TDR/GEN/Guidelines/05.1

Operational Guidelines for the Establishment and Functioning of Data and Safety Monitoring Boards

UNICEF/UNDP/World Bank/WHO
Special Programme for Research and Training in Tropical Diseases (TDR)

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INTRODUCTION

These Operational Guidelines are intended to provide international guidance to health research sponsors for the establishment and functioning of data and safety monitoring boards (DSMBs). The guidelines are based on a review of the existing guidances and requirements for DSMBs from national and international organizations, as well as on observation of existing practices of DSMBs in countries and institutions around the world.

Ethical and scientific standards for carrying out biomedical research on human subjects have been developed and established in international guidelines, including the Declaration of Helsinki, the Council of International Organizations of Medical Sciences (CIOMS) International ethical guidelines for biomedical research involving human subjects, and the WHO and ICH Guidelines for good clinical practice. The WHO/TDR Operational guidelines for ethics committees that review biomedical research have contributed to the development of ethical review practices in health research, establishing an international standard for promoting quality and consistency in ethical review. Compliance with international ethical and scientific guidance in health research contributes to ensuring that the dignity, rights, safety, and well-being of research participants are promoted and that the results of investigations are valid.

For more than 50 years, the randomized controlled clinical trial has been recognized as the standard method for evaluating the safety and efficacy of a medical intervention. The process of comparing alternative treatments and arriving at conclusive results is rigorous and complex. An essential ethical consideration in research involving human subjects is that studies should not be continued if the design of the study is no longer appropriate. Studies may also require early termination if there is strong evidence that the study has already achieved its primary objectives, the accrued evidence indicates the primary objective(s) will likely not be achieved, or there is a negative trend in the benefit/risk(harm) ratio. Furthermore, a study may need to be modified if it is observed that the accrued

data are not in line with the study design assumptions. These considerations may be especially appropriate for studies with serious outcomes or endpoints, such as mortality, serious morbidity, or irreversible adverse effects.

To preserve the integrity of the study and/or to protect the rights and welfare of research participants, there may be a need for the DSMB to recommend, at certain points, modifications to the study. These recommendations generally relate to patient safety and may include recommendations concerning dosages, treatment duration, and/or concomitant therapy. DSMBs may also include recommendations regarding eligibility criteria, sample size, and/or participant recruitment rate. Under these circumstances, sponsors and investigators may need independent advice for making such decisions. In order to ensure scientific integrity of the study, protection of human subjects, credibility of data, and avoidance of conflict of interest, an independent DSMB may be essential, especially for complex or pivotal studies. It is now recognized that a DSMB is often in the best position to provide independent assessment of the continued appropriateness and safety of an ongoing study, so the highest possible scientific and ethical standards are adhered to and maintained in the study.

1 OBJECTIVE

The objective of these Guidelines is to contribute to the preservation of scientific integrity and protection of human subjects in health research. These Guidelines describe the constitution, role, responsibilities, and operating framework for DSMBs. The Guidelines are intended to complement existing regulations and practices, as well as serve as a basis upon which specific written procedures for the functions of a DSMB can be developed by the sponsor. In this regard, the Guidelines provide international guidance to assist sponsors in developing, evaluating, and progressively refining DSMB charters and operating procedures. They are also intended to assist DSMB members, sponsors, investigators, members of ethics committees, regulatory authorities, and research participants and their organizations in understanding the role and functions of DSMBs. Users of the Guidelines should be mindful of their local laws and regulations as they apply to health research, especially as they concern the establishment and operations of DSMBs. The Guidelines are not intended to supersede national laws and regulations.

2 THE NEED FOR A DSMB

All clinical studies require safety monitoring throughout the duration of the research, but not all studies require monitoring by a DSMB. DSMBs may be critical for studies intended to save lives, prevent serious disease progression, or reduce the risk of a major adverse health outcome. DSMBs are particularly important in studies where interim data analysis is required to ensure the safety of research participants. A DSMB is often considered relevant in the following kinds of studies:

2.1 Controlled studies with mortality and/or severe morbidity as a primary or secondary end-point.

2.2 Randomized controlled studies focused on evaluating clinical efficacy and safety of a new intervention intended to reduce severe morbidity or mortality.

2.3 Early studies of a high-risk intervention (risk of non-preventable, potentially life-threatening, complications; or risk of common, preventable adverse events of interest [especially type A drug reactions]), whether or not randomized.

2.4 Studies in the early phases of a novel intervention with very limited information on clinical safety or where prior information raises concern regarding potential serious adverse outcomes.

2.5 Studies where the design or expected data accrual is complex, or where there may be ongoing questions with regard to the impact of accrued data on the study design and participants' safety, particularly in studies with a long duration.

2.6 Studies where the data justify its early termination, such as the case of an intervention intended to reduce severe morbidity or mortality, which might turn out to have adverse effects or lack of effect, resulting in increased morbidity or mortality.

2.7 Studies carried out in emergency situations.

2.8 Studies which involve vulnerable populations.

Not all studies within the above categories require DSMBs. Conversely, there may be other sound reasons for establishing DSMBs for certain studies that fall outside the above categories. In general, sponsors should consider the need for establishing a DSMB prior to undertaking a particular study. An ethics committee may also suggest to the sponsor that a DSMB be established for a particular study.

Although the DSMB has no direct relationship with the ethics committee, all protocol revisions approved by the ethics committee should be submitted to the DSMB. Other site-specific amendments may require special treatment.

3 THE PLACE OF A DSMB

The DSMB occupies a unique and important place in studies requiring specialized monitoring for data and safety. Constituted and functioning under the authority of the sponsor, a DSMB is an independent advisory body responsible for assessing data during the course of a study in a manner that contributes to the scientific and ethical integrity of the study.

The DSMB's recommendations provide the sponsor with an overall scientific, safety, and ethical appreciation of the study, and should assist the sponsor in maintaining the rigour of the study design, with appropriate attention paid to the protection of human subjects.

Safety monitoring should be part of all clinical trials, but responsibility for this may never be solely that of a DSMB. Serious adverse events (SAEs) should be regularly monitored by sponsors and reported to the appropriate parties according to regulatory requirements. In addition, safety data (often still blinded) should be monitored by the study investigators and data managers.

It is essential that all parties (including research participants, investigators, sponsors, ethics committees, regulatory authorities, and other study personnel) who are engaged in a study have confidence in the function and decisions of the DSMB. While the recommendations of a DSMB are communicated directly to the sponsor, the sponsor should notify other relevant parties and ensure that the recommendations are communicated to, and acted upon by, the various parties involved during the course of the study.

4 THE ROLE OF A DSMB

At intervals defined by the protocol, the DSMB reviews and evaluates the data on clinical efficacy and safety collected during the study, and assesses reports on cumulated serious adverse events (SAEs). The DSMB may also be requested by the sponsor to conduct emergency reviews of data to assess safety-related issues. While not responsible for the quality of data, the DSMB may be asked to

monitor this aspect. At the conclusion of the review, the DSMB provides a written recommendation to the sponsor regarding whether a protocol should be amended and/or a study should proceed based on its review of the data and the progress report submitted by the sponsor.

A DSMB should provide independent, competent, and timely review of the data from an ongoing study. The composition, review, and decision-making procedures of this Board should be free from political, social, institutional, professional, and market influences. The Board's procedures should promote independence in decision-making vis-à-vis the sponsor; at the same time, the DSMB needs to demonstrate competency and efficiency in its work.

For many trials, sequential review of safety and efficacy data may be used to permit early termination in the event of extremely strong results. Such sequential designs are primarily appropriate for studies with a major outcome, e.g. death, stroke, or irreversible progression of serious disease. A DSMB may recommend that the sponsor suspends or terminates a study whenever it is deemed necessary for safety reasons.

5 CONSTITUTING A DSMB

When required by the nature of a study, a sponsor should establish a DSMB to ensure the broadest possible coverage of potential research participants, and the validity and scientific integrity of the data. The sponsor is responsible for establishing the DSMB's charter, which should be included (or referred to) in the study protocol. This may be undertaken with advice from investigators or other parties involved in the study.

The sponsor is responsible for constituting a DSMB in such a way that review and evaluation of accumulated data during the course of the study can be executed competently and free from bias or influence that could affect the independence of the DSMB decision-making. The amount of payments and/or compensations made to DSMB members should be reasonable so as not to constitute coercion.

The sponsor is responsible for the selection and appointment of DSMB members as well as for ensuring that the DSMB has the means and resources to function well. In order to generate competent reviews and sound recommendations, the DSMB should be multidisciplinary and include, as appropriate, expertise in medicine (physicians with relevant backgrounds), clinical pharmacology and/or toxicology, epidemiology, statistics, clinical trial process, and ethics. The suitability of members of a board should be determined according to the nature of the study to be monitored. Appropriately qualified members who are able to act independently are essential to the DSMB's role in ensuring integrity of the research and safety of the patients/participants. The DSMB should be fully constituted and should meet to review its charter and the study protocol before the study begins.

In international studies, representation should be considered from participating countries. For studies conducted in settings with limited healthcare research infrastructure, it may be appropriate to have additional types of expertise represented on the DSMB. For example, anthropologists or community members may be of value in assessing cultural sensitivities that may affect interpretation of data. To this end, it may also be advantageous for large, international multicentre studies to have representation on the DSMB from more than one country.

6 CHARTER AND OPERATIONS OF A DSMB

6.1 DSMB Charter

The sponsor should establish a DSMB charter that defines the relationship between the sponsor and the DSMB. The charter should be developed according to the data monitoring needs (including scientific and ethical) of the particular study. The charter should identify the study for which the DSMB is established and the role and responsibilities of the DSMB in the study.

The charter should indicate the authority under which the DSMB is constituted together with its responsibility, operational procedures, means of communications, and decision-making procedures - when and as applicable - vis-à-vis the sponsor, the investigator(s), study statistician, data manager, ethics committee(s), and regulatory authority(ies).

The relationship between the DSMB and other parties with responsibilities in the study should be clearly defined in order to avoid conflict in decision-making arising during the course of the study. The role and responsibilities of the DSMB should be clearly identified vis-à-vis those of the investigator(s) and ethics committee(s). Equally important is establishing the role and responsibilities of the DSMB in reference to the study steering committee, statisticians, data managers, clinical research associates, auditors, and other relevant offices of the sponsor.

At times a single DSMB may be established for a set or programme of studies, or for multiple studies. In this case, the charter should reflect the consistencies and specificities of the DSMB's responsibilities and activities across the studies.

The following items should be addressed in the charter. Some of the items identified may be addressed within the charter; others may be addressed in separate standard operating procedures (SOPs). The decision as to which procedures should be included in the charter and which ones in separate SOPs will be specific to the study.

6.1.1 Description

6.1.1.1 The name or description of the individual or office of the sponsor responsible for appointing members to the DSMB.

6.1.1.2 An organizational diagram indicating the relationship of the DSMB to other parties in the study: the sponsor (including the steering committee and Contract Research Organization), investigator, and ethics committee.

6.1.1.3 A description of the membership requirements of the DSMB (including qualifications, payments and/or compensations).

6.1.1.4 Arrangements for audits and/or inspections of the DSMB.

6.1.2 Objectives

6.1.2.1 Data that are to be reviewed by the DSMB.

6.1.2.2 Intervals (specific times) at which the DSMB will review and evaluate the data.

6.1.2.3 Points to be evaluated and advised on by the DSMB.

6.1.2.4 Statistical procedures to be utilized by the DSMB (including procedures for monitoring safety and efficacy outcomes, and/or ongoing benefit/risk[harm] analysis, as appropriate).

6.1.2.5 Parties to whom the DSMB report will be distributed by the sponsor (e.g. investigator(s), ethics committee(s), regulatory authority(ies), the study steering committee, data managers).

6.1.3 Meeting arrangements

6.1.3.1 Materials to be forwarded to the DSMB members and meetings.

6.1.3.2 Process and format of the DSMB meetings.

6.1.3.3 Quorum requirements.

6.1.3.4 Procedures for maintaining study confidentiality.

6.1.4 Data management and security

6.1.4.1 Where and how the data examined by the DSMB will be stored and maintained.

6.1.4.2 Who will have access to the data.

6.1.4.3 How the confidentiality and privacy of the data will be maintained.

6.1.4.4 How personally identifiable data will be handled.

6.1.5 Documentation

6.1.5.1 The confidentiality agreement(s) signed by DSMB members.

6.1.5.2 The format and content of the minutes of DSMB meetings.

6.1.5.3 The format and content of DSMB reports.

6.1.5.4 The procedure for amending the DSMB charter.

6.1.5.5 The procedure for record-keeping and archiving.

After reviewing the charter, all DSMB members should agree to, and sign, the charter at the time of their appointment to the DSMB. The members' signatures' indicate their intent to fulfil their DSMB responsibilities.

6.2 Operations of a DSMB

The responsibilities of the DSMB as outlined in the charter should be fulfilled according to the requirements of the study. The sponsor should develop its standard operating procedures (SOPs) in accordance with the needs of the charter. The SOPs may be procedures that apply to all DSMBs established by a sponsor, adapted as appropriate to the charter and needs of the particular DSMB.

6.2.1 Membership

The DSMB is an independent multidisciplinary group consisting of at least three members. It should include individuals with relevant clinical and statistical expertise. Additional expertise may be required in certain studies, e.g. in the specific disease area being studied, or in ethics. The size and necessary expertise of the DSMB will depend upon the study design. Members should not be affiliated

with the sponsor, investigator(s), ethics committee(s), regulatory authority(ies), site(s) or study staff. Members should also not have vested conflicts of interest (e.g. a financial or other interest in an intervention or product similar to the intervention being studied).

A procedure should be established concerning the requirements for candidacy, including an outline of the duties and responsibilities of DSMB members.

Procedures for membership should include the following:

6.2.1.1 The procedure for selecting members, including the method for appointing a member (e.g. by application, committee or personal invitation).

6.2.1.2 The procedure for identifying conflicts of interest, and criteria for determining unacceptable conflicts of interest.

6.2.2 Terms of appointment

A procedure should be established identifying the terms of appointment for members of the DSMB, including

6.2.2.1 The duration of appointment.

6.2.2.2 The policy for renewal of an appointment.

6.2.2.3 The disqualification procedure.

6.2.2.4 The resignation procedure.

6.2.2.5 The replacement procedure.

6.2.3 Conditions of appointment

A procedure stating the conditions of appointment should be drawn up; it should include the requirements for:

6.2.3.1 A potential member to report in writing, at the time of candidacy, all potential or real conflicts of interest to the sponsor.

6.2.3.2 A member to be willing to publicize his/her full name, profession, and affiliation(s).

6.2.3.3 All reimbursement for work and expenses, if any, within or related to a DSMB to be recorded and made available to the public upon request.

6.2.3.4 A member to sign a confidentiality agreement regarding meeting deliberations, applications, information on research participants, and related matters; this agreement should cover confidentiality requirements related to the intervention and protocol-related information as well as study results.

6.2.4 Offices

For a well-functioning DSMB, procedures for the Board's officers should be clearly defined. A description is required of: the officers within the DSMB (e.g. chairperson, secretary); the requirements for holding each office; the terms and conditions of each office; and the duties and responsibilities of each office (e.g. agenda, minutes, notification of recommendations). Procedures for selecting or appointing officers should be established.

6.2.5 Independent consultants

The sponsor may call upon, or establish, a standing list of independent consultants in accordance with the DSMB charter. Independent consultants provide special expertise to the DSMB; they may be specialists in ethical or legal aspects, specific diseases or methodologies, or they may be representatives of communities or special interest groups. For international studies, particularly those involving disease-endemic countries, efforts should be made to access expertise from countries or regions involved in the study, and there should be recognition that other expertise (e.g. anthropology or health policy) may be useful.

For studies which have mortality or major morbidity as endpoints, a medical monitor may be requested to review reports of serious

adverse events (SAEs) on an ongoing basis, in order to ensure good clinical care and identify early safety concerns. The medical monitor may be invited to report SAEs or other safety concerns at DSMB meetings.

Terms of reference for independent consultants and medical monitors should be established to identify the role of these persons vis-à-vis the DSMB and the data.

6.2.6 Conflict of interest

Procedures for reporting and addressing potential or real conflicts of interest for members and independent consultants should be clearly defined in the charter, as well as criteria for deciding whether a (potential) member or consultant has an unacceptable conflict of interest. The procedures should ensure the independence of DSMB members in decision-making (that is, in providing recommendations).

6.2.7 Education for DSMB members

The conditions of appointment should state the provisions made for training of DSMB members in the work of a DSMB. The training should include an introduction to the study the participants will be monitoring, and the charter for the DSMB on which they will be serving.

6.2.8 Staff

When appropriate, staff should be provided to support the DSMB's work. Measures to protect the confidentiality of the study and the patients/subjects should be defined for the staff.

6.2.9 Quorum requirements

The DSMB charter should establish specific quorum requirements for reviewing, and making recommendations on, the study, which should include:

6.2.9.1 The minimum number of members required to compose a quorum (e.g. more than half the members).

6.2.9.2 The professional qualifications required (e.g. physician, biostatistician, paramedic, ethics). A quorum should include at least one physician with experience in the medical field of concern, and one biostatistician.

6.2.10 Meeting requirements

The charter should specify the meetings to be held, including their expected frequency and venue. The charter should indicate whether the meetings will be held in person or by teleconference. Under exceptional circumstances, the DSMB may have to meet urgently or hold a teleconference within a short time period. Procedures for this should be described in the DSMB charter, under meeting requirements.

The meeting requirements should include the following:

6.2.10.1 Meetings should be planned in accordance with the DSMB charter.

6.2.10.2 DSMB members should be given enough time to review the materials for the meeting.

6.2.10.3 Minutes of the meeting should be documented, and finalized following an approval procedure.

6.2.10.4 Procedures for inviting the sponsor and/or investigator to the meeting should be outlined, including the measures used to ensure that the resulting recommendation is based fully on the independent decision-making of each member (e.g. the use of a closed session for discussion and arriving at a recommendation).

6.2.10.5 The procedure for inviting independent consultants to a meeting or to provide written comments should be defined, including the applicable confidentiality agreement.

6.2.11 Meeting procedures

Procedures for organization of the meetings should be developed in accordance with the meeting requirements.

6.2.11.1 Organizational meeting

This initial meeting should be attended by the DSMB members and representatives of the sponsor; members of the study staff and the investigator(s) may also be invited. The DSMB members should review and discuss the DSMB charter, including the role and responsibilities of the DSMB, the protocol safety monitoring plan, and the statistical methodology.

The DSMB should review the protocol, informed consent documents, the investigator's brochure, relevant literature(s), and other research-related document(s), posing any questions it has. The DSMB should also consider prior ethics committee(s) reviews, as well as the requirements of applicable laws and regulations. The statistical methodology described in the protocol and its role in the DSMB safety monitoring plan should be clarified at this initial meeting.

DSMB members should receive orientation regarding the procedures outlined in the charter, and training in relevant guidelines and SOPs. The DSMB may, in the context of this discussion, propose changes to the charter. The sponsor is responsible for final decisions relating to the charter. This organizational meeting takes place prior to finalization of the study protocol and review by the ethics committee(s).

6.2.11.2 Early safety review meeting

During the early stages of implementation of a study, a meeting may be held to review early safety information and factors relating to quality of conduct of the study.

6.2.11.3 Periodic review meetings

The expected frequency of these meetings should be specified. The DSMB charter should indicate whether the meetings are to be held in person or by teleconference. The meetings should review the efficacy and/or safety data generated during this period, and should include a progress report from the investigator, serious adverse events reports, and cumulative safety data. The DSMB should take into account the quality of conduct of the study and the accuracy of the data.

The agenda for each DSMB meeting should be established based on the discussions and recommendations from previous meetings as well as according to events in, or related to, the study that may have occurred since the previous meeting. Procedures regarding the: responsibility for drafting, reviewing, and approving the agenda; issues to be reviewed; consultants and other participants; and the sequence of open and closed sessions (see section 6.2.12), should be designed in advance.

The DSMB charter should indicate if the DSMB will have access to the monitors' and auditors' reports as well as other documents relating to quality assurance activities.

The DSMB charter should indicate when and how to break the code during the course of the study. A third party data analyst (e.g. an independent biostatistician) might provide a breakdown of adverse events to the DSMB members. When significant trends in the data require further interpretation, the DSMB may request unblinding of the data. In these cases, it may only be immediately necessary to unblind the statistician or epidemiologist, for example, and not all the DSMB members. The unblinded person then reports to the other members if there is cause for concern. The unblinding procedures should be defined in advance and supported by documentation which indicates who has access to the unblinded data.

When appropriate, a mechanism should be developed for timely reporting and assessment of serious adverse events, between regularly scheduled meetings of the DSMB, to ensure that participants are not put at undue risk. Designating an independent medical safety monitor to fulfil this responsibility is an effective approach.

6.2.11.4 Final study closeout meeting

At the termination or conclusion of a study, the DSMB may meet to consider the efficacy and/or safety data generated from the study and provide any final recommendation to the sponsor.

A final assessment report can be considered.

6.2.12 Format of meetings

The DSMB should ensure confidentiality and proper communication to enhance the integrity and credibility of the study. It is recommended that each DSMB meeting be divided into two sessions: an open session and a closed session. This will enable the DSMB to interact with groups and individuals who assume responsibilities for the study while ensuring the independence and integrity of the Board's recommendation.

6.2.12.1 Open session

The DSMB may request the attendance of the study team, steering committee, investigator(s) and/or independent consultant(s) to provide specific clarification or respond to issues that have arisen. Open session discussion should focus on the conduct and progress of the study, and pay special attention to the pooled safety and efficacy data.

6.2.12.2 Closed session

Only DSMB members should be present at the closed session. In this session, the DSMB should review the efficacy and safety data, at times in unblinded format. The DSMB should consider the data in relation to the conduct and progress of the study, and the study protocol. The DSMB should also decide, in closed session, on the written recommendation it will present to the sponsor.

6.2.13 DSMB review of the sponsor's report

The sponsor should report the safety and efficacy data, as well as other relevant study information, to the DSMB for its review. The sponsor's report to the DSMB is often provided in two parts: an open part and a closed part. The full report should be made available to DSMB members in advance (at least one week) of the meeting.

The contents of the report are determined by the DSMB charter and discussed in advance during the organizational meeting. The charter should specify who will prepare and provide the open part of the report, and who will prepare and provide the closed part.

The open and closed parts can be provided by two separate parties.

6.2.13.1 Open part

The open part of the sponsor's report should include blinded and non-confidential data, e.g. participant recruitment, baseline characteristics, and pooled data on eligibility violations, completeness of follow-up, protocol compliance, problems encountered in the conduct of the protocol, and any new information/publications that bear on the study.

6.2.13.2 Closed part

The closed part of the sponsor's report may include unblinded data and confidential information, as applicable, e.g. unblinded analyses of primary and secondary endpoints, analysis of SAEs for severity and seriousness, analyses of laboratory data, summary of global and site-specific safety data, and any other pertinent information from the sponsor or study sites during this or a previous confidential meeting.

In blinded studies, the charter should outline whether and when the DSMB will receive completely or partially unblinded data. The charter should outline who is responsible for unblinding the data, the procedure for unblinding the data, and all parties who will have access to unblinded data.

6.2.14 Arriving at recommendations

In advising on the continuation (without changes to the protocol or its implementation), modification, suspension, or termination of the study, the DSMB needs to take into account prior reviews, the requirements of applicable laws and regulations, and the scientific and ethical appropriateness of continuing the study. Statistical analysis may provide evidence that justifies a recommendation for continuation, modification, suspension, or termination of the study, but consideration of all available data from the study or relevant information external to the study may be necessary to arrive at a more complete judgement. A DSMB should also take the following into consideration in its decision-making process:

6.2.14.1 A member should excuse himself/herself from the meeting during the decision procedure in case of conflict of interest; any potential conflict of interest should be disclosed to the chairperson prior to the meeting and recorded in the minutes.

6.2.14.2 Recommendations should only be made at meetings where a quorum (as stipulated in the charter) is present.

6.2.14.3 The documents required for a full review of the study should be available to each member, and the relevant elements mentioned in the safety monitoring plan should be considered before a recommendation is made.

6.2.14.4 Only DSMB members who participate in the review should be involved in making a recommendation.

6.2.14.5 There should be a predefined method for arriving at a recommendation (e.g. by consensus, by vote). It is recommended that recommendations be arrived at through consensus, wherever possible; when a consensus appears unlikely, it is recommended that the DSMB votes.

6.2.14.6 A recommendation to modify, suspend, or terminate the study should be supported by clearly stated reasons. If the recommendation is based on a vote, dissenting members should have the option to append a minority view to the majority opinion.

6.2.15 Minutes of the DSMB meeting

An appropriately detailed summary of the DSMB's discussions should be recorded, with the recommendation clearly documented.

6.2.15.1 Minutes of open sessions should describe the proceedings of these sessions at DSMB meetings, and summarize all DSMB findings, including the recommendation to continue, modify, suspend, or terminate the study. These minutes should not contain any unblinded information

because they may be distributed to the sponsor, investigator(s), and oversight groups.

6.2.15.2 Minutes of closed session(s) should describe the proceedings of both the open and closed sessions. This part of the minutes should only be distributed to members of the DSMB, unless otherwise specified in the charter.

6.2.15.3 Copies of the minutes of the open sessions should be sent to the sponsor, who will distribute them and/or the recommendation further, in accordance with the DSMB charter. Copies of the minutes of closed sessions should be forwarded to the sponsor at the end of the study, or when indicated in the DSMB charter.

6.2.16 Communicating the DSMB recommendation

The recommendation should be communicated in writing to the sponsor within a predefined period, according to the DSMB charter and its procedures. This communication should include, but is not limited to, the following:

6.2.16.1 The exact title of the study reviewed.

6.2.16.2 Clearly identified date and version/number of the study.

6.2.16.3 The name and title of the principal investigator(s) or the coordinating investigator, when applicable.

6.2.16.4 The name of the study site(s).

6.2.16.5 The name (or some identifier) of the DSMB providing the recommendation.

6.2.16.6 The date and place when/where the recommendation was made.

6.2.16.7 A clear statement of the recommendation. In cases where the recommendation suggests modification, suspension, or termination of the study, clearly stated reason(s) for this need to be provided.

6.2.16.8 The signature (dated) of the chairperson (or other authorized person) of the DSMB.

6.2.13.9 Documentation of the delivery and receipt of the recommendation and its acknowledgement by the sponsor.

6.2.17 Distribution of the DSMB recommendation

The sponsor should establish a procedure for receiving and distributing the recommendation of a DSMB. The sponsor is responsible for distributing the recommendation, in a timely manner, to the steering committee, investigator(s), ethics committee(s), and regulatory authority(ies) involved in the study. Procedures for implementing the recommendation of the DSMB also need to be considered in advance.

6.2.18 Documentation and archiving

All documentation and communications of a DSMB should be dated, filed, and archived according to written procedures. A DSMB should develop an SOP to define the archival and access procedures (including naming the persons responsible for archiving the materials and those authorized to access the archived materials) for the various documents, files, and archives. The SOPs should include special precautions concerning the filing and archiving of randomization codes or lists. The documents should be archived for the duration of study. At the closure of the study, the archived materials should be forwarded to the sponsor.

Documents that should be filed and archived include, but are not limited to:

6.2.18.1 The DSMB charter.

6.2.18.2 The curricula vitae of all DSMB members.

6.2.18.3 A signed and dated statement from each DSMB member indicating that he/she understands his/her responsibilities and that he/she has no interests that

conflict with the objective performance of his/her duties and responsibilities as a member of the DSMB.

6.2.18.4 A record of all income and expenses of the DSMB, including payments and reimbursements made to the DSMB members.

6.2.18.5 The agendas of DSMB meetings.

6.2.18.6 The minutes of DSMB meetings.

6.2.18.7 A copy of all materials received by the DSMB, including the sponsor's reports.

6.2.18.8 A copy of the recommendation(s) provided by the DSMB to the sponsor.

6.2.18.9 A copy of all official DSMB correspondence.

GLOSSARY

The definitions provided within this glossary apply to terms as they are used in these guidelines. The terms may have different meanings in other contexts.

Blinded/unblinded

Data (or their format/presentation) are considered 'blinded' when those with access to the data are not informed of the significant characteristics associated with them. Often this refers to identification of the intervention associated with the data. Data (or their format/presentation) are considered 'unblinded' when those with access to them are informed of the significant characteristics (e.g. intervention) to which the data are associated.

Charter

A document prepared by the sponsor which establishes the role and responsibilities of the DSMB vis-à-vis the sponsor and other parties engaged in the study.

Conflict of interest

A conflict of interest arises when a member(s) of the DSMB holds interests with respect to specific applications for review that may jeopardize his/her (their) ability to provide a free and independent evaluation of the research. Conflicts of interests may arise when a DSMB member has financial, institutional, or social ties to the research.

Data & Safety Monitoring Board (DSMB)

An independent committee established by the sponsor to assess, at intervals, the ongoing scientific and ethical integrity of a study by reviewing and evaluating (unblinded) data and reports at regular intervals. The DSMB provides non-bonding recommendations to the sponsor regarding study modification, suspension, or termination. There is no fixed or harmonized international name for committees performing this function. Other names for

committees performing the same or similar functions include, but are not limited to: Data Monitoring Committee (DMC), Independent Data Monitoring Committee (IDMC), Monitoring Committee (MC), Data & Ethics Monitoring Committee (DEMC), Safety Monitoring Committee, Study Monitoring Committee.

Ethics committee

An independent body (an institutional, regional, national, or supranational board or committee) established to review independently proposed and ongoing research. Such committees are also known variously as Independent Ethics Committees (IECs), Institutional Review Boards (IRBs), Research Ethics Boards (REBs), Research Ethics Committees, and other designations.

Investigator

A qualified scientist who takes on the scientific and ethical responsibility, either on his/her own behalf or on behalf of an organization/firm, for the ethical and scientific integrity of a research project at a specific site or group of sites. In some instances, a coordinating or principal investigator may be appointed as the responsible leader of a team of co-investigators.

Protocol

A document that provides the background, rationale, and objective(s) of a health research project, and describes its design, methodology, and organization, including ethical and statistical considerations. Some of these considerations may be provided in other documents referred to in the protocol.

Recommendation

Non-binding decisions provided by the DSMB to the sponsor concerning the Board's scientific and ethical appreciation of the study and regarding the continuation, modification, suspension, or termination of the study following review of the accumulated safety and efficacy data.

Research participant

An individual who participates in a research project, either as the direct recipient of an intervention (for example, study product or invasive procedure), as a control, or through observation. The individual may be a healthy person who volunteers to participate in the research, a person with a condition unrelated to the research being carried out and who volunteers to participate, or a person (usually a patient) whose condition is relevant to the use of the study product or questions being investigated.

Standard operating procedures (SOPs)

Detailed, written instructions to achieve uniformity of performance of a specific function.

Sponsor

An individual, company, institution, or organization that, either singularly or collectively, takes responsibility for the initiation, management, and/or financing of a health research project. The sponsor of a study may be composed of a number of individuals, companies, institutions, or organizations that share the responsibilities of the study. In this case, it is important that the protocol clearly defines how the sponsor responsibilities are distributed, the individual(s) or organization(s) responsible for establishing the DSMB, and to whom the DSMB reports.

SUPPORTING DOCUMENTS

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8 BACKGROUND

These Operational Guidelines were developed following requests from international and national clinical research organizations and researchers for specific guidance on data and safety monitoring boards (DSMBs). The guidelines have been developed against the background of WHO experience in the management and oversight of clinical research, with the support of an international working party of experts and broad international consultation.

The first draft of these Operational Guidelines was presented at the Steering Committee and Advisory Board Meeting of the Strategic Initiative for Developing Capacity in Ethical Review at the Western Institutional Review Board in Olympia, Washington, USA, in August 2003. This was followed by a meeting of international experts at WHO/TDR in October 2003. Revisions of the draft guidelines were widely circulated for comment throughout the international clinical research community.

Agencies and individuals within the United States Department of Health and Human Services were particularly helpful in providing expert advice based on extensive experience with the establishment and functioning of DSMBs. During 2004, the revised draft guidelines were presented and discussed at regional meetings in Asia, Africa, Latin America, Eastern Europe, the European Union, and North America. The draft guidelines were then reviewed for their applicability by the WHO/TDR Clinical Trials Monitors' Network.

These Operational Guidelines represent the first international guidance dedicated to the role and functions of DSMBs. As the number of clinical trials increases globally, alongside an increasing call for greater ethical and scientific oversight of clinical research, DSMBs are becoming an increasingly established part of clinical research, and their responsibilities are increasingly pushed to the fore. The objective of these Operational Guidelines is to clarify the role and responsibilities of DSMBs based on an international reference point for constitution and function.

Comments and suggestions on all aspects of these Operational Guidelines are welcome for consideration in future revisions of this document. Please correspond with:

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