

**Operational Plan for the
Southeast Asia Infectious
Disease Clinical Research
Network
Data and Safety Monitoring
Board**

Southeast Asia Infectious Disease Clinical Research Network
Network Steering Committee

Version 2.0 October 26th, 2009

Abbreviations List

Abbreviation

Term

DSMB	Data and Safety Monitoring Board
EC	Ethics Committee
FHI	Family Health International
IRB	Institutional Review Board
NIAID	National Institute of Allergy and Infectious Diseases
NSC	Network Steering Committee
SEA-ICRN	Southeast Asia - Infectious Disease Clinical Research Network
TOC	Trial Operations Committee

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Purpose

It is the intent of the Southeast Asia Infectious Disease Clinical Research Network Steering Committee (NSC) to establish an Independent Data and Safety Monitoring Board (DSMB) for certain studies conducted under the auspices of the Southeast Asia Infectious Disease Clinical Research Network (SEA-ICRN) to address issues of research participant protection and to make recommendations regarding the continuation, termination or modification of SEA-ICRN sponsored studies. Specifically, the DSMB members are charged with the following two main functions:

1. To examine over time the endpoint and safety data from selected SEA-ICRN sponsored clinical trials and other clinical studies in order to make recommendations concerning continuation, termination or other modification of studies based on the observed beneficial or adverse effects, typically those associated with particular therapeutic or preventive interventions under study; and
2. To independently review the general progress and conduct of the aforementioned studies and to assist in resolving any problems that may arise.

The DSMB will monitor all SEA-ICRN interventional phase I, II, III and IV trials and other selected trials or studies as determined by NSC and the SEA-ICRN. Please note, however, that this operational plan applies mainly to the monitoring of phase III and late phase II trials. Operational aspects of the monitoring of other types of trials will be discussed during study previews, but will follow the general principles outline in this plan.

Composition

The DSMB will consist, initially, of 5-10 voting members invited by NSC to serve, one of whom will be designated to serve as chairperson. The Board will include at least five standing members and one to four study-specific members. Standing members will be asked to commit to 2-, 3- or 4- year terms so as to assure continuity when terms expire. Study-specific members are expected to serve on the DSMB for the duration of the specific study. Study-specific members may also serve as the study-specific member for multiple studies. To cover contingency situations, 1-2 alternates will be identified to fill in as needed. The DSMB members are required to be free from conflicts of interest with respect to the studies they will be expected to review. The DSMB can nominate a Chairperson to the NSC for approval.

The composition of the DSMB should reflect the disciplines and medical specialties necessary to interpret data from the studies being monitored, and in particular to fully evaluate the safety of participants in those studies. DSMB members must be intellectually and financially independent of study/trial investigators, and should also not be an employee of a partner within the SEA-ICRN. It is essential that DSMB members not have close current or recent affiliations with the study investigators and that they

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have absolutely no direct involvement with the studies to be monitored. DSMB members should not be directly involved in protocol development, nor supervise persons who are so involved. Each proposed member shall be asked to disclose potential conflicts of interest, including for example current or expected financial ties to any commercial concerns likely to be affected by the outcome of any trial. Only those individuals who provide such disclosure and whom NSC deems to have no such conflicts may serve on the DSMB. If a conflict arises during a member's tenure on the DSMB, he/she should bring it to the attention of the Executive Secretary or of the DSMB itself. If either the DSMB or NSC believes that the conflict or the appearance of a conflict is significant, then either the DSMB or NSC may recuse the member from monitoring the affected studies.

The DSMB will be minimally comprised of the following members:

- An emerging infectious disease specialist with clinical research and, preferably, DSMB experience, likely to be a candidate for chairperson.
- A statistician with DSMB experience.
- An ethicist with experience working in resource poor settings.
- One or more representative from Southeast Asia with pathogen expertise.
- One to four study-specific members with pathogen-specific expertise. An individual can fulfill the study-specific role for more than one study.

It is important that the statistician as well as some other members have expertise in clinical trials conduct and methodology. In addition to these 5-10 voting members, an Executive Secretary and Administrative Assistant to the DSMB will be appointed by the NSC. Although they will attend meetings or teleconferences of the DSMB, neither will have voting privileges.

The number of members assigned to monitor a particular study may vary depending on trial phase, range of medical issues, complexity of design or analysis, and potential level of risk.

Guiding Principles

Scientific Integrity

Recommendations regarding the continuation, termination or modification of the study should be based on the interpretation of the results of the ongoing trial and the existing context of relevant scientific data and other factors (internal or external to the study) that impact the ethics of continuing the study. Every effort should be made to prevent the intrusions of other considerations into the decision-making process of this panel. One way in which this principle will be acknowledged is that DSMB members will be asked to sign conflict of interest documents immediately prior to every meeting.

Participation of Protocol Team in the Monitoring Process

It is essential for adequate monitoring that the members of each protocol team be involved in monitoring their study. Regular interaction among the NSC, principal investigators, Trial Operations Committee (TOC) representatives, statisticians and others on the protocol team is required to ensure that adequate oversight information is gathered and that the study proceeds optimally with regard to patient accrual, data quality, adequacy of follow-up, protocol compliance, detection of adverse events, and any other issue which could affect the successful completion of the study.

Access to Interim Data

Access to the accumulating endpoint data will be limited to as small a group as possible. Knowledge concerning treatment differences, even when they are considered statistically non-significant, may make investigators reluctant to enter patients in the trial, or may lead investigators to limit entry to a certain subset of patients or to encourage patients to withdraw if they are assigned to what they perceive as the inferior treatment. Such attitudes and behaviors may increase selection or ascertainment bias, which will diminish the reliability of the trial's eventual results and/or may preclude the completion of the trial. Limiting access to interim data to the DSMB relieves the investigator of the burden of deciding whether it is ethical to continue to randomize patients, and helps protect the study from bias in patient entry and/or evaluation. The DSMB will work to ensure that a trial will meet its obligations first to protect individual trial participants and secondly, to the extent possible, to protect the interests of the larger public, whose welfare may be enhanced (or at least preserved) by either terminating the study early or by ensuring it continues on to a definitive conclusion.

Meetings

Regular meetings of the DSMB will likely be held at least once a year. Additional meetings and/or teleconferences may be scheduled when necessary for adequate monitoring. Meetings of the DSMB will be closed to the public. DSMB meetings should be scheduled to enable all members to attend all scheduled meetings. Study team members, TOC representatives, NSC representatives and FHI staff may also attend or be included by telephone, if deemed necessary and appropriate.

Material presented at all DSMB meetings should be considered privileged by DSMB members, who should maintain this confidentiality at all times to the extent permitted by law.

The DSMB Chairperson will prepare the agenda for each DSMB meeting in consultation with the Executive Secretary and/or NSC representatives.

In general, DSMB members are responsible for defining the process that the DSMB will use to reach recommendations concerning the continuation or termination of reviewed studies. This process should be established as early as possible, but in all cases prior to initiating any data review. Whenever possible, the DSMB should review protocols and

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monitoring plans before enrollment of participants begins. Proposed stopping guidelines (see Stopping Guidelines below) should, as a general rule, be specified in the protocol. The DSMB should confirm the appropriateness of those guidelines. Protocol changes that are made during the performance of the study and that NSC deems to be material should also be reviewed by the DSMB.

At its meetings, the DSMB primarily should address issues of patient protection and quality assurance of the research. Multiple protocols and studies may be reviewed at any given DSMB meeting. For each protocol being reviewed, the Chairperson will designate a member of the DSMB to serve as the Lead Reviewer, and one or more secondary reviewers. The Lead Reviewer may be, but need not be, one of the study-specific members of the DSMB. A member of the DSMB may serve as the Lead Reviewer for multiple protocols. For each study, the Lead Reviewer will initiate discussion of whether the study should proceed as is, be modified in any way or be terminated.

DSMB members must be satisfied that the timeliness and accuracy of the data submitted to them for review are sufficient to protect the safety and health of study participants. In particular, the DSMB should seek to discern and assess critical problems such as:

- Increased morbidity and/or mortality related to the study intervention;
- Adverse reactions to the intervention;
- Unsatisfactory performance of the data coordinating center or of any clinical sites;
- Failure to comply satisfactorily with recruitment criteria, including those related to the participation of women and minorities, or with other components of the study protocol; and
- Any other issues that would lead to important protocol changes.

DSMB members will have the option of reviewing completely unblinded data whenever they decide it is appropriate to do so. All printed reports will be at least partially blinded (unless otherwise stated in the interim analysis plan for a specific protocol). That is, no printed reports will show any results by actual treatment group, but they may show results grouped by coded treatment (e.g., A and B; conditions are indicated below). Before the start of each DSMB meeting, the lead protocol statistician will be responsible for ensuring that the DSMB Chairperson or his/her designee receives the information necessary to decode the treatment groups.

The business of the DSMB will be conducted in sessions that will generally occur in the order they are listed below. However, during closed session discussions of a particular study the DSMB may find it necessary to revert to a less restricted session, such as an Open Session. Transitions between sessions should always be done explicitly and with care to ensure that only appropriate persons are in attendance.

1. Open Sessions – At Open sessions, issues relating to the general conduct and progress of each study will be discussed. Such issues may include, for example, substantive changes made to the protocol, the rate of accrual, database status,

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completeness and interpretability of key variables (including efficacy outcomes), the adverse event experience (not by study group), comparability of study groups on baseline factors, quality control measures and results, compliance with the protocol, and follow-up schedule compliance. For multicenter studies, such critical parameters should also be examined for possible problems at individual centers.

In addition to the DSMB members, Executive Secretary and Administrative Assistant, other people who generally attend an Open Session are the Principal Investigator and lead protocol statistician of the protocol being reviewed, other investigators, as well as the FHI DSMB specialist. Additional people who may attend include other members of the study team, TOC representatives, SEA-ICRN Leaders, FHI and NSC representatives, representatives of any other sponsors and/or industrial collaborators, and representatives of relevant regulatory agencies.

2. Closed Sessions – At Closed Sessions, data pertaining to safety (which might by their nature need to include some efficacy outcomes) will be reviewed. Ordinarily, interim data with respect to efficacy considerations will be reviewed *only if and when permitted by the protocol*. Data will be presented by coded treatment arm. Closed Sessions are intended only for DSMB members, the Executive Secretary, the Administrative Assistant and, subject to the direction of the DSMB, the lead protocol or independent statistician and/or the DSMB specialist from FHI.
3. Closed Executive Sessions: These sessions are intended to provide the DSMB voting members with the opportunity to discuss their views and make final decisions on whether to recommend continuation, modifications, or termination of a particular study. Attendance is restricted to the 5-8 voting members of the DSMB only. A designated DSMB member (such as the Lead Protocol Reviewer for the study) will record all members' recommendations so the Executive Secretary can include them in the meeting summary.

The DSMB may unmask the actual treatment associated with the codes when they decide that this knowledge is necessary. However, unmasking will be done in a closed executive session with the attendance of voting members of the DSMB only.

Voting

For making decisions of a general nature, such as on operating procedures and overall policies, a quorum defined as a majority of permanent DSMB members must be present (either in person or by conference call), and decisions will require a simple majority of participating members.

For each individual study review, a quorum defined as a majority of the *total* of permanent members *plus* study-specific members must participate, and any decisions

will require a simple majority of participating members; furthermore, a member designated as the lead reviewer for the study must participate. After a thorough discussion of DSMB members' opinions and rationale and an attempt to reach clarity regarding individual recommendations, the final recommendations of each voting DSMB member may be solicited in Closed Executive Session. The final recommendations must be summarized either as majority or minority positions or as actual vote tallies for the various divergent recommendations, i.e., as number of votes for or against a particular action, such as continuing or terminating a study, etc. Specific positions will not be attributed to individual Board members.

Responsibilities

Protocol Team

1. The Protocol Team is responsible for developing the proposed data and safety monitoring plan and stopping guidelines for the study. The plan should be developed along with the study protocol and may be included as an appendix to the protocol.

DSMB

1. The DSMB is responsible for reviewing the study protocol, the safety monitoring plan and the stopping guidelines prior to initiation of the study or as soon thereafter as possible. If necessary the DSMB will make recommendations for changing them or develop their own safety and stopping plans as needed.
2. During the course of a study, the DSMB should review study conduct and performance information, such as accrual information, follow-up information and listings of protocol violations.
3. The DSMB should review all major modifications to the study.
4. The DSMB should review cumulative safety data summaries as well as interim analyses of outcome (efficacy) data, as appropriate.
5. The DSMB should also review emergent information from related studies that may impact Board members' recommendations with respect to changing or terminating the monitored study.
6. After considering all the above factors, the DSMB should recommend whether the study should continue as designed, be changed, or be terminated based on its findings. In the latter case, the DSMB may be invited to participate in planning study closure.
7. Within approximately two weeks following each DSMB meeting, the Board should finalize its written findings for all of the studies it reviewed, whereupon they will be distributed to the NSC (and secondarily to the leadership of those studies). The required content of these reports is

provided in the section on Administration, under "Reports from the DSMB".

DSMB Chairperson

1. The DSMB Chairperson will oversee the meetings, develop the agendas and ensure that meeting summaries are adequately prepared. He/she will facilitate discussions and make attempts to reach consensus among DSMB members for final recommendations whenever possible.
2. The Chairperson also will be the primary contact person for the DSMB. Individuals considered for Chairperson should have a demonstrated ability to run a meeting and handle group interactions in an effective manner, and should have previous clinical trial and DSMB experience.

DSMB Executive Secretary

1. A NIAID staff person outside the Collaborative Clinical Research Branch will function as Executive Secretary and will attend all DSMB meetings and teleconferences.
2. The Executive Secretary, with the help of the Administrative Assistant, is responsible for assisting the DSMB Chairperson in developing meeting agendas and for assuring that DSMB members receive copies of the study-specific reports at least five (5) working days prior to the DSMB meeting.
3. The Executive Secretary, with the help of the Administrative Assistant, may help in the preparation and distribution of meeting summaries, but will not have voting privileges and may not advocate specific conclusions or actions of the board.
4. After each DSMB meeting, the Executive Secretary will ensure that the meeting summary reports are properly formatted and that they are approved by all DSMB members. He/she will ensure that the final DSMB meeting summaries are distributed to the NSC Chairperson and/or NSC representative for further distribution as needed.
5. The Executive Secretary will be responsible for maintaining copies of all DSMB reports.

DSMB Administrative Assistant

1. A staff member of the FHI will serve as Administrative Assistant.
2. The Administrative Assistant will act under the direction of the Executive Secretary to accomplish all administrative and logistical tasks associated with the DSMB, e.g. facilitate meeting and teleconference arrangements, collect and distribute study reports, maintain official DSMB files, store copies of all DSMB related documents, etc.

Study Team

1. Each participating Investigator will inform his/her IRB of the operating procedures concerning data and safety monitoring (e.g., who, what, when, and how monitoring will take place). This information will serve to assure the IRB that the safety of the research participants is appropriately monitored. If the IRB is not satisfied with the monitoring procedures, it should request modifications. While it may not be possible to satisfy every IRB request completely, IRB comments will be considered seriously.
2. Appropriate members of the study team should be available during the Open Session(s) of the DSMB's review of their study to answer questions about study conduct, study progress and other appropriate areas of interest.
3. The study team should be familiar with the correct ways to perform and interpret interim analysis and should request any needed assistance through the NSC as early as possible.
4. The lead protocol statistician on the study team is responsible for delivering all tables and listings needed for the DSMB review (with the possible exception described in item 5 below) approximately two weeks in advance, as directed by the Administrative Assistant at FHI.
5. To help ensure complete masking of the study team, the protocol statistician will normally not generate any tables showing efficacy data by treatment group (masked or unmasked) until all data collection has been completed (unless otherwise stated in the study protocol). If the data monitoring plan calls for interim efficacy data to be reviewed or compared by treatment group, all interim results must be kept from the clinical team. While this is very difficult to ensure, one effective method is as follows. The protocol statistician prepares and tests programs needed to perform the planned efficacy analysis using a dummy treatment variable (instead of the actual treatment variable). The protocol statistician delivers these programs to an independent statistician not otherwise involved in the conduct of the study along with the analysis dataset (or a preliminary version of it) a few weeks prior to the DSMB meeting for testing purposes. The protocol statistician will ensure that the actual interim analysis dataset (including the actual treatment information) is delivered to the independent statistician prior to the DSMB meeting so that the latter can generate the analysis report for the Closed Session. This should happen allowing enough time for generation, distribution, and review of reports.
6. The appropriate statistician will summarize and present the data at the DSMB meeting. (Note: this may involve the team statistician, the independent statistician or both.)

7. The study team is responsible for the provision of information about important new developments outside the study. This notice should be provided in real time if sufficiently important.
8. After the DSMB's summary report for a study is forwarded to the study's principal investigator, the investigator at each of the study sites is then required to transmit the report to his/her governing IRB(s).

DSMB Specialist

1. If the data monitoring plan calls for interim data to be reviewed or compared by treatment group, the DSMB specialist will assist study teams to set up proper procedures to implement the role of the Independent Statistician when needed.
2. The DSMB specialist will maintain guidelines for the content and format of reports to be reviewed by the DSMB in order to assure their completeness, consistency and interpretability. The DSMB specialist will also provide guidelines for dataset documentation, dataset transport and other steps required when an Independent statistician analyzes interim data, so as to maintain the masking of the lead protocol statistician.

Stopping Guidelines

Guidelines for stopping trials should be carefully considered before trials begin. Ideally, and as a standard rule, the stopping guidelines will be developed by the investigators and clearly specified in the protocol. The DSMB would only have to confirm the appropriateness of those guidelines. If for any reason stopping guidelines are not specified in the protocol, then the DSMB would have to develop the guidelines for that particular study.

Stopping guidelines for each randomized trial should address trends in either direction. For example, in a superiority trial, the guidelines should address conditions for stopping the trial if a new treatment is found to be superior to the control or if it is found to be harmful. Since more evidence is generally required to demonstrate a positive benefit than a harmful effect, asymmetrical boundaries may be appropriate in many cases. In addition, guidelines for stopping trials when the likelihood of demonstrating superiority is low (given the interim results) may be appropriate in some cases (i.e., due to futility).

Repeated evaluation of study endpoints can inflate the risk of falsely declaring a treatment effect to be statistically significant when in fact the overall treatment effect is not significant. Having preplanned stopping guidelines helps to determine the impact of interim monitoring on the type I error rate. Plans for interim analysis of study efficacy endpoints should use procedures that guard against inflation of type I error rates.

Interim analysis plans for efficacy outcomes should include the following:

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- the purpose of the interim analyses
- when the interim analyses will be performed
- what hypotheses, if any, will be tested, what statistical tests will be used and the significance level for each test
- what interim results, if any, might lead to early termination of the study (i.e., any stopping guidelines)
- the impact of the interim analysis on the overall Type I error rate for the study.

Stopping guidelines for safety may be less specific, but key safety outcomes to be monitored and frequency of monitoring should be described. For some trials, it may be especially useful to identify what might be considered a clinically acceptable incidence of key safety events.

Administration

Administrative Support

Administrative support for the DSMB will be provided by the Administrative Assistant under the direction of the Executive Secretary. These two individuals should have sufficient experience to command reasonably the administrative, fiscal and other resources required to support the DSMB in the exercise of its responsibilities. All substantive communications to/from the DSMB will be handled by the Executive Secretary, in consultation with the Chairperson, to ensure that all such communications reach the appropriate parties. The Executive Secretary may assist the Chairperson by circulating draft DSMB reports to DSMB members. He/she will assure the preservation of all documentation pertinent to the work of the DSMB while assuring the security and confidentiality of information related to individual DSMB members, as permitted by law.

Reports

Interim Reports for the DSMB

The protocol statistician will prepare interim reports of safety and study progress for each study protocol being reviewed prior to each DSMB meeting. Data files used for interim analyses will be checked for errors to the extent practical, and should be considered fundamentally "clean". The Administrative Assistant will forward the reports (with each page labelled **CONFIDENTIAL, DO NOT COPY**) to the appropriate DSMB members at least 5 working days before the scheduled meeting or teleconference. These reports will generally consist of at least two parts, open and closed reports. Open Reports will provide information on study aspects such as accrual, baseline characteristics, aggregated safety data, completeness and interpretability of key variables (including efficacy outcomes) and other general information on study status. Closed Reports may contain data on study outcomes, including group-specific safety data and possibly efficacy data. The Closed Reports are strictly confidential. After each meeting, all members may keep their reports until final meeting summaries are completed, but must then either return their reports to the Administrative Assistant or inform her of their disposal. The Administrative Assistant will tally them and destroy any

remaining copies. Only one copy of each report to the DSMB will be kept in a controlled access locked file cabinet at FHI.

Reports from the DSMB

The Executive Secretary will draft a summary of the DSMB's findings. The draft summary for each study should be circulated to DSMB members, and any others designated by the DSMB within one week after the meeting. Reviewers will be asked to return their comments on the draft report within three business days of receipt. The lead reviewer, the DSMB Chairperson and the Executive Secretary will review the comments to be incorporated. The Chairperson and Executive Secretary will then jointly approve the report as final, if possible within two weeks of the meeting.

Each summary report will document that a review of data for all the study sites took place, the date of the review and the last date of collection for data reviewed. The summary will contain general recommendations and specific action items, the anticipated schedule of future reviews, any suggested protocol changes or other study implementation changes, as well as justification for the recommendations. In particular, each summary report must capture all members' overall safety assessments and the results of votes on recommendations regarding study continuation and protocol modification, as specified in the section on Voting above. No communications concerning Board findings and recommendations, either verbal or in writing, shall include unblinded data, discussion of the unblinded data or any other confidential information, although the general rationale for the DSMB's recommendations should be provided.

Based on the final decisions of Board members, the nucleus of the summary for each study should contain voting results captured using one or more of the following five types of statements:

1. Member(s) recommend(s) that the study continue without major modification. (This would occur most frequently.)
2. Member(s) recommend(s) that the study continue with specific modifications. (Recommended modifications within a specified time frame might include the collection of additional safety data, increasing the study's enrollment target, extending the length of follow up, approaches to encourage closer adherence to the existing protocol, or operational changes to improve follow-up of participants, and so forth.)
3. Member(s) recommend(s) that all or a portion of the study be stopped due to safety concerns. (This must be accompanied by an explicit description of the nature and significance of the safety concerns and recommendations for appropriately managing participants who are currently receiving the intervention as well as those who have completed the intervention.)

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4. Member(s) recommend(s) that the trial be stopped as a result of meeting the formal stopping criteria for finding efficacy. (I.e. confirm that the interim analysis fulfilled the efficacy stopping criterion.)
5. Member(s) recommend(s) terminating the study because the probability is very low that the objective of the trial will be realized by continuing (i.e. due to futility).

In cases 3, 4 or 5 above or if there is any other reason for immediate response, the NSC Chairperson and/or designee should be notified immediately within 24 hours of the DSMB decision. In addition to verbal communications, a recommendation and rationale to discontinue or substantially modify the design of conduct of a study must be conveyed to the responsible NSC official in an Immediate Action Report (in writing) on the day of the DSMB meeting.

Generally in this situation such recommendations must initially be withheld from all others, including the Principal Investigator and study team, to avoid premature unblinding and confusion. The NSC official makes the final decision to accept the recommendations or not, following any needed consultations with the trial leadership. Then, only after the recommendations have been accepted, this immediate report plus other appropriate closed information should be furnished to the study leadership. Generally the immediate report will be followed by the full, final summary report described above.

The Executive Secretary will ensure that the final DSMB meeting summaries are distributed to the NSC Chairperson and/or NSC representative, who will in turn furnish them to each Principal Investigator and to other parties as required. (See also IRB section below)

Responses to DSMB Recommendations

The DSMB will be informed of responses to its recommendations, as outlined below:

1. An NSC decision regarding a major recommendation (e.g. to stop or alter a trial) should be communicated promptly to the DSMB. If the decision is to reject it, appropriate rationale should be provided, after which the DSMB will reach a final determination regarding its recommendation and the distribution of it;
2. A timely response to the DSMB recommendations is also needed if ensuing changes are apt to affect the nature or timing of the DSMB's planned monitoring, or if the DSMB specifically requests prompt feedback.
3. Otherwise, it is generally adequate for the team to make a good faith effort to respond appropriately to the Board's recommendations, and the team need not report its responses until the time of the next scheduled study review;

Relationship of DSMB and Institutional Review Board (IRB) (or equivalently Ethics Committee - EC)

The DSMB and IRBs serve distinct but related functions. The IRB is charged with the protection of human subjects in research at a particular institution. In contrast with a DSMB, the function of the IRB is generally mandated and supported by federal regulation. The appropriate and timely use of DSMBs may assist IRBs and the study researchers in executing their mandated responsibility to protect human subjects participating in the research. Thus, both bodies are concerned with the protection of individuals participating in research studies and with the scientific integrity and validity of study design, but federal law governs the function only of IRBs.

It is a legal requirement that the IRBs of all participating sites are apprised of the findings of a DSMB. It is also appropriate that the DSMB be aware of actions taken by the IRBs. Thus, copies of substantive communications from the IRBs concerning studies being monitored should be made available to the DSMB Chairperson by each Principal Investigator, and a copy of all each summary DSMB report should be forwarded to every IRB by the respective site Investigators.