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Liability issues for data monitoring committee members

David L DeMets^a, Thomas R Fleming^b, Frank Rockhold^c, Barry Massie^d, Thomas Merchant^e, Alan Meisel^e, Barbara Mishkin^f, Janet Wittes^g, David Stump^h, Robert Califfⁱ

In randomized clinical trials, a data monitoring committee (DMC) is often appointed to review interim data to determine whether there is early convincing evidence of intervention benefit, lack of benefit or harm to study participants. Because DMCs bear serious responsibility for participant safety, their members may be legally liable for their actions. Despite more than three decades of experiences with DMCs, the issues of liability and indemnification have yet to receive appropriate attention from either government or industry sponsors. In industry-sponsored trials, DMC members are usually asked to sign an agreement delineating their responsibilities and operating procedures. While these agreements may include language on indemnification, such language sometimes protects only the sponsor rather than the DMC members. In government-sponsored trials, there has been even less structure, since typically there are no signed agreements regarding DMC activities. This paper discusses these issues and suggests sample language for indemnification agreements to protect DMC members. This type of language should be included in DMC charters and in all consulting agreements signed by DMC members. *Clinical Trials* 2004; 1: 525–531. www.SCTjournal.com

Introduction

Clinical trials have become a central medical research tool in the evaluation of new interventions, including diagnostics, drugs, biologics, devices, procedures, nutritional supplements, alternative medicines and behavioral changes. Federal regulations require that all trials funded by the National Institutes of Health (NIH) or under the regulatory jurisdiction of the Food and Drug Administration (FDA) must have data monitoring for patient safety [1,2]. NIH guidelines require the establishment of data monitoring committees for multisite clinical trials involving interventions that entail potential risk to the participants and, generally, for Phase III clinical trials [3]. FDA is developing guidance to assist clinical trial sponsors in determining when a data monitoring committee is needed for optimal study monitoring [4].

A data monitoring committee (DMC) is an independent body that periodically and objectively reviews accumulating data in a trial to: 1) determine if there is evidence establishing lack of benefit or evidence of harm from an experimental intervention; 2) determine if the evidence for benefit of the intervention is convincing; or 3) assess if the trial has a serious ethical or scientific design flaw or operational problems such as poor recruitment, adherence or retention. While the DMC would recommend termination of a trial when the evidence about patient safety, treatment efficacy or data quality provides compelling justification to do so, the DMC also serves the important role of ensuring that trials go on to completion in the majority of settings when there is not compelling evidence for termination [5–8]. The DMC process for making any recommendation is complex and must take into account many considerations

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[9–12] such as the benefit-to-risk profile of the intervention, the internal consistency among primary and secondary outcomes, and the relevant data from sources external to the trial.

The challenge is how to determine what constitutes compelling evidence. Trials typically have multiple outcome variables, one or two being declared to be the primary outcome and others, while important, being relegated as secondary or even tertiary outcomes. Some measure clinical dimensions while others measure physiologic or biological markers. Some are more relevant to benefit while others focus on safety. As noted above, consistency among these variables is one important factor in determining whether a trial should be continued or terminated. For example, an experimental intervention may show impressive positive benefits for the primary clinical endpoint such as “stroke-free survival” but may have a negative trend for “overall survival” alone. Intervention effects on clinical outcomes may all be favorable but critical laboratory measures such as liver function tests may indicate potential longer term safety concerns. On occasion, a trial may be testing an intervention, already in common use for one indication, for a new indication. During the course of the trial, the DMC may observe that, contrary to expectations, a negative harmful trend for the primary clinical outcome or for mortality has emerged and the trial is unlikely to demonstrate the intervention to be beneficial in the new indication. However, the DMC must decide whether to let the trial proceed to determine if the intervention, already in use, is simply “not beneficial”, or is, in fact, “harmful”. This is an extremely challenging issue and one that must be evaluated for each individual trial and circumstance.

Monitoring the ebb and flow of accumulating data provided at interim analyses is difficult. An early trend for either benefit or harm can emerge, and then can become stronger or simply disappear as more data become available. Available statistical methods can assist DMCs in determining when a trend is sufficiently strong and persistent to be judged significant in the statistical sense. However, no single statistical method or analysis is adequate to assess fully the interim data for early evidence of intervention benefit or harm. Thus, the DMC members must rely ultimately on their experience and reasoned judgment in making any recommendations. Members of DMCs may, in fact, have differing opinions as to what actions to take. Furthermore, due to the complexities and uncertainties inherent in interim data, two different hypothetical DMCs reviewing the same data could come to different recommendations.

The choice between allowing a trial to continue too long or terminating too quickly creates a natural

tension. DMCs are constituted largely to protect current and future patients in the trial from exposure to a harmful intervention without an adequate compensating benefit. However, terminating a trial too early before the data are mature and convincing also raises ethical dilemmas. A prematurely terminated trial may fail to resolve the merits of a new or available intervention, either possible benefits or potential harm. Continuing the trial to provide longer follow up may have revealed the safety concern to be transient and the benefits very compelling. In this case, future patients might be denied access to a beneficial treatment. In another case, continuation of the trial may have revealed that a commonly used but untested intervention would be not only without benefit but actually harmful. Here, premature termination may lead to more patients outside the trial being exposed to a harmful intervention if that is the current medical practice. In some cases, decisions made during the course of the trial with partial data may appear incorrect when the data later on become fully updated and finalized. Knowledge that this could occur can weigh heavily on some decisions, but it is critical that important decisions on safety monitoring be guided by the available data, the predetermined monitoring plan and the DMCs ultimate responsibility to the trial participants.

The DMC is largely an advisory body to the trial sponsor and the steering committee. It carries out its responsibilities primarily on behalf of the participants in the trial, and secondarily on behalf of the study investigators, the steering committee, the sponsor and future patients. DMCs also have responsibilities to the local Institutional Review Boards (IRBs) and to governmental regulatory authorities. The DMC's charter usually describes its composition, responsibilities, and operational procedures [5].

Given the responsibilities of DMC members and the recent increase in litigation in human subject research [12], the topic of legal liability for their actions has received surprisingly little attention. For NIH-sponsored trials, the institute director usually writes a very brief letter of invitation without any mention of liability. Individual members are not asked to sign documents that address liability. For industry-sponsored trials that use an external DMC, DMC members usually sign a consulting agreement. Such agreements typically include explicit language on indemnification, the purpose of which is to protect the sponsor from any liability that may arise as a consequence of the DMC's functioning, rather than to protect the members of the DMC from liability. For NIH-sponsored trials, liability coverage for DMC members is handled on a case-by-case basis and is dependent on the mechanism by which the member is appointed. Recently, in recognition of

the importance of the vital role of data and safety monitoring boards, NIH has begun to assess the adequacy of existing options and to consider whether to implement more uniform approaches to ensure consistent liability coverage. The approaches routinely used in current practice are inadequate for the protection of DMC members and inappropriate in light of the special circumstances of the DMC and the trial it oversees. Given the special role of a DMC, the members should have the same level of protection as investigators. These aspects of DMC liability have not been widely discussed previously and are presented more fully below.

Potential areas of DMC liability

Monitoring of accumulating data can be quite complex, relying not only on the technical expertise of the DMC but also on their experience and judgment [9–12]. Often, the DMC is the only body, other than the statistical team that generates the reports providing the interim results to the DMC, with access to unblinded efficacy and safety data. The role of the DMC to monitor for early evidence of benefit, lack of benefit or harm raises the real possibility of civil legal liability for DMC members should a subject in a monitored clinical trial feel they were harmed by a recommendation of the DMC. Even if the likelihood of a law suit is low, the serious consequences make the issue important. Defending a lawsuit can entail significant financial and emotional costs. At least one DMC for a high visibility NIH funded trial recently resigned because of the sponsor's failure to provide adequate legal protection for its members [13].

The following paragraphs present three hypothetical examples of situations that could lead to liability claims even though the DMC may have responded appropriately in carrying out their responsibilities on behalf of patients, investigators and sponsors:

Example 1

A trial comparing two marketed therapeutic regimens provides substantial evidence of a difference in the primary endpoint of all-cause mortality, but these results have not yet crossed the predefined conservative sequential boundaries for early termination. The trial continues and, when these boundaries are subsequently crossed, the DMC recommends early termination. Subsequently, the family of a study participant, who died shortly before the DMC recommended termination, considers instituting a lawsuit against the sponsor,

the DMC members and the statistician for not terminating the trial when strong positive trends first emerged in the trial, a decision that they claim caused the subject's death.

Example 2

The protocol for a trial has a composite primary endpoint of death, nonfatal MI and nonfatal stroke. The trial has appropriate sequential monitoring boundaries for the composite endpoint for evidence of benefit, lack of benefit or harm. While the interim results for the composite endpoint indicates a strong trend favorable for the new treatment, the results also show a statistically nonsignificant excess of disabling hemorrhagic strokes. A patient in the experimental arm of the trial suffers a disabling stroke and sues the treating physician, the sponsor and the DMC members for not revealing this excess in nonfatal strokes during the course of the trial, which he claims would have led him to withdraw from the trial before he suffered the stroke.

Example 3

In a variation of the previous scenario, the evidence for treatment effect on the primary composite endpoint of death, nonfatal MI and nonfatal stroke crosses the monitoring boundary for benefit as a result of a large reduction of risk of nonfatal MI. However, the DMC recommends continuation because of a worrisome unfavorable trend in mortality. A patient in the control arm of the trial suffers an MI late in the trial and sues the DMC, claiming that terminating this trial when the benefit on MI was apparent would have prevented this event, because such action would have enabled patients in the control arm to obtain earlier open label access to the experimental treatment.

Protection of DMCs from liability risk

Until recently, concerns about the imposition of liability on DMC members have been theoretical. However, the death in 1999 of a patient in a gene therapy trial brought widespread public attention to the fact that patients entering trials do incur risks [14], and that some trials may be conducted in a manner that rises to the level of legal negligence. This event triggered two new policies in the US relevant to the issue of DMC liability: 1) that all clinical trials funded by the NIH, regardless of their phase of development, are required to have a monitoring plan [4]; and 2) that for randomized trials, regardless of sponsor, where the disease or treatments create serious risks, an independent

DMC is generally warranted [3]. As a consequence of this heightened public awareness of research risks, DMCs' recommendations may be subject to scrutiny not only by peers, IRBs and regulatory agencies but also by subjects and/or their families, patient advocacy groups and the public at large. There is an increased concern that the actions of a DMC may be used inappropriately as a basis for litigation. DMC members can be protected in a number of ways if litigation emerges.

Protections based on law

The most fundamental protection would be based on a claim that members of DMCs owe no legal duty to subjects in clinical trials. If such a claim were successful, the case would be dismissed before it ever went to trial. Given the trends in modern tort law, this is not a particularly promising means of protection for DMC members. Furthermore, the uncertainty and substantial costs of any litigation, leads to tremendous pressure to settle cases, typically with a monetary payment. Thus, a DMC member might be financially liable for injuries to a subject even if no legal duty to subjects were established.

If a case went to trial, a number of defenses could be raised. First, for an injured subject to prevail, he or she must demonstrate that that DMC members were "*negligent*" in their conduct – that is, that they failed to conform to recognized standards of practice among DMC members. If such standards do not exist or if there is considerable dispute as to what they are, this poses a significant hurdle to the injured subject's success in the lawsuit. Even if it is determined that the DMC members were negligent, the subject must also establish that this negligence was the *cause* of the subject's injury – that is, that the subject would not have been injured if the DMC had acted in conformance with the established professional standard. Thus, in Example 3 above, the patient would have to show that he would not have suffered an MI if the trial had been stopped and he had, as a result, gotten access to the new experimental medication. Proof of causation could also be a particularly onerous burden for a subject to meet. Even if DMC members were found liable, an appeal could be made, and settlement discussions would certainly continue before and during the appeal.

Protections based on contract

Even if ultimately successful, in the sense that no liability is imposed or settlement payment made, legal proceedings are a lengthy, expensive and

arduous process. Although these burdens cannot be eliminated, they can be significantly mitigated if the DMC members' defense costs and possible financial liability are borne or reimbursed ("indemnified") by a third party.

Indemnification is ordinarily obtained through an insurance policy, but it is uncertain at this time that there is any market for such a specialized form of insurance or, if there is, whether such a policy would be affordable. In theory, indemnification can also be provided by a third party other than an insurance company and that is most likely to be either the employer of the DMC member or the trial's sponsor. Such an agreement would be established in a contract that requires one of these parties to reimburse the DMC member for any liability incurred while acting in that capacity, under specified conditions. Even in the absence of a prior indemnification agreement, a sponsor or an employer may agree at some later time (e.g., in the course of litigation, or after liability is imposed) to indemnify the DMC member, but this leaves the DMC member at the mercy of that party's goodwill.

As an alternative to contractual indemnification for liability, an employer or a sponsor might, through in-house counsel, provide a legal defense for DMC members without agreeing to indemnify against liability that might be incurred through judgment or settlement. If this approach were to be used, it should be accompanied by notice to the DMC members of a possible conflict between the DMC member's interests and the employer's interests and the DMC member's consent to be represented in this way nonetheless.

Indemnification of a DMC member by his or her employer is not likely. DMC members are usually drawn from academic or research institutions, which typically do not indemnify against liabilities incurred through an external consulting activity, no matter how valuable or academically justifiable that service might be. Furthermore, many universities and research institutions do not have in-house counsel, or do not have sufficient in-house counsel to provide a legal defense.

Government-sponsored trials

The level of protection that is provided for those who serve on government-sponsored trials varies depending on the mechanism by which the DMC member's services are obtained. Recipients of NIH grants, cooperative agreements and contracts may charge the costs of insurance to the award. This is typically charged as part of the administrative portion of the facilities and administrative (F&A) rate. For colleges and universities, the Office of Management and Budget has capped the administrative portion of the

F&A rate to not exceed 26%. For some NIH-sponsored trials, members are appointed as special government employees (SGEs) for the days that they are serving on a DMC. The Federal Torts Claims Act (FTCA) covers members serving as SGEs for their DMC activity. Under this act, the US assumes liability for common law torts committed by its employees within the scope of their employment. Subject to the approval of the Department of Justice, the FTCA may cover uncompensated volunteers. In other cases, members of DMCs for NIH-sponsored trials may be appointed as a contractor either by the NIH or by another entity such as a research institution or trial coordinating center. Although the FTCA does not cover contractors and their employees, they can be provided liability coverage through other mechanisms. NIH is in the process of reviewing the adequacy and consistency of the use of liability coverage mechanisms for DMC members who serve as contractors. Given the modest level of compensation provided to DMC members by the federal government for their service on DMCs, one immediate solution proposed might be for the NIH to obtain justice department approval and allow all members to serve as unpaid volunteers, being reimbursed only for travel expenses to DMC meetings.

Industry-sponsored trials

The agreement a consultant signs when becoming a DMC member, sometimes includes language about liability and indemnification. However, the agreement generally removes, rather than provides, protection to DMC members. These agreements are usually standard consulting contracts written by the sponsor's legal department, with the intention of assuring that any legal liability is imposed on the members of the DMC rather than on the sponsor. Such contracts not only put DMC members at considerable risk, they may actually increase their risk by requiring them to indemnify the sponsor if the sponsor is held liable as a consequence of DMC decisions. An example of such language is shown in Figure 1.

A DMC member provides expertise and service to the sponsor for the benefit of the subjects in the clinical trial. Therefore, it is fair that the sponsor should not only avoid attempting to shift liability to DMC members, but should provide legal protection to DMC members – in the form of indemnity for liability and for the costs of retaining legal counsel – in the remote event that this is needed.

Potential solutions

There are a number of possible options to address the issue of DMC members' liability. First, the

Member shall indemnify, defend and hold Sponsor harmless from and against any claim, loss or damage whatsoever (including reasonable attorneys' fees and expenses) arising out of Member's performance of this Agreement. The foregoing obligation is in addition to, and not in limitation of, any other rights and remedies Sponsor may have against Member arising in connection with this Agreement. In addition, Sponsor shall not be liable for any personal injury to Member nor for loss or damage to any personal property belonging to Member or in Member's custody or possession while using or accessing Sponsor's facilities other than that arising from the active negligence of Sponsor.

Figure 1 Example of standard indemnification agreement

sponsor's legal office could provide any necessary legal defense and indemnification of awards of damages, and some DMCs do operate under such an arrangement. However, while such support from a sponsor's legal office would be more desirable than having no defense, the lawyers assigned to such a case would have split loyalties since the preferred solution for the DMC members might differ from that preferred by the sponsor. The optimal arrangement for DMC members is for the sponsor to pay for DMC members to retain legal counsel to represent the members, who would work in collaboration with the sponsor's legal office unless there were conflicts, and to indemnify against an award of damages. A few trials have put such agreements into effect using language such as that shown in Figure 2.

This approach gives the DMC member reasonable legal protection. It also better serves the interests of the clinical trial and the investigators because this kind of arrangement frees the DMC to make its best judgments and recommendations without undue

Sponsor agrees to indemnify and hold harmless consultant and its academic institution from any and all third party claims, actions, lawsuits, losses, and reasonable expenses ("Claims"), including reasonable legal fees and expenses, related to services that Consultant provides pursuant to this Agreement, except with regard to Claims brought by Sponsor or Contract Research Organization (CRO), and except to the extent finally determined to have resulted from the willful misconduct or fraudulent acts of the Consultant relating to such services.

Figure 2 Phrasing from a DMC consultant contract

concerns about legal liability. DMC members would not be entirely free of concerns about legal liability because they would still be required to act in good faith, or risk loss of their indemnification, and the law generally prohibits indemnification for intentional wrongdoing. However, indemnification for negligence committed in good faith would free DMC members from being inappropriately concerned about their own personal liability rather than the well-being of study subjects.

The language of the indemnification agreement, shown in Figure 2, is far better than that in Figure 1. The contents of Figure 3 represent wording recently negotiated for several other trials in the industry setting, and seems to be the minimum standard that DMC members should expect for either industry- or government-sponsored trials.

The Company [i.e., sponsor] will defend, indemnify and hold harmless the Consultant from any liability, loss, damage, costs and expenses of claims and suits (including reasonable attorneys' fees, costs and expenses of handling such claims and defending such suits) resulting from the participation of the Consultant on the Data Monitoring Committee as part of the Services, except that the Company will not be required to defend, indemnify and hold harmless the Consultant where any claim or suit arises from:

- (i) the failure of the Consultant to comply with any applicable laws or regulations or to adhere to the terms of the Data Monitoring Committee Charter for the clinical trial; or
- (ii) a judicial finding of willful misconduct of the Consultant.

The Company's obligation to defend, indemnify and hold harmless the Consultant is subject to the following conditions:

- (i) that the Company is provided with written notice of any claim or suit within seven (7) days of receipt thereof by the Consultant;
- (ii) that the Company retains the right to defend the claim or suit, in any manner it deems appropriate, including the right to retain the legal counsel of its choice;
- (iii) that the Company has the sole right at its expense to settle the claim or suit; and
- (vi) that the Consultant tenders the defense of any such claim to the company and co-operates fully in the investigation and with defense of any such claim or suit.

Figure 3 Indemnification for DMC members

Conclusions

The methodology for the design, conduct and analysis of clinical trials continues to improve. One area of improvement is the development of the science of trial monitoring, including the role of DMCs. As this methodology evolves, new issues emerge. A uncharted territory that is becoming increasingly important in both industry and federally sponsored trials is the liability that a DMC as a whole or its individual members may assume in carrying out their critical function. While we know of no instances in which a lawsuit has yet been brought against members of a DMC, the possibility exists. Given long-standing trends in tort law, it seems just a matter of time before this theoretical possibility materializes. The potential loss in resources, time, and reputation in the event of a lawsuit could be devastating to the DMC members and to their families. Such a lawsuit might also be destructive to the clinical trial enterprise, as it would provide a major disincentive to service on a DMC that had no liability protection.

The language currently used in many consulting agreements inappropriately puts DMC members at risk for lawsuits, or at least puts them in a position where protecting their personal financial interests could conflict with their mandate to protect the interests of subjects and the integrity of science. Thus, to provide necessary protection for DMC members, sponsors must develop more appropriate language in letters of appointment or in formal contracts used to engage DMC members. Sponsors should use generic language such as that in Figures 2 and 3 in these formal agreements with DMC members as well as in DMC charters.

Legal liability is an omnipresent fact of all aspects of contemporary life, both personal and professional. DMC members should not be, and are not, seeking special protection not accorded others. DMC members should assume a fair allocation of legal responsibility. What this means in practice is that DMC members should neither be free from legal liability nor should they be forced to bear the entire brunt of it through one-sided contractual arrangements. A fair allocation of legal liability needs to take into account the role of sponsors as well as that of DMC members. In the final analysis, subjects will be better protected by an equitable distribution of legal responsibility. A too-heavy allocation of responsibility to DMC members could make them overly cautious in their judgments. On the other hand, providing too much protection to DMC members would afford inappropriate liability protection for willful misconduct. It is in the best interests of all for an equitable balance to be struck.

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