sup> The Randomization Manager is usually another statistician who is in charge of generating and maintaining the randomization schedule.

should be also be available to perform any additional interim analyses that the DSMB may request.)

- iii. Separately, the Randomization Manager will provide the actual identity of all the coded treatment groups to the DSMB Executive Secretary in one or more completely opaque, sealed envelopes, as directed, so the DSMB can fully unblind the report during their review if necessary.

NOTE: Depending somewhat on circumstances, the DSMB sees the use of an independent statistician as generally preferred. (There may be variability in how critical the blinding of reports is, in how independent the study statistician already is, in feasibility, etc.) Investigators' plans for maintaining confidentiality of interim data, whether or not they involve an independent statistician, should be carefully described. The DSM plan should include details regarding the roles of all people involved in the preparation of the report (statistician(s), PIs, field personnel, etc.).

The DSM plan should describe any relationship between an unblinded or partially unblinded statistician and the study team, so that his/her degree of independence can be assessed. For instance, even if a statistician is not directly involved with the study at hand, s/he might not qualify as an independent statistician if s/he is overseeing or supporting other studies by the same investigator or organization or studies with related objectives. The statistician should also be free of financial or other interests that could cause real or even apparent conflicts of interest.

The DSMB will evaluate the proposed plans and determine whether the blinding is adequate or whether a more independent statistician is needed to generate the unblinded reports. See Section VI below regarding how FHI may assist with the implementation of the independent statistician role.

- e. The use of other safety monitoring groups. If there will be safety monitoring by other people or groups, such as an independent safety monitor (ISM), the DSM plan should describe their roles and their interactions with the DSMB.

#### **IV. Additional Documents**

Ideally, the documents listed in this section, perhaps even if only partially complete, should also be submitted to the DSMB for their review during the initial preview meeting. However, recognizing the potential importance of other factors, including time pressures that PIs may face during protocol review and study initiation, the DSMB may allow the full documents in this section to be submitted after the DSMB preview. All of them must be submitted well before the first scheduled DSMB review of interim study data.

## **4.1 Case Report Forms (CRFs) and Data Management (DM) Plans**

Review of the CRFs and DM plan (if separate from the protocol) is needed to enable the DSMB to ensure that the data actually collected will satisfactorily address both safety and key efficacy outcomes.

## **4.2 DSMB report shell**

DSMB report templates consisting of several sections as appropriate for the open and closed sessions of the meeting and the type of data to be presented (i.e., safety and efficacy) have been prepared to guide investigators in preparing their interim reports. The templates can be downloaded from the SEAICRN website (<http://www.seaicrn.org/>). The template should be adapted as needed to suit the specific circumstances of each study. That is, each study team (PI/statistician) should prepare a report shell (i.e., without data) to elicit DSMB feedback before submitting an actual report. If the report shell is not reviewed at the preview meeting, it should be completed months before the first interim review.

## **V. The DSMB meeting itself**

In addition to the PI, the study statistician is generally encouraged to attend the meeting for the DSMB preview. At that meeting, the PI may be asked to provide a very brief oral presentation of the study. DSMB members will be particularly interested in getting a clearer understanding of the rationale for the plans for collecting and/or monitoring both safety data and efficacy data. Because not all members will have expertise in the specific pathogen area, members may ask questions about background information.

Examples of specific areas that the PI may need to address in describing the protocol (depending on what is relevant in the given circumstances) are:

- Background/rationale
- Study design
- Patient population
  - inclusion/exclusion criteria
- Rationale for dosage selection
- Endpoints
- Sample size, power and related statistical considerations
- Number of anticipated safety and efficacy events and basis for projections
- Anticipated timelines for accrual, follow up, analysis
- Recruitment procedures and anticipated problems
- Process of informed consent
- How safety data are collected, reported and monitored
- Plans for formal clinical monitoring visits

- Procedures for blinding and for emergency unblinding
- Data management procedures and confidentiality
- Feasibility of study as designed

## **VI. FHI assistance**

Family Health International (FHI) assists investigators in implementing International Standards and DSMB requirements and recommendations, as well as, in interacting with the DSMB. FHI can assist with any aspects described in this document, although the following are the areas in which the FHI assists most regularly:

- Finalizing various aspects of the DSM plan. In particular, FHI can facilitate the discussion on how to fulfill a DSMB requirement for an independent statistician for the generation of the DSMB reports.
- Adapting the DSMB report templates to better reflect the characteristics of the study.
- Defining a timeline for the generation of a DSMB report. Careful planning for processing the data for the report (entering, checking, querying, cleaning, and freezing) is needed. The report should include data collected as close to the date of the DSMB meeting as possible, while still allowing sufficient time to complete all the steps. Therefore, a realistic timeline for key data management activities is important.
- Coordinating the submission of all the necessary documents to the DSMB in a timely manner.

## **VII. The SEAICRN DSMB coordinators**

All the activities related to the operation of the SEAICRN DSMB are coordinated by the Executive Secretary (ES), the Administrative Assistant (AA), and the DSMB specialist (DS). This group works closely to link the DSMB with the study teams and to provide investigators with assistance for successful submissions of reports and other documents to the DSMB. Although these people attend DSMB meetings, they do not have voting privileges. Investigators should feel free to contact them regarding any questions concerning the SEA-ICRN DSMB. Currently these positions are held by:

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