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The role of data and safety monitoring boards in implementation trials: When are they justified?

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Abstract

The National Institutes of Health requires data and safety monitoring boards (DSMBs) for all phase III clinical trials. The National Heart, Lung and Blood Institute requires DSMBs for all clinical trials involving more than one site and those involving cooperative agreements and contracts. These policies have resulted in the establishment of DSMBs for many implementation trials, with little consideration regarding the appropriateness of DSMBs and/or key adaptations needed by DSMBs to monitor data quality and participant safety. In this perspective, we review the unique features of implementation trials and reflect on key questions regarding the justification for DSMBs and their potential role and monitoring targets within implementation trials.

As implementation scientists, we became interested in the purpose and role of data and safety monitoring boards (DSMBs) for implementation trials while conducting effectiveness-implementation trials [1,2]. Currently, we are conducting an implementation trial of evidence-based interventions to reduce cardiovascular risk factors [1]. This trial is part of ‘ImPlementation REsearCh to Develop interventions for People Living with HIV’ (PRECluDE – RFA-HL-18-007): a National Heart, Lung, and Blood Institute (NHLBI)-funded study of implementation strategies for evidence-based interventions to reduce cardiovascular or pulmonary risk for people living with human immunodeficiency virus (HIV).

When we reviewed the DSMBs published literature, we found no articles that specifically discussed DSMBs for implementation trials. In this perspective, we reflect on this topic beginning with DSMBs’ purpose and history as well as the National Institutes of Health (NIH) and the NHLBI requirements, DSMBs’ relevance to implementation trials and whether DSMBs should be universally required. Additionally, we include a discussion of expanding the concept of individual participant risk to include risk to organizations and staff. We conclude with suggestions for implementation issues and outcomes that might be considered for advancing the field and enhancing the safety not only for patients, but also for organizations, settings, and staff participating in studies to implement evidence-based practices.

DSMB Purpose, History, and Policies

DSMBs are committees of independent members with methodological and content expertise relevant to the particular trial that conduct interim monitoring, analysis, and oversight [3]. Thus, NIH policy requires DSMBs where there is heightened risk to individual participants. Notably, only individuals are addressed by The Common Rule, US 45 Code of Federal Regulations 46.102(e) [4]. The primary purpose of a DSMB is to ensure the safety of study participants [5] where study participants are generally limited to individuals who are directly impacted by the intervention. A secondary purpose is to protect and preserve data quality in order to safeguard the interests of participants and to produce reliable scientific findings that justify ongoing risk to participants [6]. The DSMB’s role in conducting periodic benefit–risk assessments and their authority to recommend trial termination distinguishes them from other research oversight and advisory groups [7].

Although DSMBs may issue recommendations to improve participant protections and/or improve data quality and trial integrity, trial stoppage decisions are typically based on: (1) individual participant safety concerns; (2) overwhelming benefit; or (3) futility. DSMBs have a unique role in trial monitoring that is different from other oversight groups, for example, institutional review boards, ethics committees, or trial steering committees, in their access to
unblinded interim results [7]. One of the earliest DSMBs was estab-
lished in the late 1960s to monitor the University Group Diabetes
Project following concerns about drug safety and adequate mon-
itoring [8]. Subsequently, the Greenberg Report to NHLBI recom-

mended requiring DSMBs for large clinical trials [9].

Current NIH policy provides latitude in appointment of
DSMBs based on risk to participants:

All clinical trials require monitoring—Data and safety monitoring is required for all types of clinical trials . . . Monitoring should be commensurate with risks—The method and degree of monitoring needed is related to the degree of risk involved. A monitoring committee is usually required to determine safe and effective conduct and to recommend conclusion of the trial when signifi-
cant benefits or risks have developed or the trial is unlikely to be concluded successfully . . . Monitoring should be commensurate with the size and com-
plexity. Monitoring may be conducted in various ways or by various individ-

uals or groups, depending on the size and scope of the research effort. These
exist on a continuum from monitoring by the principal investigator or NIH
program staff in a small phase I study to the establishment of an independent
data and safety monitoring board for a large phase III clinical trial [10].

NIH defines a phase III clinical trial as a, “study to determine
efficacy of the biomedical or behavioral intervention in large groups
of people (from several hundred to several thousand) by comparing
the intervention to other standard or experimental interventions as well as to monitor adverse effects, and to collect information that will allow the interventions to be used safely” [11]. Arguably, most
implementation trials do not fit this definition because the usual intent of implementation trials is less on evaluation of individual
effectiveness and safety, although there are potential exceptions for some hybrid trials that primarily evaluate effectiveness during
implementation [12].

Current NHLBI policy is more expansive. NHLBI requires
DSMBs “for all clinical trials that involve: investigation of a
research question having direct implications for clinical care
and/or public health (including all phase III trials), and/or a
high-risk intervention, and/or a highly vulnerable population” [13]. Further, NHLBI requires DSMBs for multicenter trials and/or trials conducted under a contract or cooperative agreement [13]. Thus, these implementation trials funded by NHLBI must have DSMBs regardless of risk to individual participants. However, NHLBI policy is silent regarding the explicit purpose of this heightened monitoring in these contexts, much less what
should be monitored during implementation trials.

**Are DSMBs Relevant to Implementation Trials?**

The term “implementation” does not appear in NIH’s “Important Clinical Trial-Related Terms.” Nonetheless, implementation research is defined by NIH “. . . as the scientific study of the use of strategies to adopt and integrate evidence-based health inter-
ventions into clinical and community settings to improve individual outcomes and benefit population health” [14]. Thus, an implement-
tation trial uses a clinical trial design to evaluate strategies to adopt and integrate evidence-based interventions into practice. In con-
trast, pragmatic trials assess the effectiveness of interventions under real-world conditions [15]. Implementation trials often
assess both effectiveness and implementation to varying degrees,
that is, hybrid trials [12]. In implementation trials, the question is which strategies promote uptake of these evidence-based interventions, under what circumstances and why and whether findings of effectiveness can be embedded and sustained in real-world settings. Given that implementation trials often involve the use of evidence-based interventions, the risk to individual

participants is often minimal, approximating the same level of risk
associated with the delivery of routine clinical care [16]. Based on
NIH guidance, DSMBs would not be generally required for clinical
trials involving minimal risk.

The unique features of many implementation trials hinder the
use of DSMB stopping rules. Primary implementation outcomes
(e.g., acceptability, adoption, appropriateness, feasibility, implemen-
tation costs, reach, penetration, and sustainability) are commonly
assessed using mixed methods [16]. The use of stepped wedge
designs often limits longitudinal assessments to existing data. The
“messiness” of multiple measures that are qualitatively and quanti-
tatively assessed hinders the development of simple stopping rules. Effectiveness is often assessed in implementation trials using existing
data (e.g., blood pressure reading or laboratory data) from electronic
medical records rather than from direct assessment of individual
participants. Adverse events for individual participants, resulting
from the evidence-based intervention, are often not routinely
collected. Among oversight groups, DSMBs have a unique role in
their access to potentially unblinded results. However, this role is
limited in the context of an implementation trial, where assessments
often focus on group-level effectiveness and implementation proc-
cesses, rather than individual-level, relative, benefit-to-harms. Many
implementation trials do not involve the collection of sufficient,
actionable, real-time data needed to inform DSMB recommenda-
tions for trial termination based on individual harm, let alone over-
whelming benefit or futility.

**What Is the Role of DSMBs in Implementation Trials?**

Based on the principle that the intensity of monitoring be commen-
surate with risk, it is reasonable to question whether DSMBs are
generally relevant for monitoring participant safety in implementa-
tion trials. Potentially, this requirement runs the risk that participant
protections and monitoring result in “over protection of the rights
and interests of patients in some cases and under-protection in
others?” [17] Thus, implementation trial participants are potentially
overprotected, while patients exposed to major changes in health
system policies or use of off-label medications might be under-
protected.

When it comes to implementation trials, NHLBI policy does
not clearly articulate what DSMBs should be monitoring and under
what circumstances, how such risks should be monitored (rather
than by whom) and what specific risks to individual participants
or the trial itself warrant more intensive monitoring. Should
DSMBs for implementation trials shift their primary focus from
monitoring benefit–risk for participants to monitoring data quality
and trial integrity? If so, how does this requirement translate into
stopping rules for an implementation trial? Should implementa-
tion trials be required to collect adverse events from participants
related to the evidence-based intervention even when risk is
minimal? How should DSMBs operationalize monitoring for
implementation trials, beyond trial accrual, dropouts, data quality,
and missing data? What stopping rules should be implemented in
this context? Most importantly, what is the evidence that DSMBs
for implementation trials reduce risk to participants or improve
data quality and trial integrity?

**Risk to Organizational Participants in Implementation Trials**

Implementation trials are often conducted at the organization
or practice level through cluster randomization and may pose

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potential risk to organizational participants [18–20]. These may be indirect and collateral participants in pragmatic clinical trials that are directly affected by the implementation of the interventions [21]. Smalley defines “indirect participants” as “...individuals who are (1) not identified as direct participants and (2) whose rights and welfare may be affected by the intervention through their routine exposure to the environment in which the intervention is being deployed” and “collateral participants” as “[P]atient groups and other stakeholder communities who may be otherwise affected by the occurrence and findings of the pragmatic clinical trial” [21]. For example, the implementation of an intervention or practice could divert attention and resources, leading to potentially diminished access or quality in other areas [22].

An implementation trial could potentially adversely impact workflow and workforce, wherein clinicians and staff may be indirect participants during a study and collateral participants during broader dissemination of study results. In theory, these organizational-level harms could be monitored using routinely gathered administrative data or through data collected during the implementation processes, such as quality metrics not related to the study, staff turnover, and patient access. This is a specific example of the more general principle of the “unanticipated consequence of purposive social actions” [23]. Significant differences in any of these measures between those randomized to different treatment arms may require a priori development of early termination decision rules similar to those carried out at the patient level [24], with interim monitoring for these types of organizational- and staff-level adverse outcomes. However, actionable DSMB decisions are likely limited by statistical power for organizational-level events, unique contextual factors, few validated measures of organizational harm, and stepped wedge designs involving staggered rollout that hinder real-time direct comparisons based on actionable data. Moreover, groups and organizations are not considered research subjects under the Common Rule [4], possibly excluding them from oversight by DSMBs who are charged with protection of individual participants. Table 1 summarizes the challenges for DSMBs and future considerations.

**Reflections Going Forward**

To spark discussion, we make the following suggestions. First, we suggest that NIH clearly distinguishes between implementation trials and phase III clinical trials of effectiveness to minimize any potential confusion among investigators regarding the scope of NIH policy on DSMBs.
Second, we suggest that NHLBI amend its current policy that universally requires DSMBs for multisite, implementation trials, and those funded through contracts and cooperative agreements. Given the dearth of data regarding the role of DSMBs for implementation trials, we propose that NHLBI defers to local institutional review boards to make individual determinations based on the justifications within proposals to ensure that DSMB appointment is commensurate with the risk, size, and complexity of the specific implementation trial. Since this determination is likely to be made after funding, we propose that NHBLI sets aside additional funding for DSMBs.

Third, we suggest that NIH promote the collection and monitoring of data addressing potential, unintended consequences for indirect and collateral participants, such as organizations and staff participating in implementation trials. Such data would inform the potential role for DSMBs in implementation trials, in addition to informing the science regarding not only the benefits, but also the potential harms of implementation strategies. Last, we encourage NIH to fund studies explicitly designed to assess whether DSMBs affect safety, data quality, or trial integrity in the context of implementation trials, including potential cost-effectiveness and cost–benefit analyses that could inform future DSMB policy and training.

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References

8. Meinerz CL. History of treatment effect monitoring. The Johns Hopkins University, Bloomberg School of Public Health, Department of Epidemiology [Internet], 2003 [cited Dec 12, 2019]. (https://jhuccs1.us/clm/PDFs/His{t_Sld.pdf)