Institutionally chartered Data and Safety Monitoring Boards: structured approaches to assuring participant safety in clinical research

Blair Holbein ,[1] Marie T Rape,[2] Barbara N Hammack,[3] Ann Melvin,[4,5] Carson Reider,[6] Tamsin A Knox[7,8]

For numbered affiliations see end of article.

Correspondence to
Dr Ann Melvin, Division of Pediatric Infectious Disease, Department of Pediatrics, University of Washington Seattle Campus, Seattle, Washington, USA; ann.melvin@seattlechildrens.org

BH deceased; TAK deceased

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ABSTRACT

Data and Safety Monitoring Boards (DSMBs) derived from the need to monitor large federally funded multi-center clinical trials and evolved to include commercial and other large and complex trials. Eventually, academic health centers also created institutionally focused trial monitoring mechanisms. The basic general principles that define traditional DSMBs extend to the institutional level. The primary responsibilities are assuring safety of the participants, preserving the integrity of the trial, and ensuring the reliability of the results. Institutionally chartered DSMBs meet these responsibilities but usually have fewer members, have a structure specific to the needs of the trial, are more focused and/or have different scope reviewing smaller, single site, higher risk, and investigator-initiated studies and are flexible to accommodate institution-specific requirements and approaches. Their purpose is to meet the responsibilities of oversight for safety and data integrity, ensure proper study design, rigor and conduct, as well as provide statistical support appropriate to the setting of the research. Academic health centers should recognize the importance and existence of institution level safety and data monitoring and provide support as much as possible. Investigators should have sufficient resources available to assemble DSMBs. The Clinical and Translational Science Awards Collaborative DSMB Workgroup provides an online manual to assist investigators.

INTRODUCTION

The National Institutes of Health (NIH) guidelines for Data and Safety Monitoring Boards (DSMBs),[1] National Cancer Institute (NCI) mandated DSMBs,[2] and Food and Drug Administration (FDA) Guidance for Industry[3] have set standards for the contemporaneous oversight of clinical research for the protection of research subjects and assurance of data integrity. DSMBs evolved from the recognized importance of monitoring the progress of NIH-funded large multi-center trials.[4] The NIH initiative established the importance of active independent oversight to promote clinical research integrity.[5 6] The essential concepts include independent review, a priori statistical rules, and an emphasis on assuring participant safety. This initial NIH model of ongoing study-specific independent oversight has evolved to a formal, highly structured process for proximal and multidisciplinary monitoring of clinical studies and has been broadened to include DSMB engagement for industry-initiated high-enrollment, multi-center trials.[6 7]

As the structure and function of DSMBs developed from the need to monitor the progress and safety of large trials, the necessity for a similar approach for smaller scale investigator-initiated studies that were not government or industry sponsored conducted primarily at academic health centers (AHCs) also arose.[8] The knowledge gained through the development of NIH and industry-sponsored multi-center trial DSMBs has yielded an approach that can be adapted for AHCs and their researchers. While these institution level safety oversight committees have existed for many years, there appear to be few available references that provide documentation and guidance for this important aspect of AHC research.

The Clinical and Translational Science Award (CTSA) established by the NIH included a component of creating collaborative work groups. The now discontinued Regulatory Knowledge and Support Key Function Committee[9] worked to establish best practices for aspects of clinical research that are subject to federal and state regulations. A subcommittee was established to specifically address academically based DSMBs. When funding for the key function committees ended, the DSMB subcommittee transitioned into an informal workgroup. Over the decade of existence, a majority of the CTSA hubs have been represented on the workgroup by institutional regulatory leaders involved with DSMBs and DSMB participants. This legacy committee, "the DSMB Workgroup", continues to work on collaboration, best practices, and training needs for members of these AHC-based committees and boards[10] and meets monthly. The workgroup has published a manual for DSMB members.[10] The purpose of this paper is to describe institutional DSMBs as well as to provide recommendations and resources derived from the experience,

observations, and opinions of the workgroup to support the unique needs of these committees and reflects information beyond that contained in the manual.

INSTITUTIONALLY CHARTERED DATA AND SAFETY MONITORING BOARDS (IC-DSMBS)

The establishment and evolution of DSMBs for commercial and large NIH trials brought an awareness of the need for structured contemporaneous oversight of other types of clinical research such as those conducted within an academic institution, especially those studies that pose concerns for participant safety and study integrity. Calis *et al*[11] referred to "internal data and safety committees". Weber *et al*[8] described "Academic Chartered Data Safety Committees" to indicate the utility of institutionally focused research oversight. Initially, these committees evolved from the early NIH guidances but have come to include oversight for safety and data integrity, and also to ensure compliance as well as independent statistical support.[12]

Significant differences exist in AHC DSMBs when compared with those established by contract research organizations, industry, and government.[8] Academic centers may have specialized therapeutic foci, including rare or neglected diseases, or may have dedicated centers or institutes with different missions or which may serve different populations than those usually represented in large trials as well as those clinical trials with significant commercial interests. These specialized areas of research which are generally the purview of AHCs reflect the more limited institutional needs beyond that of a single large trial and have become a well-established aspect of clinical research characteristic of AHCs and affiliated not-for-profit institutions. Likewise, these academic clinical trials generally differ from commercial or large multi-site trials in that they usually have lower enrollment, a limited number of investigators and sites, and are often working within a limited budget. Nevertheless, the structure, process, and methods derived from the large-trial multi-center experience have been extrapolated for use by smaller, single-site, or focused specialty review committees.[8 11] While the term "Academic Chartered Data Safety Committees" is useful, there are examples of specialized DSMBs that can be more appropriately described as "Institutionally Chartered DSMBs" (IC-DSMB) when referring to centers or institutes that are loosely affiliated with AHCs or independent entities. This term is helpful when defining and describing the composition of these DSMBs and also their unique role and responsibilities. Also note that for simplicity and consistency, we use the term "Data Safety and Monitoring Boards" (DSMBs) even though the terms "Data Monitoring Committee" (DMC), "Data Safety Monitoring Committee" (DSMC), or "Safety Boards" can all equally be used to describe similar functions.

Characterization of IC-DSMBs

A unifying concept for IC-DSMBs is their *raison d'étre* to protect the safety of human subjects in clinical trials. While these DSMBs usually have fewer members, are more focused, or different in scope than DSMBs assembled for surveillance of large multi-center clinical trials, they nonetheless have several characteristics in common. Ellenberg *et al*[6] presented four overarching principles for DSMBs: (1) Primary responsibilities are assuring safety of the participants, preserving the integrity of the trial, and ensuring the reliability of the results; (2) Multidisciplinary membership; (3) Avoidance of actual or apparent conflicts of interest (COI); (4) Maintenance of data integrity and confidentiality.

Much of the methodology and administrative approach used in structuring traditional large-trial DSMBs holds true for IC-DSMBs, although appropriately scaled.[7 11–13] The primary purpose of a DSMB is to provide contemporaneous review of a trial: evaluating data integrity and participant safety based on a priori guidance and/or rules, for example, statistical stopping rules for safety. The membership is multidisciplinary and is based on the available expertise and freedom from any administrative and financial COI. The formal structure of a charter or equivalent and the monitoring plan describe processes for oversight of an active trial and define the criteria to stop a trial for reasons beyond subject safety: recruitment, futility, and efficacy. Likewise, the reliance on a charter to define DSMB composition and its processes such as the structure of meetings, reports, and authority is an essential common characteristic for all DSMBs.

In contrast, a distinguishing characteristic of IC-DSMBs is flexibility. By definition, they are institutionally based to provide oversight that matches the environment of the trial. Some review numerous trials conducted within the institution that focus on a therapeutic or medical specialty; some are constituted for individual trials with larger enrollment; some review one enrolled subject at a time for trials involving extremely high-risk interventions or which include vulnerable or highly selected populations that require a case-by-case evaluation, for example, a high-risk medical device study, or a face or hand transplant program. Since the size or focus of the trials and the institutional resources are highly varied, the charters that define the structure and function of the boards reflect the need to adapt to the specific trial.[5] As such, the charters and IC-DSMBs may not strictly conform to NIH or FDA guidelines which were derived to meet different trial environments. IC-DSMBs also differ in the reporting structure. Typically, the reports are given directly to the Principal Investigator (PI). Occasionally, the reports are copied to other oversight entities such as a department or division head, a central committee for a therapeutic center, and/or IRB. Some of the IC-DSMBs operate within a research center or a division within an AHC. As such, the board may operate without being wholly administratively independent of the existing institutional hierarchy. There is sometimes a need for a degree of flexibility in the definition of independence of the members. Since these Boards are institutionally focused, identifying and recruiting members who do not have some degree of administrative conflict of interest or competing research may be challenging. Since many such studies are not industry sponsored, the financial COI may be less problematic. Service on these boards may not always be compensated financially and may not carry liability exposure or coverage typical to industry-sponsored boards. When independence is a concern or if expertise is lacking within the institution, board members may be drawn from outside the AHC or from the local community. Furthermore, the possibility of post hoc involvement by a member of the DSMB for data analysis, manuscript preparation, or other should be contemplated when assembling

Table 1 Comparison of Institutionally Chartered DSMBs, NIH DSMB guidelines, and FDA DSMB guidelines

Characteristics in common for all DSMBs			
Primary responsibilities	Assure safety of participants Preserve integrity of trial Ensure reliability of results Maintenance of data integrity and confidentiality		
A priori statistical determinants	Yes		
Charter or equivalent	Yes		
Multidisciplinary composition of board	Yes		
Confidentiality procedures	Defined within charter and maintained within board		
Maintenance of data integrity	Defined within charter and maintained within board		
Conflict of interest	Avoidance of any actual or apparent		
Risk assessment	Moderate to high-risk trials		
Characteristics that may differ between IC-AHC DSMBs and government-sponsored or industry-sponsored DSMBs			
Entity	AHC IC-DSMB	Government-sponsored DSMB	Industry-sponsored DSMB
Characteristic			
Structure	Institutional charter	Federal guidelines for charter	FDA guidance
Composition of members	Specific to needs; defined in charter	Federal guidelines	FDA guidance
Funding	Research grants, institutional, may be unfunded	Government	Industry
Investigational setting	AHCs	Government-funded trials and AHCs	Varied
Investigator initiated	Yes	Yes	No
Single/multi-site	Single or occasionally small or limited multi-site (4–6 sites)	Single or multi-site	Single or multi-site
Trial size	Interventional trial: small (<100) Observational study: small–intermediate (100 s)	Interventional trial: small–large (<100–1000+) Observational study: small–large (<100 to 1000+)	Small (<100 in phase I) to large interventional trial (1000+)

AHC, academic health center; DSMB, Data and Safety Monitoring Board; FDA, Food and Drug Administration; IC-DSMB, institutionally chartered Data and Safety Monitoring Board; NIH, National institutes of Health.

the Board; with primary consideration given to best practices as provided in this document as well as compliance to sponsor, institutional, and publication policies concerning COI.

While the scope and structure of the various iterations of the IC-DSMBs vary, there are some unifying characteristics as well as institution-specific characteristics. Table 1 summarizes characteristics for NIH and FDA guided DSMBs and IC-DSMBs.

It is important to distinguish how an IC-DSMB differs from an Institutional Review Board (IRB). While both are charged with the assurance of research subject safety, the purpose and governance of DSMBs is not the same as that charged to IRBs.[12] DSMBs provide time-proximal and study-focused (often singularly devoted) safety monitoring founded and guided by statistical principles to evaluate highly specialized or complex trials and to evaluate interim results. IRBs and their support offices usually do not have the requisite expertise or resources for the detailed activities of DSMBs. Thus, it is important to determine if a study would benefit from the contemporaneous safety surveillance that a DSMB would provide especially when safety assurances extend beyond the capacity of the IRB of Record for a clinical trial.[12] An IRB does not and should not review unblinded data with the intent to advise the sponsor on modifying the trial design if dictated by interim data nor recommend whether a trial should be amended or stopped based on interim data.[12] The essential distinction is that statistical expertise and reliance on well-established approaches to study design and data analyses are common to all DSMBs. Finally, the IRB typically is part of the research administration within an institution and reports to an institutional official. An IC-DSMB is independent of the IRB. However, DSMB reports and recommendations should be provided to the IRB by the PI or sponsor.[6 11]

It is useful to describe IC-DSMBs by size and scope. The utility of identifying such characteristics is that within each category, there are commonalities that make it easier to construct workable charters and inform processes and appropriate methods. Each category is defined by focus, the basic structure, and conformance with established principles.

Types of IC-DSMBs

Comprehensive IC-DSMBs

Some academic centers have assembled institution-level standing DSMBs to provide oversight/monitoring for multiple investigator-initiated phase II–III trials and encompass a wide range of drug, device, and other interventional research for all or most of the entire AHC. The trials overseen by these boards may be determined on the basis of size, scope, or risk of the trials or by PI request. Occasionally, other sponsors or an IRB may specifically request that the DSMB monitor a trial. Faculty and staff from multiple disciplines and across disease specialties comprise the membership to ensure appropriate expertise. Conflict of interest needs to be considered but is usually managed

by having members disclose any potential COI and recuse themselves from the review of a particular trial. In most AHCs, the members of the DSMB do not receive direct financial compensation for their service. Also, contrary to the reporting structure of most industry-supported DSMBs, reports from DSMB meetings are not sent directly to the funder/sponsor, but rather are shared with the investigator, IRB, and/or Dean of the investigator's school or college. These larger Boards typically have about eight members with a broad range of clinical expertise and include statistical and often regulatory and/or research ethics specialists, meet on a regular schedule—usually monthly or semi-monthly, and have pre-set, routine agenda. As an alternative approach to providing a single institutional level DSMB, a standing DSMB advisory committee is assembled at an institutional level, but instead of reviewing individual trials, these committees provide guidance and resources for investigators to form DSMBs. Some of these boards are supported by institutional grants, such as the National Center for Advancing Translation Science (NCATS)–funded CTSA which have provided funding for institutional level clinical research infrastructure.

The National Cancer Institute (NCI) requires that every clinical and comprehensive NCI-designated Cancer Center (NCI-CCC) have an institutional Data and Safety Monitoring Plan that meets the specific requirements of the NCI.[2] The NCI guidance lists essential responsibilities for members, defines criteria for membership, gives guidelines for meetings, describes the reports and recommendations from the DSMB, describes confidentiality procedures, and offers criteria for COI. As a result, many NCI-designated cancer centers have incorporated into their data safety monitoring plan a monitoring committee to provide scientific review as well as more common safety review, data monitoring, and statistical analysis of the progress of small-scale clinical trials to ensure the safety of the participants for a number of studies. These review committees typically take the structure of a DSMB with a charter or the equivalent.

Focused IC-DSMBs

These Boards may be smaller in size and narrower in scope. They are restricted to disease or center research focus. DSMB charters are developed for each study separately. These Boards typically are intermediate in size and board members are often compensated. These boards meet as needed or by charter-invoked intervals which typically are dependent on the nature of the study, associated risks, and study progress. The agenda is determined by the studies and issues requiring review. Reports from the DSMB are written by the board chair and sent to the respective investigators. For example, a therapeutically focused center at an AHC would have an IC-DSMB for all trials at that center. A special example of legislatively mandated safety oversight is the University of Colorado UC Health Hospital Denver at the Clinical and Translational Research Center Cannabis Research DSMB. Colorado Amendment 64, which was passed by voters on November 6, 2012, legalized retail or recreational marijuana in Colorado effective January 2014. The Colorado Legislature mandated that the Colorado Department of Public Health and Environment study the potential public health effects of marijuana using funds generated from taxes on marijuana.[14] The NCATS-funded Colorado Clinical and Translational Sciences Institute established an umbrella DSMB specifically to review studies using cannabis. The initial DSMB was composed of eight local faculty with expertise in cannabinoid physiology, emergency medicine, medical toxicology, biostatistics, bioethics, and other relevant clinical specialties.

Single-purpose IC-DSMB

Investigator-initiated trials that require a DSMB are the simplest application of the IC-DSMB principles. These DSMBs require the most flexibility in structure and operations. The primary principles for all DSMBs apply, but the charter, scope of review, membership size, and characteristics must reflect the trial scope and relative risk. Larger trials, such as those funded by the NIH or major donor or advocacy organization, have membership reflective of the size, complexity, and risk of the trial, meet regularly or as dictated by safety observations or enrollment, and issue detailed reports by the chairman. Smaller trials may have fewer members and may more closely resemble a trial with oversight by an independent safety officer.[15]

The final category would include highly specialized Boards with either a single focus or a multipronged project with specific review requirements that extend over several years and exist for a single overarching grant or project. This designation is to a degree different than the other listed DSMBs. These Boards are small with less than five or six members, all with relevant expertise, independence, and freedom from COI, and meet on a scheduled as well as an "as needed" basis, but nonetheless are organized and operate within a charter or mission statement and provide safety oversight beyond an IRB. As such, there is often less attention directed towards statistical review but rather immediate protection of human subject concerns.

DISCUSSION

The knowledge gained from experience in large government-sponsored trials and large industry-sponsored trials that meet FDA guidance for DSMBs provide general principles that apply at an institutional level. Principles, tools, and standards derived from the evolution of DSMBs for large, multi-center trials have been adapted to serve similar purposes in smaller, single-center, or focused research in the form of IC-DSMBs. Critically, it should be noted that there are few standards agreed on for these smaller, more focused specialized DSMBs and the illustration that general principles apply can guide future charters and DSMBs. There is a need to provide investigators the means to ensure commensurate and proximal monitoring and oversight for investigator-initiated trials. Not all institutions have access to an institutional DSMB or resources to assemble a DSMB. Equally problematic is the situation in which investigators may not recognize the need for a DSMB, or the IRB may require one and the investigator may not have the expertise, familiarity, or access to resources to write a charter and assemble a board. Not infrequently, an investigator needs to include safety planning in a grant or their NIH medical officer for a grant directs the investigator to include assembling a DSMB.

The lack of recognition of the availability of smaller institutional level DSMBs contributes to some of the perceived difficulties in planning for research that requires that level of safety oversight. It may even serve as an impediment. It could be argued that providing some support for IC-DSMBs would be useful, especially for the unique research that often is the exclusive purview of AHCs. There are additional institutional benefits for recognizing the value of IC-DSMBs. They can offer training and service opportunities for both junior and senior faculty which in turn may also assist with each's own proposal submissions as well as contributions to grant peer review panels.

There is a collaborative effort to avail the wider research community of the tools and standards for developing IC-DSMBs. This coalition is a legacy workgroup that was originally formed as a subgroup of the CTSA Regulatory Knowledge and Support Key Function Committee.[9] The CTSA Collaborative Data and Safety Monitoring Board (DSMB) Workgroup continues to meet regularly, provide educational sessions, and develop guidance, training materials, and resources in DSMB practices for investigator-initiated research studies. The Workgroup, supported by NCATS, has produced an online DSMB Training Manual for Investigators, DSMB members, IRB members, biostatisticians, and research staff involved in AHC research.[10] The manual provides instructional materials for individuals asked to serve on a DSMB. It also provides guidance as well as templates for writing charters and reports that are specifically targeted to an institutional level DSMB. The manual was first published in 2018 and will be reissued as a second edition in 2021. The manual is open access. Tufts University hosts the manual online. The workgroup also reviews and answers questions submitted to the group regarding structure and function of DSMBs.

The question arises as to how well the workgroup reflects the wider community of AHCs and whether our collective experiences and recommendations are broadly applicable. The workgroup formed in 2010. We have met for over a decade and have had attendees from many of the CTSA AHCs. When the Key Function Committees and workgroups were part of the CTSA structure, the DSMB workgroup had 45 members with participation from about 40 institutions. Early in the group's history, a survey was conducted regarding DSMB resources within each of the CTSA Consortium institutions. The results revealed that very few had policy-driven standards and even within institutions, many had no specific tracking of these boards. This lack of definitive data calls for a more structured and comprehensive survey to determine the number of IC-DSMBs that exist and how they do/do not fit the characterizations offered in this paper. The conduct of such a survey would require a committed investigator with research funding sufficient to gather these data. Importantly, this information could be used to emphasize the institutional importance of IC-DSMBs, establish conventional standards, and improve processes. Nonetheless, the response to establishing an access website[16] and the downloads of the manual could be construed as an approval or acceptance of the content. In the 2 years since establishing the website and posting of the manual (January 1, 2019 to December 20, 2020) there have been 667 unique visits to the website and 291 unique downloads of the manual (Tufts Digital Library, unpublished usage analytics data). The workgroup continues to accept and address DSMB-related questions submitted through the website.[16]

CONCLUSIONS

AHCs should recognize the existence and importance of institutional level data and safety monitoring. Some institutions have robust support for IC-DSMBs while others have minimal resources. We acknowledge that many institutions do not have the resources to fully support IC-DSMBs. Nonetheless, investigators should have sufficient resources to be able to assemble "right-sized" data and safety monitoring for their research. Research support and administration can make sure that investigators are made aware of the resources that are available. The DSMB workgroup has provided a credible open-source resource to supplement institutional support. The DSMB manual is available and is applicable for assembling IC-DSMBs for investigator-initiated trials that require increased data and safety monitoring.

Author affiliations
[1]Population and Data Sciences, University of Texas Southwestern Medical Center, Dallas, Texas, USA
[2]North Carolina Translational and Clinical Sciences Institute, University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, North Carolina, USA
[3]Colorado Clinical & Translational Sciences Institute, University of Colorado Denver – Anschutz Medical Campus, Aurora, Colorado, USA
[4]Department of Pediatrics, Division of Pediatric Infectious Disease, University of Washington and Seattle Children's Research Institute, Seattle, Washington, USA
[5]Institute of Translational Health Sciences, University of Washington, Seattle, Washington, USA
[6]College of Public Health, The Ohio State University OSUMC, Columbus, Ohio, USA
[7]Department of Public Health and Community Medicine, Tufts University School of Medicine, Boston, Massachusetts, USA
[8]Tufts Clinical and Translational Science Institute, Tufts University School of Medicine, Boston, Massachusetts, USA

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ORCID iD
Blair Holbein http://orcid.org/0000-0003-1368-4571

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