

Optimizing the Use of Data Monitoring Committees in Clinical Trials

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Key Conclusions and Recommendations

- Data monitoring committees (DMCs) provide an extra measure of credibility, safety, and validity for randomized trials that have endpoints of mortality or serious morbidity or for trials with special safety concerns.
- Though DMCs have been used for more than 30 years, the industry has not developed standard practices for them. This may change now that the Food and Drug Administration (FDA) has issued a draft guidance concerning when and how to use DMCs.
- More than 80 percent of all industry respondents to the FDA draft guidance express reluctance to relinquish control of data analysis to an independent statistician.
- Using a DMC complicates interactions among a sponsor's management, steering committees, and independent statistician, all of which must have working relationships with the DMC.
- DMC members report that sponsors commonly have problems generating current data for interim analysis, which hampers the DMC's ability to make informed decisions.
- Though some sponsors fear the FDA's guidance simply reflects distrust, DMCs represent an essential part of the safety monitoring process.
- Though some sponsors view the FDA's guidance as a reflection on their credibility, they should view DMCs as an essential part of safety monitoring for trials with mortality or serious morbidity as endpoints or for those with safety concerns.
- Sponsors risk inconsistent judgments when DMCs lack standards for making decisions.
- The risk of invalid Phase III trials far outweighs the cost of DMCs.
- FDA guidance will drive the adoption of DMCs, particularly in device companies, and will affect drugs and biologics as well.
- New developments in technology could eliminate many data-management challenges that currently undermine the potential effectiveness of DMCs.
- During 2003–4, outsourcing of interim statistical analysis will become standard practice for trials with external DMCs.
- Sponsors must learn to select, evaluate, and manage external statistical groups. Acumen Sciences recommends using niche providers to obtain this necessary expertise.
- Managing the DMC process for success requires the sponsor to provide the DMC charter, a qualified committee, an independent statistician, and current data.
- When using an external DMC, a sponsor should not outsource analysis and monitoring to the same contract research organization.
- Sponsor internal data monitoring provides flexibility while adding rigor to the monitoring process and should be used more frequently for early-stage trials.
- Industry should use external DMCs very selectively and for specific purposes.



Executive Summary

Data monitoring committees (DMCs) provide an extra measure of credibility, safety, and validity for randomized clinical trials with mortality or serious morbidity as endpoints or for trials with special safety concerns. A DMC is a multidisciplinary group of experts, independent of trial operations, who review data from an ongoing clinical trial. A monitoring committee examines the accumulating data for evidence of toxicity and efficacy and decides when a trial must be stopped or changed. There are three main reasons to terminate a clinical trial early: (1) unequivocal evidence of treatment benefit, (2) unacceptable toxicity, and (3) no emerging trends and no reasonable chance of demonstrating benefit.

The FDA issued a draft guidance in 2001 focused on when and how to use monitoring committees. Acumen Sciences believes the guidance will increase the use of DMCs, particularly in medical device companies. In comments to the draft guidance, sponsors object most strongly to its recommendation that the statistician preparing data for the DMC be independent of the sponsor. More than 80 percent of industry respondents to the draft FDA guidance expressed reluctance to relinquish control of data analysis. Some companies believe that if they construct internal firewalls to separate trial operations and monitoring staff, they can use their own statisticians. However, this practice can create a conflict of interest and undermine the credibility of trial results. Because the same could be said for contract research organizations, Acumen Sciences recommends against outsourcing analysis and monitoring to the same CRO when using an external DMC. We predict that during 2003–4, interim statistical analysis will be outsourced routinely for trials with external DMCs. Sponsors must learn to evaluate and manage these groups and should use niche providers to supply the necessary expertise.

Sponsors should view DMCs as an essential part of safety monitoring for trials, but not as the only safeguard. This report explains how to model the safety data flow in trials with a DMC, and its role and communications with other groups involved with the clinical trial. The report also discusses how to manage successfully the DMC process, from establishing a DMC charter and selecting committee members, to the necessity of using an independent statistician and the importance of proper staffing to obtain current data to support decision making. Most importantly, the report points out that a DMC needs clear standards in order to decide when to stop or change a trial. Sponsors risk unacceptable judgments about terminating or changing trials when DMCs lack these standards.

Failure to achieve validity and credibility of a clinical trial intended to provide pivotal data for licensure of a new product could result in the need to rerun the trial. Rerunning would take significant time and cause forfeiture of sales for approximately the length of time it takes to rerun a trial. The risk of invalid Phase III trials far outweighs the cost of a DMC. One case study illustrates the misuse of a monitoring committee. The firewall separating the DMC and the sponsor is also valuable when trial results if known by the sponsor must be disclosed because they are material to the firm's valuation.

Acumen Sciences believes that sponsor internal data monitoring provides flexibility while adding rigor to the monitoring process; it should be used more frequently. The internal monitoring committee can be used for early-stage trials not requiring an external monitoring committee: nonpivotal efficacy trials, dose-response and proof-of-concept trials, trials that have surrogates for clinical benefit, noncomparative post-marketing trials, etc. The internal committee provides a focal point for interactions between the external DMC and the sponsor. Also, if actions are recommended by an external DMC, the internal committee can provide the sponsor with a forum to integrate business and scientific considerations without unblinding the sponsor's project team. The internal committee should be governed by a standard operating procedure.

Acumen Sciences recommends that industry use independent DMCs very selectively and for very specific purposes and that sponsors manage the DMC process carefully. Specific recommendations are made on when to use data monitoring committees.

Context

Data monitoring committees (DMCs) provide an extra measure of credibility, safety, and validity for randomized trials that have endpoints of mortality or serious morbidity or for trials with special safety concerns.

A data monitoring committee is a group of experts, independent of trial operations, who review data from an ongoing clinical trial to ensure its continuing safety, validity, and scientific merit. A monitoring committee examines the accumulating data for evidence of toxicity and efficacy and decides when a trial must be stopped or changed. A DMC may recommend early termination of a clinical trial for three main reasons:

- Unequivocal evidence of treatment benefit (i.e., sufficient data have already been collected)
- Unacceptable toxicity (risk assessment)
- No emerging trends and no reasonable chance of demonstrating benefit

Other reasons for termination may be operational: failure to recruit enough patients, lack of compliance among a large number of patients, or external information, such as results from other trials that establish unequivocal benefit or harm.

There are several benefits to using a DMC to make these decisions.

- **Safety:** The most important objective of data monitoring is protecting the human subjects involved in the trial. Typically, the DMC will have access to unblinded treatment data. This allows comparison of safety information for differential risk caused by the study interventions during the course of a trial.
- **Credibility:** When a trial can be stopped early because efficacy has been demonstrated, an independent DMC can make the decision more credible. If a trial is stopped early by a sponsor, the medical community may suspect that the data have been manipulated or that the sponsor was biased by commercial interests. Trials that compare a sponsor's product to other products require unbiased data monitoring.
- **Validity of trial results:** Results are valid only when the data collection and analysis are unbiased. Using an independent committee means that those conducting the trial cannot access accumulating data, so they cannot be tempted to modify a trial based on preliminary treatment comparisons. Statistical analyses based on accumulating data (i.e., interim analyses) must also be prescribed in the protocol to maintain an overall level of statistical error for the trial.

Monitoring committees may be internal or external. Sponsors use an external independent committee when the credibility and validity of the trial are of most concern, usually in late-stage, randomized trials. An internal DMC is effective for early-stage trials in which the endpoints are surrogates, for proof-of-concept trials, for dose-response trials, etc. Conditions for appropriate use of these different types of monitoring committees are summarized in Table 1, below.



Table 1**Appropriate uses for different types of monitoring committees**

External independent	Internal sponsor DMC
Phase IIb, III, and IV trials, with mortality and irreversible morbidity endpoints	Mechanism for in-house monitoring of nonpivotal blinded trials
Studies where interim analyses are planned	Dose-response trials
Long-term trials	Proof-of-concept trials
Trials affected by external and/or internal developments (e.g., results from other studies)	Noncomparative post-marketing trials
Phase I and early Phase II studies that pose high risks to patients	Trial endpoints are surrogates for clinical benefit
Trials for a new chemical entity or new class of drug	
Trials intended for expedited regulatory review	

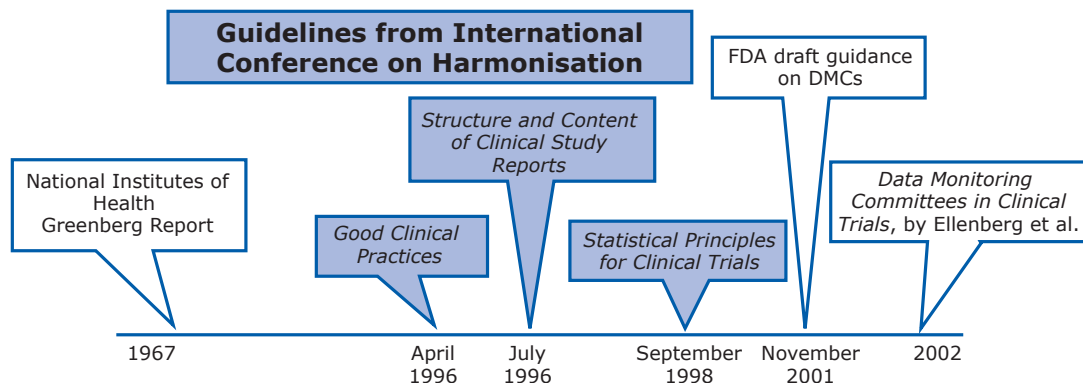
Source: FDA draft guidance¹, Acumen Sciences

Though DMCs have been used for more than 30 years, the industry has not developed standard practices for them. This may change now that the FDA has issued a draft guidance concerning when and how to use DMCs.

There is a long tradition of using DMCs in clinical trials for certain therapeutic areas. In what's known as the Greenberg Report, issued in 1967, the National Institutes of Health (NIH) originated the use of monitoring committees in clinical trials and established the principle of separating the trial monitoring group from the operations of the studies they monitor. Three regulatory documents from the International Conference on Harmonisation referencing the use of DMCs have been published in the past six years (see Figure 1).

Figure 1

Landmark publications on the use of data monitoring committees



Source: International Conference on Harmonisation^{2, 3, 4}, Acumen Sciences

In November 2001, the FDA issued a draft guidance entitled “On the Establishment and Operation of Clinical Trial Data Monitoring Committees.” This FDA guidance was precipitated partly by a report on institutional review boards (IRBs)⁵ by the inspector general of the Department of Health and Human Services, which recommended FDA guidance as part of the protections for human subjects participating in clinical investigations. Most recently, Ellenberg, Fleming, and DeMets (2002) wrote a book on the practical implementation of DMCs⁶, synthesizing works that had been published in the literature with their significant experience in the field.

DMCs are now used frequently in industry-sponsored clinical trials of drugs and biologics, though not typically in trials of medical devices. IRBs frequently now request DMCs for multicenter studies.

The following table enumerates some of the FDA positions articulated in the draft guidance that most highly affect sponsors. Clearly, sponsors must document all aspects of their relationship with a DMC: protocol, analysis plan, DMC charter, meeting notes, data, and appropriate standard operating procedures (SOPs).

Table 2**Positions detailed in the FDA's draft guidance on data monitoring committees**

Sponsor perspective on the FDA's position	Acumen Sciences comment
Knowledge of unblinded interim treatment comparisons can bias the outcome of a study. For certain pivotal trials, interim results should be accessible only to an independent DMC.	Sponsors should establish standard operating procedures to ensure the confidentiality of such data.
The sponsor should submit the DMC charter to the FDA before initiating the trial.	The charter is the sponsor's primary tool to manage the DMC process.
"The statistician preparing the reports to the DMC should ideally be independent of the sponsor and clinical investigators." ¹	Use truly independent organizations for statistical analysis. Do not create artificial firewalls within an organization that is involved with operations.
The sponsor should submit all meeting records to the FDA, with the clinical study report.	The sponsor should assign the responsibility of maintaining records to one group, preferably the independent organization preparing the reports. Sponsors should be prepared to share the interim databases as well.
Sponsors may create internal groups to monitor studies with less-serious outcomes than those monitored by independent monitoring committees.	This option provides great flexibility but is underutilized.
Special measures should be considered if the sponsor wants access to interim data for planning purposes.	This is a minefield. Sponsors risk invalidating the study. Proceed at your own risk.
DMC recommendations for protocol changes that may affect the validity of a trial should be discussed with the FDA before implementing.	Protocol changes should not be made based on the DMC's access to <i>unblinded</i> data.

Source: FDA draft guidance¹, Acumen Sciences

More than 80 percent of all industry respondents to the FDA draft guidance expressed reluctance to relinquish control of data analysis to an independent statistician.

The pharmaceutical, biotechnology, and device companies, as well as the public sector—including the National Institutes of Health, cancer coöperative groups, industry associations, and individuals—all submitted comments in response to the guidelines. These comments highlight the disagreement that exists on many issues between the FDA and those who conduct trials (see Figure 2, page 8).

The single most frequent comment was an objection to the FDA's recommendation that the statistician preparing data for the DMC be independent of the sponsor (see Table 3). This recommendation has large implications for industry, as well as others involved in conducting clinical trials, for example, cancer coöperative groups.

Table 3**Frequent responses to the FDA's draft guidance on data monitoring committees**

Issues that sponsors targeted, by frequency	The FDA's reasoning	Sponsors' objections
Use of external independent statistician	Preserves independence of sponsor with evolving data	Cost, inefficient logistics, longer time frames, perceived lack of competency
Overlap in monitoring groups	Creates fewer mistakes, higher quality of safety monitoring	Redundancies in the monitoring processes, duplicate work
Ambiguity as to which trials need a DMC	Increases safety of monitoring, reducing risk to patients	Highly subjective nature of guidance, requiring judgment for each situation
Little differentiation between types of sponsors (e.g., government or industry)	Involves different conflicts of interest, but independent DMC model still applies	Varying needs of each type of sponsor, even within industry (e.g., drugs and devices)
Little differentiation between types of trials (e.g., drug, medical device, or biologics)	Encourages use of DMCs whenever there is patient risk	Not a necessity in every industry (e.g., devices)
Requirements for composition of DMC members	Creates a multi-disciplinary team	Difficulty of recruiting experienced DMC members, limited pool of resources
No explicit mention of open-label studies	Does not differentiate between open and blinded studies—patient safety drives the need for DMCs	Possibility of preempting the external DMC by opening access to data for open-label studies
Responsibility of trial termination	Reduces potential for financial conflict if DMC recommends termination	Less control over the study (though sponsor can make the final call)

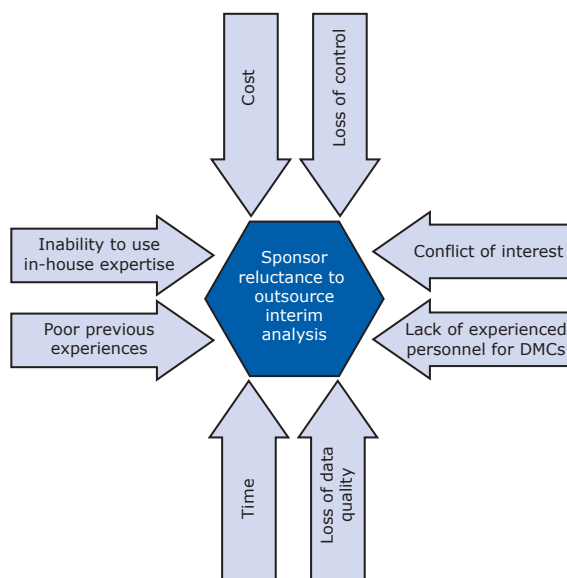
Source: FDA Docket #O1D-0489, Acumen Sciences

Though many parts of the clinical-development process are commonly outsourced, the analysis and interpretation of data has always been done by the sponsor's biostatisticians and clinicians, who justifiably claim that they have the requisite technical skills and scientific knowledge to perform this function. When they analyze final locked datasets from a concluded study, this is not a problem. However, it is a problem when team members analyze unblinded results from an ongoing study, whether or not a DMC is used.

Sponsors have tried to obviate this problem by using separate statistical teams within the company to perform interim analyses and to present them to DMCs where necessary. The FDA is uncomfortable with this arrangement because it still allows for potential (albeit subtle) influence of the sponsor, with regard to the conduct of the trial.

This discomfort led the FDA to recommend that independent statisticians perform all interim analyses. For sponsors, this represents turning over the "crown jewels" (i.e., the trial data) to outsiders who may be less versed in the science and medicine of the drug under study. It also potentially duplicates costly work and requires substantial effort to ensure that the contract statistician understands sufficiently the compound under study.



Figure 2**Pressures on sponsors to resist outsourcing statistical analysis**

Source: Acumen Sciences

Using a DMC complicates interactions among a sponsor's management, steering committees, and independent statisticians, all of which must have working relationships with the DMC.

A DMC is yet another entity involved in a trial, which already includes numerous parties and entails complex interactions (see Figure 3). Each entity has its own agenda. Simply put, the sponsor wants to enable new drug approval; investigators want publications; regulatory agencies want assurance of patient safety, transparent implementation, and data integrity. The DMC seeks to protect patient safety and to assess efficacy. Each party shares responsibility for study conduct and oversight. Using a DMC complicates communications across sponsor management, steering committees, and the independent statistician, all of which must work with the DMC. The study protocol, analysis plan, and DMC charter can clearly define roles and responsibilities. Still, the operations unit needs a talented project manager to coordinate all the activities.

In projects without a DMC, the sponsor's project statistician conducts the analysis. Using an independent statistician to prepare interim data displays and analyses for the DMC requires additional work and expense: Operations must collect accrued data; close the interim database; transfer it to the statistical contract group, who prepare summary reports; and transmit the reports to DMC members for review—all within a defined time window.

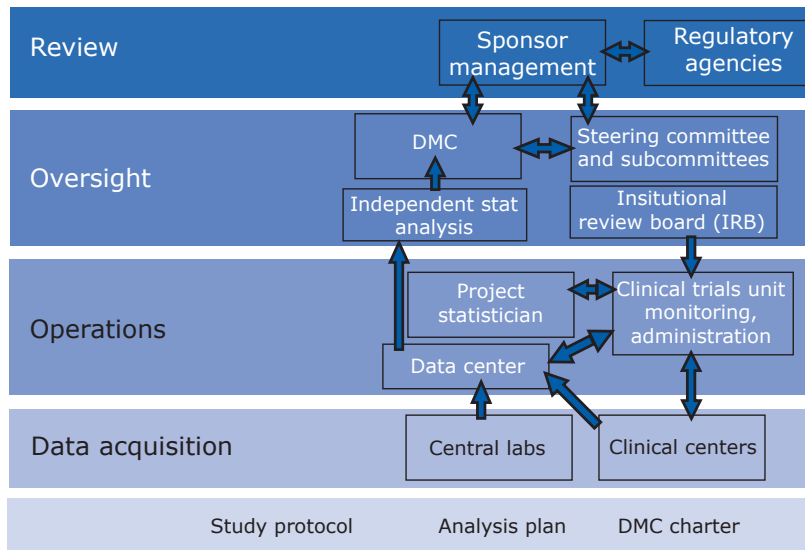
Using a DMC also affects a sponsor's relationship with an IRB, which reviews the science and ethics of each protocol conducted at its institution and is responsible for the safe conduct of trials. While an IRB receives reports of serious adverse events in trial patients at its own institution, it has no knowledge of adverse events at other centers and, thus, may lack information to evaluate patient safety. For multicenter trials, these boards are increasingly requesting that sponsors provide external DMCs. The blinded-DMC recommendation can be circulated to IRBs at participating institutions, allowing them to document ongoing safety monitoring.

DMCs usually deliver their recommendations to sponsor management (executives not involved in the conduct of the trial) or to an executive committee consisting of sponsor management members and lead investigators. When a DMC recommends changes in a trial, the sponsor and the investigators should discuss the recommendations with the DMC, so that all parties involved understand those recommendations precisely. If they involve a change

in protocol or procedure, the sponsor will usually remain blinded to comparative efficacy and safety data. When a DMC recommends stopping a trial, Acumen Sciences believes that the sponsor-and-investigator leadership team should unblind themselves and review the data that was the basis for the recommendation. Only in rare cases would one expect disagreement between the sponsor and the DMC. These processes should be governed by internal SOPs.

Figure 3

Generic communications model for a clinical trial with an external data monitoring committee



Source: Acumen Sciences

Case Studies

The following case studies show how sponsors have properly and improperly used DMCs, and how DMCs can protect patient safety.

Case Study 1. The GUSTO-I trial: use of a DMC for a large, simple trial

The GUSTO-1 (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) trial illustrates classic use of a DMC⁷.

An accelerated dosing regimen of tissue plasminogen activator, or alteplase, a thrombolytic therapy already on the market, was tested in an international trial (GUSTO-I) with more than 41,000 patients who had presented with a myocardial infarction within six hours of symptom onset. The trial included four regimens: One used accelerated alteplase infused over 90 minutes, two regimens used a standard dose of streptokinase alone infused over 60 minutes, and the fourth regimen used a combination of alteplase and a lower dose of streptokinase infused over 60 minutes. Patients in all regimens received heparin and aspirin.

In GUSTO-I, the accelerated infusion of alteplase resulted in a significantly lower death rate (6.3 percent) than either of the two standard-dose streptokinase regimens (7.2 percent and 7.4 percent). The experimental combination regimen of alteplase and a lower dose of streptokinase offered no advantages.

Increased potential for bleeding and stroke are the major safety concerns associated with these treatments. The incidence of stroke was higher among patients treated with accelerated alteplase (1.6 percent) than in patients treated with either of the two standard-dose streptokinase regimens (1.4 percent and 1.2 percent). However, the combined incidence of death or nonfatal stroke was lower in patients treated with accelerated alteplase (7.2 percent) than in patients treated with either of the two standard-dose streptokinase regimens (8.2 percent and 8.0 percent).

A DMC was used for this trial for several reasons:

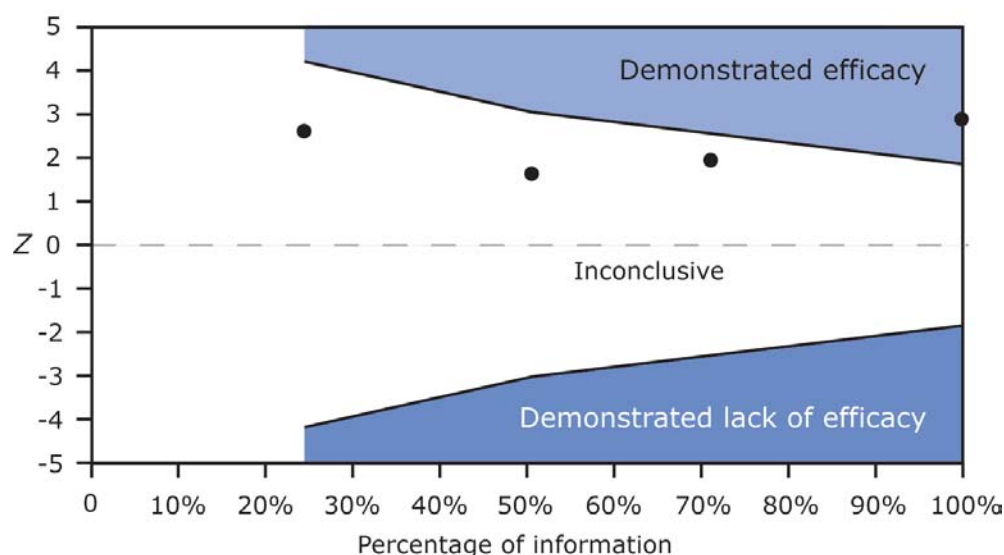
- The endpoint was mortality and serious adverse events.
- A dose-related, increased likelihood of stroke was associated with thrombolytic therapy.
- Since two drugs (alteplase and streptokinase) were competing for market share, credibility and validity of the results were critical.

There were three interim looks at the data, and the trial was run to completion. Protection of patient safety was critical in this large, simple trial. Because the accelerated dosage of alteplase had only limited testing, the frequency of intracranial hemorrhage had to be monitored carefully. Special arrangements were made to provide the DMC with current data on deaths and intracranial hemorrhage.

The trial used an O'Brien-Fleming group sequential statistical design. Three formal interim analyses were planned after approximately 10,000, 20,000, and 30,000 subjects were accrued. The statistical monitoring results for the streptokinase and alteplase arms are shown in Figure 4. Statistical significance for efficacy was almost attained at the third interim and was attained at the final analysis.

Figure 4

O'Brien-Fleming boundary: streptokinase vs. alteplase



Source: Kerry Lee, Duke Clinical Research Institute

Case Study 2: HA-1A (Centoxin) Phase III trials in sepsis

The development of this molecule involved two Phase III trials, and each used a DMC. The first trial illustrates how a DMC was used by the sponsor improperly; the second shows how using a DMC can protect patients' safety and save the sponsor millions of dollars through early termination.

HA-1A is a human monoclonal antibody developed to treat gram-negative sepsis (GNS), a leading cause of death in hospitalized patients. Septicemia is a serious disease involving multiorgan failure and requiring intensive care treatment. Thirty percent of septicemia cases are due to gram-negative bacteremia thought to be caused by an endotoxin (the lipopolysaccharide component of the cell wall of gram-negative bacteria). This trial, in which mortality was the clinical trial endpoint in very sick patients, called for use of a DMC.

After completing Phase I and II trials, the sponsor began the first Phase III trial. The initial results of the first double-blinded, randomized, placebo-controlled Phase III trial were published in the *New England Journal of Medicine*⁸. Using death at Day 28 as the endpoint, the authors concluded that HA-1A decreased the death rate in patients with GNS ($p=0.014$). The authors found that of patients with demonstrable GNS, 49 percent receiving a placebo had died by the Day 28 endpoint, compared with 30 percent of patients receiving HA-1A.

However, the FDA and other critics cited several problems with the analysis and raised safety concerns^{9, 10}. During the course of the study, sponsor personnel attended a closed session of the monitoring committee and viewed the interim data. After viewing this data, the sponsor submitted a revised analysis plan to the FDA. The changes were explained by FDA reviewer Jay Siegel¹¹:

The plan modified the primary analysis, changing from 14-day to 28-day analysis, and modified subgroups. There were different groups of gram-negative infection and sepsis and gram-negative bacteremia groups that modified which groups were important to the analysis, changed to a rank analysis from a point-in-time analysis, a landmark analysis of survival, and made many other clarifications because the original analytic plan was rather vague on a number of issues, made a lot of useful clarifications but also some significant changes.

Since these changes were made by the sponsor, who had seen the interim data, the validity of the results was questioned. FDA analysis based on the original protocol-defined analysis plan yielded a p-value of 0.6, far from the threshold for statistical significance. The FDA requested a confirmatory trial. This trial illustrates the necessity, for situations in which an external monitoring committee is used, of SOPs that restrict sponsor access to interim data.

The additional study, the CHES (Centocor: HA-1A Efficacy in Septic Shock) trial¹², was terminated after the first interim analysis by the DMC, when the mortality rate in patients without GNS who received HA-1A was higher than the rate in patients without GNS who received placebo. Only 1,086 patients were treated of the total sample, which was estimated to reach 7,500 patients eventually. The result was that thousands of patients were not exposed to a potentially harmful product, and the sponsor did not spend millions of dollars continuing the study.

This example also demonstrates the huge financial loss that a sponsor incurs with an invalid study at Phase III. If HA-1A really had proved effective, imagine the lost revenue over the period of time the second Phase III study would have run. If the repeat study took 18 months, then the sponsor would have lost \$540 million, assuming that the drug sold at a rate of \$1 million per day.

DMC members report that sponsors commonly have problems generating current data for interim analysis, which hampers the DMC's ability to make informed decisions.

Current data are critical for DMCs to evaluate safety and to make timely decisions about stopping a trial. The DMC would not want to terminate a trial early if there was a lot of data in the pipeline that could call into question the termination decision after all data were compiled. Although the definition of *current* varies from trial to trial, a good rule of thumb is that the interim data should be current as of 60 days before a DMC meeting. This becomes an operational challenge that involves handoffs among multiple groups. Minimally, sponsors must ensure that the following tasks are finished in advance of the scheduled meeting:

- Case report form (CRF) completed at sites
- Monitoring visits made to trial centers, as appropriate
- Data entered into the clinical database
- Data from the sponsor sent to the independent statistical analyst
- Analysis dataset created and statistics analyzed
- Statistical reports distributed to DMC members

Since each of these tasks requires a handoff within a tight timeline, effective coordination of the process is essential. Sometimes, with mortality endpoints or serious expected adverse events (like intracranial hemorrhage in the GUSTO-I trial), information may be sent by fax or other expedited means; this takes much less time than completing CRFs. Also, sometimes data from the treatment and control arms are collected on different schedules. For example, in unblinded cancer trials, patients on a new chemotherapeutic agent may be seen more often than those on the conventional regimen. Even if the protocol of an unblinded trial specifies equal follow-up, treated patients may be seen more often (because they have more side effects) or less often (because they receive fewer concomitant medications). Consequently, data from the treated and untreated arms may show bias; the group that is seen more frequently has a greater number of opportunities to report adverse events.

Frequently, the DMC reviews data of two types: those validated through the normal processes, including computerized data checking, and those that have not gone through the entire review cycle, like the fax mentioned above. The sponsor must indicate what variables are subject to further review, so the DMC is aware of the accuracy of the data.



Analysis

Though some sponsors view the FDA's guidance as a reflection on their credibility, they should view DMCs as an essential part of safety monitoring for trials with mortality or serious morbidity as endpoints or for those trials with safety concerns.

Some interviews suggested that sponsors believe the FDA doubts their credibility and their competence to conduct trials. The medical community and the public often distrust the pharmaceutical industry. Everyone realizes that pharmaceutical companies have a vested financial interest in the outcome of their randomized clinical trials. Many checks and balances besides DMCs (see Table 4 below) help protect against bias in the conduct and reporting of clinical trials. Nonetheless, the credibility of a trial is enhanced if the results are free of sponsor influence.

The firewall separating the DMC and the sponsor is also valuable when results of a trial could affect a firm's valuation. The Securities and Exchange Commission may require companies to disclose such information publicly. The release of interim information could bias the ultimate results and, therefore, must be avoided.

Table 4

Existing safeguards against bias in the conduct and reporting of clinical trials

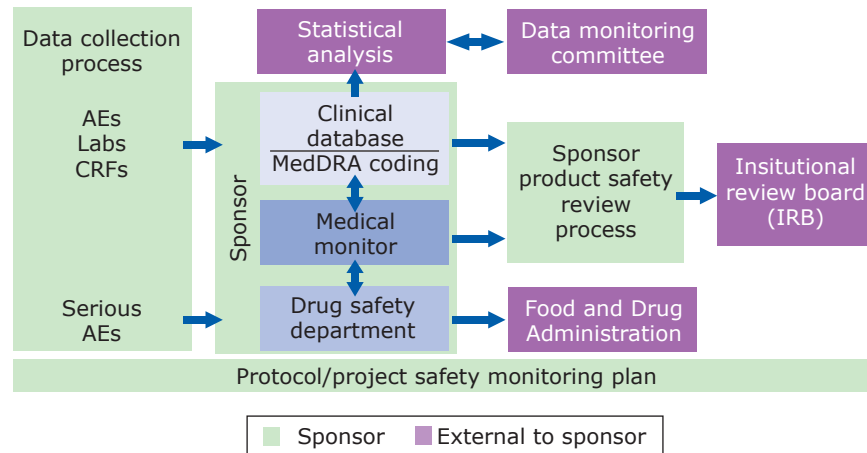
Operational	Review of trial results
Detailed protocol and analysis plan	Regulatory agencies for marketing approval
Unblinding and data dissemination plan	Independent data analysis
DMC charter	Investigators
Adherence to good clinical practice guidelines	Sponsor internal review
Field monitoring	FDA Advisory Committee
Internal quality-assurance compliance audits	Regulatory audits
Internal standard operating procedures	Peer-reviewed journals
Computer-systems validation	
Intent-to-treat analysis	
Financial disclosure guidelines	

Source: Acumen Sciences

Figure 5 shows the information flow when an external DMC is involved in a trial. The sponsor remains heavily involved in collecting data, processing individual adverse-event data, and routing serious-adverse-event reports to the FDA. Meanwhile, the DMC aggregates the safety data by treatment group for risk assessment among all patients treated. Open DMC recommendations (not incorporating relative treatment comparisons) should be distributed to IRBs by the sponsor or investigator. Because the sponsor is liable for patient safety but has little access to data, it generally tries to appoint a DMC with risk aversion similar to its own. In most cases, the sponsor will have the opportunity to review the data only at the end of the trial or if and when the DMC recommends stopping the trial early.

Figure 5

For many trials, data monitoring committees are an essential part of the safety-monitoring process, but they are only one safeguard among many



Source: Acumen Sciences

Sponsors risk inconsistent judgments when DMCs lack standards for making decisions.

The FDA draft guidance describes appropriate use and management of DMCs, but gives no real recommendations on what issues the DMC should consider when deciding to stop or change a trial. Obviously, the protocol and charter will specify statistical stopping boundaries for efficacy or futility. However, statistical considerations are only one reason to consider changing a trial⁵ (see Table 5).



Table 5**Some issues for a data monitoring committee to consider before recommending early termination of a trial**

Questions a DMC should answer before altering a trial	Acumen Sciences comment
What effect has treatment had on endpoints and side effects? Do the benefits outweigh the risks?	Secondary endpoints may be underpowered relative to the primary endpoint. However, the secondary endpoints may prove important for drug labeling. Is it worth continuing a study for additional information on secondary endpoints?
Can observed treatment effects be explained by differences in baseline distributions of risk factors or comorbid conditions?	Probably not a problem with a blinded, randomized study with a large sample, but DMCs are often reassured by an analysis showing that results are not explained by baseline imbalances.
Is there a possibility of bias in the recognition or diagnosis of the endpoints?	If there is discordance between investigator and core laboratory evaluations, use standard core lab evaluations for stopping.
Could patients in one group have received medical management that was different from the other group's because of investigator bias, side effects of assigned treatment, or unblinding?	Analyses presented to the DMC should explore this possibility before the DMC recommends major changes to or termination of the trial. Example: Medical management may vary among countries in international trials. Do positive results only depend on a subset of countries? If so, what can be generalized from the trial?
Will early adverse or beneficial trends be reversed if the study is continued to its scheduled conclusion?	Futility analysis may demonstrate that continuance of a trial is a waste of time, money, and patient resources.
Are the findings concordant for all identifiable subgroups of the study population, or is early termination warranted only in one or more subgroups?	Studies aren't normally powered for subgroup analysis. Stopping early because of a subgroup may limit the conclusion that may be drawn for the larger population.
If more than one active treatment is under study, could the placebo group be abnormally high or low in incidence of the primary endpoint, compared to all other treatment groups?	The trial may not be reproducible if stopped early, and not accepted as valid if results vary from past experience.
What is the impact of stopping a trial early, and what messages would this send to the medical community (e.g., physicians)?	The DMC needs to be sure that the message sent by stopping early will be clear and definitive to members of the medical community who are treating similar patients.

Source: (left column) Adapted from Coronary Drug Project Research Group. (1981) Practical aspects of decision making in clinical trials: the coronary drug project as a case study. *Controlled Clinical Trials* 1: 363–376

The more experienced the members of the committee are, the more adept they will be at anticipating dilemmas. When potential dilemmas do arise, the DMC may use open sessions to assess the sponsor's attitude toward multiple hypothetical outcomes and factor that information into their decision process.

The risk of invalid Phase III trials far outweighs the cost of DMCs.

The sponsor's cost of operating a DMC will vary considerably depending on the length of the study, the number of DMC meetings, the number of DMC members, and other factors. The cost of the statistical analysis alone may vary from \$100,000 to \$500,000 depending on the trial. Other expenses include the meeting venue and time and travel reimbursement to DMC members. Intangible, but real, expenses accrue in obtaining data from the field and processing it for the DMC meeting.

Although these expenses add up, they are usually quite small compared to the cost of losing the credibility and validity of a Phase III clinical trial, as shown in the CHESS case study discussed previously. In addition, if the expenses associated with clinical data monitoring are amortized over several trials, the result can actually be a significant savings, as some studies will be terminated early for safety reasons, efficacy, or futility.



Outlook

FDA guidance will drive the adoption of DMCs, particularly in device companies, and will affect drugs and biologics as well.

Several factors will increase external DMC adoption:

- **The FDA draft guidance on DMCs:** Lack of clarity and definition will increase the use of DMCs; sponsors will use them just to be certain of satisfying requirements.
- **IRB requests for monitoring:** IRBs want assurance that patient safety is being monitored carefully for multicenter trials.
- **High-risk trials:** New or novel therapeutic approaches (e.g., gene therapy) require close monitoring of patient safety.
- **Increased use by the device industry:** Device companies currently use DMCs infrequently; the adoption rate will increase as DMC usage becomes standardized. This will happen despite the fact that most device trials cannot be blinded.

Though adoption will increase overall, some factors will slow it:

- **Logistical difficulties:** Not only are DMCs expensive and time-consuming, but qualified members are hard to find.
- **Lack of need:** DMCs are not necessary when patient safety is not a major concern or when interim analyses are not planned.

Overall we think that the use of DMCs will increase modestly, driven largely by device trials, which do not have a tradition of monitoring committees.

New developments in technology could eliminate many data-management challenges that currently undermine the potential effectiveness of DMCs.

As mentioned earlier, current patient information is essential for the DMC to do its job. Historically, in trials sponsored by the pharmaceutical industry, to obtain field data for interim analysis required retrieving paper CRFs and entering data manually into a database. Remote data-capture systems could eliminate the need for both paper CRFs and manual data entry, making possible later cutoff dates for patient data. These systems might be very useful for interim monitoring, as they have shown promise in speeding data acquisition. However, Acumen Sciences is not aware of any trials that have demonstrated this possibility.

During 2003–4, outsourcing of interim statistical analysis will become standard practice for trials with external DMCs.

Acumen Sciences believes that the FDA does not recommend the sponsor's statisticians serve as the "reporting" statistician for external DMC deliberations because such an arrangement threatens the validity of a study. Furthermore, although some large firms and CROs think that they can create an effective wall between the project team and the in-house statistician, this setup has the appearance of a conflict of interest and, so, should be avoided.

An independent statistical center costs a sponsor time and money; it can even end up duplicating work that the sponsor will need to do to prepare a final study report. To save resources, some sponsors have provided ready-to-go

programs for the statistical center, but this has had mixed results. As a trial progresses, there are always requests for new information or revised presentations by the DMC. Consequently, analysis programs change during the course of a trial. Acumen Sciences’ research shows that using an independent statistical center could cost \$100,000 to \$500,000 for a multiyear, multicenter trial with three or four interim analyses. However, because this represents a small fraction of the cost to run a clinical trial, a credible independent statistics group is a good investment. Other cost benefits accrue: Because the programming must be done twice—at least once for the DMC and once for final results—a check is built in. Furthermore, if the study is complicated and the reporting statistician and DMC are competent, necessary exploratory analyses will be completed already. If the DMC has understood the trial well, it can even speed up the process at the end of the study.

Sponsors must learn to select, evaluate, and manage external statistical groups. Acumen Sciences recommends using niche providers to obtain this necessary statistical expertise.

Table 6 lists some of the capabilities of an independent statistics group. Foremost is scientific expertise. The statistician should be familiar not only with statistics, but, ideally, also with the therapeutic area and clinical trials. Often a statistical programmer will take responsibility for the programming aspects of preparing the many statistical reports. The programming activities need to be validated, because the data may affect important decisions.

Table 6

Selection and evaluation of independent statistical analysis

Vendor evaluation variables		Acumen Sciences analysis
Scientific expertise	Statistical programming and validation procedures	This is necessary to prepare tables.
	Statistical analysis	The sponsor must have confidence in the individual statistician who will do the analysis.
	Clinical trials	
	Clinical domain experience	
Process capabilities	Secure electronic data-transfer capabilities	Expediting data exchange and record keeping helps lower costs and improve quality.
	Documented processes	Sponsor should audit the vendor to be sure appropriate standard operating procedures are in place for data handling and programming. 21 CFR Part 11 regulations should be followed.
Overall company	Stability	Personnel should be available the entire length of the trial and have the ability to build additional domain knowledge.
	Conflicts of interest	Analysis activities should be kept independent of clinical trials production work.

Source: Acumen Sciences



Acumen Sciences believes that work for a DMC should be conducted with the same rigor the sponsor would use in compiling a final study report. This means that the DMC and the independent statistician should follow appropriate guidelines for software validation and electronic records and signatures. Finally, since clinical trials may last several years, the stability of the statistical center is an important consideration.

In addition to actually performing the statistical analysis, the independent statistical groups are in a good position to record the DMC proceedings. For example, all data and tables presented should be archived. All minutes should include participants, a list of topics discussed, decisions, and recommendations. Open session minutes should be available immediately. Closed session minutes should not be available until the end of the study. These minutes and reports should be included in final study reports³. Remember, minutes may become public after the study is over.

Contracts for independent statistical analysis for DMCs should be written in a way that differs from usual CRO contracts. The independent statistician reporting to the DMC must respond to requests from the DMC and often may not tell the sponsor about the analyses until the trial is over.

Acumen Sciences believes that the independent statistical group can bring business rigor to DMC operations. The DMC process can be streamlined with technologies. Although face-to-face meetings will always be preferable (especially for the initial organizational meeting), busy schedules, time, and geography may make such meetings impractical. Routine meetings can be held by teleconference. If the DMC thinks it has major recommendations, its members probably should meet in person. DMC meetings with some members present and others joining by phone reportedly do not to work well.

In these cases, it is possible to share information over the internet through secure connections, and to use electronic messaging systems for off-line communications if a sponsor's concerns for confidentiality and DMC members' comfort with electronic access permit. Collaboration and knowledge management software, such as Livelink by Open Text Corporation, may facilitate the process.

Recommendations

Managing the DMC process for success requires the sponsor to provide the DMC charter, a qualified committee, an independent statistician, and current data.

The use of DMCs requires planning and resources from the sponsor; therefore, these committees should be used only when necessary. After determining that a clinical trial needs an external DMC, the sponsor should begin writing the DMC charter and selecting committee members.

Most sponsors already have an SOP for monitoring clinical trials. The SOP outlines the responsibilities of independent DMCs and any in-house data review committees. It should define the role of the project statisticians and independent statisticians. The SOP should also clearly define the sponsor's role and procedures to control sensitive information. The SOP should require that a charter be created for DMC activities.

DMC charter. The charter identifies the committee's roles and responsibilities and its relationship to other groups involved in the study. It describes how the DMC will monitor the safety and efficacy of the study. This operational charter should be provided by the sponsor and agreed to by the monitoring committee. Table 7 shows the topics typically addressed in a DMC charter.

A DMC should have an executive session that excludes the reporting statistician, to ensure the committee operates truly independently. Often this session is very short, but it allows the DMC to discuss freely any problems it may be having with the reporting statistician. This is especially important if the group presenting to the DMC is inexperienced.



Table 7**DMC charter table of contents**

1. Introduction
2. Role of the committee
 - 2.1 Safety
 - 2.2 Efficacy
 - 2.3 Study conduct
3. Organizational flow
4. Committee membership
 - 4.1 Members
 - 4.2 Financial disclosure and conflict of interest
 - 4.3 Duration of DMC
5. Committee meetings
 - 5.1 Organizational meeting
 - 5.2 Scheduled interim analysis meetings
 - 5.2.1 Open session
 - 5.2.2 Closed session
 - 5.2.3 Executive session
 - 5.3 Unscheduled meetings
6. Communication
 - 6.1 Open reports
 - 6.2 Closed reports
 - 6.3 DMC minutes
 - 6.4 DMC recommendations
 - 6.5 Sponsor decision
7. Statistical monitoring guidelines
8. Other stopping considerations
9. Content of the DMC's open and closed reports

Source: Acumen Sciences

Select the right committee membership. The guiding principle for selecting committee members is that the study sponsor should trust the collective membership to make appropriate risk/benefit decisions. Unfortunately, qualified, experienced people are hard to find. More people need to be trained to participate in these activities.

The committee should have diverse, multidisciplinary representation. Members should be free of all conflicts of interest—professional, financial, and scientific. There should be no study sponsor, investigator, or FDA personnel

on the committee who could potentially be involved with future FDA product review. All members should support the study objectives and design. Biostatistical experience is important to interpret group sequential stopping rules and to make reasoned judgments about surprising safety signals.

There is a difference in the experience in various medical fields with randomized clinical trials and monitoring committees. For example, there is a long tradition of use of DMCs in cardiology, but this is not the case for all medical specialties. This makes it harder to find qualified people to serve on committees in some therapeutic areas. Also, for longer term trials, it is important that DMC members commit to serve for the entire length of the study.

When using an external DMC, a sponsor should not outsource analysis and monitoring to the same CRO.

If the CRO is involved with the ongoing clinical operations, even if there is a firewall between operations personnel and the independent statistician, there is no real difference between the CRO and the study sponsor. There exists at least the potential for a conflict of interest. This is true for both commercial and academic CROs. As the FDA draft guidance reminds us

...references to the sponsor with regard to trial management and decision-making should be understood to refer also to any individual or group to which the sponsor has delegated the relevant management responsibilities.

Acumen Sciences believes that operations personnel (e.g., those involved in data management or monitoring activities) should not work directly with analysis personnel who can access unblinded data. The draft guidance specifically addresses the requirement that no information be communicated even subtly during ordinary interactions among sponsor staff. This can be guaranteed *only* if the sponsor's project staff does not have access to unblinded data.

It also follows that the data center and the statistical reporting group should be independent of the investigators to avoid operational conflicts of interest. Furthermore, access to the treatment codes should be independent of the operations group and the sponsor.

Sponsor internal data monitoring provides flexibility while adding rigor to the monitoring process and should be used more frequently.

The internal monitoring committee provides a focal point for interactions between the DMC and the sponsor. It also provides the sponsor with a forum to integrate business and scientific considerations. The committee should be governed by an internal SOP and composed of sponsor medical, statistical, and regulatory personnel who have no operational responsibilities for the trial. There should be flexibility to add ad hoc members as necessary, including external members.

The internal committee has several key responsibilities:

- To approve external monitoring committee charters
- To accept or reject the recommendations of independent DMCs
- To communicate DMC decisions to the FDA prior to unblinding interim results
- To serve as an internal monitoring committee for early-stage nonpivotal efficacy trials, dose-response and proof-of-concept trials, trials that have surrogates for clinical benefit, noncomparative post-marketing trials, etc.
- To ensure that members are not involved in trial operations

This structure provides great flexibility for a variety of situations. For example, if the external DMC recommends stopping a trial, the internal DMC could review the data before acting on the recommendation. Thus, the sponsor can make an informed decision without unblinding the sponsor's project team. For nonpivotal trials, this



means there is a mechanism in place for review of safety on an ongoing basis. Internal DMCs may not be feasible for small companies that would have difficulty recruiting committee members who are not involved in trial operations.

Industry should use external DMCs very selectively and for specific purposes.

Not all trials require DMCs. Table 8 indicates that an external data monitoring committee will be most useful in the setting of randomized clinical trials for life-threatening diseases or diseases causing serious morbidity, that is, trials in which protection of subject safety is critical. These are often pivotal trials for new drug approvals or for comparative Phase IV trials. Independent DMCs should be used in trials with a strong ethical imperative and for late-stage trials in which credibility and integrity are especially important.

Table 8

Situational recommendations for use of a data monitoring committee

Setting	Imperatives		Need for DMC	
	Ethical	Credibility/ integrity	External DMC	Internal DMC
Life-threatening diseases; diseases causing irreversible serious morbidity; novel treatments for life-threatening diseases with potential for significant adverse events; vulnerable populations				
Randomized trials (Phase IIb, III, IV)	YES	YES	YES	NO
Randomized trials (Phase I, IIa)	YES	Likely	Maybe	Likely
Nonrandomized trials	YES	Maybe	Unlikely	Likely
All other settings				
Randomized (any phase trial)	Unlikely	Likely	Unlikely	Maybe
Nonrandomized	Unlikely	Unlikely	NO	Unlikely

Source: *Data Monitoring in Clinical Trials*; Susan Ellenberg, Thomas Fleming, and David DeMets; 2002; © John Wiley & Sons Limited. Adapted and reproduced with permission.

Of course, if there's uncertainty as to whether or not a trial needs a data monitoring committee, it is best to ask the appropriate regulatory authorities. Sometimes the FDA will review a protocol and ask that a DMC be used. Since protocol review at the FDA is often the last step before study initiation, you may need to set up a DMC late in the process. Though this can be done, it is better to anticipate the need than to have it forced upon you.

Disclaimer

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