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Data and Safety Monitoring

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Data and safety monitoring (DSM) refers to a set of oversight procedures in research studies involving human subjects. Depending on the nature and complexity of the study, DSM is carried out not just during the study but often before and after it as well.

Data monitoring refers to the oversight of the research data to help ensure their validity and integrity and to determine whether and to what extent they adequately serve the goals of the study and subject safety. For instance, in a clinical trial designed to test whether a given drug is more effective than placebo in reducing heart attack rates, the plan for data collection must be scrutinized for its appropriateness to achieve study goals before the study even begins. During the study, the accumulated data must be evaluated periodically to determine whether and how the study procedures need to be modified to better achieve study goals and subject safety. If at any point the data indicate with sufficient confidence that the drug is effective, ineffective, or harmful, the relevant arms of the study may have to be stopped prematurely while the other arms are allowed to proceed. Especially in such cases, data monitoring may have to proceed in ongoing arms of the study even as the results from the finished arms of the study are disseminated.

Safety monitoring refers to the oversight of the safety of human subjects participating in the research. Before the study begins, the entire protocol must be vetted for subject safety measures. During the study, incidents that potentially represent adverse or unanticipated outcomes must be examined in order to evaluate whether they are study-related and whether and how the study needs to be modified. For instance, in the aforementioned example, reported instances of fainting may or may not be caused or expected from a given study drug.

While the two types of monitoring can be conceptualized separately, it rarely makes sense to fully separate them in practice because they are intimately related. Therefore, the two types of monitoring are almost always implemented as a single, integrated package of monitoring procedures, even though the underlying responsibilities may be delegated differentially among different specialists in the DSM workflow.

This entry reviews the core principles, regulatory underpinnings, and historical background of DSM before detailing the basic elements of DSM design and operation.

Core Principles of DSM

The actual DSM practices can vary across studies, institutions, and regulatory jurisdictions. Nonetheless, certain basic principles guide DSM everywhere. Prominent among these are

1. The level and type of monitoring needed depend on multiple factors, including especially the complexity of the study and the type and level of risk to subjects.
2. The ultimate goals of DSM are distinct from, and independent of, the study goals. In case of a conflict, the former always trump the latter. Therefore, DSM should be carried out objectively, and regardless of how it may affect the study outcomes.
3. DSM should be flexible and dynamic enough to continually adapt and respond to study events and developments.
4. All the stakeholders in the study—including the principal investigator (PI), the rest of the study team, the institutional review board (IRB), study sponsors, and external monitoring entities, if any—should work cooperatively and exercise their own appropriate level of monitoring, however, formally or informally.

In sum, DSM is simply common-sense research vigilance operationalized.

Regulatory Underpinnings of DSM

In the developed world, the ultimate rules pertaining to DSM are codified in governmental regulations and therefore have the force of law. In the United States, the underlying procedural requirements are covered by the U.S. code of federal regulations Titles 21 and 45. U.S. regulations and guidelines pertaining to DSM apply

to all studies approved in the United States, regardless of whether the sponsor or the study site is within or outside the United States or whether the study is also subject to regulatory oversight in another jurisdiction.

In the United States, all clinical studies that involve greater than minimal risk to participants are required to have in place some level of DSM commensurate with the risk. Strictly speaking, DSM is not required for nonclinical trials. Nonetheless, IRBs may, and often do, require some level of DSM for such studies commensurate with the risk. While research in animal subjects in the United States is covered by an entirely independent set of regulations, the underlying DSM principles and practices tend to be similar and are routinely referred to as DSM in research protocols, funding applications, and research publications.

Numerous other countries around the world have comparable DSM requirements for clinical research. Depending on the country, these requirements tend to be more or less consistent with the international guidelines for clinical research set forth by the World Health Organization (WHO). Compliance with the international standards is especially important these days because health-care research, development, and delivery as well as pharmaceutical manufacturing and marketing are increasingly globalized, as are many of the major health concerns.

Historical Background

The origins of DSM can be traced to the landmark 1964 Declaration of Helsinki that set forth broad ethical principles for biomedical research involving human subjects worldwide and the April 1979 Belmont Report by a U.S. government-appointed commission on the topic. Many of the current practices and even the phraseology of DSM stem from a June 1979 recommendation of the Clinical Trials Committee of the U.S. National Institutes of Health (NIH) that applied the ethical principles specifically to clinical trials and called for every clinical trial to “have provision for data and safety monitoring.” Since then, other influential organizations around the world, including the WHO, European Medicines Agency (EMEA), and the U.S. Food and Drug Administration (FDA), have issued comparable guidelines that apply to clinical research carried out under their aegis.

The overall rationale for DSM rests on the fact that the success of any clinical study requires that the investigators as well as the study subjects meet certain obligations. On the one hand, the investigators must protect the health and safety of study subjects; inform the subjects about the risks, rigors, and responsibilities that participation in the study entails; afford the subjects the opportunity to withdraw from the study if they so desire; and pursue the objectives of the study with diligence. On the other hand, the study subjects must comply with the study requirements as long as they participate in the study. The sponsors and the IRB must ensure that the potential risks to the study subjects are commensurate with the potential benefits to the society and to the subjects and are properly managed throughout the study. The purpose of DSM is to ensure that all these interests are properly balanced and safeguarded throughout the study.

Basic Elements of DSM Design and Operation

Designing DSM procedures is an integral part of developing the study protocol. DSM procedures must be custom-developed for each study because there is no standard set of DSM practices that is a priori suitable for all studies.

In determining the proper level of DSM for a given study, it is wise to err on the side of caution, especially where risks to the subjects are substantial. However, unnecessary DSM has its costs too because it can be wasteful and unnecessarily impede the study. Ultimately, it is the responsibility of the PI to balance these competing considerations, plan the DSM procedures appropriately for the given study in consultation with the IRB, and obtain the approval of the IRB for the protocol prior to starting the study. Once the study gets underway, the PI is ultimately responsible for carrying out the study procedures, including DSM, according to the approved protocol.

Data and Safety Monitoring Plan (DSMP)

DSMP refers to a written document that specifies all aspects of DSM in a given study. IRBs typically require a DSMP as a part of any protocol of a clinical trial. Similarly, most sponsors of clinical trials also require a DSMP as a part of the grant application for funding. For instance, NIH requires a DSMP that addresses specific topics as a part of the Human Subjects section of all proposals for grants or contracts to fund clinical trials. As to the specific format and the required content of the DSMP, the IRB and/or the given funding agency should be consulted.

IRB

In its capacity as the intramural regulator of record, the IRB has considerable powers of oversight and enforcement pertaining to DSM. Before the study can begin, the IRB reviews the study, requires appropriate modifications where necessary, and approves the study if all aspects of the study, including the DSM plans, are adequate. While the study is ongoing, the IRB typically has two types of DSM oversight functions. First, as a part of its periodic review of the study, it monitors compliance with the approved DSM procedures. Second, it reviews, on an ad hoc basis, the reports of study developments and reportable events submitted to it by the PI or other cognizant parties such as the sponsor. Based on its review, the IRB may accept the recommendations (if any) of the cognizant parties, suspend or terminate the study activities, or require modifications to one or more aspects of the study, including DSM procedures.

Data and Safety Monitoring Board (DSMB) and Data Monitorinommittee (DMC)

The DSMB and the DMC are exactly equivalent. Both refer to a panel of independent experts tasked with carrying out DSM for a given clinical trial. The difference is that the NIH and WHO refer to these panels as DSMBs, whereas the FDA and EMEA prefer to call them DMCs (or DSM Committees, or DSMCs). The following is a general description of a DSMB in a typical National Institutes of Health sponsored clinical trial. Panels in other regulatory contexts operate broadly similarly.

NIH requires DSMBs for large, randomized multisite studies that evaluate treatments intended to prolong life or reduce risk of a major adverse health outcome, such as the rates of mortality or major morbidity. They are generally not required for most other clinical studies. For instance, DSMBs are generally not required for trials at early stages of product development or for trials addressing lesser outcomes, such as relief of symptoms, unless the trial population is at elevated risk of more severe outcomes.

Unlike the IRB, a DSMB is not a general-purpose, standing committee that concurrently oversees multiple different aspects of multiple studies. Instead, each DSMB is set up ad hoc solely to carry out DSM for one particular clinical trial. The exact composition and operation of DSMB depends on the type and complexity of the DSM needed for the given study, and the relevant guidelines of the NIH institute that sponsors the study, and are set forth in the approved protocol. A typical DSMB consists of three to seven voting members with various types of study-relevant expertise and may consist of one or more nonvoting members, such as specialists and ex officio invitees, on permanent or ad hoc basis.

To carry out the DSM functions it is tasked with, the DSMB meets at specified intervals (and more often if required by the study developments) and reviews the data related to safety and study outcomes. It has considerable leeway in carrying out its DSM functions for the study. Depending on a majority vote of its voting members, the DSMB can review any and all information germane to its DSM functions. Based on its review, it may vote to recommend modifications to, or even the termination of, the study. It can even recommend changes to its own composition and operation in certain ways. For instance, it can recommend adding members in specific areas of expertise. In studies that involve blinding, it can ask to be unblinded fully or partially to any study information as needed.

While the DSMB can make any recommendation it deems appropriate, it does not have the authority to enforce its recommendations. The PI, the sponsor (NIH, in the present example), and other designated parties will be privy to the DSMB's recommendations as set forth in the protocol. Moreover, the IRB and any external

regulators with jurisdiction over the study will have de jure access. A cognizant official of the sponsoring NIH institute will make the final decision as to whether to accept or modify the DSMB's recommendations and inform the PI and other stakeholders.

Other Mechanisms of External Monitoring

For some studies, external monitoring may be carried out by an Independent Safety Monitor or a sponsor-appointed monitoring committee. However, the use of these mechanisms is uncommon. In most cases, either a full-fledged DSMB or just in-house DSM is used.

See also Clinical Trial; Data A and Safety Monitoring Board; Declaration of Helsinki; Informed Consent; Justice in Social Science Research

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