The Multi-Regional Clinical Trials Center of Brigham and Women's Hospital and Harvard Bioethics Collaborative

Tuesday, October 5, 2021 | 1:00PM-4:00PM ET
Virtual Meeting

Navigating Interactions Between DMCs and IRBs
Meeting Summary

Background

Institutional Review Boards (IRBs) and data monitoring committees (DMCs, also termed data and safety monitoring boards, or DSMBs) play important roles in research oversight. IRBs are responsible for protecting research participants by reviewing the study at initial and periodic review and ensuring that risks are minimized and appropriately balanced with benefits, and that key features of research are adequately disclosed to participants.[1,2] DMCs play a role in protecting participant safety, ensuring the integrity and credibility of a trial, identifying beneficial treatments early, and advising termination of a trial if a treatment is or is likely to be ineffective. DMCs often have access to unblinded data and are able to perform interim statistical analyses to fulfill their oversight responsibilities, whereas IRBs typically cannot.

The extent to which IRB and DMC responsibilities overlap or diverge is often difficult to navigate in practice. Both IRBs and DMCs may and sometimes do pause studies out of safety concerns, either based on single safety events or what may appear to be a higher than anticipated rate of adverse events in a study. Responsibility for the interim analysis of study data for futility and/or efficacy typically rests with DMCs, while accrual is monitored by both.

Further complicating the division of labor between IRBs and DMCs is the fact that these parties rarely communicate directly.[3-5] DMC recommendations are typically communicated as advisory opinions to the sponsor or sponsor-investigator who in turn evaluates them, decides how to proceed, and shares that decision with the IRB as pertinent.[4] IRBs may not always be informed of the rationale or basis for DMC recommendations or sponsor decisions, which can in turn complicate the IRB's ability to satisfy its obligation to ensure adequate data and safety monitoring during a study.

The October 5 meeting of the MRCT Center Bioethics Collaborative convened IRB members, DMC members, sponsors, investigators, academicians, and patient advocates to reflect on the responsibilities of IRBs and DMCs, including their roles and responsibilities in practice and how these responsibilities should inform communication between these parties. Bioethics Collaborative attendees noted that the topic of IRB and DMC communication has been largely overlooked, and DMC training programs typically do not discuss IRB-DMC communication.

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Meeting Summary

Attendees at the Bioethics Collaborative noted the variable quality of DMCs. Some participants reported experiences with DMCs that are appropriately constituted and capable of providing high-quality data monitoring. Other participants voiced a number of concerns about the ability of certain DMCs.

Unsurprisingly, attendees accustomed to interacting with high-quality DMCs did not perceive a need for improvement in IRB-DMC communication. In their experience, DMCs successfully executed their oversight responsibilities, systems were in place to ensure that the IRB received DMC recommendations from the sponsor, and the added value of direct communication between the DMC and IRB(s) was unclear. A practical example of indirect but reliable communication was discussed during the Bioethics Collaborative. The example disease network:

- Educates DMC members
- Sends the DMC membership roster (including member expertise), charter, and if requested, financial disclosures to the IRB
- Requires that sponsors forward DMC recommendations to the IRB (in addition to and independent of the sponsor decision in response to the recommendation)
- Appoints a liaison to help each DMC navigate unexpected issues

Some attendees who serve as members or chairs of IRBs or are responsible for institutional human research participant protections, however, saw value in IRB-DMC communication even when a high-quality DMC is providing oversight. For example, DMCs often contain a depth of discipline-specific expertise that IRBs may lack. Additionally, increasing communication between DMCs and IRBs may help IRBs ask questions about and better understand DMC recommendations and their rationale, allowing IRBs to be more well-informed and confident in providing continued trial oversight.

Those more skeptical of the quality of DMCs and DMC review perceived a compelling need to increase communication between IRBs and DMCs. Some attendees noted that there are no formal requirements, training, or international standards for DMCs, and some expressed skepticism over whether DMCs know how to adequately satisfy their responsibilities. Sponsors are responsible for selecting and educating DMC members, and companies and academic institutions may both struggle to convene quality DMCs. When there is uncertainty regarding DMC quality, IRB-DMC communication can help ensure that participants are adequately protected.

Despite the arguments in favor of IRB-DMC communication, some attendees hesitated to endorse direct interactions between these parties while a study is ongoing. First, the scope of

the information that could or should be shared with the IRB is unclear. The IRB would likely be overwhelmed by the volume and complexity of the information that the DMC receives. Further, direct communication could be a potential source of misunderstanding and/or unblinding for IRB members, leading to potential bias and even error in oversight decisions. At the same time, the goal of providing IRBs with sufficient understanding of the DMC's rationale for their recommendations can be achieved by careful communication; IRBs need not receive or analyze data themselves.

A different discussion concerned whether IRBs should have access to and review the DMC charter and/or DMC membership and/or chair prior to studies commencing. As a first step, IRBs should review the data monitoring plan of a study to determine its adequacy and freedom from bias or influence. That process will involve the review of any proposal for the sponsor to establish a DMC. Beyond that, however, there was generally little agreement on what standards or expectations should be relied upon to review the data monitoring plan. This is an area for potential future work.

Whether the IRB should opine on committee membership (e.g., individuals with statistical, disease area, and/or bioethical expertise) or about the relationships and conflicts of interest between DMC members and the sponsor was discussed. Some meeting attendees felt that DMC members should be identified in order to allow the IRB to assess whether a DMC is appropriately constituted. Other attendees pointed out that some DMC members may not want their identity disclosed generally, as a safeguard against patient groups, investors, and others asking them sensitive questions about a trial. There appeared to be agreement that providing the IRB with the qualifications of DMC members and their relation to the sponsor, even if not their identities, would generally suffice for the IRB's purposes.

Attendees suggested that the sponsor should share the DMC charter with the IRB. However, the sponsor should redact statistical details that might unintentionally permit the IRB or other parties to simulate the trial and discern confidential information about trial progress. Given concerns about statistical analysis and membership confidentiality, attendees discussed creating a checklist about DMCs for the sponsors to share with IRBs that includes important but not confidential information. The checklist could include items such as the number and timeline of DMC meetings per year, what events will trigger ad hoc meetings of the committee, the composition of the DMC and the expertise of its members, and whether there is a process for mitigating potential conflicts of interest. IRB study approval could be contingent on the sponsor sharing the DMC checklist information.

Investing in DMC member professional education and development was an additional suggestion to improve the quality, number, and experience of DMC oversight. Many DMC members have not been formally trained for DMC service. There is also a lack of community representation on DMCs, particularly in multi-national trials. Attendees mentioned that even

large and well-established sponsors experience high turnover rates, and continuing education would therefore be important.

In addition to increasing DMC trust and transparency prior to study start, attendees discussed whether there should be a system or method for resolving issues when the DMC, IRB, or sponsor have differing views about the best course of action or uncertainty about whether oversight responsibilities are met. The IRB is in a difficult position, for example, if a sponsor rejects the DMC's recommendations but declines to explain their rationale. Further, DMC members, given confidentiality provisions, typically have few options for recourse beyond resigning in protest or airing their frustration publicly. One potential solution would be a DMC charter element that permits the DMC to communicate directly with the IRB, and a concrete process by which this could happen, if the DMC is concerned with the sponsor's actions. Alternatively, a liaison might be appointed to convene discussions between the DMC and IRB. At least one disease network has successfully implemented this approach, and the liaison has helped mediate direct IRB-DMC communication as well as forwarded requests from the IRB to the DMC.

When building pathways for IRB-DMC communication, stakeholders should consider the restrictions placed on communication by DMC member confidentiality agreements. The language of the confidentiality agreement will determine whether direct communication is foreclosed, but often, even if permissible, DMC members are uncomfortable. Stakeholders should also consider the timeliness of communication, to expedite recommendations and resolution of questions. Time delays are particularly problematic when there is a safety concern.

Miscellaneous Topics

Bioethics Collaborative attendees discussed several other topics. The US Food and Drug Administration (FDA) customarily requires at least two years of controlled data in order to approve the drug. On (rare) occasions, this may constitute a sponsor reason to override a DMC recommendation to stop early for efficacy, as the continued data is necessary for regulatory approval. Rarely, FDA may advise the sponsor (or the DMC) in order to establish the evidentiary basis for regulatory review. Sponsors and DMCs need to consider not only regulatory requirements but what will constitute sufficient evidence to change clinical practice.

Another topic discussed was the fact that sponsor representatives are sometimes allowed to attend closed DMC meetings, particularly for NIH-funded studies, potentially raising concerns for study integrity and affecting the DMC's ability to make recommendations free of influence. Attendance by NIH employees felt qualitatively different than commercial sponsors attending closed meetings.

Finally, it was pointed out that discussion at the Bioethics Collaborative assumed a focus on registered clinical trials. Some pragmatic clinical trials, which test approved interventions in the real world, also need DMCs to ensure data quality and study integrity and perform interim analyses. Any conclusions from the Bioethics Collaborative should be reexamined in light of pragmatic and other types of trials that require DMC and IRB oversight.

Potential Future Work

- Revisit DMC training programs and determine whether they should be updated with information on IRB-DMC communication.
- Draft standards and processes for sharing information between the DMC and the IRB at initial review and during study conduct.
- Draft a deliverable describing the tensions that can arise when navigating communication between DMCs and IRBs.
- Share disease network models for IRB-DMC communication with industry sponsors and ask sponsors to evaluate how effectively the models would translate to their context.

References

1. Criteria for IRB approval of research, 45 Code of Federal Regulations § 46.111 (2018).

2. Criteria for IRB approval of research, 21 Code of Federal Regulations § 56.111 (2018).

3. Taylor HA, Chaisson L, Sugarman J. Enhancing communication among data monitoring committees and institutional review boards. *Clin Trials*. 2008;5(3):277-282. doi:10.1177/1740774508091262.

4. Eckstein L. Building a More Connected DSMB: Better Integrating Ethics Review and Safety Monitoring. *Account Res*. 2015;22(2):81-105. doi:10.1080/08989621.2014.919230.

5. Grant AM, Altman DG, Babiker AB, et al. Issues in data monitoring and interim analysis of trials. *Health Technol Assess Winch Engl*. 2005;9(7):1-238, iii-iv. doi:10.3310/hta9070.