BEHIND CLOSED DOORS: THE DATA MONITORYING BOARD IN RANDOMIZED CLINICAL TRIALS

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SUMMARY
Many randomized clinical trials include a data and safety monitoring board (DSMB) that is responsible for reviewing accruing data, monitoring performance of the trial, assuring safety of the participants in the trial, and assessing the efficacy of treatment. The DSMB often makes recommendations about continuation of the trial or alteration of the protocol. Although such boards are very influential in both the conduct and interpretation of randomized clinical trials, there is no standard mode in which DSMBs operate nor do they routinely report publicly about their deliberations. This paper describes the composition of DSMBs as well as their functions. It concludes with a series of questions that needs to be addressed to ensure that the DSMBs operate effectively.

1. INTRODUCTION
Imagine a scientific methodology that bases its experimental technique on a technology that alters sample size, modifies the study design, and provides guidance to interpretation of data, but which the methods sections of papers rarely mention and to which papers rarely allude at all. Further, while some scientific papers describe the existence of the technology and a body of literature discusses one important technical aspect of the approach, the literature is virtually silent about the details of the method. If the experiments that used this method concerned chemical reactions, physical parameters, or laboratory animals, referees would demand more detailed documentation. But the experiments to which I refer are randomized clinical trials performed on people and few referees ask for specific information. The technique is the 'data monitoring board'. The technical aspect that is well described is the method of constructing statistically valid monitoring boundaries. Other aspects of the monitoring process, however, are only infrequently discussed. In fact, participation on a data monitoring committee requires a vow of silence, a silence that often remains unbroken for years.

Generally, the first meeting of the committee lays out the rules; those who have never before participated in a monitoring committee become apprentices who rely on the oral tradition to learn the rituals. The same faces appear and reappear in related studies, but individual boards develop their own modus operandi. Trials of cardiovascular disease include people who have had experience in monitoring cardiovascular trials; oncologists monitor cancer trials, and so forth. Since the details of methods of monitoring are not published, the network of information passes by word of mouth; statisticians and ethicists, who tend to cross disciplinary boundaries, act like the caravans of yore, passing information from one society to another. But because we statisticians see medicine with our own eyes, often focusing on the random walks embedded in ongoing data, the information we pass may neglect some insights that would be important to medical
researchers. Sometimes a few written words pass from the DSMB to the outside world; a sanitized version of the minutes may become public or a report of a specific problem may find its way to the literature, but the animated discussions, the wrangling, the agonizing over ambiguities in the ongoing data are lost. Hours of arguments about the propriety of continuing a trial become a sentence in the minutes, 'The Data Safety Monitoring Board unanimously recommended continuation of the trial'.

Not only do the styles of DSMBs in studies of various diseases differ from each other, but boards attached to the NIH tend to operate differently from those attached to the Veterans' Administration which differ in turn from boards attached to trials sponsored by industry. Because of the important influence of DSMBs, the methods must be discussed in public. I therefore applaud the efforts of the three institutes – NHLBI, NCI, and NIAID – for co-operating to sponsor this workshop and I look forward to the discussions of the next two days.

In these comments, I shall describe some common components of data safety monitoring boards, and address several questions that I believe need to be answered. I am sure this workshop will provide a valuable airing of views and sharing of experiences.

2. THE DATA AND SAFETY MONITORING BOARD

A data and safety monitoring board (DSMB), a committee attached to a randomized clinical trial, is charged with the responsibility of monitoring performance of the trial, safety of the participants, and efficacy of the treatments being tested. Some DSMBs have broader responsibilities. For example, the sponsors of the trial may ask a DSMB to review policy or to act as a scientific advisory board. The boards go by a variety of names; the name may include almost any subset of the words 'data', 'safety', 'performance', 'efficacy' and 'policy'.

The necessity of a DSMB stems from the ethical imperative to disassociate the treating physician from the accruing data in order to maintain a legitimate 'state of equipoise' regarding the therapies being studied and to remove those with vested interest in a specific treatment from deciding whether the trial should continue. I view a randomized clinical trial as a dual compact. On the one hand, a trial is a compact between those who treat and those who are treated. The patient accepts the notion that the treating physician is uncertain about therapy. It is a compact also between physician and sponsors, for the physician must trust the sponsors of the trial to protect the interest of the patients. The DSMB provides the link between the two compacts.

Sizes of DSMBs vary; the smallest board on which I have participated included only three people while the largest had a membership of more than 15. Most of the members of DSMBs are physicians involved either in the care of patients who have the disease under study or in research about it. Many boards include a 'patient advocate', such as a medical ethicist. Clinical trials that test a very new drug or biological product may include a pharmacologist or biochemist; trials of biobehavioural interventions, or trials with one or more psychosocial endpoints, often include a psychologist on the board. By definition, all boards in which I have participated have included at least one statistician; if there are DSMBs without statistical input, I would not know.

3. FUNCTIONS OF A DATA SAFETY MONITORING BOARD

3.1. Monitoring performance of the study

The first responsibility of a DSMB is to monitor the performance of the study. Some tasks are obvious – the board routinely monitors recruitment, flow of forms, quality control of the data, frequency of follow-up, and adherence to protocol. When the board identifies problems, it reports
them to the sponsor of the trial, often with recommendations for improvements. Some tasks, though important, are more subtle. For example, in studies of long-term administration of a drug, patients randomized to placebo may eventually begin to take the drug or an equivalent medication, and some randomized to the drug may stop. In trials comparing surgical to medical interventions, those randomized to medical therapy may eventually undergo surgery. The power of the study, and perhaps the interpretability of the study, will be jeopardized if the number of drop-outs from placebo or drop-ins to therapy is much larger than anticipated. The DSMB, on observing an uncomfortably large number of participants who are not adhering to therapy, may recommend strategies to encourage improved adherence. One can view performance monitoring as a set of procedures designed to assure that the study is implemented effectively enough so that if the therapies being tested differ from each other with respect to either safety or efficacy, the results will be known.

### 3.2. Monitoring safety

One of the most important functions of a DSMB is to monitor the safety of the participants of the study. The board usually conceives of safety in several broad senses. First, it asks whether participants in the study incur some excess risk of harm as a result of being in the study; the potential harm may arise either as a direct effect of the therapy being studied or as a consequence of some other aspect of the protocol. Intertwined with its responsibility to the patients in the study itself is the board’s concern for the safety of patients who may yet be treated. On observing data that suggest potential harm severe enough to contemplate early termination, a DSMB often struggles with the implications to patients that may in the future undergo the study treatment. If the study treatment is new, early evidence of harm may be sufficient to terminate an arm (for example, the high frequency ventilation arm in the High Frequency Intervention Trial (HIFI), a study that compared methods of ventilation for premature infants), but if the study treatment is one in common use, the conflict between the current patients and the potential future ones is more problematic (for example, the Cardiac Arrhythmia Suppression Trial (CAST)). In the event that accruing data point to the possibility that a new therapy is unsafe, the data coordinating centre must decide when to inform the board. Of particular difficulty in the deliberations about whether there is harm is that the speed of ascertainment of safety data may differ between the experimental groups, especially if the treatments are unblinded. Further, the ground rules for monitoring safety often cannot be specified in advance, because adverse effects of a new therapy may be a surprise.

### 3.3. Efficacy

Many DSMBs monitor efficacy as well as safety, with the view toward terminating a trial if the study therapy appears strongly favourable. Statistical monitoring for efficacy is easiest when the disease being studied is acute, the endpoint immediate, and a monitoring plan specified in the protocol. Thus, for example, the Thrombolysis in Myocardial Infarction I trial (TIMI-I), which studied patients immediately after heart attack, compared streptokinase to tissue plasminogen activator (rTPA) with respect to patency of the coronary artery 90 minutes after treatment. The trial stopped prematurely because of early evidence that the proportion of patients with patent vessels was greater among those treated with rTPA than among those treated with streptokinase. Stopping for efficacy is much more difficult when the questions relate to long-term therapy for a chronic condition. For example, the Systolic Hypertension in the Elderly Program (SHEP) studied antihypertensive medication in men and women over 60 years of age who had isolated systolic hypertension. Although the primary endpoint was fatal and non-fatal stroke, an important additional goal was to learn whether long-term treatment with antihypertensive
Table I. Number of data safety monitoring boards reported in all papers describing randomized clinical trials

<table>
<thead>
<tr>
<th>Journal</th>
<th>Years surveyed</th>
<th>Number of randomized clinical trials published</th>
<th>Number of trials reporting a DSMB</th>
</tr>
</thead>
<tbody>
<tr>
<td>New England Journal of Medicine</td>
<td>1/89–8/91</td>
<td>61</td>
<td>4</td>
</tr>
<tr>
<td>Journal of the National Cancer Institute</td>
<td>1/88–3/91</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>Archives of Internal Medicine</td>
<td>1/88–2/91</td>
<td>10</td>
<td>0</td>
</tr>
</tbody>
</table>

Table II. Survey of the 57 New England Journal of Medicine randomized clinical trials that did not report having a data safety monitoring board

<table>
<thead>
<tr>
<th>Responded to questionnaire (n = 20)</th>
<th>Did not respond</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study had a DSMB</td>
<td>Study did not have a DSMB</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>11</td>
</tr>
</tbody>
</table>

medication would adversely affect mood and cognition in elderly people. Thus, in spite of early apparent (but not statistically significant) benefit of therapy, the DSMB did not stop the trial early. One reason for continuation was the concern that early stopping would preclude ever learning about the long-term effects of therapy.9

4. HOW DOES THE SCIENTIFIC COMMUNITY LOOK AT DSMBs?

Medical journals do not appear to have standards for reporting about the existence and role of a DSMB in a randomized clinical trial. We reviewed a number of issues of three medical journals and noted for each randomized clinical trial whether a monitoring board was mentioned. Table I shows the results. Of the 82 reported randomized clinical trials, only 5 reported that the trial had a monitoring board. Since I had been a member of two DSMBs for trials that did not report the existence of a board, I know that papers reporting a randomized clinical trial do not necessarily mention all boards. Therefore, we wrote to the first authors of all trials that did not report a DSMB. The letter asked whether the trial in fact had such a board and, if so, what the composition was. Of the 20 responses, 9 reported having had a monitoring board (see Table II). While the high rate of non-response does not allow any estimate of the proportion of trials with DSMB, the fact that the publications from 9 trials with boards did not mention their existence indicates that boards frequently are unreported.

5. WHAT DO WE NEED TO KNOW?

To set the stage for the rest of the meeting, I would like to pose a number of questions. For some of the questions, I will briefly present my own views, but I want to stress that some of my opinions are quite labile. I look forward to hearing the discussion of the next two days.
(a) What clinical trials should have a DSMB?
My own belief is that all trials in which the therapy or the endpoint is masked, and all multicentre trials, whether or not therapy is masked, should have a DSMB. Clearly, however, if all such trials routinely used DSMBs, many people would be extremely busy with committees. So, the natural consequence is to explore methods of structuring meetings that are not onerous.

(b) What should be the charge of a DSMB?
Since I do not have a clear opinion, I shall simply list a number of relevant questions. Should it monitor only safety? Efficacy and safety? Quality of the study? How much should it influence the protocol? Should it set its own monitoring boundaries or should it adopt those in the protocol?

(c) To whom should the DSMB report?
Typically, in NHLBI-sponsored trials that operate under contracts, the DSMB reports to the programme that is responsible for managing the trial. In grant-supported trials, the lines of reporting are less clear. Usually, the DSMB reports to NHLBI, but sometimes the board reports to the steering committee itself. In trials sponsored by the drug industry, the board generally reports to the sponsor. Often the board is considered only advisory to the sponsor. How should recommendations of the board be reported? How can boards report back to the sponsor in ways that are responsible but do not unblind the study? What if the sponsor overrules the board?

A vexing problem pertains to the problem of inadvertent ‘reporting’ to the investigators. Investigators often make assumptions that the failure of a DSMB to recommend early termination of a trial is itself informative. Many assume that if a DSMB does not stop a trial, the accruing data must be showing neither therapeutic disaster nor therapeutic triumph.

(d) What should be the size and composition of the board?
Is there a minimum responsible size? A maximum feasible size? What disciplines should necessarily be represented?

(e) Should there be ‘litmus tests’ for members of the board?
I have participated in DSMBs on which some members were not comfortable with many of the basic premises of standard clinical trials. In particular, I have served on boards in which some members (even some statisticians) objected to analysis by randomized group. In one DSMB, several members urged ending the trial early because of an analysis that assigned people to the treatment received. Some DSMB members have expressed unease about randomization, or grave doubts about some aspects of the protocol of the study. My own belief is that litmus tests are appropriate for monitoring board members. Certain stances are inconsistent with membership in DSMBs, for example ethical qualms about randomization, substantive objections to a protocol, or unwillingness to analyse according to the randomized assignment. Just as jurors are interviewed concerning their likely reaction to certain cases, I believe the sponsor has the right to make sure that at the beginning of the study, all members of the board are satisfied with the protocol and are comfortable with the generally accepted principles of clinical trials methodology.

(f) Should there be codes of conduct for DSMB members?
I believe that members of DSMBs must not allow themselves to be in a position in which they might reap substantial monetary rewards if a trial is successful. Even an ethical board member might well be influenced by self-interest in monitoring data. Moreover, a person on a board who holds stock in a company during the course of a study may signal results to others. But I believe the stricture goes further, for I am opposed to permitting board
members to speak about the efficacy of treatments that are being given in studies they are
monitoring. I know this is not a popular position, and I look forward to hearing how others
view the issue.

(g) How should blinded data from one trial affect interpretation of accruing data from
another?

Often the same individual is on monitoring committees of similar trials or a single committee
is monitoring several related trials. What guidelines should be established to deal with data
in such cases? More generally, should DSMBs of trials asking similar questions share data?

(h) What should the sponsor do if the DSMB asks for improper analysis or makes recom-
mendations with which the sponsor strongly disagrees? Conversely, how should a board
act if its recommendations are ignored?

I am certain that during the symposium all these questions and others will be discussed. I look
forward to hearing about the experience and opinions of so many of you.

ACKNOWLEDGEMENT

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Building a More Connected DSMB: Better Integrating Ethics Review and Safety Monitoring

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Data and Safety Monitoring Boards (DSMBs) have become an increasingly common feature of clinical trial oversight, yet a paucity of legal or ethical frameworks govern these Boards’ composition or operation, or their relationship with other actors with monitoring responsibilities. This paper argues that prevailing structural gaps are impeding harmonized systems for monitoring the ongoing ethical acceptability of clinical trials. Particular tensions stem from DSMBs’ sweeping discretion in deciding whether and when to recommend that a trial should be terminated or amended based on safety and efficacy information. This discretion becomes especially challenging in light of DSMBs’ monopoly over emerging trial data, which prevents Institutional Review Boards, sponsors, and investigators from participating in certain pivotal and ethically charged decisions. To address these disconnects, I advocate for strengthened pre-trial and post-trial communication in addition to innovative strategies to support DSMB decision making through the life of a trial.

Keywords: clinical trials, data monitoring, Data Safety and Monitoring Boards, human subjects protection, Institutional Review Board, research ethics

INTRODUCTION

At the June 2012 American Society of Clinical Oncology meeting, investigators announced that a trial assessing the drug abiterone (Zytiga) in early-stage prostate cancer patients had been unblinded for efficacy based on an independent Data and Safety Monitoring Board (DSMB) recommendation (Ryan et al. 2012; 2013). The decision faced immediate controversy. The trial had only reached statistical significance for one of its primary endpoints: progression-free survival. Overall survival, the other primary endpoint, showed a strong positive trend but did not reach statistical significance. Critics noted that the
decision to unblind—effectively terminating the trial—was a missed opportu-
nity to show an unequivocal survival advantage and, therefore, “a disservice
both to medicine and the men who participated in the trial” (Droppert, 2012).
Yet, in contrast, DSMBs in other trials have recommended continuing trials
well beyond when the data reached statistical significance for efficacy, rais-
ing concerns that participants in the control arm are being sacrificed as mere
means to the end of scientific knowledge. (See, e.g., Redmond et al., 2006.)

The conflicting actions of DSMBs in these trials—that is, recommending
a sponsor terminate a trial before it reaches statistical significance versus
recommending a sponsor terminate a trial only years after such significance
is reached—reflect DSMBs’ multiple responsibilities and potential tensions
between them. First, DSMBs safeguard the interests of trial participants
by guarding against assignment to inferior trial arms. Second, they preserve
trial integrity through independent interpretation of interim data. Third, they
facilitate the availability of timely and reliable findings to the broader clinical
community. To satisfy these charges, DSMBs periodically review emerging data
to determine “the ethical and scientific appropriateness” of trial continuation
(Ellenberg et al., 2002, p. 20) Yet DSMBs are far from the only bodies respon-
sible for trials’ ongoing ethical and scientific acceptability. In the United States,
national and international research regulations give Institutional Review
Boards (IRBs) primary responsibility for safeguarding the rights, safety, and
wellbeing of trial subjects, including through continuing review of any adverse
events. Sponsors and investigators also have ongoing monitoring obligations.
Troublingly, little attention has been given to the relationship between these
various ethical oversight roles and potential rifts between them.

This paper evaluates the underexplored and important question of how
the intertwined monitoring roles performed by DSMBs, IRBs, sponsors, and
investigators should be coordinated. More specifically, it argues that prevail-
ing structural gaps are impeding harmonized systems for data monitoring. For
much of the course of a trial, interim data is locked within DSMBs, bound
by tight confidentiality requirements. While this secrecy is based on sound
practical and scientific justifications, it prevents others with regulatory moni-
toring responsibilities from participating in many pivotal and ethically charged
decisions.

Very little evidence is available about how DSMBs are making monitoring
decisions in ethically hard cases, nor the decisions that others might make if
given access to the relevant data. Yet, because of differences in their com-
positions, and real and perceived roles and responsibilities, IRBs, in particular,
might be expected to prioritize the interests of current research participants
and future patients quite differently than many DSMBs. This raises so-far
unanswered questions about whose opinion should prevail and how they should
be weighed—questions foundational to the functioning of our data monitoring
system.
This paper seeks to address these prevailing structural gaps. Part One explains the ethical need for trial monitoring and the rise of DSMBs as a means of satisfying this need. This provides important background to the structural disconnects between DSMB operations and other elements of our clinical trial monitoring system: the subject of Part Two. Finally, Part Three suggests reforms to institute more interconnected systems for ensuring the ongoing ethical acceptability of clinical trials.

**PART 1: THE NEED FOR CLINICAL TRIAL MONITORING**

During the course of a clinical trial, emerging data from the trial itself and other studies can change an initially favorable risk-benefit calculus. For instance, interim data can show the falsity of (sometimes long-held) assumptions that clinicians, patients, and others have about the safety and efficacy of medical interventions (see, e.g., DeMets and Friedman, 2006). At other times, information external to a given trial can alter what is known about the trial’s risk-benefit calculus during the course of a trial (see, e.g., Shah et al., 2011). Accordingly, monitoring accumulating clinical trial results is a crucial component of ensuring trials’ ongoing ethical acceptability. To this end, international research guidelines and national regulations place certain ongoing monitoring obligations on trial sponsors, investigators, and IRBs (for example, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 1996, para. 5.16.2; International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 1998, para. 4.10.2). Yet trials’ growing length, complexity, and geographic dispersion, can make it difficult for these parties to meet their monitoring obligations. Increasingly, DSMBs—essentially an independent group of people qualified to detect and interpret emerging safety and efficacy trends—are performing this role.

Formalized committees charged with regularly assessing a trial’s accumulating results has its genesis in the Greenberg Report, commissioned in the mid-1960s by the then National Heart Institute to advise on the organization and conduct of large, multicenter trials. Most relevantly, the report recommended establishing an advisory group of independent expert scientists and a mechanism for terminating a trial early if it became evident that it could not meet its objectives or new information rendered it superfluous (Greenberg, 1988). Following this report, DSMBs gained increasing traction in publicly sponsored clinical trials (DeMets, Furberg, et al., 2006, p. 5). By 1998, a National Institutes of Health (NIH) policy required the establishment of DSMBs for all “multi-site clinical trials involving interventions that entail potential risk to the participants” (National Institutes of Health, 1998). Based on the need for “extra caution” for interventions being tested in nonconsenting
participants, the Food and Drug Administration (FDA) also made DSMBs mandatory for research in emergency setting that seeks a waiver of the informed consent requirement (Department of Health and Human Services, 1996, amending 45 CFR Part 46).

DSMBs gained favor for several reasons. Perhaps most importantly, clinical trialists recognized the ethical need to monitor accumulating clinical trial results to ensure continued participant welfare. However, if investigators or sponsors looked at the emerging data to make such determinations, they could become unblinded, affecting the course of the trial and the validity of the results (Ellenberg et al., 2002, p. 2). Another driving factor was recognition of the limitations of IRBs—those bodies with regulatory responsibility for ongoing human subject protection—in undertaking continuing review of research (Office of the Inspector General, 1998, p. 12). While IRBs receive reports of adverse events that are observed in a clinical trial, meaningfully assessing these reports requires additional information to which these Boards are not privy: without emerging efficacy information, for example, notifications regarding potential safety signals may appear unduly alarming (Morse, 2001). Moreover, for multicenter clinical trials, IRBs often are provided with serious adverse event reports originating from all sites studying an investigational drug or device, with little if any accompanying data interpretation (DeMets, Fost, et al., 2006, p. 144). The availability of DSMBs minimizes the need to overwhelm IRBs with this vast quantity of information, much of which they have limited expertise in assessing.

In contrast to publicly sponsored trials, DSMBs were relatively uncommon in industry-sponsored trials until the early 1990s (Ellenberg et al., 2002, p. 9). Despite some initial concerns, clinical trials may now be more likely to report the use of DSMBs when pharmaceutical companies are involved in the trial (Sydes et al., 2004, p. 52). The DSMB benefits previously discussed in the context of publicly sponsored trials apply equally to industry-sponsored trials, but several commercial benefits also could help explain their increasing ubiquity in this context. For one, DSMBs can mitigate regulatory bodies’ concerns about the potential that sponsor companies have made changes to trials based on commercial incentives rather than legitimate scientific rationales. (See Herson, 2009, p. 5.) DSMBs also have protected sponsor companies against claims of misleading stockholders by providing a legitimate argument that the company did not have prior knowledge of safety or efficacy concerns (Ellenberg et al., 2002, pp. 9-10).

In sum, DSMBs are likely to be an increasingly important component of clinical trial oversight. When constituted appropriately, they satisfy the ethical and scientific imperative for the review of emerging trial data by independent people qualified to detect and interpret complex efficacy and safety trends. By shielding them from knowledge of emerging interim data, DSMBs also minimize the real and perceived potential for sponsor or investigator actions
to bias trial findings. Finally, DSMBs have certain commercial benefits that may make them increasingly attractive for trials sponsored by pharmaceutical companies. Yet, as explored in the remainder of this paper, they also raise significant questions about the appropriate regulatory framework for making decisions about a trial’s ongoing ethical acceptability.

**PART 2: AN OPAQUE DSMB MONITORING PROCESSES**

The manner in which DSMBs perform their roles is presently somewhat opaque to many outside observers. Few federal or state regulations govern the composition or conduct of these Boards, and none at a sufficient level of specificity to comprehensively guide implementation (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 1996; International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 1998, para. 4.6). The only time that U.S. federal legislation or regulations expressly refer to DSMBs is in provisions governing the waiver of consent for research in emergency settings (21 CFR 50.24). However, these simply state that approval requires the existence of a DSMB without specifying any requirements for the Board’s operations. The most comprehensive advice available on DSMB operations is a 2006 FDA guidance document, which provides useful advice on a range of aspects relevant to DSMB constitution and operation. However, the guidance carries no direct legal weight nor seeks to resolve processes for dealing with hard ethical cases (Food and Drug Administration, 2006).

Trial protocols frequently include data monitoring plans, which IRBs may review as a part of their risk-benefit assessment. Yet, to accommodate the multitude of factors that feed into DSMB decision-making—many of which will be unknown at the time of drafting—these almost always include considerable scope for DSMB discretion. Moreover, once a trial is in process, much of the information to which a DSMB has access is regarded as strictly confidential, as are DSMB deliberations surrounding this information. Accordingly, once a DSMB issues a recommendation, anyone who challenges it must, at least initially, do so without being privy to the interim data (Grant et al., 2005, p. 45).

After explaining the confidentiality and decision-making discretion central to DSMB decision-making, this Part canvasses their potential implications for the integrity of our clinical trial-monitoring framework.

**2.1. DSMB’s Monopoly on Interim Trial Data**

DSMB members usually are the only people allowed access to unblinded safety and efficacy information. In the absence of a recommendation for trial amendment or termination, interim data (with exceptions for certain toxicity information) usually must not be released outside of the DSMB. Indeed, the
FDA Guidance Document goes so far as to advise DSMBs to limit the disclosure of even aggregate safety and efficacy information to “those who cannot otherwise carry out their trial management responsibilities” (Food and Drug Administration, 2006, p. 11). In this way, DSMBs take on a gatekeeper role for the flow of information about interim findings.

Accordingly, extensive DSMB practices and procedures have evolved to limit the disclosure of emerging trial data. In large part, this is achieved through the use of “open” and “closed” DSMB meetings. The open sessions are attended by DSMB members, trial investigators, and possibly sponsor representatives. These sessions review the progress of the trial, including participant accrual and data quality. The Data Monitoring Committees: Lessons, Ethics and Statistics (DAMOCLES) study group—who the U.K. National Health Service commissioned to improve the evidence-base surrounding DSMBs and make recommendations for reform—advise that toxicity might be discussed “in general terms” at the open meeting, but they do not recommend even general discussion of efficacy (Grant et al., 2005, p. 23). Participation in closed sessions is restricted to those who may see unblinded data: usually just DSMB members and the trial statistician.

Confidentiality is an important factor in DSMBs’ role of promoting the scientific integrity of trials. Most clearly, it guards against erroneous conclusions about trial results and potentially premature adoption of study findings by investigators, participants, and the public more generally (Fleming et al., 2002, p. 2850). DSMBs have expertise in distinguishing possible from probable trends, and probable trends from statistical certainties. For those without this technical expertise, or with a greater stake in the outcome, this task can be overwhelming. By only releasing information once it reaches a specific threshold, DSMBs ensure that decision-makers are basing their actions on factually sound trade-offs. DSMB members have criticized, for example, risks to trial integrity that arise from releasing interim analysis results, which arguably eventuated from routinely providing interim data to investigators in the Princess Margaret Hospital trial (Fleming et al., 2008). When early results failed to show any survival trend, the study “died a natural death” (Rider et al., 1977). A further trial enrolling 824 participants was needed to provide more reliable evidence of lack of benefit (Duncan et al., 1984).

DSMB confidentiality also protects against claims by regulatory authorities that any amendments to a trial’s design were biased by a sponsor’s knowledge of interim data. Notably, these concerns can jeopardize marketing applications even in the absence of any information that interim analysis information was responsible for prompting proposed changes to study design (see case study in Ellenberg and Siegel, 2006, p. 43).

Finally, trials sponsored by companies listed on the Securities and Exchange Commission have another (less morally praiseworthy) incentive for DSMB confidentiality. Stock market rules mandate disclosure if these sponsors
become aware of “material” safety or efficacy information. Since material information is not constrained by statistical significance, a company with knowledge of a negative trend that cannot justify trial termination may nevertheless have to disclose it. This can damage the trial’s ongoing feasibility. A DSMB protects a company from this situation by shielding the company from knowing the trend at all.

Despite the compelling scientific and practical reasons for DSMBs to keep interim data confidential, such secrecy prevents others with monitoring responsibilities from reaching their own view about a trial’s ongoing ethical acceptability. As the biostatistician Janet Wittes reflects on the gatekeeping process and its consequent limitations on outside reflection:

Sometimes a few written words pass from the DSMB to the outside world; a sanitized version of the minutes may become public or a report of a specific problem may find its way to the literature, but the animated discussions, the wrangling, the agonizing over ambiguities in the ongoing data are lost. Hours of argument about the propriety of continuing a trial become a sentence in the minutes, “The Data Safety Monitoring Board unanimously recommended continuation of the trial.” (Wittes, 1993, p. 420)

From a regulatory perspective, the knowledge gaps arising from DSMBs’ information monopoly become especially problematic when viewed alongside Boards’ considerable decision-making discretion.

### 2.2. DSMB’s Decision-Making Discretion

Usually, DSMB decision-making is guided by data monitoring plans, which specify the point at which the DSMB may recommend trial termination based on statistical significance (the “stopping boundary”). Some monitoring decisions involve straightforward applications of trial stopping boundaries. This will likely apply, for example, where no clear safety or efficacy trends emerge through the course of the trial or where the interim data show that the efficacy and safety of one therapy is clearly superior to the other. However, numerous situations arise in which trial termination or amendment may not be warranted even once a stopping boundary has been reached, and sometimes termination may be warranted even before the data reach a stopping boundary. For this reason, DSMB members stress that stopping boundaries are “guidelines, nothing more, and need to be interpreted wisely” (Wheatley and Clayton, 2003; see also Grant et al., 2005, p. 38).

These decisions typically involve complex ethical trade-offs. Consider, for example, a trial that meets a stopping boundary for efficacy but raises certain safety questions. A DSMB could recommend terminating the trial in accordance with the stopping boundary, prioritizing the provision of a more
efficacious treatment to current control arm participants and others while lessening the scientific knowledge attained by the trial. Alternatively, the DSMB could recommend trial continuation, prioritizing the accretion of additional safety and efficacy information over early access to the (now known to be efficacious) interventional treatment for control arm participants.

Precisely these questions arose in the Breast Cancer Prevention Trial, a placebo-controlled trial to investigate whether tamoxifen could prevent the occurrence of cancer in high-risk women. DSMB members agreed that they would consider stopping the trial if evidence showed that tamoxifen significantly prevented breast cancer and the “global statistic” (a figure that amalgamated a number of adverse effects using a weighting based on severity of outcome) was supportive (Redmond et al., 2006, p. 127). At the second interim efficacy review, the data showed a significant preventative tamoxifen effect and a slightly positive global statistic. Although the data met the previously decided-upon stopping boundary, the Committee recommended that the study continue to get more evidence about long-term effects. This pattern continued until the fourth interim review, when the DSMB recommended that the trial terminate for efficacy. This came two years after study findings crossed the stopping rule for benefit and after an additional 65 breast placebo-arm participants were diagnosed with breast cancer. DSMB members justify their decisions, noting:

The rationale for continuations was not related to doubt within the committee that there was substantial underlying decrease in incident breast cancer for participants who received tamoxifen that might diminish over time. Rather, [DSMB] members believed that there should be more reliable evidence relating to long-term adverse effects in order to predict the net benefit both for women who had participated in the [trial] and for women who might consider taking tamoxifen as a preventative after the trial ended. (Redmond et al., 2006, p. 134)

Other ethical trade-offs arise when the investigational drug becomes unable to meet its efficacy goals. Particularly in situations in which the investigational drug is already in use, a DSMB may recommend continuing a “futile” trial in order to more persuasively guide future clinical practice. Yet, the trade-off is exposing current participants to the prospect of harm without the chance of improved efficacy. These dilemmas were well illustrated in the Carotene and Retinol Efficacy Trial (CARET), designed to test the hypothesis that beta-carotene prevented lung cancer. During the trial, a related study reported that the trial regimen was associated with an increased incidence of lung cancer, rather than the assumed protective effect. The CARET DSMB analyzed their trial’s interim data and found a statistically insignificant excess incidence of lung cancer in the trial regimen. Some members advocated trial continuation and argued that they “owed it to science to be absolutely certain of the adverse
effect before stopping the trial” (Miller et al., 2006) Others recommended immediate termination, opining that they “owed it to participants to prevent possible further harm to them” (Miller et al., 2006). Given the lack of agreement among members, the DSMB decided to allow outcome events to continue to accumulate for another six months.

A foundational problem underpinning DSMB decision-making in each of these case studies is a lack of a consensus regarding the ethical principles underpinning certain trial monitoring decisions and how these relate to prespecified stopping boundaries. That is, how to balance what David Buchanan and Franklin G. Miller describe as “the dual obligations of clinical research”: the protection of human subjects and the generation of new medical knowledge (Buchanan and Miller, 2005).

Perhaps the most widely held position is that a trial should be stopped when “clinical equipoise” is disturbed (Freedman, 1987). On this view, trials should terminate when there is convincing enough evidence to resolve the dispute among clinicians about the therapeutic merits of the investigational arms. Buchanan and Miller argue instead that “trials are designed to gather as much data as possible regarding the overall risk-benefit ratio of the treatments being evaluated and other critical clinical issues by the end of the trial” (Buchanan and Miller, 2005, p. 168). They therefore propose a nonexploitation framework, under which trials should be stopped “when the anticipated level of harm from withholding the treatment is judged to be disproportionate or unreasonable based on the seriousness of targeted condition, the degree of evident therapeutic efficacy, and the risks of toxicity” (Buchanan and Miller, 2005, p. 172). These frameworks ascribe different importance to the welfare interests of current research participants and future patients, yet neither fully resolves the inherent tensions between these interests. Both at some point require choices to be made: for example, the amount of evidence that is taken as needed to disturb equipoise; the extent to which the welfare interests of participants can be traded off for benefits to future patients until the tradeoff constitutes exploitation (Malmqvist et al., 2011).

Given these underlying ambiguities in judging the ethical acceptability of trial termination, formulating and applying stopping boundaries remain malleable to individual and institutional assumptions and biases. Clearly, this is problematic in and of itself. However, the opaque nature of DSMB decision-making exacerbates such concerns. Most overtly, it raises questions about possible discrepancies between DSMB stopping decisions and the decisions that others with monitoring responsibilities could make if given the requisite information. The questions for the remainder of this paper are if such differences are plausible and, if so, whose opinion should prevail and how they should be weighed?
2.3. Structural Tensions Stemming from DSMB Decision-Making

There is limited evidence on the manner in which DSMBs, as compared with IRBs and others, make ethical trade-offs in trial monitoring. Yet given the highly discretionary nature of DSMB decision-making and a lack of clear principles on which decisions are made, conflicting ethical interpretations are far from fanciful. Problematically from a structural perspective, a DSMB may recommend that a trial should continue without amendment in circumstances in which a reviewing IRB would disagree. Without disputing the potential for either or both of these decisions to be ethically defensible, this discrepancy raises concerns for current regulatory frameworks for governing research. Essentially, the DSMB’s role in gatekeeping the flow of information means that an IRB—the body specifically tasked with safeguarding participants’ rights safety and well-being—is blocked from information about the trial that could ground its regulatory power of termination.

Several important differences between DSMBs and IRBs suggest the plausibility of such a scenario. First, DSMB and IRB compositions differ. Federal regulations require that IRBs include diverse membership, including members with “sensitivity to community attitudes” (45 CFR 46.107(a)). Many have noted the challenges and inadequacies in IRB membership (Anderson, 2006; Sengupta and Lo, 2003), yet it still appears to be considerably broader than membership of DSMBs, which comprises almost exclusively clinicians and biostatisticians. (Grant et al., 2005, p. 90; Tereskerz et al., 2011). While the practical implications of these differing memberships requires further dedicated attention, one study has shown that IRB community members, investigators, and biostatisticians vary in how they think DSMBs should operate. Generally, IRB community members supported more stringent DSMB structure and management requirements than investigators and biostatisticians. Community members also were significantly less concerned with blinding sponsor companies than biostatisticians (Tereskerz et al., 2011).

Systematic differences in IRB and DSMB monitoring decisions also may stem from differences in these Boards’ overarching roles and responsibilities, or at least their perception thereof. Since the Nuremberg Code, IRB decision-making has tended to prioritize the protection of current research participants, a focus supported by a range of pivotal research ethics guidance documents. Most explicitly, art 8 of the Declaration of Helsinki provides, “While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects” (World Medical Association, 2013).

In comparison, the available DSMB literature expressly seeks to balance Boards’ roles in protecting individual participants with their responsibilities to further clinical knowledge for the benefit of future patients. So, for example, the DAMOCLES Group advise that “Unlike ethics committees . . . whose
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remit is aimed almost exclusively towards the protection of the interests of the trial participants (individual ethics), [DSMBs] also have ethical responsibilities to future patients (collective ethics)” (Grant et al., 2005, p. 41). Such balancing played out, for example, in the first major randomized trial to test the widespread belief that hormone therapy would prevent coronary heart disease. During the final year of the trial the power to discover an overall benefit in the primary endpoint became “nearly zero.” DSMB members justified their decision to continue the trial based on the importance of producing the most definitive conclusions possible, in order to best challenge widespread clinical beliefs (Hulley et al., 2006). Although this approach clearly is ethically defensible, IRBs’ focused more exclusively on protecting current research participants would quite plausibly recommend a different course of action.

Of course, conflicting monitoring perspectives are not limited to those between IRBs and DSMBs: sponsors and investigators also may differ in their interpretations of emerging trial data. As with IRBs, information locked within the DSMB may be sufficient, in the views of a sponsor or investigator, to terminate or cease involvement with a trial. On the flip side, DSMBs may present a sponsor with a recommendation to terminate in a situation in which the sponsor does not think that the data are sufficient to ground such a decision. While this scenario may raise fewer ethical issues, since all parties have access to information relevant to make their own interpretations of a trial’s ongoing acceptability, it has troubling practical implications. In particular, it becomes much harder for the sponsor to make any necessary changes to trial design without incurring a high level of regulatory scrutiny. The information also may affect the feasibility of further trial recruitment and randomization. (For a practical example, see Pocock et al., 2004.)

PART 3: BUILDING A MORE CONNECTED DSMB SYSTEM

This paper has demonstrated that DSMBs have considerable discretion and an information monopoly that precludes most meaningful oversight of their decision-making during the course of a trial. The resulting fragmentation has serious implications for DSMB members, sponsors, investigators, IRBs, and others with a stake in the clinical trial system. The final Part provides a proposal for a more transparent and consistently understood data-monitoring framework. Although the diverse persons and bodies tasked with monitoring responsibilities will not always reach consistent determinations about a trial’s ongoing ethical acceptability, the availability of clear and consistent procedures for making such decisions can at least bring us closer towards informed and ethically reflective decisions.

Below, I propose strategies for promoting this more connected data monitoring framework, including through pre-trial and post-trial information sharing
among sponsors, IRBs, and DSMBs, as well as avenues for DSMBs to converse with reviewing IRBs during the course of a trial. Potential reforms in this regard are underexplored in the literature. While Holly A. Taylor and her colleagues advocate the importance of communication between DSMBs and IRBs, their proposals for reform are limited to DSMB sharing of nonconfidential information through the life of a trial (Taylor et al., 2008). I adopt far more comprehensive and broad-reaching suggestions for collaboration and information sharing among DSMBs, IRBs, and others.

The proposals set forth in this Part are limited in many ways by the widespread fragmentation that characterizes U.S.’s (and most other countries’) research oversight framework, including relatively isolated IRBs operating at a local institutional level. The fragmentation becomes more marked still when considered at the global level on which most clinical trials operate. As more streamlined national and international ethical review frameworks are implemented, new options may emerge for interconnecting the activities of DSMBs and other bodies with monitoring responsibilities. However, in light of the challenges of meaningful harmonization, the below proposals for reform are designed to work with, and hopefully improve, the current oversight framework.

3.1. Pre-Trial Communication

Providing DSMB members with guidance about their role and decision-making processes through clear and specific monitoring plans provides an incremental but important step forward in creating integrated data monitoring systems. As one example, sponsors could develop, and IRBs review, monitoring plans that permit DSMB recommendations for termination only once the trial meets the stopping boundaries for primary and secondary endpoints as well as a minimum period of exposure to the study drug, or a minimum number of expected deaths (or other adverse events) have been observed (see, e.g., Thomas and Snappin, 2002, p. 8). In particular, this should minimize open-ended discretion when it comes to DSMB monitoring and instead require sponsors—potentially in collaboration with investigators and IRBs—to institute more structured decision-making frameworks. In addition, developing such plans may further understandings among sponsors, IRBs, and others of the nuances of data monitoring practices, and how these are being applied in the context of a specific trial. This may guard against concerns about assumptions “that if a DSMB does not stop a trial, the accruing data must be showing neither therapeutic disaster nor therapeutic triumph” (Wittes, 1993, p. 423). Monitoring plans also can specify DSMB membership to allow IRBs to satisfy themselves as to members’ competence and independence.

However, the extent to which monitoring plans can resolve the decision-making disconnects at the heart of this paper is questionable. Consider, for
example, the difficulty of specifying in advance strategies for dealing with those ethical dilemmas and case studies outlined in Part Two. Pre-specifying how DSMBs should weigh information from other emerging trials also is exceedingly difficult given the paucity of information trial sponsors and DSMBs may have about these trials at the time they formulate a data monitoring plan. While more carefully constructed data analysis can minimize DSMBs' decision-making discretion, it cannot (and likely should not attempt to) remove it altogether. Additional strategies will be necessary to deal with these exigencies.

3.2. Post-Trial Communication

A further step in opening up debate about DSMB processes is expanding discussions in clinical trial publications. With notable exceptions (perhaps, most instructively, DeMets, Furberg, et al., 2006), few open reflections on the data monitoring process—including its inherent ethical tensions—are available in the clinical trials literature. Indeed, what information is available can unhelpfully simplify data monitoring decisions to straightforward applications of stopping boundaries. For example, the pivotal investigator publication on the Breast Cancer Prevention Trial explains that trial termination in March 1998 was the result of an “independent data-monitoring committee” determination that “in accordance with prespecified rules for stopping the study, the findings indicating a reduction in breast cancer risk were sufficiently strong to justify disclosure of the results” (Fisher et al., 1998). Nowhere do the authors raise the committee's decision to delay termination until well after the tamoxifen arm reached the prespecified stopping boundary for efficacy for the purpose of obtaining additional safety information. Whether this was a strategic decision on the part of the authors to avoid possible criticism or even participant lawsuits, or the investigators simply did not know that the committee made such a trade-off is unclear.

In order to counteract this effect, published reports should include details about the information available at interim analyses, and the stopping rule used to inform any decision whether to stop the trial. This recommendation is broadly consistent with the Consolidated Standards of Reporting Trials (CONSORT) guidelines, which seek to improve the reporting of randomized controlled trials. In particular, the CONSORT group recommends that authors report whether they, or a DSMB, conducted any interim analyses and, if so, “how many there were, what triggered them, the statistical methods used (including any formal stopping rule), and whether they were planned before the start of the trial, before the data monitoring committee saw any interim data by allocation, or some time thereafter” (Moher et al., 2010; Slutsky and Lavery, 2004). The CONSORT group notes that this information is often not included in published trial reports, even in trials that report early termination.
This information also may be suitable for publication on clinical trials registries such as ClinicalTrials.Gov.

Extending this requirement somewhat further, at the conclusion of a trial, DSMBs could provide a complete report of the information available to them at given points in time and their decision-making process to trial sponsors, along with investigators and reviewing IRBs. This debrief would give the Board’s rationale for recommending trial continuation or termination after specific interim analyses, thereby opening up their decision-making practices to scrutiny from those who may ultimate be held responsible. To some extent, discussions along this line happen when DSMBs justify to sponsors and others, such as executive committees, a recommendation to terminate a trial early. Yet no such discussions take place in situations in which interim data cross a stopping boundary and the DSMB decides not to make a recommendation for trial termination or amendment.

One advantage to open discussions of this nature is fostering a greater appreciation among IRB members and others of DSMB roles and processes, and an understanding of what to look out for when drafting and reviewing future data monitoring plans. For DSMB members, a formal debrief should foster a greater appreciation of the monitoring ethos of others with intersecting monitoring responsibilities. This could be especially valuable for standing DSMBs—for example, Boards established to monitor trials undertaken by specific NIH Institutes and Centers—which usually oversee trials reviewed by the same IRB and with a common pool of investigators. Ideally, these discussions could move individual institutions, cooperative groups, and the clinical trial community more broadly towards a shared ethics of data monitoring.

The extent to which such discussions happen already is unclear, although several recommendations in this vein have been put forward. National Cancer Institute (NCI) biometricians, for example, recommend that DSMBs provide an explanation when they do not follow a monitoring plan with respect to stopping, or not stopping, a trial for inefficacy (Korn and Freidlin, 2011). The DAMOCLES group template DSMB Charter advises that “Reasons should be recorded for disregarding a stopping guideline,” which implies a debriefing discussion of some nature with the trial sponsor and possibly others (Grant et al., 2005, p. 133). However, a thorough literature review revealed few, if any, published case reports of these discussions. To the extent such debriefings are actually occurring, they warrant dedicated attention in case study reports. If they are not currently commonplace, pilot studies of debriefing discussions with DSMB members, trial sponsors, and reviewing IRBs would be instructive. In particular, these could track various parties’ understandings of the ethical issues associated with data monitoring and strategies for resolving them, along with any changes in these views following the debriefing.
3.3. Communication during Trials

Open discussions at the start and conclusion of a trial are a promising start to fostering a shared understanding of clinical trial monitoring among sponsors, investigators, DSMB members, and IRBs. However, they do little to support DSMBs in the throes of tough decisions. Instead, their information monopoly and decision-making discretion demand that DSMBs grapple alone with the implications of interim data until they agree on a recommendation for termination or amendment. The sponsor is normally authorized to overrule the DSMB’s recommendation, but the associated disclosure can lead to practical problems, including for subsequent trial recruitment. Processes are needed to provide DSMBs with decision-making support as interim data trends emerge, including further attention to the circumstances in which DSMB recommendations may be subject to challenge and, in contentious cases, whose views on a trial’s ongoing ethical acceptability should prevail.

Most debates, to date, focus on releasing preliminary data to allow investigator, patient, and physician decision-making. Richard Lilford and his colleagues forcefully denounce DSMBs for making “big decisions using opaque (and doubtless variable) heuristics while ignorance is perpetuated to stop potential participants voting with their feet” (Lilford et al., 2001, p. 441). In response, they advocate making all interim results publicly available to enable participants, potential future participants, and others to use the data to make their own decisions. However, this proposal faces strong criticism from many DSMB members who decry consequences including the risk of persons prejudging unreliable early results, diminished enthusiasm among investigators for enrolling patients, and potentially biased assessments of outcome measures. Given the potential for disclosure of interim data to participants and the broader public to preclude many important DSMB benefits, it does not appear to be a promising pathway for future reform. Rather, there may be a role for DSMBs to enter into more targeted interactions with sponsors, investigators, and—most particularly—reviewing IRBs to address emerging dilemmas.

3.3.1. Sponsors and investigators

Since DSMBs usually are only empowered to make recommendations about trial termination or amendment to study sponsors, DSMB and sponsor agreement on the criteria for a trial’s ongoing ethical acceptability is crucial. In particular, sponsor disagreement with a DSMB recommendation for trial termination can lead to damaging procedural impasses (Pogue and Yusuf, 2006). One option for reform is involving select sponsor representatives or trial investigators in DSMB meetings as nonvoting members, as applies in some NIH Institutes and Centers. At least theoretically, such representatives could act as a bridge between potentially competing understandings of best-practice monitoring.
Yet considerable concerns have been raised about sponsor and investigator representation in closed DSMB meetings (Dixon et al., 2011; Department of Health and Human Services Office of Inspector General, 2013). Most pressing, exposure to unblinded safety and efficacy data raises the potential for real or perceived bias, thereby obviating one of the strongest reasons for establishing a DSMB in the first place. These concerns are theoretically surmountable, provided stringent procedural safeguards are in place. Guidance, in particular, can be drawn from the “ethical wall”—a screening mechanism used, in particular, by law firms to protect client confidences from improper disclosure. But whether ethical walls would prove of widespread utility is open to question. In addition to the requisite procedural safeguards they—despite best intentions—remain open to perceptions of bias, and they require institutional divides that may not be possible for small sponsor companies or investigative teams. Depending on how any ethical wall is instituted, a publicly-listed sponsor company may remain open to securities disclosures. For reasons I explore below, IRBs are more promising bodies from which DSMBs may obtain decision-making support.

3.3.2. IRBs

Despite their overlapping mandates, little is written on how IRBs relate to DSMBs, and, in practice, there is usually no direct communication between them (Grant et al., 2005, p. 42). To the extent that guidance exists, it focuses on ensuring that IRBs have a baseline level of information about DSMB operating procedures and (usually nonconfidential versions of) DSMB meeting minutes. By circulating to reviewing IRBs the key recommendations of DSMB meetings (without providing unblinded and/or comparative data), the goal is to provide IRBs with “the assurance that a knowledgeable group had performed a thorough review of the interim data and determined that the trial should continue as planned, or made recommendations for changes.” (Ellenberg et al., 2002, p. 112). In other words, the expectation is a largely passive, one-way information exchange, usually mediated through a trial investigator.

Few commentators have taken the step of considering more active IRB roles when it comes to reviewing DSMB reports. Holly A. Taylor and her colleagues have presented perhaps the most far-reaching proposal for IRB/DSMB interactions, based on a review of the communication of DSMB actions with IRBs affiliated with Johns Hopkins institutions. Reporting a lack of consistency in the communication of DSMB actions and considerations, they recommend the systematic sharing of DSMB reports with IRBs. The authors further critique the informativeness of some DSMB communications, suggesting that these should include enough information about DSMB deliberations concerning any issues on which the IRB needs to be positioned to act. However, the kinds of information that they recommend including (aggregate evaluation
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of adverse and serious adverse events, significant protocol violations, recruitment concerns and plans to modify the protocol) do little to make DSMB decision-making more transparent. Notably, they explicitly state that none of the information shared should compromise the trial blind (Taylor et al., 2008).

Taylor and her colleagues further opine that IRB chairs should have the option to communicate directly with DSMBs (Taylor et al., 2008). Yet even here their unwillingness to unblind IRBs would preclude Boards from conducting an informed risk-benefit assessment. In the absence of unblinded safety and efficacy information, an IRB chair often would have no indication that the trial may be approaching (or, indeed, have reached) a stopping boundary. How a chair would know to contact the DSMB, and what the DSMB may tell the IRB chair should such contact be established, remains unclear. In sum, few options have been published that may challenge a DSMB’s informational monopoly when it comes to an ongoing clinical trial and, accordingly, to capacitate IRBs in performing their continuing clinical review role. Nor do they provide DSMBs with the option of accessing additional sources for ethical reflection.

I suggest empowering IRBs with a more consequential monitoring role. Specifically, in a limited and predefined set of circumstances, which would be agreed to by the sponsor, DSMB and IRB prior to trial commencement, DSMBs should be required to consult with the reviewing IRB (or, for multicenter studies, the principal reviewing IRB) on the ongoing ethical acceptability of a clinical trial.

Most clearly, a consultation requirement could apply in the event that a trial reaches a stopping boundary, or approaches a stopping boundary in circumstances in which the DSMB is considering termination. Consider here, for example, the situation that arose in the Breast Cancer Prevention Trial. In brief, interim data reached the point where the DSMB had no doubts that the trial intervention led to a decrease in incident breast cancer for participants. However, it sought more reliable evidence about potential long-term toxicity prior to trial termination. Notable in this scenario is the clear ethical trade-off and potential for ethical conflict: the DSMB had solid evidence that the trial intervention was efficacious, but terminating the trial early diminished potentially important opportunities to gather safety information.

A requirement for a DSMB to consult with the reviewing IRB has several advantages in this context. Perhaps most importantly, involving IRBs in these challenging decisions respects the broad regulatory schema for human subjects protection: namely, that a review body established in accordance with a slew of regulatory requirements oversees a trial’s ethical acceptability through the trial’s life. Moreover, a consultation requirement can lead to better monitoring decision-making by opening up the discussion to a wider set of perspectives. DSMBs are comprised principally of clinicians and biostatisticians, often numbering as few as three members (Herson, 2009, p. 22). In contrast, IRBs must be constituted with an eye to racial, gender, and cultural diversity, along with
at least one nonaffiliated and nonscientist member (45 CFR §46.107). While criticisms validly can be raised about the limited extent to which many IRBs operationalize these membership requirements, and the importance of further strengthening and delineating the role of nonaffiliated, nonscientist members (see, e.g., Anderson, 2006; Sengupta and Lo, 2003), IRB membership remains considerably broader than that of DSMBs. Once supplemented by DSMBs’ expertise in accurate data interpretation, this provides a firmer grounding for understanding the risks and benefits of trial continuation as perceived by trial participants and the community more generally. Collaborative ethical reflection by IRB and DSMB members on a trial’s ongoing ethical acceptability also confers considerable weight to their decision, increasing the likelihood of sponsor and investigator acquiescence.

On the flip side, a consultation requirement raises certain implementation questions. Perhaps most challenging is what should occur in the event of an unresolvable conflict between the DSMB and IRB on the acceptability of continuing a trial? Hopefully this will be a rarity: collaborative decision-making and consensus-building is undoubtedly the objective of this proposed reform. However, in the event of intractable conflict, I suggest that either party is entitled to take actions available to it (i.e., IRB termination of ethical approval, DSMB recommendation to trial sponsor for termination). So, an IRB could terminate its approval for a trial in situations in which a DSMB judges to be premature. Some may object that this jeopardizes scientific progress by expanding the situations in which a trial may be terminated early. Yet, it is important to recognize that DSMBs are only going to consult with reviewing IRBs in limited circumstances: namely, when a trial reaches a stopping boundary, or when it approaches a stopping boundary and the DSMB is considering termination. In these grey zones of data monitoring, an IRB decision to terminate ethical approval falls squarely within its regulatory remit. An IRB also will have had the opportunity to discuss the emerging data with the DSMB so a decision to terminate should be grounded in an accurate understanding of the emerging information—the biggest concern when it comes to IRBs’ satisfaction of their continuing review obligations. Remaining disagreements, therefore, will be grounded in different prioritizations of current participants as compared with future patients. Similarly, DSMBs should retain the right to recommend amendment or termination to the trial sponsor.

A related issue is the question whether such a consultation requirement would essentially lead to the creation of a second, competing, DSMB. Rather than value-add, such a body could be redundant, stretching limited trial monitoring expertise even further. If this proposal is implemented as intended, however, this should not be the result. As is the case now, the trial DSMB would be responsible for monitoring unblinded data, and making recommendations to trial sponsors, investigators, and IRBs for continuation up until the point of reaching a stopping boundary or another prespecified event. Only then
would IRB consultation be required: in other words, at the time of reaching a monitoring milestone that relevant parties, prior to trial commencement, have agreed warrants input beyond the confines of the DSMB. A collaborative consultation process of this nature is consistent with IRBs’ expertise in research subject protection and their regulatory responsibility to reevaluate trial risks and benefits based on emerging information.

3.4. Integrating DSMBs and IRBs?

Given the overlapping roles of DSMBs and IRBs in protecting the ongoing welfare of trial participants, a much broader question is whether their monitoring responsibilities should remain distinct. A few scholars have assessed the respective costs and benefits of integrating monitoring responsibilities, with contrasting positions on which Board should take ultimate responsibility. On the one hand, Valery Gordon and her colleagues suggest that DSMBs should operate in an advisory capacity to IRBs. They provide few details on how this relationship would function, relying primarily on pre-trial negotiations among investigators, IRBs, and DSMBs to determine, for example, the data to which IRBs will have access (Gordon et al., 1998). David DeMets and others propose the opposite hierarchy when it comes to trial monitoring, advocating the delegation of responsibility for monitoring participant safety to a centralized trial DSMB, which should operate on the basis of a “locally reviewed” DSMB charter. This, they argue, “would relieve local IRBs from [their monitoring] responsibility” (DeMets, Fost, et al., 2006). Essentially, the result is bifurcating regulatory responsibility for a trial’s ethical acceptability: localized IRBs would have regulatory responsibility for trial approval, while a centralized DSMB would have regulatory responsibility for trial monitoring. This would alleviate the need for IRB/DSMB communication since each would have clearly demarcated roles, the boundaries of which would be made clear to sponsors, investigators, and trial participants.

Despite the intuitive appeal of integrating IRB and DSMB monitoring responsibilities, strong arguments stand in the way of relinquishing power to either Board, at least as they are currently operate. The local, institutional basis of IRBs means that, for multisite trials, no single Board will have a good sense of the trial in its entirety (Califf et al., 2003). Nor do most IRBs have access to unblinded safety and efficacy information. Even if they did, most would not have the requisite biostatistics expertise to analyze such information. However, delegating IRBs’ monitoring responsibilities to DSMBs also seems unsatisfactory. Previous sections of this paper have shown the underregulated nature of DSMB structure and operations. New regulations presumably could be drafted to deal specifically with DSMBs; however, a more fundamental question surrounds the acceptability of tasking different bodies—with different expertise, membership, mandates, and so forth—with responsibility for
assessing the risk-benefit profile at a trial’s inception as compared with while
a trial is ongoing.

While integrating monitoring responsibilities appears vexed in the current
schema for human subjects protection, the push towards single ethical review
of multisite research may provide a more promising framework for integra-
tion. A principal reviewing IRB overcomes concerns about IRBs’ fragmented
understanding of the trial. To the extent that a single ethical review system
manages to lessen IRB workload concerns, the reviewing IRB may have greater
time and resources to undertake meaningful monitoring. Finally, to address
issues surrounding some IRBs’ limited expertise in biostatistics and clinical
trial design, reviewing IRBs could constitute trial monitoring subcommittees,
with similar membership to current DSMBs. These subcommittees, on condi-
tions of confidentiality, could be entrusted with reviewing unblinded safety and
efficacy information. In essence, DSMBs would be rebranded and resituated as
a trial monitoring subcommittee of the IRB. Clearly, such an overhaul raises
considerable practical questions (how flexible is subcommittee membership to
accommodate the clinical expertise necessary to monitor a given trial, would
the relationship between trial sponsors and the subcommittee be sufficiently
transparent, etc.). However, should single ethical review of multisite research
become ubiquitous, the benefits of integrating monitoring responsibilities in
this way warrants serious consideration.

CONCLUSION

DSMBs are an important innovation in trial monitoring with the potential
to ensure rigorous and independent monitoring of trial data. Yet DSMB deci-
sions about a trial’s ongoing ethical acceptability are highly discretionary and
steeped in confidentiality, raising structural concerns about our trial monitor-
ing framework. Most notably, DSMBs may employ different decision-making
matrices than by IRBs—those bodies with regulatory responsibility for safeg-
�guarding the rights and interests of research participants. No systems exist to
harmonize the ethical reasoning employed by DSMBs, IRBs, and others with an
interest in a trial’s ongoing acceptability, including sponsors and investigators.

In this paper, I suggest a range of reforms to promote a more connected data
monitoring system. In particular, I advocate better communication between
DSMBs, IRBs, and others at the pre-trial and post-trial stage. More contro-
versially, I suggest mechanisms to facilitate shared ethical reflection in limited
circumstances during the course of a trial. These “grey areas” of trial mon-
itoring decision-making include when a trial crosses a stopping boundary in
circumstances in which a DSMB considers recommending trial continuation
and when a trial approaches (but does not yet cross) a stopping boundary in
circumstances in which a DSMB considers recommending trial termination.
These reforms have the potential to promote a holistic and ethically robust
framework for monitoring clinical trials.
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NOTES

1. A more cynical interpretation would also reflect potential conflicts of interest a DSMB faces; in particular, a Board constituted by a commercial sponsor eager to market a new drug or indication for a drug. While recognizing the potential role that such conflicts of interest play in DSMB decision-making, this paper focuses, instead, on the structural disconnects that limit transparency even in the most well-intentioned and conflict-free Board.

2. At the second interim review, a total of 134 incident invasive breast cancers had been reported, including 89 in those randomized to placebo versus 45 among those randomized to tamoxifen. At the fourth and final review, a total of 239 incident breast cancers had been reported, including 154 in the placebo group versus 85 in the tamoxifen group. Presumably at least some of these women would have been diagnosed with breast cancer even if they had received tamoxifen; however, it is fair to suppose that at least some of them could have been prevented.

3. Essentially, ethical walls work by limiting disclosure of information to certain individuals who may be subject to a conflict of interest. These have been upheld as means of rebutting the presumption that an attorney has shared confidential information his or her law firm, thereby mitigating the effects of certain conflicts of interest in law firm representation.

REFERENCES


