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TRANSLATIONAL TOOLBOX

# Data Safety and Monitoring Boards Should Be Required for Both Early- and Late-Phase Clinical Trials

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## SUMMARY

Phase I and II clinical trials increasingly combine therapeutic and toxicity endpoints. Recently, therapeutic agents have even achieved U.S. Food and Drug Agency approval based on early phase trials alone. These developments point to new challenges in assuring the safety of human research subjects and patients. Given their size and use of real-world patients, phase III studies warrant independent monitoring by a Drug Safety Monitoring Board (DSMB). Requirements should also be extended to include many phase I and II clinical trials. Measures should be taken to establish and standardize minimum qualifications for service on a DSMB. (J Am Coll Cardiol Basic Trans Science 2021;6:887–896) © 2021 The Author. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Data Safety and Monitoring Boards (DSMBs), also referred to as Data Monitoring Committees (DMCs), were first established in the 1960s to ensure the safety of subjects in clinical trials (1). A critical difference between DSMBs and other research oversight bodies is that a DSMB undertakes periodic risk-benefit assessments during the clinical trial using the data gathered in the course of the study to look for the emergence of serious or unexpected adverse outcomes or, alternatively, signs of a significant beneficial effect. The DSMB may recommend stopping a trial for evidence of harm (eg, the ALTITUDE (ALiskiren Trial In Type 2 diabetes Using cardiovascular and renal Disease Endpoints) trial, which was stopped prematurely because patients treated with aliskiren had higher occurrence of cardiovascular morbidity and mortality endpoints than the placebo control group [2]) or for futility (eg, echoCRT [Echocardiography guided Cardiac Resynchronization Therapy], which was stopped prematurely at the recommendation of its DSMB for futility and potential increase in mortality [3]). For less serious outcomes, the DSMB may serve as a conduit for relevant information to the study sponsor that can trigger protocol amendments, changes in surveillance or further training of study investigators. They may also expedite early termination or rapid completion of a trial that shows significant clinical benefit (eg, the ASCOT-BPLA (Ango-Scandanavian Cardiac Outcomes Trial—Blood Pressure Lowering Arm) trial in which the trial's DSMB found a significant therapeutic advantage of amlodipine/perindopril versus atenolol/thiazide in the prevention of cardiovascular disease in patients with hypertension [4]). Early termination of trials can be indicated to protect current subjects in the treatment arm from harm as well as to protect future patients from the harm of delayed access to efficacious treatments. Early terminations because

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**ABBREVIATIONS AND ACRONYMS**

**DMC** = Data Monitoring Committee

**DSMB** = Data Safety and Monitoring Board

**FDA** = U.S. Food and Drug Administration

**IRB** = Institutional Review Board

**NIH** = National Institutes of Health

of adverse outcome or futility are important, both to protect patients from the harm of unexpected or unexpectedly high adverse outcomes and to eliminate costs of completing a clinical trial that will not result in a viable therapeutic outcome. DSMBs are crucial in maintaining the scientific integrity of a large clinical trial by providing for an interim review of data that is independent of the sponsor but that also avoids introducing potential bias into the study before data have "matured"—that is, accumulated sufficient power to ensure that the results reflect the true outcomes of the completed study.

The decisions of DSMBs can have profound effects on several groups of people:

- prospective trial subjects (who may or may not be patients with the target disease) who will be recruited around the time the DSMB makes an interim audit of the trial;
- current and future patients with the disease who may benefit from the study agent once the trial is either complete or terminated early for benefit;
- current and prospective study enrollees who avoid harm when they are not exposed to a hazardous study agent because the DSMB determines at the interim analysis that there is either no benefit (the therapy is futile) or that the therapy poses a significant and unwarranted adverse risk;
- current and future patients who may be denied beneficial therapy when a DSMB determines that early trial termination is warranted, and an important late beneficial effect of the study agent goes undetected.

Because early termination can deny patients both benefits and harms, a major challenge for DSMBs is to determine when the interim analysis of the data crosses some determinative boundary and becomes conclusive as beneficial versus harmful. Deciding when to terminate a trial presents complex ethical and statistical questions.

DSMBs face several ongoing challenges that are not currently optimally addressed by regulations. These include a lack of regulatory requirements for DSMB involvement in clinical studies, including early-phase clinical studies; a lack of regulatory authority with which to enforce the safety issues they discover; a lack of required education and experience in issues that are key to service on a DSMB; and a lack of a uniform approach to safety issues, which results in inconsistencies in monitoring the scientific integrity and safety of otherwise similar clinical studies.

## REGULATION OF DSMBS

Despite the critical nature of a DSMB's role in analysis and recommendations in monitoring and ensuring the safety of study subjects and patients, DSMBs have surprisingly limited authority over clinical studies of drugs, biologics, and devices; are not actually required except in extremely narrow circumstances; and are currently recommended for use in only a small set of studies. Gewandter et al (5) found that of randomized clinical trials reported in 6 high-impact journals, 40% failed to state whether a DSMB was used, although half had indicated in a clinical trial entry or published protocol that they intended to do so (5). In addition, service on a DSMB is minimally regulated, does not require specific training, and is generally controlled by the study sponsor through its nomination of members.

DSMBs operate under contracts that have legally binding operational aspects, and the DSMB charter states that its purpose is to ensure the study is conducted in a manner that protects the safety of patients and the ability of the trial to yield scientifically valid information. In 1998, the National Institutes of Health (NIH) began to require DSMBs for all NIH-sponsored phase III multicenter clinical trials (6,7). In 2011, the National Heart, Lung, and Blood Institute extended this to include requiring a DSMB for National Heart, Lung and Blood Institute-sponsored studies "with greater than minimal risk" (8). Although these facts suggest that DSMB recommendations are binding, regulatory bodies such as the U.S. Food and Drug Administration (FDA) (9) and the European Medicines Agency (10) place ultimate control over decisions related to the design and conduct of clinical trials with the trial sponsors themselves. When a DSMB makes recommendations that warrant discussion between the sponsor and the FDA, the FDA specifies that it is the sponsor's responsibility to initiate that discussion and not the DSMB's (9). Thus, the DSMB remains a "consultative" scientific body—although one with considerable clout (11). Indeed, the FDA does not require that a clinical trial establish a DSMB at all (except in emergency trials in which informed consent cannot be obtained) (12) but merely outlines the types of studies for which one is recommended.

The FDA recommends consideration of a DSMB in late-phase studies when: 1) the study endpoint is such a highly beneficial or harmful result that interim analysis might ethically require early termination of the study; 2) some aspect of the study other than the treatment itself presents safety concerns—for

example, the procedure for administering the treatment is particularly invasive; 3) there is prior information suggesting potential serious toxicity with the study treatment; 4) the study is being performed in a particularly fragile patient group, such as children, elderly individuals, patients who are terminally ill, or persons of diminished mental capacity; 5) the study is being performed in a population at elevated risk of death or other serious outcome; and 6) the study is large, of long duration, and multicenter (9). The FDA comments that DSMBs are not usually warranted in early-phase studies but "might be considered" when risk to study subjects appears to be particularly high, such as when novel approaches to treating a disease or condition are being tested. When the investigator is also the sponsor, the FDA suggests that the added independent oversight of a DSMB may enhance subject safety as well as the credibility of the product development. Interestingly, the FDA further comments that in early-phase studies "in which the potential for scientific gain from continuing a study must be evaluated in the context of ethical considerations for ensuring subjects' rights and welfare," a DSMB can provide independent, objective expert counsel—a role traditionally allotted to an Institutional Review Board (IRB) (9).

FDA guidance on DSMBs does not distinguish between the entities being studied, and FDA guidance for DSMBs applies equally to clinical trials involving drugs, biologics, and medical devices. Although DSMBs have been convened to oversee clinical trials involving devices, DSMBs are most often used in clinical trials of drugs and biologics in the treatment of disease rather than devices. One reason for this may be the different process that most devices take compared to drugs and biologics to achieve FDA approval, because most do not require clinical trials in humans at all (13). Class I and II devices (ie, those that pose only low or moderate risk to patients, such as suture) can be approved on the basis of laboratory and animal studies, and even class III devices (such as implantable cardiac devices) may bypass clinical trials entirely if they are based on a predicate (similar) device that has already won approval.

Although the FDA and European Medicines Agency limit their strongest recommendations as well as their limited requirements for a DSMB to larger clinical trials and emergency studies in which the subjects are unable to give informed consent, other types of trials can benefit from DSMBs, including multiple parallel studies involving the same agent, to maintain continuity and maximize knowledge and experience across all studies in the parallel set (14), and pragmatic clinical trials comparing alternate interventions in heterogenous health care settings (ie, "real-world" pragmatic trials) (15). In addition, DSMBs are increasingly useful in early clinical phase I and II trials.

## DSMBS FOR PHASE I AND II CLINICAL TRIALS

Traditionally, phase I clinical trials have been referred to as "toxicity trials" and are used to uncover adverse events and elucidate the pharmacokinetic profile of a drug or biologic agent and have limited therapeutic intent. Phase II clinical trials traditionally incorporate the first "patient subjects"—patients who have the target disease—and are engaged in further discovering adverse events and searching for clinically relevant dosage (so-called "dose-finding" trials). However, the separation between clinical trial phases is increasingly becoming blurred. With the advent of molecularly targeted agents associated with biomarkers that enable finer selection of patients/subjects, not only is it possible for a phase I trial to have a therapeutic endpoint, but phase I trials increasingly incorporate phase II extensions (phase I/II clinical trials) and often used surrogate outcomes, Bayesian principles, and adaptive design requiring sensitive and specialized statistical analysis. More and more, the small phase I clinical trial using unselected subjects is disappearing (16), and the FDA has now even approved investigational drugs on the results of phase I studies alone. Ceritinib, for example, was approved based on a 58% response rate seen in a phase I study in patients with lung cancer. Pembrolizumab was approved for the treatment of melanoma on the basis of responses seen in the expansion phase of a first-in-human phase I trial (16). Many such studies are carried out in terminally ill patients, for whom mortality is an expected outcome whether or not related to the study agent. Under current regulatory language, the incorporation of a DSMB in such trials is not even recommended, even though the subjects of these trials are particularly vulnerable.

Despite the FDA's downplaying of the utility of DSMBs in early-phase clinical studies, it is becoming clear that DSMBs would be useful and should even be required in many smaller phase I and II trials (17), particularly if there is potential for significant risks; if the patient population being studied is particularly vulnerable because of either the severity of disease or other factors (eg, young age, developmental delay, elderly individuals, or people in prisons); for therapies that are complex, novel, or for which little is known; and for trials for which the study design and statistical complexity warrant independent monitoring and evaluation, such as in phase I/II

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seamless trials and phase II adaptive trials. In a seamless phase I/II design, for example, specific patient populations are identified in the early part of the trial to continue on in a confirmatory phase, rather than employing 2 sequential but entirely different groups of subjects.

Adaptive trial design, even in early clinical phases, presents new and unique challenges in safety analysis and can benefit from DSMB monitoring. A changing primary endpoint or changes in trial size in an adaptive trial can also be problematic for analyzing clinical benefit (18). It can be tempting to jump to a decision to terminate a trial that shows early benefit, but such a decision can prove to be premature because of the high variability of early results. One example can be found in the CHARM (Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity) trial. At the fourth interim analysis, there appeared to be a 24% reduction in the risk of mortality that met a predetermined stopping boundary for benefit. However, other reasons caused the DSMB to vote to continue until the next interim analysis. At subsequent interim analyses, the risk reduction was attenuated and did not reach significance ($P = 0.055$). Because early trial termination was avoided, an overly optimistic assessment of overall mortality reduction was avoided, and the trial duration exposed important long-term benefits in other outcomes, such as cardiovascular death and heart failure hospitalizations (19,20).

Montori et al (21) examined 143 randomized clinical trials that were stopped early for benefit (25% of which were cardiovascular studies) and found that the decision making for early termination was often inadequately explained and that trials often showed implausibly large treatment effects. They concluded that many such trials should be "viewed with skepticism." Of the 143 randomized controlled trials that were terminated for benefit, just 85 were stopped because of a decision involving a DSMB. In the remaining 58 cases, the party that determined that the trial be terminated early was either not identified (n = 24) or was a party associated with the trial, either via the executive committee without DSMB recommendation (n = 32) or by the sponsor itself (n = 2). These findings raise the possibility of overzealous interpretation of positive results by commercial sponsors, among other conflicts of interest.

Whether and to what extent the sponsors or investigators should have access to interim trial results in a phase I/II seamless trial remains an unanswered question: the sponsor's perspectives on the trial may be key in determining whether to continue. Indeed, currently, the sponsor may be the sole entity responsible for the analysis that determines whether to continue. FDA guidance for DSMBs, however, stipulates that such sponsor involvement must be clearly justified and implemented with strict controls, and the entire process of sponsor involvement should be transparently presented to regulators.

## INCREASING SCOPE OF DSMBS

The scope of potential roles for the DSMB has expanded in recent years, with DSMBs being requested to weigh in on study design and protocols before initiating a study; make recommendations about stopping or modifying a trial for ethical reasons; weigh in on modifying or stopping a trial based on inaccuracy in its design assumptions or because of emerging external information; and participate in implementing an adaptive design after interim data analysis (11).

Clinical trials are increasingly complex; entail many components; and, most importantly, are performed on human subjects as well as actual patients. They bring together the motivations, hopes, desires, and values of many people, from the theoretical scientist to the clinical investigator, the commercial sponsor and the subjects and patients. Not all of these people will necessarily have identical goals and interests, and there will be legitimate differences of opinion regarding the interpretation of trial data. Thus, each trial is its own complex "ecosystem," involving many components and leading to complex and frequently unpredictable outcomes. In addition, all clinical studies involve explicit and implicit ethical rules and standards. Performing a clinical study consequently requires human deliberations and not merely protocols. Statistical rules and clinical judgment are not by themselves sufficient to ensure the integrity of a clinical trial.

All clinical trials benefit from some form of oversight, which currently is provided by a variety of entities, such as regulators, IRBs, study Steering Committees, and DSMBs. Of these, the DSMB has the strongest combination of the most specific expertise for the study it oversees, plus relative independence from conflicts of interest and undue influence.

The DSMB is in a tempting position to be able to implement adaptive trial methods after the examination of interim data. This currently runs specifically against the regulatory concepts of adaptive trial designs, in which adaptive designs must be prespecified before an interim analysis, as the FDA draft guidance for adaptive trial designs describes (22), but might be permissible under the independent oversight of a DSMB. The FDA does recognize that during the course

of a trial, outside information may become available that suggests that trial changes should be made to protect patient safety. FDA guidance comments that in such a case, an adaptive implementation may be warranted, and the sponsor should still remain blinded to the interim results (9). The DSMB may thus be the best positioned to help with a conversion to an adaptive design.

## IRBS ARE NOT DSMBS

Most small, single-institution trials currently do not involve a DSMB, and oversight is usually provided by an IRB. However, this practice leaves a substantial void in monitoring the safety of clinical studies—most IRBs do not generally proactively monitor studies but rather rely on the investigator-generated reports that are required periodically or in instances of significant adverse events. Relying on the investigator for safety reports imperils impartiality in such oversight. IRBs lack the specialized expertise of a DSMB to contextualize such adverse events within often esoteric studies and to determine how significant the event might be in a specialized patient population. IRBs also have a more diverse composition (scientists, physicians, ethicists, community members, etc) than DSMBs, which are more focused on the specific charges of analyzing study data and assessing patient safety. They do not have automatic access to emerging data that might affect decisions to terminate or continue a study (9). IRBs also generally do not have sufficient bandwidth within their many duties to monitor the implementation and organizational aspects of a study nor to do interim data analysis in complex adaptive protocols. They depend heavily on the study's own statistician for data interpretation, again raising questions about potential bias. Most IRBs lack both the study-specific expertise and the time to carry out rigorous analysis for all entries in a heavy docket of institutional studies.

In a traditional phase I or phase II study that is not intended to be therapeutically definitive (such as a dose-finding study), interim statistical analysis is generally not required, currently bypassing FDA recommendations for a DSMB altogether. In such cases, studies may rely on trusted individuals with expertise to help oversee the trial in a less formal arrangement than a DSMB. However, such arrangements still have significant disadvantages compared to a DSMB. If monitoring is insufficiently rigorous or involves too few individuals, important issues can be missed. In addition, the advantage of having multiple perspectives and group discourse in making important trial safety decisions is sacrificed when an individual becomes the primary overseer. DSMBs have the capability of carrying out both rigorous evaluation of the scientific integrity of a study and thorough consideration of various safety aspects of a study from multiple perspectives.

Much that has been learned from the operational organization of IRBs can be applied to DSMBs to manage workload, promote financial and organizational efficiency, and provide consistency.

Institutions generally do not have different IRBs for each clinical study, for example, but rather have an institutional committee that is responsible for most IRB decisions. By combining IRB functions across multiples studies, not only is organizational efficiency established, but there is also potential considerable cost savings. In one study (23), IRB costs per action (ie, individual services provided, such as study review, review of adverse events, and other handling of research materials) for "high-volume" IRBs (those fulfilling more than 1,000 actions per year) were significantly lower than those for "low-volume" IRBs (those fulfilling 125 actions or fewer per year) by about two-thirds.

Combining DSMB general functions in a similar fashion is possible and can provide financial and operational efficiency. The structure of a standing committee might also provide more consistency in methods and decision making. Tannock et al (6) describe development of an institutional, semi-independent DMC at the University of Kentucky. The committee has a standing membership of a small group of faculty that includes at least 2 physician-scientists with clinical research experience, a research pharmacist, a biostatistician, a safety officer, and ad hoc members appointed as needed to supply special expertise related to a specific research study.

## COMPOSITION, CONFLICT, AND CONFIDENTIALITY

DSMBs avoid some of the pitfalls of having only a single individual—or individuals with less specific expertise—monitoring safety and carrying out interim data analyses. DSMBs are generally composed of biostatisticians, scientists, bioethicists, and clinicians knowledgeable about the question being studied. Because of the increasing complexity of clinical trials, some authors also now recommend that such committees include bioethicists, patient advocates, and patients (24,25). Candidates for board membership of a DSMB are generally proposed by the study sponsor (which may be a commercial entity, a funding source that is not a commercial entity, or an individual sponsor) (9) or the Steering Committee of the clinical trial, if there is one.

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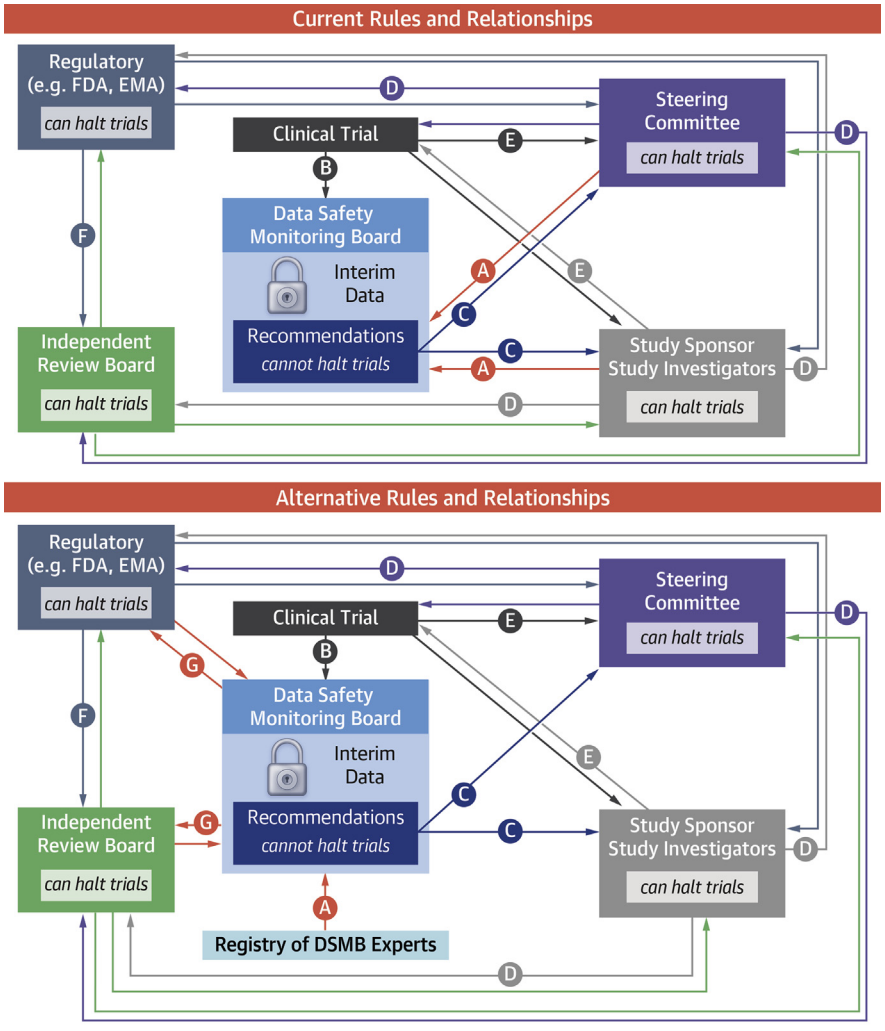
**CENTRAL ILLUSTRATION** **Basic Current and Alternative Data Safety Monitoring Board Clinical Trial Relationships**

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Part I: Basic processes. **(A)** Although individual trials may vary, under current rules, the sponsor or clinical trial Steering Committee nominates experts to serve on the DSMB. **(B)** Clinical trial investigators provide data to the DSMB for interim analysis. The data are held secure and, except in extraordinary circumstances, are not released to the Steering Committee and/or trial sponsor/investigators. **(C)** The DSMB communicates recommendations to the Steering Committee and study sponsor/investigators regarding continuing the trial, terminating the trial, and possible changes in protocol during the trial. **(D)** The Steering Committee and/or study sponsor/investigators are responsible for reporting adverse events and changes in protocol to the IRB and FDA. **(E)** The Steering Committee and/or study sponsor/investigators are also responsible for communicating to trial investigators changes in protocol and DSMB recommendations. **(F)** Communication occurs between the FDA and IRB in cases of serious safety events. Part II: Alternative rules. **(A)** DSMB members are assigned by an independent registry of experts who have experience in DSMB actions and expertise in the field being studied. Ad hoc members with specific knowledge of the study therapy may also be assigned, but they may or may not have voting privileges. **(B)** Clinical trial investigators provide data to the DSMB for interim analysis. The data are held secure and, except in extraordinary circumstances, are not released to the Steering Committee and/or trial sponsor/investigators. **(C)** The DSMB communicates recommendations to the Steering Committee and study sponsor/investigators regarding continuing the trial, terminating the trial, or possible changes in protocol during the trial. **(D)** The Steering Committee and/or study sponsor/investigators are still responsible for reporting adverse events and changes in protocol to the IRB and FDA. **(E)** The Steering Committee and/or study sponsor/investigators are also responsible for communicating to trial investigators changes in protocol and DSMB recommendations. Communication occurs between the FDA and IRB in cases of serious safety events **(F)**. **(G)** In addition, the DSMB has new direct reporting duties to the IRB and FDA when significant adverse events occur; changes in protocol are recommended; and termination of the trial for benefit, futility, or adverse outcomes is contemplated. The IRB and DSMB work hand in hand to resolve ethical issues and protect patient safety. DSMB = Data Safety Monitoring Board; EMA = European Medicines Agency; FDA = U.S. Food and Drug Administration; IRB = Institutional Review Board.

Avoiding both actual conflicts of interest and undue influence, as well as the appearance of the same, is critical to patient safety and is integral to the functioning of a DSMB; thus, DSMBs remain independent of the trial itself, must be able to maintain strict confidentiality, and cannot have direct or indirect financial interests in the trial or its outcomes. That being said, complete autonomy of board members from the trial may be problematic, because the very composition of the DSMB relies on sponsors or investigators who have the best knowledge of who possesses the appropriate expertise to serve, particularly when the study involves novel or esoteric therapies.

**COMPOSITION.** DSMBs usually consist of 3 to 5 members, including a statistician (nonvoting) member with sufficient specialty experience in the particular field of the trial and physicians with relevant clinical training and experience. General principles are to keep the DSMB as small as possible while still encompassing all relevant expertise. An odd number of members is often recommended to avoid tie votes (26), although DSMB recommendations should ideally be arrived at by consensus rather than voting. Individuals on the DSMB should have a thorough understanding of the relevant aspects of the disease and treatment that are affected by the specific study. It would not usually be sufficient for members to have, for example, only broad knowledge of the medical specialty in which the study is concentrated. Previous experience is important, but restricting membership to only those with past experience on a DSMB would prevent new dedicated parties from participating in the nuanced safety board review process and decision making. Some authors recommend, therefore, that mentoring programs be implemented to provide opportunities for individuals to participate as nonvoting members of the DSMB, in order to work directly alongside experienced members and gain the skills required for their own DSMB service (14). The Clinical Trials Transformation Initiative suggests other measures to increase the experience, expertise, and consistency of DSMB members, including the development of didactic educational programs and case studies (24).

Zuckerman et al (27) found only 2 formal training workshops for DSMB members: an in-person workshop at Johns Hopkins University in 2008 and a web-based training module targeted to statisticians. A recent survey of DSMBs and sponsors revealed that only 8% of DSMB members received formal training, and 94% were not aware of any training programs (27). These findings lead to concerns about the inconsistency of DSMB reviews and decisions. Trachtman and Caplan (25), for example, describe DSMB decisions regarding 2 studies of almost identical size—the AURA-LV (Aurinia Urinary Protein Reduction Active-Lupus With Voclosporin) and TESTING (Therapeutic Evaluation of Steroids in IgA Nephropathy Global) trials, in which 1 trial was terminated and 1 allowed to proceed despite both having similar serious adverse event rates, including clinically significant mortality. Such disparate decisions can compromise trial safety and integrity and raises questions of whether more consistency in DSMB operation and more formal preparation of individuals for DSMB service are needed.

**CONFLICT.** Avoiding both actual conflicts of interest and undue influence, as well as the appearance of the same, is critical to patient safety and is integral to the functioning of a DSMB, and thus, DSMBs remain independent of the trial itself. That being said, complete autonomy of board members from the trial may be problematic because the very composition of the DSMB currently relies on sponsors or investigators who have the best knowledge of who possesses the appropriate expertise to serve, particularly when the study involves novel or esoteric therapies. In addition, it is nearly impossible to totally divorce the influence of trial investigators on DSMB decisions because trial statisticians are almost always used to create the very unblinded interim data reports that the DSMB reviews (28).

Other kinds of conflicts are not necessarily limited to financial conflicts (such as financial linkage with the sponsor entity) or to study involvement but can include more subtle conflicts, such as personal relationships. Even intense intellectual investment can also present significant conflicts (9). An individual responsible for developing the original concept being tested or for the early research establishing the rationale for the therapy under investigation, for example, might be more reluctant, consciously or subconsciously, to stop a trial for futility than someone without such an investment because continuing or terminating the trial may reflect on their own work (24,29).

**CONFIDENTIALITY.** The confidentiality of interim results is of particular concern to the FDA (9). The FDA guidance warns that sponsor knowledge of interim data can bias study outcomes, both by influencing the further conduct of the trial and by affecting analysis planning (30). Interim results can also be misinterpreted and are “unstable” in the sense that it is not uncommon for them to change as the trial progresses. Early knowledge of interim

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results can have serious effects, as demonstrated in the LIGHT (Cardiovascular Outcomes Study of Naltrexone SR/Bupropion SR in Overweight and Obese Subjects with Cardiovascular Risk Factors Trial) trial, which evaluated the long-term cardiovascular effects of naltrexone-bupropion versus placebo in 9,000 randomized patients. More than 100 people had access to the data, including the company's board of directors. Based on the interim data, the commercial sponsor, Orexigen, filed for a patent and filed a report with the Securities and Exchange Commission claiming a positive effect of the drug that had not been proven by the interim data. This led to early termination of the LIGHT trial by investigators, and subsequent analysis found that risk of strokes, myocardial infarctions, and death increased in treated subjects, not decreased (31).

To protect separation of the DSMB from study investigators, general FDA guidance suggests that changes to study design be made only by individuals who are independent of the DSMB—such as a Steering Committee or other trial managers—unless patient safety is at stake. Having said that, FDA guidance is not forthcoming about changing trial enrollments, protocols, and other issues apparent in adaptive trial designs. In 2019, the FDA finalized guidance for adaptive trial design; the agency states that although a DSMB might be used to make adaptation recommendations already present in a well-designed prospective plan, it should not be used to identify new design aspects for adaptation based on the interim results (22).

## RECRUITMENT OF DSMB MEMBERS

The confidentiality and sensitivity with which a DSMB performs its tasks leads naturally to an atmosphere of "secrecy" to the performance of DSMB reviews and a lack of transparency about DSMB recruitment and training.

Because sponsors themselves are largely responsible for recruiting DSMB members for their studies, there are concerns that bias in recruitment of DSMB members is leading to an accumulation of an "aging power elite" among DSMB members (32), which may not adequately represent the talents, knowledge, and perspectives of younger researchers. This, in turn, raises questions about influence on DSMBs, as well as lack of structured experience among many members in the analysis needed in DSMB decisions (33).

At a recent international workshop formed by the Heart Failure Association of the European Society of Cardiology and the Clinical Trials Unit of the European Heart Agency of the European Society of Cardiology, experts suggested addressing this problem in part by developing a registry of DSMB members so that smaller companies or new sponsors might have access to a pool of experienced individuals from which to draw (34). Shifting the initial nominating process for DSMB membership away from the sponsor and to such a registry may have additional beneficial effects in reducing undue influence of sponsors over DSMBs. Information regarding potential conflicts of interest could also be maintained in such a registry and facilitate the exclusion of individuals from a DSMB due to such issues (see **Central Illustration**).

## CONCLUSIONS

Boundaries between the traditional phases of clinical therapeutic trials are increasingly becoming blurred, with phase I and II clinical trials often larger in size and increasingly combining therapeutic and toxicity endpoints. Recently, therapeutic agents have been approved by the FDA through phase I clinical trials alone. These changes bring added challenges to patient safety, with trial designs that require increasingly specialized and sophisticated interim data analyses.

Historically, the primary founding mission of the FDA was to provide consumer assurance of the safety of medical therapies, a mission that gradually evolved to include demonstration of efficacy. Above all, regulatory agencies should bear in mind the safety of trial subjects. In fact, recent changes in clinical trial design and purpose should still place the founding purpose of drug approval safety ahead of all others.

Given their size and the fact that real-world patients are used as subjects, most if not all phase III studies warrant independent monitoring by a DSMB, and DSMB involvement should be required and not merely recommended. Furthermore, the requirement for a DSMB should now also be extended to include many phase II and phase I clinical studies. Indeed, it may be more efficient for the FDA to describe which, if any, clinical trials should not require such an important safety aspect as part of their design.

As clinical trials become more complex and therapeutics more esoteric and specialized, the work of a DSMB requires increasingly experienced and safety-specialized members. Although it is impossible for all safety board participants to have experience and knowledge in all therapeutics, the qualifications of a "core" board member should no longer be left to the subjective and potentially biased decisions of parties associated with the investigative study, either as Steering Committee members or sponsor associates. To increase both the qualifications and independence

of DSMBs, there should be minimum requirements for training and experience that include didactic material as well as apprenticeships/mentorships with actual DSMBs. Establishing a registry of experienced DSMB members, their qualifications, their experience, and their potential conflicts of interest should be a priority in enhancing the quality and consistency of DSMBs. Ad hoc DSMB members should be considered when the studied therapy warrants highly specialized input, although the question of whether such members should be allowed voting status remains to be considered, because they may of necessity have some associations with the study or its sponsors.

Increasing the demand for DSMB monitoring will certainly increase workload. IRBs are both ill-prepared and underqualified to assume the specialized work of data and safety monitoring for studies that currently are not required to use a DSMB. Rather, both IRBs and DSMBs should work hand in hand to ensure that patient rights and safety are assured in clinical trials. To manage the increase in demand for DSMBs and interim data analysis, regulatory agencies could adopt the concept of semi-independent (ie, institutional) DSMBs such that DSMB experience can better be concentrated on DSMBs, and organizational and administrative functions can be consolidated for maximum economic and administrative efficiency.

The construction and/or modification of regulatory rules and guidelines is needed to provide the long-overdue widening of clinical trial safety monitoring, address the qualifications of DSMB membership, and define more efficient organization of institutional DSMB workflow for the purpose of enhancing the independence and consistency of DSMB decision making.

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