Guidance for Clinical Trial Sponsors

On the Establishment and Operation of Clinical Trial Data Monitoring Committees

DRAFT GUIDANCE

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For questions on the content of this draft document contact Mary Foulkes (CBER), 301-827-3034, Robert Temple (CDER), 301-594-6758, or Joanne Less (CDRH), 301-594-1190.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Center for Drug Evaluation and Research (CDER)
Center for Devices and Radiological Health (CDRH)
November 2001

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Office of Communication, Training and
Manufacturers Assistance, HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Rockville, MD 20852-1448
Internet: http://www.fda.gov/cber/guidelines.htm.
Fax: 1-888-CBERFAX or 301-827-3844
Voice information System: 800-835-4709 or 301-827-1800
or

Office of Training and Communications
Division of Communications Management
Drug Information Branch, HFD-210
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane, Rockville, MD 20857
(Phone 301-827-4573)
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or

The Division of Small Manufacturers Assistance (DSMA), HFZ-220
Center for Devices and Radiological Health
Food and Drug Administration
1350 Piccard Drive, Rockville, MD 20850
800-638-2041 or 301-443-6597
Internet: DSMA@CDRH.FDA.GOV
Fax: 1-301-443-8818
Facts-On-Demand (FAX) at 800-899-0381 or 301-827-0111

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GUIDANCE FOR CLINICAL TRIAL SPONSORS

On the Establishment and Operation of Clinical Trial Data Monitoring Committees

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1. INTRODUCTION AND BACKGROUND

This guidance discusses the roles, responsibilities and operating procedures of Data Monitoring Committees (DMCs) that carry out important aspects of clinical trial monitoring. The document is intended to assist sponsors of clinical trials in determining when a DMC is needed for optimal study monitoring, and how such committees should operate. We recognize that in many clinical trials the sponsor delegates much decision-making regarding the design and conduct of the trial to some other entity such as a Steering Committee (see Section 3.2) or Contract Research Organization (CRO) (see 21 CFR 312.3(b)). In this document, 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.

Sponsors are required to monitor studies evaluating new drugs, biologics, and devices (see 21 CFR 312.50 and 312.56 for drugs and biologics, as well as 21 CFR 600.80, and 21 CFR 812.40 and 812.46 for devices). Various individuals and groups play different roles in clinical trial monitoring. One such group is a DMC, appointed by a sponsor to evaluate the accumulating outcome data in some trials.

A DMC is a group of individuals with pertinent expertise that reviews on a regular basis accumulating data from an ongoing clinical trial. The DMC advises the sponsor regarding the continuing safety of current participants and those yet to be recruited, as well as the continuing validity and scientific merit of the trial.

Many different models have been proposed and used for the operation of DMCs. Experience has shown that some of these approaches have particular advantages or disadvantages. In this document we highlight these advantages and disadvantages, with particular attention to the setting in which investigational products are being evaluated for possible marketing approval. The intent of the document is not to dictate the use of any particular approach but rather to ensure wide awareness of potential concerns that may arise in specific situations.

1.1. History of DMCs

DMCs have been a component of some clinical trials since at least the early 1960's. DMCs were initially used primarily in large randomized multicenter trials sponsored by Federal agencies, such as the National Institutes of Health and the Veterans Administration in the U.S. and similar bodies abroad, that targeted improved survival or reduced risk of major morbidity (e.g., acute myocardial infarction) as the primary objective. In 1967, an NIH external advisory group first introduced the concept of a formal committee charged with reviewing the accumulating data as the trial progressed to monitor safety, effectiveness, and trial conduct issues in a set of recommendations to the then-National Heart Institute. The recommendation for the establishment of such committees was based on the recognition that interim monitoring of study data was essential to ensure the safety of trial participants, but that individuals closely involved with the design and conduct of a trial may not be able to be fully objective in reviewing the interim data for any emerging concerns. The involvement of expert advisors external to the trial organizers, sponsors, and investigators was intended to ensure that such problems would be addressed in an unbiased way by the trial leadership.

Few trials sponsored by the pharmaceutical/medical device industry incorporated DMC oversight until relatively recently. The increasing use of DMCs in industry-sponsored trials is due to several factors, including:

- the growing number of industry-sponsored trials with mortality or major morbidity endpoints;
- the increasing collaboration between industry and government in sponsoring major clinical trials, resulting in industry trials performed under the policies of government funding agencies, which often require DMCs;
- heightened awareness within the scientific community of problems in clinical trial conduct and analysis that might lead to inaccurate and/or biased results, especially when early termination for efficacy is a possibility, and demand for approaches to protect against such problems.

1.2. Current Status

DMCs are currently used in a variety of situations, and different models of operation have been employed. Although no single model may be optimal for all settings, and there is not necessarily consensus about the optimal model in any given setting, advantages and disadvantages can be described for some of the different approaches that have been taken.

As noted above, government agencies that sponsor clinical research, such as the National Institutes of Health and the Veterans Administration, have required the use of DMCs in certain trials. Current FDA regulations impose no requirements for the use of DMCs in trials except for research studies in emergency settings conducted under 21 CFR 50.24(a)(7)(iv), in which the informed consent requirement may be waived. FDA believes that the issues discussed in this document arise in both industry- and government-sponsored trials, and therefore has not differentiated between them. We recognize that the potential conflicts of interest faced by government sponsors are somewhat different from those of industry sponsors, so that the implications for the approach to monitoring, particularly with regard to confidentiality and independence issues (see Section 4.2 and Section 6), may also differ to

some extent. Nevertheless, we believe that the discussion of advantages and disadvantages of various approaches to DMC operation is relevant to all trials, regardless of the sector of the sponsor.

2. DETERMINING NEED FOR A DMC

All clinical trials require safety monitoring (21 CFR 312.32(c)), but not all trials require monitoring by a formal committee external to the trial organizers and investigators. As noted earlier, DMCs have generally been established for large, randomized multisite studies that evaluate interventions intended to prolong life or reduce risk of a major adverse health outcome such as a cardiovascular event or recurrence of cancer. Because monitoring of accumulating results is almost always essential in such trials, DMCs should be established for controlled trials with mortality or major morbidity as a primary or secondary endpoint. They may also be helpful in settings where trial participants may be at elevated risk of such outcomes even if the study intervention addresses lesser outcomes such as relief of symptoms. Although DMCs may prove valuable in other settings as well, a DMC is not needed or advised for every clinical study. Several factors are relevant to determining whether or not to establish a DMC for a particular trial. These relate primarily to safety, practicality, and scientific validity.

2.1. Risk to Trial Participants

A fundamental consideration is the safety of those who would be at potential risk due to their participation in the trial. Is the study endpoint one for which a favorable or unfavorable early result might ethically require termination of the study before its planned completion? Is there reason for a particular safety concern (for example, if the method of administering the test treatment involves unusually high risk)? Is the treatment to be tested novel, so that there is little prior information on clinical safety, or is there specific prior information that raises concerns about the potential for serious toxicity? Safety concerns are usually heightened in studies performed in potentially fragile populations such as children or the very elderly, or in any group at relatively high risk of death or morbid events in whom a medical intervention might increase such risk or cause unanticipated adverse events. The oversight of a DMC in addition to typical sponsor-conducted safety monitoring can provide further protection of study participants. A trial that is large, of long duration, and multi-center raises more possibilities of safety concerns because of the greater overall exposure and because prolonged exposure may cause adverse effects not readily recognized as such. DMCs may be more important in these trials.

2.2. Practicality of DMC Review

A second consideration is whether a DMC is practical. If the trial is likely to be completed quickly, a DMC might not have an adequate opportunity to contribute. In short-term trials with important safety concerns that may warrant a DMC, sponsors need mechanisms to permit the DMC to be informed and convened quickly in the event of unexpected results that raise concerns.

2.3. Assurance of Scientific Validity

A third consideration in the decision of whether to have a DMC for a trial is whether a DMC can help assure the scientific validity of the trial. Trials of any appreciable duration can be affected by changes over time in the understanding of the disease, the affected population, and the standard treatment used outside the trial. These external changes may prompt an interest in modifying some aspects of the trial as it progresses. When a DMC is the only group reviewing unblinded interim data, the trial organizers are free to make changes in the ongoing trial that may be motivated by newly available data outside the trial or by accumulating data from within the trial (e.g., overall event rates). In general, recommendations to change the inclusion criteria, the trial endpoints, or the size of the trial are most credibly made by those without knowledge of the accumulating data. When the trial organizers are the ones reviewing the interim data, their awareness of interim comparative results cannot help but affect their determination as to whether these changes should be made. Such changes would inevitably impair the credibility of the study results. We will address this problem more fully in section 6.3.

3. DMCs AND OTHER OVERSIGHT GROUPS

Several different groups and individuals may assume or share responsibility for various aspects of clinical trial monitoring and oversight, and it is important to recognize the different roles they play.

3.1. IRBs

An Institutional Review Board (IRB) is responsible for evaluating a trial to determine, among other things, whether "risks to subjects are minimized" and "risks to subjects are reasonable in relation to anticipated benefits" (21 CFR 56.111(a)(1) and (3)). An IRB's evaluation entails review of the trial protocol, relevant background information, the informed consent document, proposed plans for informing participants about the trial, and any other procedures associated with the trial. For ongoing trials, the IRB is responsible for considering available information arising from the trial that may bear on the continued acceptability of the trial at that site. Unlike a DMC, an IRB generally does not review unblinded summaries of interim safety and effectiveness data, but the IRB may take action based on recommendations from a DMC to the trial sponsor.

3.2. Clinical Trial Steering Committees

A Steering Committee, when it exists, has primary responsibility for designing the study, maintaining the quality of study conduct, and writing the final study report. It is appointed by the sponsor and is comprised of investigators, possibly other experts not otherwise involved in the trial, and, usually, representatives of the sponsor. When there is a Steering Committee, the sponsor may elect to have the DMC communicate with this committee rather than directly to the sponsor.

3.3. Endpoint Assessment/Adjudication Committees

Endpoint Assessment/Adjudication Committees review important endpoints reported by trial investigators to determine whether they meet protocol-specified criteria. Information reviewed on each presumptive endpoint may include laboratory, pathology and/or imaging data, autopsy reports, physical descriptions, and any other data deemed relevant. The committee should be masked to assigned study arm when performing its assessments, whether or not the trial itself is conducted in a blinded manner. Such committees are particularly valuable when endpoints are subjective and/or require the application of a complex definition, and when the intervention is not delivered in a blinded fashion. Although such committees clearly do not share responsibility with DMCs for evaluating interim comparisons, their assessments (if performed at frequent intervals throughout the trial with results incorporated into the database in a timely manner) help to ensure that the data reviewed by DMCs are as accurate and free of bias as possible.

3.4. Site/Clinical monitoring

Staff internal to the sponsor or a group under contract to the sponsor generally perform site/clinical monitoring. They perform "on site" monitoring of individual case histories, assess adherence to the protocol, ensure the ongoing implementation of appropriate data entry and quality control procedures, and in general assess adherence to good clinical practices. In blinded studies, these monitors remain blinded to study arm assignment.

3.5. Others with Monitoring Responsibilities

In addition to the groups defined above, other trial components have important monitoring responsibilities. Study investigators, of course, have the front-line responsibility for identifying potential adverse effects experienced by study participants, adjusting the intervention accordingly and reporting the experience to the sponsor. The sponsor is responsible for tracking these investigator reports and relaying them as required to FDA, IRBs (medical devices only), and other investigators (21 CFR 312.32(c)). FDA, in turn, is responsible for ongoing consideration of adverse experience reports from all trials of a given product.

4. DMC ESTABLISHMENT AND OPERATION

4.1. Committee Composition

The selection of DMC members is extremely important as the DMC is assigned critical responsibilities. A DMC that fails to note problems that should be addressed, or that makes recommendations that are unwarranted or whose consequences are inadequately considered, can undermine the safety of participants as well as the value of the trial. Thus, the ability of DMCs to provide the anticipated additional assurance of patient safety and trial integrity depends on appropriate selection of DMC members.

The trial sponsor and/or trial Steering Committee generally appoints a DMC. Factors to consider in the selection of individuals to serve on a DMC should include relevant expertise,

experience in clinical trials and in serving on other DMCs, and a lack of serious conflicts of interest as discussed below. The objectives and design of the trial and the scope of the responsibilities given to the DMC determine the types of expertise needed for a particular DMC.

Most DMCs are composed of clinicians with expertise in relevant clinical specialties and at least one biostatistician knowledgeable about statistical methods for clinical trials and sequential analysis of trial data. Some DMCs may include a medical ethicist knowledgeable about the design, conduct, and interpretation of clinical trials. Prior DMC experience is helpful, but not essential, although it is desirable that at least some members have prior DMC service. Some trials may require participation of other types of scientists; for example, a study in which the investigational drug has variable absorption or excretion might include a clinical pharmacologist on the DMC; toxicologists, epidemiologists, and laboratory scientists could be included in particular cases. One or more individuals (often non-scientists) who may help bring to the DMC the perspectives of the population under study may be a useful addition in some settings. That individual should not be participating in the trial, but could be someone with the disease under study or a close relative of such an individual, for example. DMCs for international trials should have representation from participating countries or regions to the extent practical. Appropriate representation of gender and ethnic groups may be of particular importance for some trials. All appointees should be prepared to maintain confidentiality of the interim results they have reviewed (see Section 4.2).

A DMC may have as few as 3 members, but may need to be larger when representation of multiple scientific and other disciplines, or a wider range of perspectives generally, is desirable. For logistical reasons it is sensible to keep the DMC as small as possible, while still having representation of all needed skills and experience. Some redundancy may be desirable, however, in scientifically and/or ethically complex trials, trials of long duration in which DMC attrition might be anticipated, or in trials in which the DMC must meet fairly frequently so that not all members would likely be able to attend all meetings.

Conflicts of interest deserve special consideration in choosing individuals to serve on a DMC. Potential DMC members should be free of financial interests that could be substantially affected by the outcome of the trial. Investigators entering subjects into the trial should not be members of the DMC for that trial to avoid any possible influence of knowledge of interim results on their conduct of the trial. An investigator who is aware of early trends might change his or her pattern of recruitment, or modify his or her usual way of monitoring the status of participants. Also, individuals known to have strong views on the relative merits of the interventions under study may have an "intellectual" conflict of interest and might not be able to review the data in a fully objective manner. Ideally, DMC members should not have relationships with those in trial leadership positions that could be considered reasonably likely to affect their objectivity. Sponsors should have their own established procedures in place to assess potential conflicts of interest of proposed DMC members, to ensure that those with serious conflicts of interest are not included on the DMC, and to provide disclosure to all DMC members of any minor conflicts that are not thought to impede objectivity.

The study sponsor usually appoints the DMC chair. Prior DMC experience is more important for the chair than for other DMC members, as members will look to the chair for leadership on administrative as well as scientific issues. (If the DMC includes only one statistician, however, it is desirable for the statistician to have had prior DMC experience as well.) The chair should be capable of facilitating discussion, integrating differing points of view and moving toward consensus on recommendations to be provided to the trial sponsors. It is particularly important for the chair to make a firm commitment to participate for the duration of the trial.

4.2. Confidentiality of Interim Data and Analyses

Knowledge of unblinded interim comparisons from a clinical trial is not necessary for those conducting or those sponsoring the trial; further, such knowledge can bias the outcome of the study by inappropriately influencing its continuing conduct or the plan of analyses. Therefore, interim data and the results of interim analyses should generally not be accessible by anyone other than DMC members. Sponsors should establish procedures to ensure the confidentiality of the interim data (see Section 4.3.1.4.).

4.2.1. Interim Data

The interim unblinded data will be most securely protected from inadvertent or inappropriate access by the sponsor if it is prepared for analysis by an entity independent of the sponsor and investigators (see Section 6.4). The lead investigators, the study Steering Committee, or the sponsor generally develops the analytical plan, but these individuals should generally not be involved in the actual preparation of the interim results, for reasons discussed in Section 6.4. They should, however, work with the statistician who will be preparing and presenting the interim analyses prior to the first analysis of unblinded data to develop a template for the interim reports.

4.2.2. Interim Reports to the DMC

Any part of the interim report to the DMC that includes comparative effectiveness and safety data presented by study group, whether coded or uncoded, should generally be available only to DMC members during the course of the trial, including any follow-up period—that is, until the blind is broken. If such reports are shared with the sponsor, it may become impossible for the sponsor to make potentially warranted changes in the trial design or analysis plan in an unbiased manner (see Section 6.3).

In many cases, the DMC receives reports in two parts: an "open" section, which presents data only in aggregate and focuses on trial conduct issues such as accrual and dropout rates, timeliness of data submission, eligibility rates and reasons for ineligibility; and a "closed" section, in which the comparative outcome data are presented. The DMC may share the open section of these reports with sponsors, who may convey any relevant information in these reports to investigators, IRBs, and other interested parties, as the data presented in the "open" section are not likely to bias the future conduct of the trial and are often important for improving trial management.

4.3. Establishing Standard Operating Procedures

All DMCs should have well-defined standard operating procedures (SOPs). The sponsor may draft these SOPs and present them to the DMC for agreement, or the DMC may draft the SOPs with subsequent concurrence by the sponsor. Topics to be addressed would normally include a schedule and format for meetings, format for presentation of data, specification of who will have access to interim data and who may attend all or part of DMC meetings, procedures for assessing conflict of interest of potential DMC members, and the method and timing of providing interim reports to the DMC. The sponsor should submit a description of the SOPs to FDA well in advance of the performance of any interim analyses, optimally before the initiation of the trial.

4.3.1. Considerations for Standard Operating Procedures

4.3.1.1 Meeting Schedule and Format

The initial frequency of DMC meetings will depend on the expected rate of accrual and event occurrence at the time the trial is designed as well as the perceived risk of the experimental and/or control interventions. Annual meetings may be adequate for some studies; many (perhaps most) trials will require more frequent review. The study protocol should describe the schedule of interim analyses to be considered by the DMC, or the considerations that will determine the timing of meetings. The study protocol should also clearly describe the statistical approach to the sequential analysis of trial data, which may be addressed in greater detail in an analytical plan. These descriptions should be complete before the conduct of any interim analyses.

Face-to-face meetings are generally preferable, but telephone meetings may be necessary in some situations, particularly when new information must be urgently considered. In some settings, when the DMC has already had numerous meetings and the committee is very familiar with the trial and the analytical issues, telephone meetings may be sufficient.

4.3.1.2 Meeting Structure

Attendance at meetings raises the same confidentiality issues as access to interim reports to the DMC. Although confidentiality of the interim data should be maintained, the DMC may interact with the study sponsor and/or trial lead investigators to clarify issues relating to the conduct of the trial, potential impact on the trial of external data, or other topics. In order to permit such interaction without compromising confidentiality, many DMC meetings include an "open" session in which information in the open report is discussed. These non-confidential data may include, for example, status of recruitment, baseline characteristics, ineligibility rate, accuracy and timeliness of data submissions, and aggregated safety and outcome data. Open session discussions might include representatives of the study sponsor, Steering Committee, study investigators, and FDA. There is a benefit to having a wider attendance at these sessions, since they

provide an opportunity for those with the most intimate knowledge of the study to share their insights with the DMC and raise issues for the DMC to consider. The DMC then considers the comparative interim data contained in the closed report in a "closed" session attended only by the DMC members and the statistician who prepared and is presenting the interim analyses to the Committee. Following the closed session, the DMC may meet again with the study sponsor to relay any recommendations the Committee has made.

Section 6 describes the risks to study integrity when sponsor representatives have access to unblinded interim data and attend closed sessions of DMC meetings. In settings in which sponsors choose to permit its representatives or other non-DMC members to attend the closed session despite the risks of such arrangements, the DMC should have the option of conducting an "executive" closed session with no participants other than DMC members.

4.3.1.3 Initial Meeting

The initial meeting of a DMC should occur before the start of the study if at all possible. At this meeting, the DMC should discuss the protocol and analytic plan, model informed consent form, data collection instruments and other important trial documents, and present any suggestions for modifications to the sponsor and/or Steering Committee. Meeting participants should discuss and complete plans for monitoring the safety and effectiveness data, including:

- scheduling of meetings;
- format for the interim reports to the DMC;
- timing of the delivery of the report to the DMC members prior to the meeting;
- definition of a "quorum" of DMC members, including representation of essential scientific and other disciplines;
- handling of meeting minutes;

and other aspects of the process. It is particularly important that the sponsor and the DMC agree on the approach to early termination when multiple primary endpoints or important secondary endpoints, or composite endpoints with multiple components (for example, death and relapse) are to be evaluated.

4.3.1.4 Format of Interim Reports to the DMC and Use of Treatment Codes

The sponsor should ensure that the general format and content of reports to the DMC are acceptable to the DMC. At its first meeting, as noted above, the sponsor should propose a template for these reports, so that changes requested by the DMC may be implemented before the time when interim data will actually be presented. The statistician preparing the reports to the DMC should ideally be independent of the sponsor and clinical investigators (and a Steering Committee if there is one) to avoid inadvertent influence of data trends on the conduct of the trial (see Section 6.3 and Section 6.4).

A DMC should generally have access to the actual treatment assignments for each study group. Some have argued that DMCs should be provided only coded assignment information that permits the DMC to compare data between study arms but does not reveal which group received which intervention, thereby protecting against inadvertent release of unblinded interim data and ensuring a greater objectivity of interim review. This approach, however, could lead to problems in balancing risks against potential benefits in some cases. To maintain blinding of the actual study arm assignments, safety outcomes would have to be coded differently from effectiveness outcomes when adverse effects would reveal the assigned intervention. This would prevent the DMC from balancing risks and benefits of the active interventions, its most critical responsibility. Also, decisions about a trial are often asymmetric with respect to study arm. Additionally, a trend suggesting a safety concern with a new intervention could be sufficient to suggest the need for trial modification, while a similar trend in the opposite direction (new intervention looks better than standard) might not.

The statistical group responsible for preparing the reports to the DMC should present results in printed copy using codes (for example, Group A and Group B) to protect against inadvertent unblinding should a report be misplaced, and provide separate access to the actual study arm assignments for DMC members. A process should be in place to ensure rapid unblinding of treatment codes to DMC members when needed. For example, DMC members might routinely receive the unblinded treatment codes in a mailing separate from that containing the interim reports.

4.3.2. Statistical Methods

The International Conference on Harmonization guidance document, "Statistical Principles in Clinical Trials" (ICH E9), addresses the statistical monitoring of trials, describes available statistical approaches, and presents the principles involved in their implementation. Planners of clinical trials most commonly use group sequential methods, in which interim analyses are performed at regular intervals based either on chronological time or amount of information accrued, but other approaches, such as those based on Bayesian methods, have been and may be used as well. Statistical methods are also available to support stopping for futility; that is, when the likelihood that the treatment effect being sought, based on the interim data, is very unlikely to be established. The sponsor and/or trial Steering Committee usually proposes the particular statistical approach, but the DMC should generally review it before being made final, to ensure that the DMC agrees to be guided in its actions by the planned approach. Once a final plan has been put in place, the sponsor should submit it to FDA before the initiation of interim monitoring. Because statistical approaches based on classical hypothesis testing methods are by far the most common, the remaining discussion in this section will focus on issues within that framework.

One of the major responsibilities of a DMC is to evaluate the relative treatment effects based on protocol-specified endpoints to determine if the trial is meeting its objectives. A major concern when data on group differences are assessed repeatedly as they

accumulate is that the Type I error (false positive) rate may be inflated if adjustment is not made for the multiple looks at the data. Typically, procedures should specify a statistical approach in advance of the trial's initiation that permits multiple interim reviews while maintaining the Type I error rate at the desired level. These approaches usually generate boundaries for interim estimates of benefit that indicate the magnitude of benefit needed to support stopping the trial at interim points prior to its planned completion, while maintaining the desired overall probability of Type I error. Such boundaries can serve as useful guidelines to the DMC in making recommendations regarding continued accrual to and conduct of the trial. The DMC will usually recommend termination when these thresholds are crossed, but it is not obligated to do so, since other aspects of the interim data may complicate the issue. For example, the data on effectiveness may be very strong, with a stopping boundary being exceeded, but emerging safety concerns may make the benefit-to-risk assessment non-definitive at that interim review. The sponsor should expect the DMC to exercise its own judgment in such circumstances. If the DMC recommends early termination for efficacy before a boundary is crossed, and this recommendation is implemented, the Type I error cannot be preserved and the study results may be difficult to interpret.

Statistical assessment may also suggest that early termination of a trial should be considered on the basis of futility—that is, when the probability, given the interim results, that the trial will ultimately be able to demonstrate the effectiveness of the investigational product is very low. In this case, a DMC may recommend early termination on the grounds that the trial is unlikely to meet its objectives and there is therefore no basis for continuing enrollment and/or follow-up. Stopping on the basis of futility does not raise concerns about Type I error in that trial, since the conclusions of the trial will not be positive. Nevertheless, protection of Type I error is important even when there is a stated intention to stop early only for futility reasons since interim review of outcome data always raises the possibility that the DMC may find early results so persuasive that it would recommend early termination of the trial.

4.4. Potential DMC Responsibilities

4.4.1. Interim Monitoring

Most experience with DMCs has been in the setting of studies that address major outcomes such as mortality or serious irreversible morbidity. Although many such studies focus on short-term endpoints such as 30-day survival, other studies often use endpoints that require a substantial duration of follow-up after the intervention delivery has been completed. In all studies, it is essential that the DMC carefully monitor the interim data throughout the duration of the study, regardless of the duration of treatment.

4.4.1.1 Monitoring for Effectiveness

In studies with serious outcomes, all would wish that any major treatment advance be identified and made available as soon as possible. It is critical, however, that the study yield a valid and definitive result. Thus tensions between ethical and scientific considerations may arise. Consider, for example, a placebo-controlled trial of a new product for a serious illness or condition for which there

is no standard treatment. If the emerging data suggest that those receiving the treatment are doing better, one might consider whether the study should be terminated earlier than planned. Estimates of treatment effect, however, will be unstable at early points in a study, and the chance of observing a nominally statistically significant benefit (e.g., $p<0.05$) at some point during a study of an ineffective product is substantial (see Section 4.4.2). A DMC, guided by a pre-specified statistical monitoring plan, will be charged with recommending early termination on the basis of a positive result only when the data are truly compelling and the risk of a false positive conclusion is acceptably low.

A second type of consideration is whether the hypothesized benefit is likely ultimately to be achieved. If the interim data suggest that the new product is of no benefit—that is, there is no trend indicating superiority of the new product—or that accrual rates are too low or noncompliance too great to provide adequate power for identifying the specified benefit, a DMC may consider whether continuation of the study is futile and may recommend early termination on this basis. In this case, false negative conclusions are of concern; statistical procedures are available to guide such determinations (see Section 4.3.2).

4.4.1.2 Monitoring for Safety

There are several aspects to safety monitoring in long-term outcome studies. First, the primary efficacy endpoint itself often has safety implications. If those individuals given the investigational intervention are found to be at higher risk for the outcome of interest (e.g., mortality, disease progression, loss of organ function) sooner than those given the control, the DMC may consider recommending early termination on safety grounds. Such assessments have potential implications for falsely concluding that there is an adverse effect, just as regular assessments of efficacy have the potential to lead to false positive conclusions about benefit. Statistical considerations for early stopping when the data are trending in the direction of harm are often different from the case of trends in the direction of benefit, however. It is usually appropriate to demand less rigorous proof of harm to justify early termination than would be appropriate for a finding of benefit. In some cases, however, it may be appropriate to establish a harmful effect more definitively—for example, if a positive effect on the primary endpoint has been demonstrated or appears to be emerging, a precise assessment of a negative trend on a potentially important safety endpoint may be required for benefit-to-risk considerations.

A second aspect of safety monitoring in these trials is the interim review of adverse events observed in each study arm. In some cases, one can predict adverse events of concern in advance of the study, but the sponsor should provide the DMC with summaries of the adverse events observed. This is particularly important when the event may result from the disease being treated as well as the intervention itself. For example, individuals with diabetes are at elevated risk of myocardial infarction. Thus, a specific case of myocardial infarction in a participant in a trial of a new antidiabetic therapy cannot be readily attributed to

the new therapy. A DMC, however, will regularly review the number of myocardial infarctions observed in each study arm. If an imbalance between groups emerges, concerns will arise that some of the myocardial infarctions may be due to the intervention rather than the disease itself. Since a potentially large number of adverse event categories may be observed and compared between the study arms, the interpretation of safety findings by the DMC must be sensitive to the issues of multiplicity.

Concerns about the extent and type of adverse events observed may lead to early termination of the trial when the DMC judges that the potential benefits of the intervention are unlikely to outweigh the risks. In other cases, a DMC may recommend measures short of termination that might reduce the risk of adverse events. For example, the DMC might recommend changing the eligibility criteria if the risks of the intervention seem to be concentrated in a particular subgroup. The DMC might recommend an alteration of the product dosage and/or schedule if the adverse events observed appear likely to be reduced by such changes. It might recommend that screening procedures be instituted that could identify those at increasing risk of adverse events. The DMC could also recommend that current and future study participants be informed of newly identified risks via changes in the consent form and that, in some cases, re-consent of current participants to continued study participation be obtained.

Although a DMC should always review summary adverse event data, it will not usually review in detail every adverse event reported, or even every serious adverse event. This responsibility generally lies with the sponsor who reviews such events promptly, usually blinded to study arm assignment, and has the responsibility of reporting serious, unexpected adverse events in drugs and biologics trials to FDA under 21 CFR 312.32 and unanticipated adverse events in the case of device trials under 21 CFR 812.150(b)(1). The involvement of a DMC in the review of individual adverse event reports will vary from case to case. In some studies, it may be important for the DMC to see detailed information on all deaths or other specified events. In other studies, where many such events are expected, the DMC may view only the summary tabulations and comparative statistics to determine whether there appears to be an excess of an important adverse event in one of the study arms. The DMC should always be prepared to review any individual event thought to be of major significance by the study's medical monitor; such events would generally include deaths or other serious outcomes for which a causal connection with the intervention is plausible. The DMC should learn in a timely manner of any cases for which unblinding of treatment code at the clinical site or by the treating clinician is thought to be necessary to provide an appropriate intervention.

4.4.1.3 Monitoring Study Conduct

A DMC will generally review data related to the conduct of the study (that is, the quality of the study and its ultimate ability to address the scientific questions of

interest), in addition to data on effectiveness and safety outcomes. These data may include, among other items:

- rates of recruitment, ineligibility, noncompliance, protocol violations and dropouts, overall and by study site;
- completeness and timeliness of data;
- degree of concordance between site evaluation of events and centralized review;
- balance between study arms on important prognostic variables;
- accrual within important subsets.

Assessment of conduct-related data is a responsibility shared with the sponsor, the study leadership (such as a Steering Committee), and to some extent with IRBs. The DMC may issue recommendations regarding trial conduct when concerns arise that some aspects of trial conduct may threaten the safety of participants or the integrity of the study. For example, if the data presented to the DMC are not current, the DMC will not be able to meet its responsibility of ensuring that the study continues to be safe for its current and future participants. As another example, an excess of dropouts may endanger the ultimate interpretability of the study results.

4.4.1.4 Consideration of External Data

A DMC may consider the impact of external information on the study being monitored. Release of results of a related study may have implications for the design of the ongoing study, or even its continuation. In some cases, the study sponsor may bring external data to the attention of the DMC; in other cases, the data may be publicly reported. Such data may lead to recommendations ranging from termination of the study, termination of one or more study arms, changes in target population, dose and/or duration of the intervention, use of concomitant treatments, etc. The DMC may also recommend changes to the consent form or investigator's brochure, and/or letters from the sponsor to study participants describing the new results.

The role of the DMC in considering interim changes to a study protocol or other aspects of study conduct raises some issues that merit further discussion.

In many cases, access to the blinded data will be essential to making the best decision regarding changes to an ongoing trial. For example, if external reports indicate that use of the study drug in a different indication raised serious, unexpected safety concerns, a decision about continuing the ongoing trial may depend on whether the interim data suggest important benefits that may make the newly found risks acceptable, or the extent to which the newly identified concerns are evident in the ongoing study.

In some cases, however, significant involvement of the DMC in considerations of changes based on external data could have undesirable consequences. Many trial

modifications (e.g., changing endpoints, changing or adding to prespecified analysis subgroups) could have a different impact on type 1 error and interpretation of final results depending on whether the modifications were based solely on external data or based in part on knowledge of the interim efficacy data. In general, the trial leadership, rather than the DMC, should be addressing potential changes other than those driven by safety considerations.

4.4.1.5 Studies of Less Serious Outcomes

Many clinical trials evaluate interventions to relieve symptoms. These studies are generally short-term, evaluating treatment effect over periods of a few days to a few months. These studies tend to be smaller than major outcome studies and, therefore, are completed more quickly. Because the primary endpoints of such studies are not serious irreversible events, as in a major outcome study, the ethical issues for monitoring are different. In these studies, valuable secondary objectives such as characterization of the effect (i.e., magnitude, duration, time to response), assessment of the effect in population subsets, comparison of several doses and/or comparison of the new product to an active control can be ethically pursued even when the conclusion regarding the primary outcome is clear. Early termination for effectiveness is rarely appropriate in such studies. First, the study may be essentially completed by the time any interim analysis could be undertaken. Second, the effectiveness of an intervention to relieve symptoms would not generally be so compelling as to override the need to collect the full amount of safety data, or to collect other information of interest and importance that characterizes the effect, as noted above.

DMCs have not been commonly established for short-term studies of interventions to relieve symptoms. The need for an outside group to regularly monitor data to consider questions of early stopping for efficacy or protocol modification is certainly less compelling in this situation. For such products, however, an expert group to oversee all studies at all stages of development, monitor the developing safety database and make recommendations for design of successive studies based on early results may be useful. The sponsor or investigator could refer an unusual safety concern arising in any study to this type of external group for review, while maintaining its own primary role in monitoring the accumulating results. Such a group may be particularly valuable when the patient population is at relatively high risk of serious events; for example, in studies of drugs to control symptoms of angina, congestive heart failure, or chronic obstructive lung disease. The external group would independently evaluate individual events and overall event rates in ongoing studies and advise the sponsor about emerging concerns. Clearly, monitoring considerations of this type are more clinical than statistical. Sponsors frequently constitute internal groups to monitor these types of studies, and these may be satisfactory in many cases; nevertheless, external advisors, who will be less committed to the existing development plan, may identify problems more readily than internal reviewers.

4.4.2. Early Studies

DMCs may be useful for certain types of early clinical studies such as Phase 1 or early Phase 2 studies in special circumstances. An external group overseeing safety may be valuable when risk to participants appears unusually high, e.g., with particularly novel approaches to treating a disease or condition. When the investigator is also the product manufacturer or IND/IDE sponsor, and thereby subject to potentially strong influences related to financial and/or intellectual incentives, a DMC could provide additional, independent oversight that would enhance safety of study participants and the credibility of the product development. Sponsors should therefore seriously consider establishing DMCs in such settings.

A DMC's role in early phase studies would be different from that in late Phase 2 or Phase 3 studies. Early studies are often not randomized or controlled, accumulating results are known to the investigators and sponsor, and information about previous and ongoing trials of the product play a greater role in the monitoring of an individual trial. Issues regarding statistical interpretation of interim data, or confidentiality of interim data, are therefore generally less relevant in this setting. Nevertheless, for difficult situations in which ethical considerations must be evaluated in the context of the potential scientific gain from continuing a study, particularly in settings such as those described above, DMCs may be helpful to investigators, sponsors and IRBs by providing independent, objective expert counsel. We expect that such situations will be infrequent.

4.4.3. Other Responsibilities

4.4.3.1 Making Recommendations

A fundamental responsibility of every DMC is to make recommendations to the sponsor concerning the continuation of the study. Most frequently, a DMC's recommendation after an interim review is for the study to continue as designed. Other recommendations that might be made include study termination, study continuation with major or minor modifications, or temporary suspension of enrollment and/or study intervention until some uncertainty is resolved.

The DMC should express its recommendations very clearly to the sponsor. Both a written recommendation and oral communication, with opportunity for questions and discussion, are valuable. Recommendations for modifications other than termination should be accompanied by the minimum amount of data required for the sponsor to make a reasoned decision about the recommendation and the rationale for such recommendations should be as clear and precise as possible. The DMC should document its recommendations and their rationale in a form that can be reviewed by the sponsor, IRBs, regulatory agency, or other interested parties as appropriate (see section 5).

4.4.3.2 Maintaining Meeting Records

As noted in the ICH E6 (Good Clinical Practices) document, the DMC should keep minutes of all meetings. After each meeting, the DMC should issue a written report to the sponsor based on the meeting minutes. This report does not have to be extremely detailed but should include sufficient information to explain the rationale for any recommended changes. The DMC should divide meeting minutes into two parts, according to whether or not they include discussion of confidential data (usually unblinded comparative data). Reports to the sponsor should include only those data generally available to the sponsor (e.g., number screened, number enrolled at each site). The report should include a summary of the discussion in any open session of the meeting and should document any information provided verbally to the sponsor that was not included in the written report. The sponsor may convey the relevant information in this report to other interested parties such as the study investigators, who should provide any such information, as appropriate, to participating IRBs. Of course, any changes in the protocol or study procedures made as a result of DMC recommendations must go to study investigators and participating IRBs, as well as to FDA (see 21 CFR 56.108(a)(3) and (4) and 312.30 for drugs and biologics, and 812.40 for devices). The second part of the minutes should summarize discussion of the comparative unblinded outcome data and provide the rationale for the recommendations made to the sponsor. Generally, the DMC will not circulate this portion of the minutes outside the DMC membership until the trial is terminated.

The DMC or the group preparing the confidential interim reports to the DMC should maintain all meeting records. The sponsor should submit to FDA all meeting records, including the non-confidential and confidential interim reports to the DMC, with the clinical study report (see 21 CFR 314.50(d)(5)(ii)). The sponsor should arrange for archival of electronic data sets used for each set of interim analyses; these data sets should be available on request from FDA after the study is completed.

5. DMCs AND REGULATORY REPORTING REQUIREMENTS

5.1. Safety Reporting

All clinical trials conducted under an IND or IDE are subject to regulatory safety reporting requirements. These requirements include prompt reporting to FDA of unexpected adverse events (see 21 CFR 312.32(c), 21 CFR 312.52, 21 CFR 812.46(b), 21 CFR 812.150(b)(1)). In general, for events that are individually recognizable as a serious unexpected event (e.g., agranulocytosis, hepatotoxicity), the sponsor (sometimes through a CRO running the trial) will retain responsibility for notifying FDA (see 21 CFR 312.52). The sponsor may make the report with or without unblinding the case, as appropriate.

A causal relationship between some serious adverse events and an investigational intervention might, however, be detectable only by comparison of rates in the two arms of a controlled trial, i.e., would not be recognizable as an intervention-related event except by greater frequency (see Section 4.4.1.2). Such findings conveyed to a sponsor by a DMC as part of a recommendation to modify the trial would invariably be considered serious and unexpected, and the sponsor would be required to report them to FDA and to all study investigators according to 21 CFR 312.32 (drug trials) and 21 CFR 812.150(b)(1) (device trials). Study investigators are generally responsible for reporting such findings to their IRBs, according to 21 CFR 312.66 (drug trials) and 21 CFR 812.150(a)(1) (device trials), although direct reporting from sponsors to responsible IRBs may be arranged and may be preferable in some situations, e.g., when a central IRB has been established. For a device trial, however, the sponsor is clearly responsible for notifying all participating IRBs of unanticipated adverse events (21 CFR 812.150(b)(1)).

Sponsors should notify FDA and the responsible IRBs of any recommendations or requests made by a DMC to the sponsor that address safety of participants—for example, recommendations to lower the dose of a study agent because of excess toxicity, or to inform current and future trial participants of an emerging safety concern that had not been recognized at the start of the trial. Such recommendations would always be presumptively based on findings that would meet the definition of a serious and unexpected adverse event. When mutually agreed to by the sponsor and the DMC, a DMC may be delegated responsibility for reporting directly to FDA, although in most cases the sponsor will make such reports.

5.2. Expedited Development

New therapies intended to treat persons with life-threatening and severely debilitating diseases are in some cases developed with particular attention to expediting their evaluation and marketing. For such products, FDA may be more actively involved in reviewing and facilitating the progress of clinical trials and may need on occasion to interact with a DMC of an ongoing trial. In this setting, the sponsor should consider the possibility of such interactions prior to the initiation of the trial, and establish procedures under which such interactions would take place. The sponsor should construct such procedures to maintain the integrity of the trial while providing flexibility for sharing of interim data in the unusual circumstances when such data are considered essential for regulatory decision-making.

6. INDEPENDENCE OF THE DMC

An *independent* DMC is a committee whose members are considered to be independent of those sponsoring, organizing, and conducting the trial. That is, they have had no previous involvement in the design of the trial, are not involved in its conduct except through their role on the DMC, and have no financial or other important connections to the study sponsor or other trial organizers.

DMCs are rarely, if ever, entirely independent of the sponsor as the sponsor generally selects the members, gives the committee its charge, and pays committee members for their expenses and

services. Furthermore, the DMC generally conveys its recommendations to the sponsor or to a Steering Committee in which the sponsor is nearly always represented and the DMC is usually not empowered to stop or change a trial on its own.

Sponsors have taken various roles with respect to the DMC, with varying levels of access to interim data. It is important to consider the potential implications of various arrangements in this regard.

Arrangements have included:

- Sponsor representative as voting member
- Sponsor representative as non-voting member
- Sponsor representative only in open meeting; may see enrollment, compliance and event rates but no study arm specific data.
- No sponsor representation

The committee is considered independent only in the latter 2 cases.

6.1. Desirability of an Independent DMC

Independence of the DMC from the sponsor offers several advantages.

1. The principal responsibilities of the DMC are first, to ensure protection of study participants and second, to protect the scientific validity of the trial. Independence from the sponsor helps ensure that the DMC is not unduly influenced by sponsor interests. In this manner, independence promotes objectivity that benefits not only the participants and the trial but the sponsor as well, in that the credibility of the trial's conclusions is enhanced.

2. Independence of the DMC and complete blinding of the sponsor to interim outcome data preserve the ability of the sponsor to make certain modifications to a trial in response to new external information without introducing bias.

3. Independence of the DMC, by maintaining the sponsor in a fully blinded situation, protects the sponsor (and thus the trial) from pressures toward premature disclosure of results due to SEC requirements, fiduciary responsibility, or other business considerations.

6.2. Value of Sponsor Interaction with the DMC

A sponsor's decision to establish an independent DMC does not preclude interaction of the sponsor with the committee. Sponsor involvement in an open part of the DMC meeting, at which data such as enrollment, compliance, and event rates may be viewed in aggregate but not separately by study arm, has significant advantages. The sponsor may provide important information to the committee regarding the sponsor's goals, plans, and resources that the committee can later integrate into its deliberation. These interactions may provide the sponsor with information relevant to the costs, timetable, and likely interpretability of the study that can be of significant value in planning future studies and/or other aspects of

product development. The risk to the study of such sponsor involvement can be quite limited provided that (1) appropriate care is taken to ensure that the sponsor does not see outcome data separately by study arm and (2) the sponsor does not unduly influence the closed deliberations of the committee.

6.3. Risks of Sponsor Exposure to Interim Comparative Data

Sponsor exposure to unblinded interim data, through the DMC or otherwise, can present substantial risk to the integrity of the trial. One concern is that unblinding of the sponsor increases the risk of further unblinding, e.g., of participants, potential participants, or investigators, thereby potentially compromising objective safety monitoring, equipoise, recruitment, administration of the intervention, or other aspects of the trial. In some cases, this risk may be limited and manageable. However, even when unblinding is limited to a small group or a single individual within the sponsoring organization who do maintain confidentiality of the results, it should be appreciated that an individual with knowledge of interim data may reveal, or be perceived to reveal, information even inadvertently, e.g., by facial expression or body language.

An additional problem arising from a sponsor's access to interim data is the diminution of the sponsor's ability to manage the trial without introducing bias. Many trials, particularly those with DMCs, take place over several years. During that time, it is not uncommon for scientific developments, e.g., development of new tests, approval of new products, announcement of results of other trials, to significantly affect a given trial. Such developments may suggest a need for modifications of the experimental protocol, e.g., allowing certain concomitant treatments, changing endpoints. Non-scientific developments, such as new financial considerations, production problems, enrollment problems, and missing data, may also suggest the need for protocol changes. If the sponsor has had access to interim data, it may be impossible to avoid allowing that knowledge to influence decisions regarding modifications of the trial; it may also be impossible for outside evaluators to assess the impact of that influence. For example, if a sponsor is considering, based on external developments, terminating accrual in one subgroup or changing an endpoint, knowledge of current results in that subgroup or with regard to that endpoint would introduce unavoidable but unmeasurable bias. Thus, the sponsor that knows interim data may well find itself in a position where a protocol change that appears to be in the interest of the trial or even essential for continuing the trial, cannot be made without potentially introducing biases that can be neither quantified nor corrected. This may lead to major difficulties in interpreting the results of statistical comparisons.

6.4. Conduct of the Interim Analyses

Sponsors often wish to maintain control of the data and have their own statisticians perform the analyses, including the unblinded analyses for the DMC. Typically and appropriately, such statisticians are instructed not to disclose interim data to others within the sponsoring organization. Questions can always arise, however, as to whether the statisticians are adequately separated from others within the sponsoring organization involved in managing the trial. FDA has been aware of several cases in which statisticians with knowledge of interim data have been at meetings in which potential changes to study size, entry criteria, or

endpoints are discussed. Even if the statistician remains quiet about the interim data, it is essentially impossible for any opinion he or she may express not to be influenced by knowledge of these data. When the statistician is present for such discussions and knows which course of action is more likely to result in the experimental intervention being shown effective, even unintentional non-verbal communication (e.g., nervousness, smiling) may reveal some of that knowledge. Furthermore, if an executive officer of the sponsor must make a decision with major financial implications and knows a statistician in the sponsor's employ possesses information critical to that decision, both may be placed in a very uncomfortable position in which the risk is high of verbal or non-verbal transmission of information regarding interim data. For all these reasons, the integrity of the trial is best protected when the statistician preparing unblinded data for the DMC is external to the sponsor, especially for critical studies intended to provide definitive evidence of effectiveness. In any case, the statistician should have no responsibility for the management of the trial and should have minimal contact with those who have such involvement.

6.5. Sponsor Access to Interim Data for Planning Purposes

Often, sponsors wish to have access to unblinded interim data for the purpose of planning product development, e.g., designing/initiating further trials or making decisions regarding production facilities. This interest is understandable, but such access is problematic for reasons already discussed. In general, sponsors should avoid seeking information about unblinded interim data and should consider the significant possibility that they may wind up impairing trial management or even making the trial results uninterpretable by doing so. Where the sponsor nonetheless has a compelling need to review such information, the sponsor should follow certain approaches that may lessen, though by no means eliminate, risks to the trial:

- The sponsor should consider discussing such an action with FDA in advance. This is particularly advisable when the sponsor intends to use the study in support of a licensing or marketing application.
- Any viewing of study arm-specific effectiveness data by the DMC and/or sponsor in a study of a serious illness raises the possibility that an unanticipated extreme finding of effectiveness might create an ethical imperative to stop the trial. Such a possibility should be considered before performing any unblinded interim analysis. The sponsor should develop appropriate stopping rules and apportionment of type I error (α) before examining the data.
- The sponsor should determine the minimum amount of information needed. For example, rather than viewing all outcome data or all primary endpoint data, the sponsor may just need to know whether the conditional probability of success on the primary endpoint is more or less than a specified magnitude.
- The sponsor should formulate written questions, preferably with yes/no rather than numerical answers, that will elicit only that minimal required information and nothing more.
- The sponsor should receive only written information regarding the requested data (thereby documenting what was received and avoiding additional unnecessary

communications) and should not participate in closed DMC meetings or discussions of data with unblinded DMC members (except as otherwise requested by the DMC).

- The SOP should identify individuals with a critical "need-to-know" and SOPs should ensure that no one else has access to such information.
- Individuals with access to the information should avoid any further role in the management of the trial and should minimize interactions with others in that role.
- Where possible, individuals who have access to such information should avoid taking actions that will assist others in inferring what the information is.

6.6. Use of Interim Data in Regulatory Submissions

A special circumstance is the case in which the sponsor wishes to use interim data in support of a regulatory submission, with the intent to continue the trial to its conclusion. Because of the risks to the trial's credibility, analysis and use of interim data for this purpose is often ill advised. Exceptional circumstances may arise, however, in which such use could be appropriate. Before accessing and using interim data for this purpose, sponsors should confer with FDA and the DMC (or DMC chair) and consider all potential implications of such actions.

7. SPONSOR INTERACTION WITH FDA REGARDING USE AND OPERATION OF DMCs

There are many situations, several mentioned earlier, in which a sponsor should consult with FDA on matters regarding a DMC.

7.1. Planning the DMC

In planning a clinical trial, a sponsor makes several decisions regarding use, types of membership, and operations of a DMC. Many of these can be critical to the success of the trial in meeting regulatory requirements. The present guidance document is intended to provide general FDA guidance regarding those decisions, but each set of circumstances can raise unique considerations. Issues regarding use of DMCs are appropriate topics for FDA-sponsor meetings (in person or by telephone) at the sponsor's request.

7.2. Accessing Interim Data

As discussed above, accessing interim data by the sponsor carries many risks, not all of which may be fully appreciated by the sponsor. The sponsor should contact FDA before initiating communication with the DMC regarding access to interim data from a trial likely to be an important part of a regulatory submission. While FDA permission is not required, a discussion regarding the potential risks and implications of that action and of methods to limit the risks may contribute to informed decision making.

7.2.1. DMC Recommendations to Terminate the Study

In almost all cases, a DMC is advisory to the sponsor; the sponsor decides whether to accept recommendations to discontinue a trial. FDA will rarely, if ever, tell a sponsor which decision to make. In certain settings, however, consultation with the FDA before making a decision may provide the sponsor with important information regarding the regulatory and scientific implications of a decision and may lead to better decisions. For trials that may be terminated early because a substantial benefit has been observed, consideration may still need to be given to the adequacy of data with regard to other issues such as safety, duration of benefit, outcomes in important subgroups and important secondary endpoints. For trials that may be terminated because of safety concerns, timely communication with FDA is required (21 CFR 312.56(d)). In such cases, the sponsor should initiate discussion as soon as possible about the appropriate course of action, for the trial in question as well as any other use of the investigational product.

7.3. DMC Recommendations for Protocol Changes

A DMC may in some instances recommend changes to the study protocol. Many protocol changes have little impact on the usefulness of a trial to gain regulatory approval. Certain types of changes to the protocol—e.g., changes in the endpoints, changes in permissible concomitant medications or in dose/schedule of study medication—could, however, have substantial impact on the validity of the trial and/or its ability to support the desired regulatory decision. Sponsors should discuss changes of the latter type with FDA before implementation.