# Addendum to
# FDA Briefing Document
# Oncologic Drugs Advisory Committee Meeting

## April 12, 2011

## NDA 21938/S013
## Sutent® (sunitinib malate)
## Applicant: Pfizer, Inc.

---

1. FDA Guidance for Clinical Trial Sponsors – Establishment and Operation of Clinical Trial Data Monitoring Committees. March 2006. (available at: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127073.pdf

***Disclaimer****: The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the sunitinib PNET application to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.*

# Guidance for Clinical Trial Sponsors

## Establishment and Operation of Clinical Trial Data Monitoring Committees

For questions on the content of this guidance, contact the Office of Communication, Training, and Manufacturers Assistance (CBER) at 800-835-4709 or 301-827-1800.

.

**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)**
**March 2006**

**OMB Control No. 0910-0581**
**Expiration Date: 6/30/2012**
**See additional PRA statement in Section 8 of this guidance**

**Contains Nonbinding Recommendations**

# Guidance for Clinical Trial Sponsors

## Establishment and Operation of Clinical Trial Data Monitoring Committees

*Additional copies of this guidance are available from:*
*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*
*Phone: 800-835-4709 or 301-827-1800*
*Internet: http://www.fda.gov/cber/guidelines.htm*
*or*
*Office of Training and Communication*
*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*
*Internet: http://www.fda.gov/cder/guidance/index.htm*
*or*
*The Division of Small Manufacturers, International, and Consumer Assistance (DSMICA)*
*Center for Devices and Radiological Health*
*Food and Drug Administration*
*1350 Piccard Drive, Rockville, MD 20850*
*Phone: 800-638-2041 or 301-443-6597*
*Internet: http://www.fda.gov/cdrh*
*Email: DSMICA@cdrh.fda.gov*
*Facts-on-Demand (faxback): 800-899-0381 or 301-827-0111*

## Table of Contents

**1. INTRODUCTION AND BACKGROUND ..... 1**
**1.1. History of DMCs ..... 2**
**1.2. Current Status ..... 3**
**2. DETERMINING NEED FOR A DMC ..... 3**
**2.1. What is the Risk to Trial Participants? ..... 4**
**2.2. Is DMC Review Practical? ..... 4**
**2.3. Will a DMC Help Assure the Scientific Validity of the Trial? ..... 5**
**3. DMCs AND OTHER OVERSIGHT GROUPS ..... 5**
**3.1. Institutional Review Boards ..... 6**
**3.2. Clinical Trial Steering Committees ..... 6**
**3.3. Endpoint Assessment/Adjudication Committees ..... 7**
**3.4. Site/Clinical Monitoring ..... 7**
**3.5. Others with Monitoring Responsibilities ..... 7**
**4. DMC ESTABLISHMENT AND OPERATION ..... 8**
**4.1. Committee Composition ..... 8**
**4.2. Confidentiality of Interim Data and Analyses ..... 10**
4.2.1. Interim Data ..... 10
4.2.2. Interim Reports to the DMC ..... 11
**4.3. Establishing a Charter Describing Standard Operating Procedures ..... 12**
4.3.1. Considerations for Standard Operating Procedures ..... 12
4.3.1.1. Meeting Schedule and Format ..... 12
4.3.1.2. Meeting Structure ..... 13
4.3.1.3. Initial Meeting ..... 13
4.3.1.4. Format of Interim Reports to the DMC and Use of Treatment Codes ..... 14
4.3.2. Statistical Methods ..... 15
**4.4. Potential DMC Responsibilities ..... 16**
4.4.1. Interim Monitoring ..... 16
4.4.1.1. Monitoring for Effectiveness ..... 17
4.4.1.2. Monitoring for Safety ..... 17
4.4.1.3. Monitoring Study Conduct ..... 20
4.4.1.4. Consideration of External Data ..... 20
4.4.1.5. Studies of Less Serious Outcomes ..... 22
4.4.2. Early Studies ..... 23
4.4.3. Other Responsibilities ..... 24
4.4.3.1. Making Recommendations ..... 24
4.4.3.2. Maintaining Meeting Records ..... 24
**5. DMC RECOMMENDATIONS AND REGULATORY REPORTING REQUIREMENTS ..... 25**
**6. INDEPENDENCE OF THE DMC ..... 26**
**6.1. Desirability of an Independent DMC ..... 27**
**6.2. Value of Sponsor Interaction with the DMC ..... 27**
**6.3. Risks of Sponsor Exposure to Interim Comparative Data ..... 28**
**6.4. Statisticians Conducting the Interim Analyses ..... 29**
**6.5. Sponsor Access to Interim Data for Planning Purposes ..... 31**

**7. SPONSOR INTERACTION WITH FDA REGARDING USE AND OPERATION OF DMCs ..... 32**
**7.1. Planning the DMC ..... 32**
**7.2. Accessing Interim Data ..... 32**
7.2.1. DMC Recommendations to Terminate the Study ..... 33
7.2.2. FDA Interaction with DMCs ..... 33
**7.3. DMC Recommendations for Protocol Changes ..... 34**
**8. PAPERWORK REDUCTION ACT OF 1995 ..... 34**

## Guidance for Clinical Trial Sponsors

# Establishment and Operation of Clinical Trial Data Monitoring Committees

*This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.*

## 1. INTRODUCTION AND BACKGROUND

This guidance discusses the roles, responsibilities and operating procedures of Data Monitoring Committees (DMCs) (also known as Data and Safety Monitoring Boards (DSMBs) or Data and Safety Monitoring Committees (DSMCs)) that may carry out important aspects of clinical trial monitoring. This guidance is intended to assist clinical trial sponsors in determining when a DMC may be useful for study monitoring, and how such committees should operate. We recognize that in many clinical trials the sponsor delegates some 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 Code of Federal Regulations (CFR) 312.3(b)). This document, while pertaining primarily to the sponsor with regard to trial management and decision-making, may also be relevant to any individual or group to whom the sponsor has delegated applicable management responsibilities (see Section 3). This guidance finalizes the draft guidance entitled "Guidance for Clinical Trial Sponsors: On the Establishment and Operation of Clinical Trial Data Monitoring Committees" dated November 2001.

Sponsors of studies evaluating new drugs, biologics, and devices are required to monitor these studies (see 21 CFR 312.50 and 312.56 for drugs and biologics, and 21 CFR 812.40 and 21 CFR 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.[1]

A clinical trial DMC is a group of individuals with pertinent expertise that reviews on a regular basis accumulating data from one or more ongoing clinical trials. The DMC advises the sponsor regarding the continuing safety of trial subjects and those yet to be recruited to the trial, as well as the continuing validity and scientific merit of the trial. When a single DMC is responsible for monitoring multiple trials, the considerations for establishment and operation of the DMC are generally similar to those for a DMC monitoring a single trial, but the logistics may be more

[1] Some government agencies that sponsor clinical research have required the use of DMCs in certain clinical trials. Current FDA regulations, however, impose no requirements for the use of DMCs in trials except under 21 CFR 50.24(a)(7)(iv) for research studies in emergency settings in which the informed consent requirement is excepted.

complex. For example, multiple conflict of interest determinations may be needed for each DMC member.

Many different models have been proposed and used for the operation of DMCs. Although different models may be appropriate and acceptable in different situations, experience has shown that some 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 in well-controlled clinical trials. The intent of this guidance document is to ensure wide awareness of acceptable practices and of potential concerns regarding operation of DMCs that may arise in specific situations.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA guidances means that something is suggested or recommended, but not required.

### 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 (NIH) and the Department of Veterans Affairs (VA) 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. (Heart Special Project Committee, 'Organization, Review and Administration of Cooperative Studies (Greenberg Report): A Report from the Heart Special Project Committee to the National Advisory Heart Council, May 1967;' *Controlled Clinical Trials*, vol. 9, 137-148, 1988.) The recommendation for the establishment of such committees was based on the recognition that interim monitoring of accumulating study data was essential to ensure the ongoing 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. The operational and functional aspects of these committees, based on experience over several decades, were discussed in a 1992 NIH workshop (Ellenberg, S., Geller, N., Simon, R. and Yusuf, S. (eds.): Practical Issues in Data Monitoring of Clinical Trials (workshop proceedings). *Statistics in Medicine*, 12:415-616, 1993.)

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 the result of 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 need for approaches to protect against such problems;
- Concerns of IRBs regarding ongoing trial monitoring and patient safety in multicenter trials.

### 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, there are advantages and disadvantages with respect to some of the different approaches that are in use.

As noted above, government agencies that sponsor clinical research, such as the NIH and the VA, have required the use of DMCs in certain trials. Current FDA regulations, however, impose no requirements for the use of DMCs in trials except under 21 CFR 50.24(a)(7)(iv) for research studies in emergency settings in which the informed consent requirement is excepted. FDA believes that the issues discussed in this document arise in trials with both private and public sponsorship. We recognize that the potential conflicts of interest faced by government sponsors can be 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 in which the use of a DMC is appropriate, regardless of the sponsor's funding (i.e., public or private sector), the investigational setting of the trial (academic or other), trial size, or the phase of development. In general, DMC models used in federally funded trials that are established in accordance with policies of the funding agencies are acceptable to FDA.

## 2. DETERMINING NEED FOR A DMC

All clinical trials require safety monitoring, but not all trials require monitoring by a formal committee that may be external to the trial organizers, sponsors, and investigators. As noted earlier, DMCs have generally been established for large, randomized multisite studies that evaluate treatments intended to prolong life or reduce risk of a major adverse health outcome

such as a cardiovascular event or recurrence of cancer. DMCs are generally recommended for any controlled trial of any size that will compare rates of mortality or major morbidity, but a DMC is not required or recommended for most clinical studies. DMCs are generally not needed, for example, for trials at early stages of product development. They are also generally not needed for trials addressing lesser outcomes, such as relief of symptoms, unless the trial population is at elevated risk of more severe outcomes (see Sections 4.4.1.5 and 4.4.2 for further discussion).

Although the value of a DMC is well accepted in settings such as those described above, it is important to recognize that DMCs add administrative complexity to a trial and require additional resources, so we recommend that sponsors limit the use of a DMC to the circumstances described in Section 2.1. There are several factors to consider when determining whether to establish a DMC for a particular trial. These factors, discussed below, relate primarily to safety, practicality, and scientific validity.

### 2.1. What is the Risk to Trial Participants?

A fundamental reason to establish a DMC is to enhance the safety of trial participants in situations in which safety concerns may be unusually high, in order that regular interim analyses of the accumulating data are performed. We recommend that sponsors consider using a DMC when:

- The study endpoint is such that a highly favorable or unfavorable result, or even a finding of futility, at an interim analysis might ethically require termination of the study before its planned completion;
- There are *a priori* reasons for a particular safety concern, as, for example, if the procedure for administering the treatment is particularly invasive;
- There is prior information suggesting the possibility of serious toxicity with the study treatment;
- The study is being performed in a potentially fragile population such as children, pregnant women or the very elderly, or other vulnerable populations, such as those who are terminally ill or of diminished mental capacity;
- The study is being performed in a population at elevated risk of death or other serious outcomes, even when the study objective addresses a lesser endpoint;
- The study is large, of long duration, and multi-center.

In studies with one or more of these characteristics, the additional oversight provided by a DMC can further protect study participants. In other studies, such as short-term studies for relief of symptoms as noted above, such committees are generally not warranted.

### 2.2. Is DMC Review Practical?

A second consideration is whether DMC review is practical. If the trial is likely to be completed quickly, the DMC may not have an opportunity to have a meaningful impact. In short-term trials with important safety concerns, however, a DMC may still be

valuable. In such cases, in order for the DMC to be informed and convened quickly in the event of unexpected results that raise concerns, special mechanisms would have to be developed to permit DMC evaluation and input. Alternatively, the trial could build in "pauses" so that interim data could be reviewed by a DMC before an additional cohort of participants would be enrolled.

### 2.3. Will a DMC Help Assure the Scientific Validity of the Trial?

A third consideration in the decision of whether to have a DMC for a trial is whether a DMC can help assure scientific validity (and perception of such) 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, trial organizers faced with compelling new information external to the trial may consider making changes in the ongoing trial without raising concerns that such changes might have been at least partly motivated by knowledge of the interim data and thereby endanger trial integrity. Sometimes accumulating data from within the trial (e.g., overall event rates) may suggest the need for modifications. Recommendations to change the inclusion criteria, the trial endpoints, or the size of the trial are best made by those without knowledge of the accumulating data (with the exception of changes the DMC might recommend on the basis of emerging safety concerns, as discussed in Section 4.4.1.2). 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 such changes should be made. Changes made in such a setting would inevitably impair the credibility of the study results. This problem will be addressed 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. These groups are all components of a system that assists sponsors in conducting trials that are ethical and that produce valid and credible results. The sponsor of a clinical trial takes responsibility for and initiates the investigation (21 CFR 50.3(e); 21 CFR 312.3; 21 CFR 812.3(n)). Typically, the sponsor holds the Investigational New Drug Application or Investigational Device Exemption (IND/IDE) (21 CFR 312.40(a)(1); 21 CFR 812.40).[2]

[2] This guidance document may also be relevant to parties who participate in leadership roles in a clinical investigation other than sponsors, including funding organizations and/or others who share decision-making authority for a trial. The sponsor may be an individual, committee, company, university, or government agency, or some combination, that holds the IND or IDE and/or has responsibility for designing, initiating, funding, managing, coordinating, continuing and/or concluding the clinical trial. If a product manufacturer initiates a trial and delegates decision-making authority to a steering committee on which it has a representative, the manufacturer and the steering committee may also share certain responsibilities typically held by a sponsor. When the holder of the IND or IDE is also a study investigator, that individual is considered a sponsor-investigator (21 CFR 312.3(b); 21 CFR 812.3(o)).

The responsibilities delegated to steering committees or contract research organizations (CROs) by a manufacturer and/or funding agency can vary considerably. It is important that the responsibilities and authorities of the product manufacturer, the funding organization (if different) and any other entity be clearly defined and understood by all parties at the start of the endeavor. Potential conflicts of interest of each party, especially sponsors and clinical investigators (see 21 CFR Part 54) should be carefully considered when determining roles and responsibilities.

### 3.1. Institutional Review Boards

An institutional review board (IRB) is responsible for evaluating a trial to determine, among other things, whether "[r]isks to subjects are minimized" and "[r]isks to subjects are reasonable in relation to anticipated benefits" (21 CFR 56.111(a)). An IRB's evaluation entails review of the study protocol, relevant background information, the informed consent document, proposed plans for informing participants about the trial, and any other procedures associated with the trial. To determine whether risks to subjects are minimized by "using procedures which are consistent with sound research design" (21 CFR 56.111(a)(1)(i)), an IRB may appropriately request information about the approach to trial monitoring, including the statistical basis for early termination, when relevant, and what steps the sponsor is taking to minimize the risks to patients. As part of its oversight, therefore, an IRB may appropriately inquire as to whether a DMC has been established and, if so, seek information about its scope and composition.

For ongoing trials, the IRB is responsible for considering information arising from the trial that may bear on the continued acceptability of the trial at the study site(s) it oversees (see 21 CFR 56.103). A DMC, on the other hand, generally has access to much more data than the IRB during the trial, including interim efficacy and safety outcomes by treatment arm, and makes recommendations with regard to the entire trial. Given its obligation to minimize the risks to patients, an IRB may take action based on information from any appropriate source, including recommendations from a DMC to the sponsor. A trial may have multiple IRBs, each responsible for the patients at a single site, but only one DMC. Under 21 CFR 56.103, 21 CFR 312.66, 21 CFR 812.40, and 21 CFR 812.150(a), individual investigators (or the sponsor of investigational devices) are responsible for assuring that IRBs are made aware of significant new information that arises about a clinical trial. Such information may include DMC recommendations to the sponsor that are communicated to IRB(s), either directly or through individual investigators or sponsors. Additionally, it may be useful for sponsors to ensure that IRBs are informed when DMCs have met, even when no problems have been identified and the DMC has recommended continuation of the trial as designed.

### 3.2. Clinical Trial Steering Committees

In some clinical trials the sponsor may choose to appoint a steering committee; this committee may include investigators, other experts not otherwise involved in the trial, and, usually, representatives of the sponsor. A sponsor may delegate to a steering committee the primary responsibility for designing the study, maintaining the quality of

study conduct, ongoing monitoring of individual toxicities and adverse events, and, in many cases, writing study publications. When there is a steering committee, the sponsor may elect to have the DMC communicate with this committee rather than directly with the sponsor. Interactions between the steering committee and the DMC consist primarily of discussions during "open sessions" (see Section 4.3) of DMC meetings and the communication of recommendations following each DMC review of the trial. More extensive interactions might occur when early termination is being considered, or when external forces (e.g., announcement of results of related studies) impact the ongoing trial.

### 3.3. Endpoint Assessment/Adjudication Committees

Sponsors may also choose to establish an endpoint assessment/adjudication committee (these may also be known as clinical events committees) in certain trials to review important endpoints reported by trial investigators to determine whether the endpoints 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. These committees are typically masked to the assigned study arm when performing their assessments regardless of whether 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 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

The sponsor or a group under contract to the sponsor generally performs site/clinical monitoring of a clinical trial to assure high quality trial conduct. 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 those described above, other groups 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 monitoring and analyzing these investigator reports and relaying them as required to FDA, other regulatory authorities (as appropriate) and other investigators (21 CFR 312.32(c), 21 CFR 812.40). The sponsor and FDA, respectively, also review adverse experience reports from all trials of a given product (21 CFR 312.32(c); 21 CFR 812.150(b)). In addition, for medical device studies, sponsors are responsible for

ensuring that FDA and any reviewing IRB(s) are promptly informed of significant new information about an investigation (21 CFR 812.40). For drug and biologic studies, sponsors must notify IRBs, as well as FDA and other investigators, if the sponsor withdraws the IND for a safety reason (21 CFR 312.38(c)).

# 4. DMC ESTABLISHMENT AND OPERATION

## 4.1. Committee Composition

The selection of DMC members is extremely important, as DMC responsibilities relate to the safety of trial participants. A poorly constituted DMC may fail to note problems that should be addressed, or may make recommendations that are unwarranted or whose consequences are inadequately considered, thereby undermining the safety of participants as well as the value of the trial. The ability of DMCs to provide the anticipated additional assurance of patient safety and trial integrity therefore depends on appropriate selection of DMC members.

The sponsor and/or trial steering committee generally appoint members of a DMC. Factors to consider in the selection of individuals to serve on a DMC typically include relevant expertise, experience in clinical trials and in serving on other DMCs, and absence 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. For trials with unusually high risks or with broad public health implications, the DMC may include a medical ethicist knowledgeable about the design, conduct, and interpretation of clinical trials. Prior DMC experience is important when considering the committee as a whole; it is highly desirable that at least some members have prior DMC service. Prior DMC experience is particularly important for the statistical DMC member if there is only one statistician serving on the DMC.

Some trials may require participation of other types of scientists. Toxicologists, epidemiologists, and clinical pharmacologists, for example, could be included in particular cases when such expertise appears important for informed interpretation of interim results.

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. Generally, such a DMC member would not also be a participant in the trial, since awareness of the accumulating data could affect compliance or other aspects of trial participation. Rather, the member could be someone with the disease or condition under study or a close relative of such an individual, for example.

Appropriate representation of gender and ethnic groups may be of particular importance for some trials. DMCs for international trials will usually include representatives from at least a subset of participating countries or regions; however, it is often not feasible to have every participating country represented on the DMC. For the reasons discussed at the beginning of Section 4.1, we recommend that the primary criterion for selecting all appointees should be their respective expertise and experience. An important practical consideration would be their ability to commit to attending DMC meetings and to maintaining 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, sponsors typically wish 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. The most obvious conflict is financial interest that could be substantially affected by the outcome of the trial. (See Section 6 for further discussion. See also Department of Health and Human Services, Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection, available at http://www.hhs.gov/ohrp/humansubjects/finreltn/fguid.pdf.)

Investigators entering subjects into the trial have a different type of conflict of interest—their knowledge of interim results could influence 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. We therefore recommend that DMC members for a given trial not include investigators in that trial.

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; such individuals may therefore not be optimal DMC members. We recommend that sponsors avoid appointing to a DMC any individuals who have relationships with trial investigators or sponsor employees that could be considered reasonably likely to affect their objectivity.

We recommend that sponsors establish procedures to:

- Assess potential conflicts of interest of proposed DMC members;
- Ensure that those with serious conflicts of interest are not included on the DMC;
- Provide disclosure to all DMC members of any potential conflicts that are not thought to impede objectivity and thus would not preclude service on the DMC;
- Identify and disclose any concurrent service of any DMC member on other DMCs of the same, related or competing products.

The sponsor often appoints the DMC chair, but may seek advice from trial investigators or trial steering committee members. 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. Sponsors will typically want to select a chair who is capable of facilitating discussion, integrating differing points of view, and moving toward consensus on recommendations to be provided to the sponsors. Sponsors may also want to be assured that a potential chair is willing to make a firm commitment to participate for the duration of the trial (or for the term of the appointment, for chairs of DMCs monitoring multiple trials).

## 4.2. Confidentiality of Interim Data and Analyses

As described in 21 CFR 314.126(b)(5) (drugs) and 21 CFR 860.7(f)(1) (devices), sponsors of well-controlled studies should take appropriate measures to minimize bias.[3] Knowledge of unblinded interim comparisons from a clinical trial is generally not necessary for those conducting or sponsoring the trial; further, such knowledge can bias the outcome of the study by inappropriately influencing its continuing conduct or the plan of analyses. Unblinded interim data and the results of comparative interim analyses, therefore, should generally not be accessible by anyone other than DMC members or the statistician(s) performing these analyses and presenting them to the DMC (see id.). Consistent with 21 CFR 314.126(b)(5) (drugs) and 21 CFR 860.7(f)(1) (devices), sponsors should establish written procedures, which may be included in the DMC charter, to ensure the minimization of bias, such as maintaining confidentiality of the interim data (see Section 4.3.1.4). Sponsors may, of course, also address such confidentiality issues in written agreements between the sponsor and members of the DMC as well as written agreements between the sponsor and investigators.

Even for trials not conducted in a double-blind fashion, where investigators and patients are aware of individual treatment assignment and outcome at their sites, the summary evaluations of comparative unblinded treatment results across all participating centers would usually not be available to anyone other than the DMC. Section 6 addresses the particular confidentiality issues for the statistician/statistical team performing the interim analyses.

### 4.2.1. Interim Data

Interim comparative data, whether treatment assignment is revealed or coded, will be most securely protected from inadvertent or inappropriate access by the sponsor or its project team if the data are prepared for analysis by a statistical group that is independent of the sponsor and investigators—that is, the group is not otherwise involved in the trial design or conduct and has no financial or other important connections to the sponsor or other trial organizers (see Section 6). The

[3] All discussions in this guidance relating to adoption of procedures for the minimization of bias refer to the minimization of bias in adequate and well-controlled clinical trials for drugs, as described in 21 CFR 314.126, and well-controlled clinical trials for devices, as described in 21 CFR 860.7(f).

lead investigators, the study steering committee, and/or the sponsor generally develop the analytical plan (often collaboratively), but problems can arise when these same individuals are involved in the actual preparation of the interim results, for reasons discussed in Section 6.4. They may, 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. Procedures should be established to safeguard confidential interim data from the project team, investigators, sponsor representatives, or anyone else outside the DMC and the statistician(s) performing the interim analyses (see 21 CFR 314.126(b)(5) (drugs) and 21 CFR 860.7(f)(1) (devices)).

Although assigning responsibility for interim analysis to individuals employed by the sponsor is generally discouraged, such assignment may be appropriate if sufficiently secure procedures are in place to credibly ensure that the results of such analyses are not revealed to other sponsor employees or to anyone other than DMC members. We recommend that a description of such procedures be included in the DMC charter (see Section 4.3).

4.2.2. Interim Reports to the DMC

We recommend that any part of the interim report to the DMC that includes comparative effectiveness and safety data presented by study group, whether coded or completely unblinded, be available only to DMC members during the course of the trial, including any follow-up period—that is, until the trial is completed and the blind is broken for the sponsor and investigators. If interim 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). Even aggregate data on safety and efficacy may be informative; these data may be needed for some trial management functions (e.g., sample size adjustments, centralized endpoint assessment), but are best limited to those who cannot otherwise carry out their trial management responsibilities.

In some cases (for example, in open-label trials with special concerns about safety), there may be a rationale for the sponsor and/or investigators to have access to the ongoing comparative safety data to ensure continuous monitoring. Such access should be specified and justified in the study protocol and understood by the DMC (see 21 CFR 314.126(b)(5) (drugs) and 21 CFR 860.7(f)(1) (devices)).

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 open section of these reports is usually provided to 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 a Charter Describing Standard Operating Procedures

DMCs typically operate under a written charter that includes well-defined standard operating procedures. Such charters are important for the same reason that study protocols and analytical plans are important—they document that procedures were pre-specified and thereby reduce concerns that operations inappropriately influenced by interim data could bias the trial results and interpretation. The sponsor may draft this charter and present it to the DMC for agreement, or the DMC may draft the charter 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, the method and timing of providing interim reports to the DMC, and other issues relevant to committee operations. FDA may request that the sponsor submit the charter to FDA well in advance of the performance of any interim analyses, ideally before the initiation of the trial (see 21 CFR 312.23(a)(6)(iii)(g); 21 CFR 312.41(a); 21 CFR 812.150(b)(10)). In such cases, FDA would usually consider the charter when FDA reviews the study protocol.

### 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; other trials will require more frequent review. Occasionally, there may be a need for extra meetings, when, for example, there is concern about potentially emerging safety problems, or when important new information external to the trial arises. The study protocol will generally describe the schedule of interim analyses to be considered by the DMC, or the considerations that will determine the timing of meetings (e.g., a plan for interim analysis after a certain number of primary outcomes have been reported). The study protocol will also typically describe the statistical approach to the interim analysis of trial data. To minimize the potential for bias, these descriptions should be complete before the conduct of any unblinded interim analyses (see 21 CFR 314.126(b)(5) (drugs) and 21 CFR 860.7(f)(1) (devices)).

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. When telephone meetings are held, precautions may be needed to assure the confidentiality of the proceedings, and to prevent inadvertent access to conversations.

*4.3.1.2. Meeting Structure*

Attendance at meetings raises the same confidentiality issues as access to interim reports provided to the DMC. A central tenet of clinical trials is the importance of maintaining confidentiality of interim comparative data (see the Guidance for Industry, ICH E9, Statistical Principles for Clinical Trials, available at http://www.fda.gov/cder/guidance/ICH_E9-fnl.pdf). Although FDA typically expects that confidentiality of the interim data will be maintained, the DMC may interact with the 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 other administrative data. Sponsors may also use open sessions to provide external data to the DMC that may be relevant to the study being monitored. Open session discussions might include representatives of the sponsor, steering committee, study investigators, FDA representatives, or others with trial responsibilities. 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 generally 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 DMC. Following the closed session, the DMC may meet again with the sponsor to relay any recommendations the DMC 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 a sponsor chooses to permit its representatives or other non-DMC members to attend the closed session despite the risks of such arrangements, we recommend that the DMC have the option of conducting an "executive" session with no participants other than DMC members.

*4.3.1.3. Initial Meeting*

Scheduling the initial meeting of a DMC before the study is initiated has many advantages. At this meeting, the DMC can 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. Regulatory considerations may also be discussed. Meeting participants typically 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 data monitoring plan, including the approach to early termination.

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

It is important that the general format and content of interim reports to the DMC be acceptable to the DMC. This may be accomplished most efficiently if the sponsor proposes a template for these reports at its first meeting, so that changes requested by the DMC may be implemented before interim data are first presented. However, the templates may change during the course of the trial as experience is accrued. Further, the DMC will generally need easy and timely access to any additional data and analyses deemed important, and may request such additional material when needed.

We recommend that a DMC 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. For example, to maintain blinding of the actual treatment 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 evaluating the balance of risks and benefits of the active interventions, its most critical responsibility.

Also, decisions about a trial are often asymmetric with respect to study arms; that is, a DMC may recommend termination of a study with a trend toward showing harm on the basis of data that, were they in the other direction, would

not be considered strong enough to terminate early with a conclusion of benefit. Similarly, 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.

A common approach is presentation of results in printed copy using codes (for example, Group A and Group B) to protect against inadvertent unblinding should a report be misplaced, with separate access to the actual study arm assignments provided to DMC members by the statistical group responsible for preparing DMC reports. To ensure the DMC's and sponsor's ability to address an emerging safety concern rapidly, they should establish a process to unblind treatment codes to DMC members in a timely fashion when needed (cf. 21 CFR 312.32(d); 21 CFR 812.46(b)(2)). 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

Statistical approaches to monitoring trials, and the principles involved in their implementation, are addressed in Guidance for Industry, ICH E9, Statistical Principles for Clinical Trials, available at http://www.fda.gov/cder/guidance/ICH_E9-fnl.pdf [4]. 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 used as well. Statistical methods are also available to assess 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. Other statistical strategies for monitoring may also be appropriate.

The sponsor or trial steering committee usually proposes the particular statistical approach to interim monitoring, but the DMC should generally review it before it is made final, to ensure that the DMC agrees to be guided in its actions by the planned approach. FDA will typically request that the sponsor submit a final monitoring plan once it has been put in place, and before the initiation of interim monitoring, as such a plan would typically be considered a critical component of the study protocol (see 21 CFR 312.23(a)(6)(iii)(g); 21 CFR 312.41(a); 21 CFR 812.150(b)(10)). 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. As noted earlier, other monitoring strategies may also be appropriate.

[4] Although ICH documents are meant to provide guidance for drug and biologics sponsors, the statistical monitoring principles in ICH E9 could be used in the evaluation of medical devices as well.

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, the monitoring plan will specify a statistical approach 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 having been crossed, but emerging safety concerns may make the benefit-to-risk assessment non-definitive at that interim review. FDA expects the sponsor to direct the DMC to exercise its own judgment in such circumstances; the DMC can be flexible in assessing the data relative to the stopping boundaries. If the DMC recommends early termination for efficacy before a boundary is crossed, however, 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 be considered on the basis of futility, as defined previously. 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. Before recommending that a trial be terminated due to futility, a DMC will typically consider the Type II error, the chance of making a false negative conclusion. 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 may be 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. The need for monitoring in such

studies often extends beyond the time when individuals are treated, since trends in survival or other serious outcomes may not become evident until some time during the follow-up period. Thus, the DMC's responsibility to monitor the study generally continues until the planned completion of follow-up, regardless of the duration of treatment.

*4.4.1.1. Monitoring for Effectiveness*

In studies with serious outcomes, all parties 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 expect that a DMC would 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 is substantial of observing a nominally statistically significant benefit (e.g., $p<0.05$) at one of multiple interim analyses during a study of an ineffective product (see Section 4.4.2). A DMC, guided by a pre-specified statistical monitoring plan acceptable to both the DMC and the study leadership, will generally 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 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 important aspect of safety monitoring in these trials is comparison of adverse event rates in each treatment arm. In some cases adverse events of particular concern can be identified in advance of the trial, and particular attention will be given to monitoring these events. For example, in a large trial of hormone replacement therapy, specific monitoring plans were established to detect a possible increase in breast cancer incidence in women taking active therapy. Because many types of adverse reactions cannot be anticipated prior to a large-scale study, the DMC should generally be provided with interim summaries by treatment arm of adverse events observed, not limited to those identified in advance. This is particularly important for serious events that may result from the disease being treated as well as the intervention itself, or occur at an observable background rate in the population under study. An effect of the drug on these events can only be detected by comparing the rates of the events in treatment and control groups.

To illustrate the process, consider acute myocardial infarctions (AMIs) occurring during a study of an antidiabetic therapy. Diabetics are at increased risk of AMI so that a specific AMI in a participant could not be attributed to the new drug. A DMC for such a trial, however, would 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, sensitivity on the part of the DMC to the issues of multiplicity, i.e., the elevated probability of "false positives" when performing multiple analyses, is warranted. Not all potential risks can be identified in advance of the trial, so pre-specifying risks of concern cannot always be done.

A third aspect of safety monitoring is consideration of individual events of particular concern. Although a DMC typically reviews summary adverse event data as discussed above, 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 must assure review of such events promptly (see, e.g., 21 CFR 312.32(b); 21 CFR 812.42(d); 21 CFR 812.46(b)). The sponsor has the responsibility of reporting to FDA serious,

unexpected adverse events in drugs and biologics trials under 21 CFR 312.32 and unanticipated adverse events in the case of device trials under 21 CFR 812.150(b)(1). For clinical trials involving drugs and biologics, we recommend that sponsors notify DMCs about any waivers granted by FDA for expedited reporting of certain serious events.

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, particularly events that are likely to have been caused by the product being tested (e.g., acute liver failure in a drug study). In other studies, where many deaths or other serious 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. Simple listings of adverse outcomes, especially without treatment assignments, are rarely useful for DMC discussion.

The sponsor may ask the DMC 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. We recommend that the DMC be informed 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, so that the DMC can assess the potential impact of such actions on the overall study blind. Review of individual cases by the DMC does not relieve the sponsor of the regulatory responsibilities, discussed above, regarding evaluation of these events and reporting as required to FDA.

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.
- Altering the product dosage and/or schedule if the adverse events observed appear likely to be reduced by such changes.
- Instituting screening procedures that could identify those at increased risk of a particular adverse event.
- Informing current and future study participants of newly identified risks via changes in the consent form and, in some cases, obtaining re-consent of current participants to continued study participation.

*4.4.1.3. Monitoring Study Conduct*

The DMC typically shares responsibility for assessment of data related to study conduct with the sponsor, the study leadership (such as a steering committee), and to some extent with IRBs. 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.

The DMC may issue recommendations to the sponsor 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 be asked to 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, particularly when unexpected safety issues arise in related studies, the 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, or use of concomitant treatments. 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 in response to external information raises additional issues that merit consideration.

In many cases, access to the unblinded data will be essential to making the best decision regarding changes to an ongoing trial that are suggested by

external data. 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 circumstances, DMCs of separate but closely related trials (e.g., trials of the same product in different patient populations) may consider sharing confidential interim data when unexpected safety issues arise in one trial and information from the two trials together may improve decision-making in both trials. Because such sharing limits the extent to which the trials can be considered independent, it should be pursued only in the rare situations when early stopping might be considered, but the issues leading to this consideration are ambiguous, for example, when a safety concern arises that appears biologically implausible. Both DMCs would typically require the express consent of the respective sponsors prior to sharing such information.

In some cases, however, significant involvement of the DMC in considerations of changes based on external data could have undesirable consequences precisely because the DMC is aware of the interim study results. Many kinds of trial modifications (e.g., changing endpoints, changing or adding to prespecified analysis subgroups) could, if made with knowledge of trial results, have significant effects on type I error and interpretation of final results. If it is perceived that emerging results could have influenced these types of interim protocol changes, the credibility of the trial may be severely damaged. In general, to minimize the potential for bias, the trial leadership, which is insulated from knowledge of the interim data, rather than the DMC, should be responsible for proposing potential changes other than those driven by safety considerations (cf. 21 CFR 314.126(b)(5), 21 CFR 860.7(f)(1)).

The principle that interim protocol changes should not be influenced by emerging results has implications for sponsors, who would initiate requests for protocol changes, and FDA staff, who would need to evaluate any such requests for protocol changes for INDs under 21 CFR 312.30 and for IDEs under 21 CFR 812.35. Sponsors who wish to have the ability to request interim protocol changes without raising concerns about biasing the study should establish procedures to minimize bias, such as ensuring that they are completely unaware of unblinded comparative data (see 21 CFR 314.126(b)(5), 21 CFR 860.7(f)(1)). If the study is performed with blinded treatment allocation, and access to unblinded data is limited to the DMC, making such changes as requested by the sponsor is straightforward. If treatment allocation is not blinded, it is more difficult to maintain confidentiality of interim comparative results, as sponsor staff such as medical monitors will be reviewing data on each case. In such circumstances it may be very advantageous for the sponsor to set up a "firewall" to ensure that those

who would be proposing interim protocol changes based on external data are insulated from knowledge of interim comparative results. To avoid any influence of interim data on consideration of protocol changes, FDA staff will also generally remain blinded to the interim results. Under 21 CFR 312.41(a) (drugs) or 21 CFR 812.150(b)(10) (devices), we may request additional information or data to aid in FDA's review of protocol amendments and other aspects of clinical trials under an IND or IDE, respectively. Under these authorities, we will typically request that, once interim data have been seen by the sponsor, such data should also be available to FDA, provided such data form the basis for a request by the sponsor to amend a study protocol. It may be necessary for FDA to play a more active role regarding interim results in rare cases when there is an immediate need to evaluate a serious safety concern, especially when we may have important relevant information that may not otherwise be available to the DMC. Even in such cases, however, it will generally be preferable for FDA to provide such information to the DMC, where possible, rather than taking a direct role in interim evaluations.

#### *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 monitor data regularly to consider questions of early stopping for efficacy or protocol modification is usually not compelling in this situation. Such a group is probably warranted only when termination of the trial for efficacy, even at the expense of obtaining more complete safety information, would be indicated for ethical reasons.

For products intended solely to relieve symptoms, as opposed to curing or delaying progress of a serious disease or medical condition, 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 most cases. Nevertheless, external advisors, who will be less committed to the existing development plan, may identify some problems more readily than internal reviewers. Thus, sponsors may find it valuable to augment such internal groups with one or more external advisors.

4.4.2. Early Studies

DMCs are not usually warranted in early studies such as Phase 1 or early Phase 2 studies, or pilot/feasibility studies, but formal monitoring groups may be useful for certain types of early clinical studies. While these formal monitoring groups will often consist of individuals internal to the sponsor and/or investigators, a DMC overseeing safety may be considered 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 may therefore wish to 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 exploratory in nature; they are frequently not randomized or controlled and therefore accumulating results are known to the investigators and sponsor. 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 the potential scientific gain from continuing a study must be evaluated in the context of ethical considerations for ensuring subjects' rights and welfare, 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,

however, that the need for independent DMCs in early phase studies will be infrequent.

4.4.3. Other Responsibilities

*4.4.3.1. Making Recommendations*

A fundamental responsibility of a DMC is to make recommendations to the sponsor (and/or, as noted in the Introduction, a steering committee or other group delegated by the sponsor to make decisions about the trial) 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.

Because a DMC's actions potentially impact the safety of trial participants, it is important that a DMC express its recommendations very clearly to the sponsor. Both a written recommendation and oral communication, with opportunity for questions and discussion, can be valuable. Recommendations for modifications are best 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. Sponsors may wish to develop internal procedures to limit the interim data released by a DMC after a recommendation until a decision is made regarding acceptance or rejection of the recommendation, to facilitate maintaining confidentiality of the interim results should the trial continue. We recommend that a DMC document its recommendations, and the rationale for such recommendations, in a form that can be reviewed by the sponsor and then circulated, if and as appropriate, to IRBs, FDA, and/or other interested parties. Sections 5 and 7.2.1 address implications for reporting to FDA of DMC recommendations for major study changes such as early study termination.

*4.4.3.2. Maintaining Meeting Records*

We recommend that the DMC keep minutes of all meetings (see Guidance for Industry, ICH E6, Good Clinical Practice: Consolidated Guidance, Section 5.5 at 5.5.2, available at http://www.fda.gov/cder/guidance/959fnl.pdf). We also recommend that the DMC divide meeting minutes into two parts, according to whether they include discussion of confidential data (usually unblinded comparative data). The second part of the minutes will typically summarize discussion of the comparative unblinded outcome data and provide the rationale for the recommendations made to the sponsor. Generally, the DMC does not circulate this portion of the minutes or the interim study reports for the closed session outside the DMC membership until the trial is terminated.

We also recommend that after each meeting, the DMC 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. Sponsors should establish procedures to minimize the potential for bias, such as requiring that reports to the sponsor include only those data generally available to the sponsor (e.g., number screened, number enrolled at each site) (see 21 CFR 314.126(b)(5) (drugs) and 21 CFR 860.7(f)(1) (devices)). If no changes are recommended, the report may be as simple as "The DMC recommends that the study continue as designed." We further recommend that the report to the sponsor include a summary of the discussion in any open session of the meeting and document any information provided orally 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, sponsors and/or investigators must report to participating IRBs, as well as to FDA, applicable changes in the protocol or study procedures made as a result of DMC recommendations (see 21 CFR 56.108(a)(3) and (4) and 312.30 and 312.66 for drugs and 21 CFR 812.40 for devices).

We recommend that the DMC or the group preparing the confidential interim reports to the DMC maintain all meeting records in order to best ensure continued confidentiality of interim data. We may request copies of these records when the study is completed (21 CFR 312.58 (drugs); 21 CFR 812.150(b)(10) (devices)). We may also request access to the electronic data sets used for each set of interim analysis. We therefore recommend that sponsors arrange for archiving such electronic data sets.

## 5. DMC RECOMMENDATIONS AND REGULATORY REPORTING REQUIREMENTS

All clinical trials conducted under an IND or IDE are subject to regulatory safety reporting requirements. These requirements include prompt reporting to FDA of certain serious and 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 an event that is individually recognizable as a serious event potentially related to administration of a medical product (e.g., agranulocytosis, hepatotoxicity for drug studies), the sponsor (sometimes through a CRO managing that aspect of the trial, see 21 CFR 312.52) is responsible for notifying FDA (21 CFR 312.32, 21 CFR 812.150(b)(1)). The sponsor may make this notification with or without unblinding the individual case, as appropriate.

As discussed above in Section 4.4.1.2, evidence of a possible relationship between many serious adverse events and an investigational drug might be detectable only by comparison of rates in the two arms of a controlled trial and not by review of individual cases. For example, in a drug trial carried out in patients with coronary artery disease, in whom heart attacks and strokes would be expected to occur, an increased heart attack or stroke rate would not be recognized except by

comparison to the rate in the control group; if such comparison demonstrated an increase in heart attack and stroke rate, it could be presumed that the increase in heart attack and stroke rate was drug-related. Such a finding involving a serious adverse event, conveyed to a sponsor by a DMC with a recommendation to change the trial (e.g., design, informed consent), could represent, on its face, a report of one or more serious unexpected adverse event(s). As required by 21 CFR 312.32(d)(1), the sponsor would need to investigate a DMC's recommendation relating to such events as potentially reportable to FDA under 21 CFR 312.32. If the sponsor concluded that the increased rate of serious unanticipated adverse events was "associated with the use of the drug," the finding, and support for it (which could include the DMC report, any analysis, and pertinent data) would need to be submitted as a serious unexpected adverse experience. These considerations would also apply to unanticipated adverse device effects under 21 CFR 812.50(b)(1).

Findings conveyed to a sponsor by a DMC as part of a recommendation to modify the trial could therefore mean that serious and unexpected events were occurring, and the sponsor would consequently be required to report an analysis of these events to FDA and to all study investigators according to 21 CFR 312.32(c)(1)(B)(ii) (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) and 21 CFR 812.40 (device trials), although direct reporting from sponsors to responsible IRBs may be arranged and may be preferable in some situations; for example, when a central IRB has been established. For a device trial, however, the sponsor is responsible for notifying all participating IRBs when an evaluation of an unanticipated adverse event is conducted (21 CFR 812.150(b)(1)).

The requirement to report DMC recommendations related to serious adverse events in an expedited manner in clinical trials of new drugs (21 CFR 312.32(c)) would not apply when the DMC recommendation is related to an excess of events not classifiable as serious. Nevertheless, we recommend that sponsors inform FDA about all recommendations related to the safety of the investigational product whether or not the adverse event in question meets the definition of "serious." Examples might be 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.

## 6. INDEPENDENCE OF THE DMC

Independence of a DMC depends on the relationships of its members to those sponsoring, organizing, conducting, and regulating the trial. Independence is greatest when members have no involvement in the design and conduct of the trial except through their role on the DMC, and have no financial or other important connections to the sponsor (other than their compensation for serving on the DMC) or other trial organizers that could influence (or be perceived to influence) their objectivity in evaluating trial data.

Independence is defined on a continuum. 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. Aside from being compensated for their duties as DMC members, however, we recommend that these members generally have no

ongoing financial relationship with a trial's commercial sponsor and not be involved in the conduct of the trial in any role other than that of a DMC member.

A critical issue in planning and managing operations of a DMC is resolving the tension that can arise between having a maximally independent DMC and having a DMC that is well informed about the trial: its objectives, its design, and its conduct. To narrowly defining "independence" may result in eliminating from consideration the most knowledgeable researchers, who are likely to have had some past interaction with others sponsoring or performing research in their area of expertise. Additionally, while sponsor involvement in looking at comparative data threatens independence, sponsor representatives, study statisticians, and study investigators may contribute valuable perspectives regarding the trial that may not be available to the committee from more independent sources. With regard to sponsor/investigator involvement with the DMC, this tension is best resolved by permitting interaction with the committee in a carefully defined and limited manner, as described in Section 4.3.1.2. The involvement of such individuals with the DMC will typically be limited in terms of what interim data may be viewed, which sessions may be attended, what topics may be discussed, and what roles (e.g., observer, consultant, member), may be played. Some of the considerations in addressing these issues are discussed below.

### 6.1. Desirability of an Independent DMC

Independence of the DMC from the sponsor offers the following advantages:

- Independence from the sponsor helps ensure that sponsor interests do not unduly influence the DMC, promoting objectivity that benefits the subjects and the trial.
- Through enhancement of objectivity and reduction of the possibilities for bias, independence of the DMC increases the credibility of the trial's conclusions.
- 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.
- In a commercially sponsored trial, independence of the DMC may shield the sponsor (and thus the trial) from securities issues by maintaining the sponsor in a fully blinded situation.

### 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 DMC. Sponsor involvement in an open part of the DMC meeting, during 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 DMC regarding the sponsor's goals, plans, and resources that the DMC can later integrate into its deliberation. Further, the review of interim comparative data may raise certain questions that the DMC might want to address to the sponsor. These interactions may improve the quality of the monitoring process and may also 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.

On the other hand, involvement by sponsor representatives and certain investigators in the portion of the DMC meeting where unblinded data are reviewed presents substantial disadvantages, as discussed in Sections 6.1 and 6.3. Even so, such involvement is not entirely without rationale. When a DMC is facing difficult decisions based on interim safety or efficacy data, the sponsor representatives, study statisticians, and study investigators may contribute valuable perspectives that may not be available from more independent sources. For example, such individuals might point out that unanticipated difficulties in collecting certain data may affect their reliability. In addition, such individuals might have detailed knowledge of other relevant information about the drug (or disease) gained from the trial in question or from other studies that could enhance the DMC's ability to monitor the current trial. To the extent such perspectives can be obtained through a combination of having independent DMC members who are very familiar with the drug, the disease, and trial and having sponsor involvement in open session only, some risks (see Section 6.3) will be minimized. When a trial's procedures are such that sponsor representatives or investigators do see unblinded data with the DMC, the DMC may wish to develop its recommendations in an executive session (see Section 4.3.1.2).

### 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 maintains confidentiality of the results, it is possible that an individual with knowledge of interim data may reveal, or be perceived to reveal, information 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 advancements, 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 based on external developments, a sponsor were considering 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 who 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.

In certain situations, exceptions to the strict maintenance of confidentiality of interim data will be warranted. For example, as noted earlier, in trials in which severe toxicity or other severe morbidity is expected and ongoing continual monitoring is required to ensure maximal protection of trial participants, the sponsor may need to be more actively involved in monitoring unblinded safety data despite the risks to confidentiality of the interim results.

### 6.4. Statisticians Conducting the Interim Analyses

As discussed in Section 2.1, DMCs add administrative complexity to a trial, adding complexity to the statistician's analyses of the trial. Traditionally, the primary trial statistician performs interim analyses and reports to the DMC. "Primary trial statistician" may refer to an individual statistician or statistical group responsible for designing the trial and managing its conduct in collaboration with the study chair and others in the trial leadership. This arrangement can be appealing because the primary trial statistician will be extremely knowledgeable about the study and will be able to provide the most informative interaction with the DMC.

Assigning the primary trial statistician the responsibility for interim analysis and reporting to the DMC can be problematic, however. When issues arise that might suggest changes to the trial design, a statistician performing both the primary collaborative and the interim analysis functions including reporting to the DMC, will probably be the only member of the trial management team with knowledge of the interim data. In considering possible changes, the statistician’s objectivity will inevitably be compromised by the knowledge of the potential impact of such changes on the outcome of the trial. When statisticians with knowledge of interim data participate in trial management meetings in which potential changes to study size, entry criteria, or endpoints are discussed, perceptions of biased decision-making could arise. Even if the statisticians remain silent about the interim data, it is essentially impossible for any opinion they may express not to be influenced by knowledge of these data. When the statistician is present for such discussions and knows which of the alternative courses of action is more likely to result in the experimental intervention being shown effective, even unintentional non-verbal communication may reveal (or may be perceived to reveal) some of that knowledge. Furthermore, if the sponsor must make a decision with major financial implications and 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 this reason, when there is a DMC and a formal mechanism for interim analyses, it is advantageous for the statistician performing the interim analysis to be uninvolved in managing the conduct of the trial, especially in regard to making decisions about design modifications. This could mean that a statistician other than the primary trial statistician would take responsibility for the interim analysis and reporting to the DMC. Alternatively, the primary statistician could maintain this role, but forego further involvement in trial management once interim analysis was undertaken. Sponsors may identify and develop other approaches to reduce potential inappropriate influence of interim data on trial management.

Another important issue relating to the role of the statistician arises when the statisticianis employed by the sponsor. Elsewhere in this guidance, we have described the concerns associated with sponsors being aware of the interim comparative data. For purposes of quality assurance, 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.

For these reasons, the integrity of the trial may be best protected when the statisticians preparing unblinded data for the DMC are external to the sponsor and uninvolved in discussions regarding potential changes in trial design while the trial is ongoing. This is an especially important consideration for critical studies intended to provide definitive evidence of effectiveness. Balanced against this concern, however, is the need for the statisticians reporting to the DMC to be very familiar with details of the study and have ample opportunity to assess the interim data. The primary trial statistician, whether or not employed by the sponsor, is usually best situated to play this role. We recognize that an external statistician contracted by the sponsor to perform interim analysis may not be entirely free from the types of pressures and concerns that may affect a statistician employed by the sponsor.

There has been substantial experience with the model in which the primary trial statistician also analyzes interim data and reports to the DMC. This arrangement has worked well, for the most part. In the admittedly infrequent situation in which interim protocol changes need to be considered, however, participation of statisticians with knowledge of interim data could complicate the interpretability of the data. Sponsors may wish to take the above considerations into account in establishing procedures for the operation of the DMC and the process of interim monitoring.

If the statistician reporting unblinded data to the DMC is not the primary trial statistician, it is particularly important that efforts be made to ensure both that the unblinded statistician is very familiar with the design, setting, and objectives of the trial, and has

sufficient time and access to the data to provide insightful analyses responsive to the DMC's needs.

If the primary trial statistician takes on the responsibility for interim analysis and reporting to the DMC, we recommend that this statistician have no further responsibility for the management of the trial once interim analysis begins and have minimal contact with those who have such involvement. In this case, we recommend that sponsors establish and document procedures to ensure this separation, and designate a different statistician to advise on the management of the trial.

If the primary trial statistician takes on the responsibility for interim analysis and reporting to the DMC, and it appears infeasible or highly impractical for any other statistician to take over responsibilities related to trial management, we recommend that sponsors consider, develop and document procedures to minimize the risks of bias that are associated with such arrangements, as described above.

If the statistician responsible for interim analysis and reporting to the DMC is employed by the sponsor, special care should be taken to minimize the potential for bias, such as ensuring that confidential interim data are not revealed to anyone else within the sponsor organization (see 21 CFR 314.126(b)(5) (drugs) and 21 CFR 860.7(f)(1) (devices)).

While the sponsor or the DMC may suggest to the statistician the nature of the analyses and tables they wish reported to the DMC, we recommend the statistician also have the familiarity with the study and data access necessary to perform additional analyses that might be suggested by the accumulating data and/or requested by the DMC.

### 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 are advised to avoid seeking information about unblinded interim data because of the significant possibility that they may wind up impairing trial management or even making the trial results uninterpretable by doing so. Further, plans or decisions based on statistically imprecise interim data may often be suboptimal. Where the sponsor nonetheless has a compelling need to review such information, certain approaches may lessen, although they do not eliminate, risks to the trial:

- Discussion of 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.
- Development of appropriate stopping rules and apportionment of type I error ($\alpha$) before performing any unblinded interim analysis. This is important because 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, and it would not be possible to quantitate the level of evidence provided by the data if the monitoring plan had not been established prior to data review.

- Determination of the minimum amount of information needed. For example, to assist in defining eligibility criteria for a subsequent trial, the sponsor may wish to know only whether estimates of treatment effect in a subgroup are less or greater than in the overall data set.
- Formulation of written questions, preferably with yes/no rather than numerical answers, that will elicit only that minimal required information and nothing more.
- Receiving only written information regarding the requested data (thereby documenting what was received and avoiding additional unnecessary communications) and abstaining from participation in closed DMC meetings or discussions of data with unblinded DMC members (except as otherwise requested by the DMC).
- Identification of those sponsor employees with a critical "need-to-know" and restriction of such information to those individuals only.
- Ensuring that individuals with access to the information avoid any subsequent role in the management of the trial and minimize interactions with others in that role.
- Ensuring that individuals who have access to such information make every effort to avoid taking actions that will assist others in inferring what the information is.
- Ensuring that reports of study findings describe any access to interim data by individuals involved with study management, and steps taken to prevent such access from potentially biasing the study results.

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

There are many situations, several mentioned earlier, in which sponsor consultation with FDA on matters regarding a DMC is advisable.

### 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. This 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. We recommend that sponsors 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. For trials that may be terminated early because a substantial benefit has been observed, however, 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. We recommend that sponsors of trials that could potentially be terminated early for efficacy reasons discuss these issues with FDA prior to implementing the trial, when the statistical monitoring plan and early stopping boundaries are being developed. In these settings, consultation with FDA may provide the sponsor with important information regarding the regulatory and scientific implications of a decision and may lead to better decisions. Sponsors are encouraged to revisit these issues with FDA when considering DMC recommendations for early termination if new issues have arisen and/or if the regulatory implications of early termination were not adequately clarified at the outset of the trial.

For trials that may be terminated because of safety concerns, timely communication with FDA is often required (see, e.g., 21 CFR 312.56(d) (drugs); 21 CFR 812.150 (devices)). In such cases, we recommend that the sponsor 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.

We strongly recommend that sponsors initiate discussion with FDA prior to early termination of any trial implemented specifically to investigate a potential safety concern.

#### 7.2.2. FDA Interaction with DMCs

In rare cases, we may wish to interact with a DMC of an ongoing trial to ensure that specific issues of urgent concern to FDA are fully considered by the DMC or to address questions to the DMC regarding the consistency of the safety data in the ongoing trial to that in the earlier trials, to optimize regulatory decision-making. An example might be a situation in which FDA is considering a marketing application in which a safety issue is of some concern, and the sponsor has a second trial of the investigational agent ongoing. In such a situation, we might wish to be sure that the DMC for the ongoing trial is aware of the existing safety data contained in the application and is taking those data into consideration in evaluating the interim safety data from the ongoing trial. In such a case, we could request that the sponsor arrange for FDA to communicate with, or even

meet with, the DMC (see 21 CFR 312.41(a); 21 CFR 812.150(b)(10)), and care should be taken to minimize the possibility of jeopardizing the integrity of the ongoing trial.

### 7.3. DMC Recommendations for Protocol Changes

A DMC may, in some instances, recommend changes to the study protocol, particularly in the context of their responsibilities for monitoring patient safety. Many protocol changes have little impact on the usefulness of a trial to gain regulatory approval. Certain types of changes to the protocol, however, such as changes in the primary endpoints, could have substantial impact on the validity of the trial and/or its ability to support the desired regulatory decision if they potentially could have been motivated by the interim data. We recommend that sponsors discuss proposed changes of the latter type with FDA before implementation.

## 8. PAPERWORK REDUCTION ACT OF 1995

This guidance contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520).

The time required to complete this information collection is estimated to average 11.75 hours per response, including the time to review instructions, search existing data resources, gather the data needed, and complete and review the information collection. Send comments regarding this burden estimate or suggestions for reducing this burden to:

Food and Drug Administration
Center for Biologics Evaluation and Research (HFM-99)
1401 Rockville Pike, Suite 200N
Rockville, MD 20852-1448

This guidance also refers to previously approved collections of information fund in FDA regulations. The collections of information in §§ 312.30, 312.32, 312.38, 312.55, and 312.56 have been approved under OMB Control No. 0910-0014; the collections of information in § 314.50 have been approved under OMB Control No. 0910-0001; and the collections of information in §§ 812.35 and 812.150 have been approved under OMB Control No. 0190-0078.

| |
|---|
| An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB Control No. The OMB Control No. for this information collection is 0910-0581 (Expires 6/30/2012). |