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Data Monitoring Committees: Current issues

Thomas R Fleming[1], Susan S Ellenberg[2] and David L DeMets[3]

Abstract

Maintaining confidentiality of emerging data and ensuring the independence of Data Monitoring Committees are best practices of considerable importance to the ability of these committees to achieve their mission of safeguarding the interests of study participants and enhancing the integrity and credibility of clinical trials. Even with the wide recognition of these principles, there are circumstances where confidentiality issues remain challenging, controversial or inconsistently addressed. First, consider settings where a clinical trial's interim data could provide the evidence regulatory authorities require for decisions about marketing approval, yet where such a trial would be continued post-approval to provide more definitive evidence about principal safety and/or efficacy outcomes. In such settings, data informative about the longer term objectives of the trial should remain confidential until pre-specified criteria for trial completion have been met. Second, for those other than Data Monitoring Committee members, access to safety and efficacy outcomes during trial conduct, even when presented as data pooled across treatment arms, should be on a limited "need to know" basis relating to the ability to carry out ethical or scientific responsibilities in the conduct of the trial. Third, Data Monitoring Committee members should have access to unblinded efficacy and safety data throughout the trial to enable timely and informed judgments about risks and benefits. Fourth, it should be recognized that a mediator potentially could be useful in rare settings where the Data Monitoring Committee would have serious ethical or scientific concerns about the sponsor's dissemination or lack of dissemination of information. Data Monitoring Committee Contract Agreements, Indemnification Agreements and Charters should be developed in a manner to protect Data Monitoring Committee members and their independence, in order to enhance the Data Monitoring Committee's ability to effectively address their mission.

Keywords

Independence, mission, indemnification, confidentiality, mediator

Introduction: the mission of the Data Monitoring Committee and an overview of Data Monitoring Committee best practices

The mission of Data Monitoring Committees (DMCs) is to safeguard the interests of study participants and to enhance the integrity and credibility of clinical trials. Of considerable importance to the DMC's ability to achieve this mission are best practices that include maintaining confidentiality of emerging data and ensuring the independence of DMCs from sponsors and investigators.[1–6]

An earlier article provided in-depth consideration of DMC best practices and operating principles to enhance their independence and effectiveness.[1] That article addressed the importance of better training opportunities for DMC members, approaches to protect DMC members against legal liability arising from their service, avoiding DMC Charters that specify overly rigid procedures rather than principles to guide the DMC process, developing DMC recommendations through a consensus rather than voting process, structuring DMC meetings in a way that maintains the independence of the DMC and clearly establishes the leadership of the DMC chair, and ensuring that the independent statistical group that generates the reports

[1]Department of Biostatistics, University of Washington, Seattle, WA, USA
[2]University of Pennsylvania, Philadelphia, PA, USA
[3]University of Wisconsin–Madison, Madison, WI, USA

Corresponding author:
Thomas R Fleming, Department of Biostatistics, University of Washington, Box 357232, Seattle, WA 98195-7232, USA.
Email: tfleming@uw.edu

reviewed by the DMC has sufficient depth of knowledge about the study at hand and experience with trials in general to provide the DMC with timely, reliable and readily interpretable insights about emerging evidence in the clinical trial.

In this article, we will expand on DMC best practices and operating principles that enhance its independence and effectiveness, by considering some important confidentiality issues and procedures for engagement and indemnification of DMC members.

Confidentiality issues

Overview

A widely recognized principle is that "members of the DMC should ideally be the only individuals (other than the statistician(s) performing the interim analyses) with access to interim data on the relative efficacy and relative safety of treatment regimens."[2,7,8] Maintaining confidentiality of interim data reduces the risk that unreliable and potentially misleading results will be disseminated. Furthermore, it protects against prejudgments that can result in declining enrollment, and reduced adherence, retention and flexibility to implement modifications to trial design motivated by emerging data from sources external to the trial.[7,9] The "Data Monitoring Committees: Lessons, Ethics Statistics Study Group" (DAMOCLES) project commissioned by the United Kingdom National Health Service Health Technology Assessment Program stated, "There is near unanimity that the interim data and the deliberations of the DMC should be absolutely confidential."[10]

Even with such wide consensus, there continues to be some occasions where interim data from ongoing trials have been released or even published, inappropriately, and other circumstances to be discussed in this section where confidentiality issues remain controversial, challenging or inconsistently addressed.

When interim data are unblinded for regulatory review in ongoing clinical trials

Some clinical trials are designed to provide interim data to regulatory authorities in support of initial marketing approval, and then to be continued post-approval to provide more definitive evidence about principal safety and/or efficacy outcomes. In such trials, there clearly is a risk that confidentiality of emerging data about these principal outcomes will not be properly maintained, posing challenges to successfully accruing the required longer term information about the intervention's benefit-to-risk profile.

Such concerns arise in some regulatory settings, where "replacement" endpoints such as biomarkers or intermediate clinical measures can support regulatory approval, but with the expectation that the trial continue in order to provide evidence about longer term measures of clinical benefit such as irreversible morbidity or mortality. Hence, when the initial data are released for regulatory review, it is important to continue to protect the confidentiality of the emerging data on the longer term outcomes. This will require limiting access to these emerging data to the DMC until prespecified criteria for trial completion have been met.

Cardiovascular safety trials in type 2 diabetes mellitus or in obesity raise similar challenges. In these trials, marketing approval may be granted if large relative increases in cardiovascular risk can be ruled out by the interim data, but with the understanding that the trial must be continued post-marketing to assess whether a pre-specified smaller increase in risk could be ruled out. At a Food and Drug Administration (FDA)–sponsored Open Public Hearing held in August 2014, contributors from industry, government and academia agreed that sponsors and regulators should maintain confidentiality of these interim data in order to protect the ability of the trial to provide the required long-term safety assessment. Toward this end, we advocate development of a Data Access Plan that restricts access to these interim data to a small group of sponsor representatives on an "unblinded team" who can prepare reports to regulatory authorities and who agree to maintain confidentiality of the emerging data.[11] Regulatory authorities should also agree to maintain the confidentiality of these interim data.

Sponsors and regulatory authorities generally have been successful in maintaining the confidentiality of interim data in this setting. However, the ramifications from a failure to do so are illustrated by the experience of the LIGHT trial; in this trial, interim data unfortunately were broadly released by the sponsor, with major adverse consequences.

This trial was designed to provide a placebo-controlled evaluation of the cardiovascular safety of naltrexone–bupropion in overweight and obese subjects with cardiovascular risk factors.[12] The primary endpoint was the composite of cardiovascular death, stroke and myocardial infarction. The 9000 enrolled subjects were to be followed until 378 primary events were reported, providing high power for determining whether a non-inferiority margin of 1.4 could be ruled out. By design, FDA would consider marketing approval if the data from the first quadrant of the trial (i.e. at the interim analysis with approximately 87 events) ruled out a non-inferiority margin of 2.0, with the understanding that the trial would continue in a blinded manner until the planned total of 378 primary endpoints had been observed.

Approximately 18 months into the trial, the DMC reviewed interim data from the first quadrant. As shown in Table 1, these data with 94 primary endpoint events were favorable for naltrexone–bupropion, clearly

Table 1. Interim results[12] from the LIGHT trial evaluating cardiovascular safety of naltrexone–bupropion in overweight and obese subjects with cardiovascular risk factors.

	CVD/stroke/MI	Overall deaths			Stroke	MI	Death/stroke/MI
		CV	Non-CV	Total			
"First Quadrant": Events up to November 23, 2013							
Naltrexone–bupropion	35	5	5	10	7	24	40
Placebo	59	19	3	22	11	34	62
Hazard ratio	0.59						0.64
"Second Quadrant": Events between November 23, 2013, and March 3, 2015							
Naltrexone–bupropion	55	12	21	33	15	31	74
Placebo	43	15	14	29	10	23	57
≈ Hazard ratio	1.29						1.29
"End of Study": Publication of final results (on March 8, 2016)							
Naltrexone–bupropion	119	26	39	65	31	69	156
Placebo	124	42	29	71	23	71	151
Hazard ratio	0.95						1.02

CV: cardiovascular; CVD: cardiovascular death; MI: myocardial infarctions.
These results appear (or are directly derived from data) in Tables 2–4 in Nissen et al.[12] "Hazard Ratio" denotes the estimated hazard ratio.
"≈ Hazard Ratio" denotes the approximate estimated hazard ratio when using only events in the "second quadrant," as computed from results in Tables 2 and 4 of Nissen et al.[12]

ruling out the 2.0 margin. The DMC recommended that regulatory authorities and the sponsor's "unblinded team" receive access to these data and that the trial be continued with confidentiality maintained according to specifications in the trial's Data Access Plan. FDA granted marketing approval on the basis of these data, although expressing concern when informed that "more than 100 people, including the board of directors, had had access to the unblinded interim results." FDA stated that those actions by the sponsor had "the potential to compromise the integrity of the LIGHT trial."[13]

Sixteen months after the first interim analysis, the DMC performed the second interim analysis on data from the first and second quadrants. As seen in Table 1, the evidence from the second quadrant was quite inconsistent with the favorable evidence from the first quadrant. Recognizing that the cumulative data clearly did not cross the pre-specified monitoring boundaries for establishing superiority or harm, the DMC recommended that the trial continue and that confidentiality of interim data be maintained. Unfortunately, on that same day, the sponsor publicly released the data from the first quadrant as part of a report filed with the Securities and Exchange Commission on a patent that claimed "a positive effect ... on [cardiovascular] outcomes." This report of early results was seriously misleading, since the aggregate data at this point in the trial were very inconsistent with the data from the first quadrant only and it was unclear what the final conclusions would be. This release of information, in violation of the prior agreements (and in fact not formally required by Securities and Exchange Commission regulations), led the steering committee of the LIGHT trial to recommend that the trial be terminated; the sponsor agreed.[12]

The final report of the LIGHT trial was based on 243 events, 64% of the target number[12]; the estimated naltrexone–bupropion to placebo hazard ratio was 0.95, much higher than the first quadrant estimate of 0.59 that had been released to the public (see Table 1). Furthermore, non-cardiovascular deaths that were excluded from the primary endpoint were more frequent on naltrexone–bupropion. The estimated hazard ratio for the composite endpoint that included all deaths in addition to strokes and myocardial events was 1.02.

The 1.4 safety margin could not be reliably addressed due to the irregularities in trial conduct. Therefore, the FDA and the authors of the LIGHT trial publication[12] recognized that the sponsor would need to conduct a new adequately powered cardiovascular safety trial. This experience illustrates the instability of interim data, how seriously the public can be misled and trial integrity can be harmed by breaches in confidentiality and the additional resources that could be required as a consequence of inappropriate early data release.

Access beyond the DMC to aggregate data on safety and efficacy outcomes

Aggregate data on efficacy and safety outcomes—that is, outcome data pooled across all study groups—are sometimes presented in Open Sessions of DMC meetings and thus have been broadly available to sponsors, investigators and even investors. However, since such data could provide insights regarding the relative benefit-to-risk profiles of the treatments being compared, these data usually should not be broadly shared during the trial. For illustration, in a clinical trial of an

experimental drug in advanced cancer patients, suppose historical evidence suggests 2-year survival should be approximately 15% in the control arm. When one-half of the trial's targeted number of endpoints has occurred, if estimates of 2-year survival in the pooled treatment and control group were 25% or 10%, these pooled results would give a strong impression that the experimental regimen is effective or ineffective, respectively. Whether or not that impression is correct, resulting actions taken by trial investigators, sponsors or patients could compromise trial integrity and credibility.

Some circumstances do require access to aggregate data by at least some members of the investigative team. Among these are the needs to consider the adequacy of the sample size, or to perform adjudication of reported endpoints, or to more effectively monitor adherence. For example, in a major morbidity/mortality outcome trial when treatment effects on a supportive biomarker such as blood pressure, CD4 cell count or hematocrit levels previously have been well-documented, access to pooled data (or even data by study group) regarding effects on that biomarker would not provide new insights about efficacy yet could enhance quality of trial conduct by alerting investigators if targeted levels of adherence were not being achieved. Access by non-DMC members to aggregate data on efficacy or safety outcomes should be on a "need to know" basis relating to the ability to safeguard patient interests and protect trial integrity, and should be provided to as small a group as possible to limit violations of confidentiality.

DMC access to unblinded efficacy and safety data throughout the clinical trial

Some have advocated that DMC members review data only by treatment codes (e.g. A vs B), without access to the actual treatments. This practice, presumably intended to enhance the objectivity of the DMC, is misguided, as it can hamper rapid recognition of potential emerging harm.[1–4,14] In addition, it is impractical in many studies in which the comparison of rates of specific adverse events would reveal the actual treatments.

The Cardiac Arrhythmia Suppression Trial[15] illustrates the risks for delayed recognition of harm in a trial that used such A/B coding in presentation of interim results to the DMC.[2] The DMC for that trial was not provided unblinded data by the statistical center until the numbers of sudden deaths were 33 versus 9, and for overall mortality, 56 versus 22, both favoring placebo. While the DMC then promptly recommended the trial be terminated, this blinding potentially caused a delay in this action and reduced the time the DMC had to thoughtfully respond to the emerging evidence.

Some sponsors have tried to limit the role of the DMC to reviews of "safety data." This practice prevents a risk–benefit assessment. For example, in a trial of antiplatelet therapy, bleeding is a key safety outcome. However, noting an increase in the risk of bleeding without any information regarding the potentially decreased risk of ischemic events or even mortality would create a one-sided and misleading view of safety.[16]

The DMC should have ongoing access to any available data needed to carry out their primary responsibilities. The DMC, selected for its expertise and lack of major conflicts of interest, is properly positioned to assess interim data without an undue risk for prejudgment or breaches in confidentiality. The DMC's ongoing access to unblinded safety and efficacy data enables more timely recognition of an emerging problem and thereby increases its ability to protect trial participants.[14] Furthermore, the DMC's access to efficacy as well as safety data is essential to making an informed decision about safety in the context of a benefit-to-risk assessment.

Access to unblinded efficacy and safety data on an ongoing basis also increases the DMC's ability to identify irregularities in trial conduct and then to recommend approaches to improve the timeliness and reliability of data capture. Such access has also assisted the DMC in identifying coding errors in the generation of the DMC reports.[2] For example, in two clinical trials, one conducted in an acute care setting (see example 2.5 in Ellenberg et al.[2]) and the other an oncology trial, the DMC, with full access to emerging data, was able to identify a reversal of treatment codes in the DMC report in a timely manner, based on their recognition of unexpected patterns in the relationship of the intervention with some measures of safety, efficacy and treatment discontinuation.

Balancing legal and ethical responsibilities: the need for a mediator?

While infrequent, there have been situations where the DMC has believed the sponsor's dissemination or lack of dissemination of information to the trial participants and the public to be scientifically misleading or ethically inappropriate. How should the DMC proceed in such settings?

For illustration, consider a setting where a sponsor, after receiving unblinded comparative data at trial completion, makes public statements that the DMC believes substantively misrepresent trial results and could lead to inappropriate use of a treatment. Furthermore, as a reviewer of this article noted, DMC members who have been acknowledged in the study publication could be perceived (improperly) as being aligned with the sponsor's interpretation of trial data, even though they had not been provided any opportunity to influence the public presentation of results. While the DMC would

have completed its formal responsibilities to protect study subjects during trial conduct, members may want to speak out to protect the interests of the broader public. Yet, speaking out in such instances could place the DMC members at significant risk of litigation, in part through violations of confidentiality agreements in their contracts that typically remain in effect for a substantial period of time after trial completion.

These types of situations have occurred, both in public- and private-sector trials, and have motivated consideration about whether some type of mediation process for DMCs is needed.[1] This process would enable the DMC members and the sponsor to share their concerns with a mediator having expertise in the issues addressed by the trial and who would be judged objective and impartial by both DMC members and the trial sponsor. After hearing concerns from both sides, the mediator would render their opinion or conclusion about what information should be disseminated to the public in a timely manner.

Important motivations for sponsors to agree to such a mediation process would include their desire to maintain or heighten their reputation for both strong science and ethics. Both trial sponsors and DMC members would need to perceive the mediator to be an impartial arbiter who is appreciative of the issues faced by commercial sponsors as well as the scientific and/or ethical issues motivating the need for mediation. Possible organizations that could take responsibility for selecting mediators and sponsoring the mediation process could include an industry trade association such as the Pharmaceutical Research and Manufacturers of America, a scientific research institution such as the National Academy of Medicine, or a professional society such as the Drug Information Association, the Society for Clinical Trials or Public Responsibility in Medicine and Research (PRIM&R).

Procedures for engagement and indemnification of DMC members

DMC contracting process in industry-sponsored trials

DMC contracts over the past three decades have become longer and more complex. Frequently, companies offer potential DMC members a standard outsourcing contract that covers many areas not relevant to the functioning of a DMC. Such contracts tend to use technical and legally binding language that is inconsistent with the DMC's role as independent scientists whose primary focus is to safeguard the interests of study participants and to enhance trial integrity rather than to support product development.

Ideally, DMC members should be engaged through "independent scientist agreements," to reduce the risk of real or perceived conflicts of interest. Using the language of "independent scientist" emphasizes that these individuals are independent of the sponsor, using their scientific expertise to interpret the emerging data and trial progress without bias.

A DMC contract should cover five basic areas. First, the contract should briefly state the purpose and areas of responsibility of the DMC for a particular trial.

Second, the contract should address the issue of confidentiality. While it should recognize that the DMC needs access to interim emerging data by treatment arm to address its mission, the DMC contract should indicate that the DMC members are obligated to keep these interim data absolutely confidential. Leaks could jeopardize interests of the sponsor and the public, including protecting the scientific integrity of the trial and achieving its successful completion.

Third, contracts should state that the scientific insights learned from the conduct of the clinical trial are intellectual property owned by the sponsor and that the data from the trial could be used for regulatory submission and commercial purposes. These contracts also should indicate that methods for the design or analysis of trials that were previously or newly developed by the DMC member, even if this development had been motivated in part by this trial, are the intellectual property of the DMC member.

Fourth, the DMC contract should specify terms of indemnification, provided directly by the sponsor or the entity issuing the contract. Unless this is spelled out in the DMC contract, DMC members typically would not be covered for liability by the sponsor because they are not employees of the sponsor (nor would they be covered by many academic or research institutions that view DMC activity in support of industry trials as being external to the member's institutional responsibility).

Finally, the contract with the DMC member should outline the honorarium amount per meeting or per hour that will be paid to the individual member. That amount usually is determined separately for each member since it depends on the role and level of effort expected or required. For example, greater effort usually is required from the DMC's chair.

DMC indemnification agreement

Indemnification for DMC members is needed, given several sources of possible liability that they face from clinical trial stakeholders.[1,17,18]

For trials sponsored by industry, Box 1 provides a template for standardized indemnification wording to be included in legal agreements with DMC members and is similar to that provided in Figure 2 of DeMets et al.[19] DMC members should not be required to indemnify the sponsor. Furthermore, an "opt-out" of indemnification (i.e. circumstances removing the sponsor's requirement to indemnify the DMC members) should not be based on "negligence," which is a very low bar, but rather should require the higher standard

Box 1. The DMC Indemnification Agreement Template.

Re: Study Identification (including specification of the clinical setting and regimens being evaluated).
[Sponsor name] ("Sponsor") agrees to indemnify and hold harmless [DMC Member's Name] (the "Indemnitee"), from any and all third party claims, actions and lawsuits ("Claims"), including any liability, losses, costs (including reasonable attorneys' fees and expenses), arising as a result of performance of Data Monitoring Committee membership duties relating to the above-referenced study, except with regard to Claims brought by Sponsor or Contract Research Organization, and except to the extent the Claims are judicially determined to have resulted from the gross negligence, willful misconduct, or fraudulent acts of the Indemnitee relating to such services. The Sponsor's obligations in the foregoing sentence are conditioned upon the Indemnitee: (a) providing the Sponsor prompt notice of any such Claims; (b) providing the information and assistance necessary for the defense and settlement of such Claims; and (c) not entering into any settlement with respect to such Claims without the express consent of the Sponsor. The Sponsor's obligation to indemnify the Indemnitee will survive the termination or expiration of this legal agreement.

of "a judicial finding of gross negligence, willful misconduct, or fraudulent acts."[19]

In the industry setting, while an increasing fraction of DMC members are indemnified by sponsors, very often such protection is provided only when it is specifically requested by DMC members. Furthermore, the negotiation process to finalize an indemnification agreement can be lengthy. The efficiency and effectiveness of this process might be improved if those involved in negotiating an indemnification agreement for a planned trial could have access to indemnification language that had been accepted by that sponsor in other trials. Potential approaches to broadly achieve such access could include developing and making accessible either a list of sponsors who have agreed to indemnification language that is similar to that given in Box 1 or a compendium of indemnification paragraphs with linkage to corresponding sponsors.

In trials sponsored by the National Institutes of Health, since the federal Antideficiency Act, Pub.L. 97-258, 96 Stat. 923, specifically prohibits indemnification of nongovernment employees, approaches to achieve liability coverage could be through external sources such as home institutions of DMC members or the coordinating center for the trial.[1]

DMC Charter

The DMC Charter should define the primary responsibilities of the DMC, its relationship with other trial components, its membership and the purpose and timing of its meetings. The Charter also should provide procedures for ensuring confidentiality and proper communication, and an outline of the content of the Open and Closed Reports that will be provided to the DMC. The DMC Charter usually also should provide the statistical monitoring guidelines to be implemented by the DMC. Inclusion of these guidelines in the Charter ensures that they are properly discussed and approved by both the DMC and sponsor at the time of the DMC Organizational Meeting, ideally held prior to initiation of the trial. (While these monitoring guidelines typically would be included in the trial's Statistical Analysis Plan as well, that document often is still under development at that time of the DMC Organizational Meeting.) An outline of a DMC Charter is provided in Table 2.

Table 2. The Data Monitoring Committee (DMC) Charter Outline.

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Importantly, the DMC Charter should "articulate principles guiding the DMC process rather than providing a rigid set of requirements,"[1] since DMCs need flexibility to address unexpected challenges.[20] For example, a DMC Charter should not specify limits on the frequency of DMC reviews or on the extent of those reviews, such as indicating that only safety data would be reviewed. It should be recognized that DMC recommendations should be developed through a

process of consensus development rather than voting. The proper focus should be empowering the DMC regarding its mission, not a set of detailed and rigid rules and procedures.

Conclusion

While maintaining confidentiality of emerging data and ensuring the independence of DMCs are widely recognized DMC best practices, there are circumstances where confidentiality issues remain challenging, controversial or inconsistently addressed. We have reviewed a number of areas requiring special consideration of confidentiality issues, including trials for which interim data may be submitted for marketing approval with the trial continuing post-approval to provide more definitive evidence about principal safety and/or efficacy outcomes, access to pooled safety and efficacy outcomes during trial conduct by those who are not on the DMC, DMC access to unblinded efficacy and safety data throughout the trial and the potential utility of a mediator in the rare settings where the DMC has serious ethical or scientific concerns about the sponsor's public reporting of trial results.

Properly formulated DMC Contract Agreements, Indemnification Agreements and Charters also are important in protecting DMC members and their independence, thereby enhancing the DMC's ability to safeguard the interests of study participants and to enhance the integrity and credibility of clinical trials.

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ORCID iD

Susan S Ellenberg https://orcid.org/0000-0002-2364-5253

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