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Independent data monitoring committees: Preparing a path for the future

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Abstract

Independent data monitoring committees (IDMCs) were introduced to monitor patient safety and study conduct in randomized clinical trials (RCTs), but certain challenges regarding the utilization of IDMCs have developed. First, the roles and responsibilities of IDMCs are expanding, perhaps due to increasing trial complexity and heterogeneity regarding medical, ethical, legal, regulatory, and financial issues. Second, no standard for IDMC operating procedures exists, and there is uncertainty about who should determine standards and whether standards should vary with trial size and design. Third, considerable variability in communication pathways exist across IDMC interfaces with regulatory agencies, academic coordinating centers, and sponsors. Finally, there has been a substantial increase in the number of RCTs using IDMCs, yet there is no set of

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qualifications to help guide the training and development of the next generation of IDMC members. Recently, an expert panel of representatives from government, industry, and academia assembled at the Duke Clinical Research Institute to address these challenges and to develop recommendations for the future utilization of IDMCs in RCTs.

Randomized clinical trials (RCTs) are often overseen by a data monitoring committee (DMC), also known as a data and safety monitoring board. The concept was introduced in the 1967 National Heart Institute–sponsored Greenberg Report.¹ Subsequently, the Food and Drug Administration (FDA) issued an initial draft guidance in 2001, updated in 2006,² suggesting standards for DMCs in trials subject to FDA oversight.

Critical issues have emerged regarding the future of DMCs, including uncertainty about when a DMC is necessary or preferred, variation in roles and responsibilities across trials, a lack of standards for operating procedures, variability in communication pathways between DMCs and other trial stakeholders, the increased use of DMCs, and the lack of a formal mechanism to train the next generation of DMC members. Therefore, representatives from government, industry, and academia convened at the Duke Clinical Research Institute to discuss the future of DMC activities. Among other conclusions discussed hereafter, there was agreement that the independent functioning of DMCs should be highlighted by referring to them as independent data monitoring committees (IDMCs).

Contemporary IDMC use

Initially, IDMCs were principally used for large outcome studies, mostly due to concerns that interim findings could indicate substantial benefit or harm and that these findings need to be independently monitored. However, IDMC use has expanded to smaller trials not powered to detect effects on clinical outcomes. In a recent analysis of 662 RCTs published in high-impact medical journals in 2000, 18% reported IDMC use; factors associated with IDMC use included examination of survival outcomes, multicenter involvement, and larger trial size.³ Another study examined interventional RCTs from cardiovascular, mental health, and oncology specialties registered on ClinicalTrials.gov from 2000 to 2010.⁴ Of 79,413 trials, the IDMC status variable was missing for 41.2%. Among 46,699 trials reporting on IDMC status, 42.6% indicated that an IDMC was used, a marked increase from the year 2000 observation. Wide variation in IDMC use was reported according to funding source, with a far greater likelihood of use in trials sponsored by the National Institutes of Health (NIH) versus other entities (adjusted odds ratio = 9.09; 95% confidence interval: 7.38–11.34). Finally, IDMC use varied by trial phase, with a 17% lower rate of use in phase 1 to 2 trials compared with phase 3 trials (adjusted odds ratio = 0.83; 95% confidence interval: 0.76–0.91). Given that such early studies are different from the trials considered in the Greenberg Report and FDA guidance, no consensus exists regarding standardization of continuous safety monitoring in contemporary trials.

Unpublished ClinicalTrials.gov data presented at the meeting revealed that among 18,802 clinical trials registered from 2011 to 2012, IDMCs were used in 35% of industry-funded trials, 68% of NIH-funded trials, and 47% of trials funded through other mechanisms.⁵ The numbers of studies with IDMCs were similar in drug/device (45%) and nondrug/device

interventional trials (41%). Larger trials were more likely to use an IDMC: among 11,796 trials with more than 50 participants, 47% reported IDMC use, versus 36% of 5,186 smaller trials. These results highlight the increasing variability in IDMC use across contemporary clinical trials. Because the volume of clinical trials appears to be growing rapidly (approximately 330 registered each week on ClinicalTrials.gov), the role of IDMCs will increasingly be scrutinized.⁶

Notwithstanding variation in IDMC use across trials, meeting participants did not agree on which trials might benefit from IDMC use. According to the FDA guidance for clinical trial sponsors, although all trials require safety monitoring, an IDMC “is not required or recommended for most clinical studies.”² The FDA requires IDMC use for trials conducted without true informed consent but recommends discretionary IDMC use in other cases according to the following factors: safety risk, practicality of IDMC review, and whether IDMC use will help ensure scientific validity (Table I). Thus, the FDA guidance generally recommends limiting IDMC use to large, multicenter studies examining interventions that may prolong life or reduce risk of major adverse health outcomes, or to RCTs comparing mortality or nonfatal outcomes reflecting major morbidities. This view was supported by FDA participants at the meeting.

However, the high rate of IDMC use suggests that the NIH, academia, and perhaps, industry support have more frequent IDMC involvement. Many local institutional review boards (IRBs) and the clinical research community expect independent safety monitoring for site participation in trials of all sizes. Given IDMCs’ apparent range of roles, the optimal use of IDMCs within clinical trials requires further discussion.

Reconsidering the IDMC role

A general consensus, although opinions vary, is that the primary responsibility of an IDMC is to monitor the overall safety of RCT participants, focusing on serious outcomes, where unblinded comparisons are needed. In contrast, rare safety events can be handled by reporting to IRBs. In carrying out this responsibility, IDMCs have typically performed interim evaluations of accrued data to evaluate safety end points and adverse events. Although investigators and site IRBs are also responsible for participant safety and can examine individual cases, their interpretations of events that are not obviously drug-related are limited by lack of access to unblinded, aggregate data. Independent data monitoring committees evaluate aggregate data across the entire trial and may review unblinded data when necessary.

The potential for a broader role of IDMCs was noted at the meeting. Historically, IDMCs have been used to arbitrate safety, interim efficacy, and futility analyses that may lead to recommendations for adapting trial design or termination, even if safety concerns are not detected.^{7–9} These activities are most relevant to large outcome trials or smaller, shorter trials in high-risk participants. Recently, IDMCs have also been asked to monitor issues related to trial operational conduct, data quality, and end point adjudication quality. These activities, typically based on blinded data, were previously performed by trial leadership committees.

Given these expanding roles, suggestions have been made to enact IDMCs in a “fit for purpose” manner, where the primary responsibilities of the committee are determined by trial type and design. For example, large, phase 3 trials would use a multidisciplinary IDMC with broad expertise for traditional safety monitoring and other roles that are becoming increasingly common. Drug-development programs might use a single, multi-disciplinary IDMC across concurrent studies of the same therapy to ensure consistency of safety monitoring and accumulation of study effectiveness results. Another model has been demonstrated in National Cancer Institute–sponsored trials that use a single IDMC for related trials investigating different drugs for the same disease state.¹⁰

There is also growing interest in safety monitoring over a whole development program, stimulated by the FDA’s change in rules for prompt reporting of serious unexpected adverse events. Doing this properly may involve a single, multidisciplinary committee that would consider all studies of the new therapy and examine safety data from all trials within the program but would not perform efficacy assessments. This type of committee, potentially termed a *safety assessment committee*, would convene more frequently than a classic IDMC and would contain members with clinical safety expertise. Such committees—which typically include firewalled clinical, biostatistical, and safety employees from the trial sponsor as well as external members—have already been implemented by some pharmaceutical companies. Importantly, this approach differs from that delineated in the current FDA guidance, which refers mostly to large, phase 3, clinical outcome trials.

IDMC composition and member roles and responsibilities

Meeting participants agreed that IDMC composition should be multidisciplinary, with all members contributing unique and necessary skillsets and should include clinician experts in the field of study and fields relevant to specific safety concerns. Members should be experienced clinical trialists who can quantitatively analyze and interpret data. An IDMC should also include a biostatistician experienced in trial design and interpretation as well as a nonvoting, independent biostatistician who analyzes data and prepares data reports.

Prior IDMC experience is valuable, as members must understand that random fluctuations in data may not reflect the truth, and performing too many interim data analyses can alter the probabilistic assessment of treatment effects, with potentially serious clinical consequences when inappropriate conclusions are drawn. Members should also be familiar with event adjudication and trial operations such as “data cleaning” to inform data interpretation based upon site investigator reported versus independently adjudicated events. Because a recommendation for early trial termination can have significant consequences, members should also consider not only statistical boundaries and stopping rules but also nonstatistical factors, including clinical context and biologic plausibility of the findings.

The IDMC chairperson plays a critical role and is tasked with many responsibilities, including reviewing events or data between scheduled meetings, arbitrating differences of opinion, and periodically evaluating members’ conflicts of interest. The chairperson must also manage group dynamics to allow for full discussion of data and should ensure that prespecified communication pathways are maintained.

Particularly difficult issues to arbitrate include independence and conflicts of interest. “Independence,” a prerequisite for IDMC participation, connotes both financial and intellectual separation from the trial sponsor and study investigators to allow for unbiased assessments. A conflict of interest arises when an IDMC member has a stake in the trial outcome. Completely eliminating conflicts of interest may not be possible or desirable if the goal is to draw on the wisdom of experienced members. Perhaps for this reason, parameters of independence and conflicts of interest for IDMC participants remain poorly defined. For example, due to a relatively small pool of eligible IDMC members, service on multiple, simultaneous IDMCs is common. This could represent a conflict of interest if a given member is also serving on an IDMC for a competing agent. However, knowledge of a similar compound or trial structure might be advantageous in guiding attention and vigilance toward previously encountered safety concerns. Ascertainment and management of conflicts of interest within an IDMC is complex and requires a transparent approach.

Charter

Defining responsibilities

Drafting a clear IDMC operating plan is critical to ensuring effective and optimal committee functioning, but this task is not always performed. A well-developed charter allows for structured consideration of critical concepts, improves effectiveness, bolsters trial integrity, and may even provide protection against legal liability. Common elements that should be considered for inclusion in charters are listed in Table II.^{10–12} To date, no standards for charters have been endorsed for clinical trials; consensus among meeting participants was that this has resulted in substantial variation in IDMC operations.

Communication pathways and strategies

Independent data monitoring committees must communicate with multiple stakeholders, but lines of communication may be complex and ambiguous (Figure). Communication pathways should be prospectively delineated within the IDMC charter. Sponsor type can affect the communication and reporting structure. In most NIH-funded trials, the IDMC is appointed by and reports to the NIH. Independent data monitoring committee recommendations are thus passed indirectly to investigators through the NIH. In contrast, industry sponsors, preferring to be dissociated from IDMC activities to minimize conflicts of interest, may allow a committee of academic investigators to appoint IDMC members or to participate in a collaborative process to establish it. In this situation, the IDMC directly reports to investigators on the steering/executive committees and advises the sponsor. A variation would be a joint-reporting mechanism of the IDMC to the executive committee chair and a senior representative of the sponsor. Communication between IDMCs and regulatory agencies is typically conducted via trial sponsors, who are ultimately responsible for trial conduct, but direct communication may sometimes be necessary.¹³ In addition, the IDMC may directly contact site IRBs about safety concerns or informed consent form updates.

Given the complex communication pathways, clear lines of reporting are important for effective IDMC functioning. Each trial should have a clearly defined primary reporting structure and communication mechanism detailed in the IDMC charter. In cases where the

investigators or sponsor disagree with IDMC recommendations, a plan of recourse, perhaps through an independent arbitration board, can be helpful. It is also critical that the basis for an IDMC recommendation be clearly articulated to provide transparency and insight about rationale. Therefore, meeting participants proposed that IDMC decisions/recommendations and official meeting minutes be formally published after trial completion. In addition, communication timelines should also be delineated within the IDMC charter to ensure rapid initiation of corrective actions and to minimize potential risk to enrolled participants.

Legal issues: contracts and liability

Financial and legal issues are crucial but often overlooked aspects of IDMC participation and are often not addressed in IDMC charters.¹⁴ Given the time and effort required for IDMC service as well as the need to attract qualified individuals, financial compensation for IDMC participation is reasonable. However, to avoid perceived conflicts of interest with trial sponsors that often pay IDMC members directly, alternatives for organizing IDMC payments should be considered. These include payment via an academic coordinating center (if one is used), an independent body established and administered through regulatory agencies (with proportional contribution from sponsors based upon needs for IDMC participation), an independent clinical research organization that handles functions such as meeting arrangements, or payment to the respective members' academic institutions for salary supplementation. These approaches ensure payment oversight by a body charged with other societal oversight functions.

Independent data monitoring committees protect sponsors against litigation regarding trial safety issues but face liability for their own actions. Independent data monitoring committee responsibilities vary across trials, and difficult decisions are often based on dynamic statistical data, judgment, and experience without a clear right or wrong recommendation. Independent data monitoring committees are also obligated not only to enrolled patients but also to future patients, study investigators, sponsors, and regulatory agencies. An IDMC decision may therefore be viewed as benefiting one group at the expense of another. In the context of a litigious society and close scrutiny by peers, regulatory agencies, patients, and the public, IDMC members face a risk of legal action for their decisions, and this can be an important deterrent for IDMC service.¹⁰

Current mechanisms for protecting IDMC members against litigation are sparse and poorly detailed within IDMC charters. Sponsors or employers could provide legal counsel in the event of a lawsuit, which may defray some cost. However, if a sponsor and IDMC member enter into an adversarial legal relationship, an inherent conflict of interest exists in having the sponsor-employed counsel also representing the IDMC member. More complete protection is afforded by third-party indemnification, which covers defense costs and financial liability. Although indemnification can be provided by sponsors, it is usually not offered through academic institutions that may view IDMC service as external consulting.¹⁵ Meeting participants recommended that indemnification language within IDMC charters should allow members to choose independent legal counsel at the expense of the sponsor or another entity and that nondisclosure agreements should not prohibit discussion of

indemnification terms. These legal issues threaten the viability of IDMCs, and guidance should be provided.

A call to action

Critical need for experienced members

The anticipated increasing demand for IDMCs highlights the shortage of available, experienced IDMC participants. This mismatch may arise from excessive use of IDMCs in settings where other organizations could perform this function combined with a lack of systematic training for IDMC participation. Independent data monitoring committee participation requires a unique set of knowledge and skills and has been described by Drazen¹⁶, editor of *The New England Journal of Medicine*, as “the toughest job in clinical medicine.” As such, IDMC members are typically senior investigators who have extensive experience, but the “next generation” of members remains relatively unidentified.

Another important issue is the perceived lack of academic value for IDMC service,¹⁵ which may be considered personal consulting work and is rarely associated with conventional academic output. To maintain independence, IDMC members are sequestered from trial activities in which their institutions are involved and may be prohibited from participating in other trials sponsored by the same company or in the same field. This need for independence could exclude IDMC members from activities deemed valuable for consideration of promotion and tenure. Such disincentives may contribute to a decreasing number of interested, qualified IDMC members and highlight the need to reconsider the value of IDMC participation at academic institutions.

Training the next generation

No formal infrastructure or expectations for training IDMC members exist, which could result in a shortage of qualified participants. Currently, IDMC experience is often a prerequisite for IDMC participation, resulting in selection of the same IDMC members. A “pipeline” system is needed to develop new IDMC participants. Formal didactics will likely be a necessary component of such training.

The vision for such IDMC training starts with the basic knowledge of clinical trial operations, focuses next on the specific skills and knowledge required for IDMC participation, and then addresses advanced issues related to IDMC functions and predictive and decision sciences. Web-based education might provide a more convenient and accessible option. Case-based studies would comprise an important component of IDMC training, highlighting the educational value of required posttrial IDMC publications regarding decision-making strategies and rationale. Similarly, real data sets from completed trials could allow for data simulations for mock meetings. Coursework should also be supplemented with real-world experience, obtained perhaps through apprenticeships and mentorships. Finally, a certification process will probably be needed, perhaps via cooperation among regulatory, industry, and academic stakeholders.

Conclusions

Randomized clinical trials assess risk-and-benefit balances of novel therapies but have covered only a fraction of relevant questions. The continued ability of RCTs to meet society's needs with assurances for safety and integrity depends upon reinvigoration of the IDMC construct. Given the variability and heterogeneity in IDMC use and conduct, stagnant supply of qualified participants, lack of formal training, and increasing utilization of IDMCs, there is concern that IDMC credibility could limit trial conduct. The path forward is not entirely clear, but meeting participants agreed that broad appreciation of the unmet need for IDMCs and creatively thinking about educating future generations of IDMC participants will be necessary. Recommendations generated from the meeting are summarized in Table III. It is hoped that these recommendations stimulate development of concrete approaches to address these important issues.

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Appendix A. Think tank meeting participant list

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Figure.

Independent data monitoring committee communication pathways. *ARO*, academic research organization; *CRO*, commercial research organization; *EC*, executive committee; *IDC*, independent data center.

Table INonbinding FDA guidance recommendations for IDMC use in RCTs²

Factor to consider	IDMC use
No informed consent	Required
High risk to trial participants	Consider
Practicality of IDMC review (eg, may be impractical for short trial unless high risk)	Consider
Presence of IDMC desired to ensure scientific validity	Consider
Trial of any size examining mortality or major morbidity	Recommended
Trial of early stage of product development	Generally unnecessary
Trial examining less serious outcomes (eg, symptom relief)	Generally unnecessary

Table II

Common elements for inclusion in an IDMC charter

Elements	Example issues for consideration
Primary responsibilities of IDMC	<ul style="list-style-type: none"> • Assess safety and efficacy • Monitor overall trial conduct • Provide recommendations on patient selection and enrollment, data management, quality control
Membership	<ul style="list-style-type: none"> • Areas of expertise needed • Conflicts of interest (financial and other) • Role of the chair to stay apprised of conflicts of interest and to review data between meetings
IDMC meetings	<ul style="list-style-type: none"> • Frequency of meetings (eg, based on timing or number of events) • Early review of data for potential safety signal • Formal interim analysis • Who will conduct analyses? • Unscheduled meetings
Confidentiality and communication pathways	<ul style="list-style-type: none"> • Closed versus open sessions • Recording and approval of IDMC meeting minutes • Process and pathways for reporting recommendations after meetings • Timeliness of communicating recommendations
Statistical guidelines	<ul style="list-style-type: none"> • Stopping rules for early termination for benefit, harm, or futility • Guidelines for adjusting sample size or follow-up duration to increase power • Blinded versus unblinded assessments of data
Contracting	<ul style="list-style-type: none"> • Details regarding agencies that will handle contracting for members • Information regarding legal liability and indemnification for members

Adapted from Ellenberg et al¹⁰.

Table III

Recommended next steps to address current IDMC issues

1	Delineation of optimal communication pathways for the IDMC with various stakeholders to standardize trial conduct
2	Development of formal educational programs to train the next generation of IDMC members, including tiered didactics with increasingly complex topics appropriate for not only IDMC participants but also clinical trial operational personnel
3	Development of mentoring and apprenticeship programs for IDMC trainees
4	Publication of IDMC decision-making rationale after trial conclusion to enable normative understanding of IDMC activities for training purposes and to provide transparency regarding trial proceedings
5	Advocacy for formal acknowledgement by academic institutions of the value of IDMC service and, consequently, awarding of academic credit for such participation
6	Provision of standardized indemnification policies by trial sponsors for IDMC members to ensure that potential legal liability does not continue to serve as a disincentive to IDMC participation