Use of Data Monitoring Committees in Clinical Trials

Guidance for Industry

DRAFT GUIDANCE

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Use of Data Monitoring Committees in Clinical Trials Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance provides recommendations to help sponsors[2] of clinical trials[3] determine (1) when a data monitoring committee (DMC) (also known as a data and safety monitoring board (DSMB) or a data and safety monitoring committee (DSMC) or an independent data monitoring committee (IDMC)) would be useful for trial monitoring and (2) what procedures and practices should be considered to guide their operation.[4] This guidance revises the guidance for clinical trial sponsors *Establishment and Operation of Clinical Trial Data Monitoring Committees* issued in March 2006 (the 2006 guidance). When finalized, this guidance will supersede the 2006 guidance.[5]

[1] This guidance has been prepared by the Office of Medical Policy in the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research and the Center for Devices and Radiological Health at the Food and Drug Administration.

[2] A *sponsor* of a clinical trial evaluating a new drug or biological product is defined under 21 CFR 312.3(b) as "a person who takes responsibility for and initiates a clinical investigation." A *clinical investigation* is defined under 21 CFR 312.3(b) as "any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects." A *sponsor* of a clinical trial evaluating a device is defined under 21 CFR 812.3(n) as "a person who initiates, but who does not actually conduct, the investigation, that is, the investigational device is administered, dispensed, or used under the immediate direction of another individual."

[3] For the purposes of this guidance, the terms *clinical trial* and *clinical investigation* are used interchangeably.

[4] Sponsors of clinical investigations evaluating investigational drugs, biological products, and devices may be required to monitor these investigations (see 21 CFR 312.50 and 312.56 (for drugs and biological products) and 21 CFR 812.2(b)(1)(iv), 812.40 and 812.46 (for devices)). Certain categories of devices are exempt from some provisions of 21 CFR part 812 (see 21 CFR 812.2(c)). This guidance does not pertain to the applicability of part 812; the language in this guidance discussing the requirements of part 812, including language discussing monitoring and reporting requirements, is relevant to a particular investigation only to the extent those requirements of part 812 actually apply to such investigation.

[5] For the purposes of this guidance, references to *drugs* includes drugs approved under section 505 of the FD&C Act (21 U.S.C. 355) and biological products licensed under 351(a) of the PHS Act (42 U.S.C. 262(a)) that are regulated as drugs. Hereafter, unless otherwise specified, the term *drug* will be used to refer to all such products.

Significant changes in DMC structure and practice since the 2006 guidance was issued include:

- The increased use of DMCs in trials (Califf et al. 2012) of modest size as reflected in the clinical trials data bank housed at ClinicalTrials.gov[6]
- A trend for DMC charters to become longer and more detailed
- An increased use of DMCs to implement certain adaptive clinical trial designs[7]
- An increased use of some DMCs to oversee an entire clinical development program rather than a single clinical trial[8]
- The potential for expansion of functions of a DMC; for example, for review of aggregate[9] data for safety reporting for trials under an investigational new drug application (IND)
- An increased globalization of medical product development and use of multiregional trials with DMCs[10]

For the purposes of this guidance, a clinical trial DMC is a group of individuals with relevant expertise that reviews accumulating data on a regular basis from one or more clinical trials and recommends to the sponsor whether to continue, modify, or stop a trial or trials. A clinical trial DMC is established by the sponsor but should be independent of the sponsor and the trial conduct (see section VII of this guidance).

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only

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[6] ClinicalTrials.gov is a database of privately and publicly funded clinical studies conducted around the world and is a resource provided by the U.S. National Library of Medicine. Listing a study does not mean it has been evaluated by the U.S. Federal Government; not all listed studies are regulated and/or evaluated by FDA. Information on whether a DMC has been appointed for a registered trial can be provided on ClinicalTrials.gov using the optional Data Monitoring Committee data element (Y/N) (https://www.clinicaltrials.gov/prs-info/protocol-definitions#study-oversight).

[7] See the guidance for industry *Adaptive Designs for Clinical Trials of Drugs and Biologics* (December 2019) and the guidance for industry and Food and Drug Administration staff *Adaptive Designs for Medical Device Clinical Studies* (July 2016). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[8] See Clinical Trials Transformation Initiative (CTTI) Overview: Data Monitoring Committees, available at https://ctti-clinicaltrials.org/our-work/ethics-and-human-research-protection/data-monitoring-committees/.

[9] For the purposes of this guidance, the term *aggregate* refers to data within a treatment arm or across treatment arms.

[10] See the International Council for Harmonisation (ICH) guidance for industry *E17 General Principles for Planning and Design of Multiregional Clinical Trials* (July 2018).

as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. SCOPE

This guidance pertains primarily to the sponsor's responsibility for clinical trial management and decision-making but may also be relevant to any individuals or group to whom the sponsor has delegated applicable trial management responsibilities (see section V of this guidance).

III. BACKGROUND

DMCs have a unique role in clinical trial oversight because they are often the only group with access to accumulating unblinded safety and efficacy data. In order to adequately assess the benefits and risks of an intervention, the DMC should evaluate safety data within the context of the intervention's efficacy, such that the DMC should have access to safety results as well as comparative efficacy results. Generally, a DMC monitors accumulating safety data and advises the sponsor regarding the safety of the interventions in trial subjects, monitors interim effectiveness results to see whether they support benefit (or futility), and helps to ensure the scientific merit and integrity of the trial. In most cases, a DMC is responsible for a single trial. When a single DMC is responsible for monitoring multiple related trials, the considerations for the establishment and operation of the DMC are generally similar to those for a DMC monitoring a single trial, but the logistics may be more complex.

Different designs for DMCs may be appropriate in different situations, and experience has shown that no single design is optimal for all settings.

A. Evolution of the Role of DMCs

DMCs have been a component of some clinical trials since the early 1960s (see the appendix for a brief history).

Beginning in the 1990s, the use of DMCs for clinical trials sponsored by the pharmaceutical industry became more common, especially in clinical trials of conditions associated with significant morbidity or mortality. At the same time, more sophisticated statistical methods for conducting interim analyses of accumulating clinical trial data were being developed. These included methods that control the overall false positive rate while allowing for planned interim assessments, as well as methods for computing predictive probabilities that a trial, if run to completion, would be successful (Ellenberg et al. 2002; Balakrishnan 2014; DeMets and Lan 2013; Proschan et al. 2006). With the use of these methods, it became common for industry-sponsored trials to include interim monitoring for administrative purposes (e.g., audits to ensure the correct data is being collected), and with this practice came an increasing reliance on DMCs to assist in this monitoring. The International Council for Harmonisation (ICH) guidance for

industry *E9 Statistical Principles for Clinical Trials*[11] provides recommendations on the appropriate conduct of interim analyses, including the establishment and operation of DMCs, in part because of this increasing use of DMCs in industry-sponsored clinical trials.

Since 2006, there has been an increase in the use of DMCs in many disease areas beyond those involving serious morbidity or mortality. For example, DMCs can provide the specialized expertise to evaluate emerging efficacy and safety data for trials in rare diseases (e.g., certain genetic disorders), for trials in vulnerable populations (e.g., neonates), and for oncologic therapies with highly specific targets and potential serious risks (e.g., biological products for genetic targets, immunotherapies). They are also being used in early phase trials in serious diseases or conditions. With the growth of DMC oversight, a variety of approaches to DMC operations has been developed. In some cases, sponsors have engaged a single DMC to oversee a clinical development program encompassing multiple trials.

B. Current Status

Under FDA regulations, sponsors are not required to use DMCs in clinical trials except under 21 CFR 50.24(a)(7)(iv), where an institutional review board (IRB) can approve a clinical trial in an emergency setting without requiring informed consent from all research subjects, provided certain requirements are met, including the establishment of an independent DMC.

IV. DETERMINING WHETHER TO USE A DMC

As stated previously, DMCs are established to monitor accumulating data from an ongoing trial and make recommendations concerning the safety and effectiveness of an investigational product or the futility of an ongoing trial (see section V1.C of this guidance). A prominent responsibility is also to help ensure subject safety. Although all clinical trials have a plan for monitoring data and subject safety, not all trials call for involvement or monitoring by a DMC (see section V of this guidance).

An important consideration in determining whether to use a DMC in a development program is whether DMC review is practical for the particular clinical trial. Although the practicality of having a DMC for long-term trials is well established, it is not as clear for short-term trials. If the trial is likely to complete enrollment quickly and the follow-up period is short, convening a DMC to review interim data to assess continued exposure of subjects to investigational interventions may be impractical and of little value. Careful consideration should therefore be given to whether a DMC could have a meaningful impact on the conduct of the trial. Where sponsors consider DMC oversight critical for safety monitoring of short-term trials, specific mechanisms should be developed to permit timely DMC evaluation (e.g., pauses in advance of dose escalation) or to conduct data and safety oversight in an expedient manner (e.g., by an independent monitor(s)).

[11] See the ICH guidance for industry *E9 Statistical Principles for Clinical Trials* (September 1998).

Other factors can suggest the value of using a DMC, such as a limited experience in a therapeutic area or participation of subjects from a vulnerable population. Instances may also occur in which a DMC can be useful in the context of a single-arm trial (e.g., using historical control data). For example, if the single-arm trial has adaptive elements, it may be preferable to use an independent group to determine if a prespecified adaptation is to be implemented.

FDA strongly recommends establishing a DMC if trial subjects are at risk of serious morbidity or mortality (e.g., hospitalization, heart attack, stroke, death). In addition to the effects of the subject's condition, investigational products may cause serious unexpected adverse events—an important reason to consider monitoring interim results using a DMC. In cases where an assessment of causality can be made on the basis of a single event (e.g., agranulocytosis, Stevens-Johnson syndrome), the sponsor's internal safety management team or other entity responsible for reviewing safety data (see section V.E of this guidance) may be able to identify a potential risk and bring it to the attention of the sponsor and regulators. In cases where the event may be anticipated to occur in the population enrolled in the trial regardless of the intervention (e.g., myocardial infarctions in an older population) or could be related to other treatments being administered, the relationship between the investigational product and the adverse events will be less clear. In these cases it is often critical to conduct an analysis of safety data to determine whether, for investigational drugs, there is a reasonable possibility that the adverse event was caused by the investigational drug[12] or whether, for investigational devices, it was caused by or associated with the investigational device.[13] In such cases, a DMC or another independent entity should review aggregate safety reports across study arms.

Sometimes the DMC is used to make recommendations on operational matters based on accumulating noncomparative[14] safety and efficacy data (e.g., fewer than expected outcome events or a higher than anticipated rate of dropouts). These findings can also be addressed by other groups (e.g., clinical trial steering committees). Changes to the trial design that involve an analysis of results by study group are best performed by a body independent of the sponsor, the investigators, and the subjects.

V. DMCS AND OTHER OVERSIGHT GROUPS

Various parties may have or share responsibility for aspects of clinical trial monitoring and oversight, and it is important to recognize the roles they play and how responsibilities are assigned among these entities. These parties are all part of a system that helps to ensure the conduct of trials that produce valid, reliable, and credible results. As noted however, DMCs play

[12] See 21 CFR 312.32(c).

[13] See 21 CFR 812.3(s), 812.46(b), and 812.150(b)(1).

[14] A noncomparative analysis is an examination of accumulating trial data in which the treatment group assignments of subjects are not used in any manner in the analysis. A comparative analysis is an examination of accumulating trial data in which treatment groups are identified, either with the actual assigned treatments or with codes (e.g., labeled as A and B, without divulging which treatment is investigational). For more information about comparative and noncomparative analysis, see the guidance for industry *Adaptive Designs for Clinical Trials of Drugs and Biologics*. It should be noted, reporting data with codes can be informative and should be best treated as unblinded.

a unique role in providing clinical trial oversight, given that they are generally the only oversight group that has access to accumulating unblinded safety and efficacy data. The relationship between the DMC and other groups commonly associated with clinical trials is described in the following subsections.

A. Institutional Review Boards

An IRB is responsible for evaluating a trial both before and after it is initiated to determine whether "[r]isks to subjects are minimized" and "[r]isks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may be expected to result," in accordance with 21 CFR 56.111(a)(1) and (2). An IRB may request more information be given to subjects when, in the judgment of the IRB, the additional information would add meaningfully to the protection of the rights, safety, or well-being of the subjects.[15]

In trials in which there is the possibility of serious morbidity or involvement of vulnerable populations, an IRB should inquire as to whether a DMC has been established and, if so, seek information about its scope and composition as part of its oversight.

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 trial sites it oversees (see 21 CFR 56.103 and 21 CFR 56.109), but it will generally only have access to blinded (i.e., noncomparative) data and will not see unblinded interim results. A DMC, on the other hand, has access to detailed data during the trial, including unblinded interim efficacy and safety outcomes by treatment arm. Under 21 CFR 312.66, 812.40, and 812.150, individual investigators or sponsors are responsible for assuring that IRBs are made aware of significant new information that arises about a clinical trial (e.g., DMC recommendations) (see section VI.C.4 of this guidance). In multi-site studies where a single IRB serves as the IRB of record for research involving multiple institutions, the individual investigators or sponsors should also report the collected information to investigators at all sites, as appropriate, in accordance with the single IRB's communication plan.

B. 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. The steering committee may consider many aspects of trial performance (e.g., rate of recruitment, loss to follow-up, overall event rates, whether prognostic or predictive enrichment strategies are being implemented, demographic inclusion), but it should always be blinded to outcomes by study arm. It may also recommend, based on trial performance (e.g., recruitment and loss to follow-up), additional measures to identify possible subjects, elimination of exclusion criteria (e.g., age limitations), and additional efforts to identify reasons for discontinuation. Because of the various roles and responsibilities a steering committee may have, it is important that the responsibilities of the steering committee and the

[15] See the ICH guidance for industry *E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1)* (March 2018).

DMC be clearly delineated while the clinical trial is being planned. 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 should occur during *open* sessions (see section VI.C of this guidance) of DMC meetings and when the recommendations following each DMC review of the trial are communicated, so that the confidentiality of interim results of unblinded cumulative safety and efficacy data is maintained. More-frequent interactions may occur when early termination is being considered or when external events (e.g., announcement of results of related trials) could affect the ongoing trial.

C. Endpoint Assessment/Adjudication Committees

Given that DMCs have access to unblinded data (e.g., unblinded, comparative data), they should not adjudicate trial endpoints. To determine whether the endpoints meet protocol-specified criteria, sponsors may choose to establish an endpoint assessment/adjudication committee (also known as a clinical events committee) to review important endpoint data reported by clinical investigators.[16] These committees are expected to be blinded to the assigned intervention when performing their assessments, regardless of whether the trial itself is conducted in a blinded manner. The committee's assessments help ensure that the data reviewed by DMCs are as accurate and free of bias as possible, provided the adjudication results are completed and transferred in a timely manner to the DMC for its deliberations.

D. Clinical Site Monitors and Entities Reviewing Safety Reporting

1. Clinical Site Monitors

The sponsor or a contract research organization[17] hired by the sponsor generally performs clinical site monitoring of a clinical trial to assure high-quality trial conduct. Clinical site monitors perform central and/or on-site monitoring of subject-level data to assess protocol compliance and adherence to good clinical practice.[18] They should also review individual case report forms, with particular attention to adverse events. These monitors should remain blinded to treatment assignments and should never review accumulating effectiveness data for trial decision-making purposes.

All clinical trials conducted under an IND or an investigational device exemption (IDE) are subject to regulatory safety reporting requirements. These requirements, for example, include prompt reporting to FDA of serious and unexpected adverse events when, based on the available evidence, the sponsor (or, if applicable, the contract research organization, see 21 CFR 312.52)

[16] See the guidance for industry *Adaptive Designs for Clinical Trials of Drugs and Biologics* and the guidance for industry and Food and Drug Administration staff *Adaptive Designs for Medical Device Clinical Studies.*

[17] See 21 CFR 312.3(b), defining a contract research organization as "a person that assumes, as an independent contractor with the sponsor, one or more of the obligations of a sponsor, e.g., design of a protocol, selection or monitoring of investigations, evaluation of reports, and preparation of materials to be submitted to the Food and Drug Administration."

[18] See ICH E6(R2).

concludes that there is reasonable possibility the investigational product caused the event (i.e., it is a *serious and unexpected suspected adverse reaction* (see 21 CFR 312.32(c)) or when the event is an unanticipated adverse device effect (see 21 CFR 812.46(b), and 812.150(b)(1)). Safety monitoring should generally be assigned to individuals or entities that review adverse events for safety reporting.

2. Entities Reviewing Safety Data

When the potential relationship between a serious and unexpected adverse event and the investigational product can be assessed only by comparing event rates in treated and control groups, an entity (either a DMC or an independent safety team) that can potentially review unblinded safety data reporting will be critical to evaluate the adverse events, looking for evidence of emerging safety signals.[19] If the entity that reviews safety data is unblinded to information regarding the subjects experiencing the adverse event, it should be blinded to efficacy data.

An entity that reviews aggregate data for safety reporting should review unblinded accumulating safety data across multiple trials in a product development program. Whether those entities are managed by contract research organizations or are internal to the sponsor, the role of an entity that reviews safety data is distinct from how a traditional DMC operates. Such entities can have different operational practices, but there should be separation between individuals reviewing unblinded safety data and those involved in the conduct of a trial.

Based on its review of unblinded safety and effectiveness data, a traditional DMC can recommend that the sponsor modify or stop the trial because the investigational product (1) is not effective; (2) has caused an unexpected adverse event in a drug or biological product trial under 21 CFR 312.32 or an unanticipated adverse device effect that presents an unreasonable risk to subjects in the case of a device trial under 21 CFR 812.46(b) and 812.150(b)(1); or (3) has clearly been shown to be effective, generally using planned interim analysis procedures. By contrast, the role of an entity that reviews accumulating safety data would generally be to determine whether to recommend that the sponsor submit an IND or IDE report to FDA and all participating investigators.[20] It will usually be critical to unblind the interventions assigned to subjects who have serious adverse events of interest to make this determination, but the entity that reviews aggregate data for safety purposes should not have access to data on effectiveness.

The threshold that a DMC would use for reporting safety concerns to the sponsor and recommending termination or significant modification to the trial may be higher than the threshold for reporting potential serious risks obtained from aggregate data in an IND or IDE

[19] See the guidance for industry *Safety Reporting Requirements for INDs and BA/BE Studies* (December 2012).

[20] For example, see the draft guidance for industry *Safety Assessment for IND Safety Reporting* (December 2015). When final, this guidance will represent FDA's current thinking on this topic. For trials conducted under an IDE, sponsors must also report the results of the evaluation of an unanticipated adverse device effect to all reviewing IRBs within 10 working days after the sponsor first receives notice of the effect (21 CFR 812.2(b)(1)(iv), 812.46(b), and 812.150(b)(1)).

report to FDA.[21] Although DMCs and entities that review accumulating safety data have distinct roles in characterizing safety, it may be possible in some settings to have the DMC conduct these safety evaluations and provide recommendations to sponsors about whether a difference in the occurrence of safety events in the investigational arm compared to the control arm suggests a causal relationship between the investigational product and the adverse event. Even if a causal relationship is suspected for a particular type of serious adverse event, it may still be appropriate to continue the trial (Bhattarcharya et al. 2018).

E. Adaptation Committee

For trials utilizing an adaptive design,[22] a dedicated independent adaptation body could be established that is distinct from a DMC. Alternatively, the adaptive decision-making role could be assigned to the DMC, although its primary responsibility should remain subject safety and trial integrity. Using a DMC to support adaptive trials might best be reserved for group sequential designs and other relatively straight forward adaptive designs with simple adaptation algorithms. Depending on the specific trial design, either approach may be appropriate. Use of separate bodies might facilitate the inclusion of more-relevant expertise on each committee and allow the DMC to focus most effectively on its primary responsibilities. Alternatively, use of a single body—such as a DMC—for both purposes avoids the logistical challenges of information sharing with, and interactions between, multiple monitoring groups.

The committee tasked with making adaptation recommendations should include appropriate expertise, including a statistician or statisticians knowledgeable about the adaptation methodology, monitoring plan, and decision rules. Furthermore, the responsibility of this committee should be to make adaptation recommendations or decisions based on appropriately implementing a carefully designed and prespecified adaptation plan—not to identify potential design aspects to adapt after reviewing comparative interim results. Therefore, it is important that the DMC or adaptation committee be involved at the trial design stage in detailed discussions with the sponsor about hypothetical scenarios. The DMC or adaptation committee should also determine whether actions dictated by the adaptation plan are considered reasonable by all parties involved.

[21] See the draft guidance for industry *Safety Assessment for IND Safety Reporting*.

[22] The term *adaptive design* means a clinical trial design that allows for prospectively planned modifications to one or more aspects of the design based on accumulating data from subjects in the trial. See the guidance for industry *Adaptive Designs for Clinical Trials of Drugs and Biologics* and the guidance for industry and Food and Drug Administration staff *Adaptive Designs for Medical Device Clinical Studies*.

VI. DMC ESTABLISHMENT AND OPERATION

A. Committee Composition

1. Membership

The sponsor or trial steering committee, or both, generally appoint members of a DMC. Most DMCs are composed of individuals with expertise in current clinical trial conduct and clinicians with expertise in relevant clinical specialties. DMCs should also include one biostatistician knowledgeable about statistical methods for clinical trials (including the methods anticipated for the trial under its oversight) and sequential analysis of trial data, if applicable. The importance for including individuals on the DMC with expertise in informatics and technology should also be assessed. It is generally important to have some members with experience in serving on DMCs and some members familiar with FDA regulatory requirements for clinical trials. Both types of experience are typically critical for the DMC chair. All DMC members should be screened for conflicts of interest (see sections V1.A.2 and VII of this guidance).

A well-constructed DMC should be equipped to identify unexpected issues and mitigate problems that could otherwise cause risk to subjects or could adversely affect the quality of the data and integrity of the trial. The objectives and design of the trial and the scope of the responsibilities given to the DMC should determine the types of expertise needed for a particular trial. For example, for trials with unusually high risks to subject safety or with broad public health implications, the DMC should consider including a medical ethicist knowledgeable about the design, conduct, and interpretation of clinical trials.

DMCs will often be supported by an independent statistician or statistical group that is responsible for providing and presenting statistical analyses and reports to the DMC during closed sessions—they are not considered part of the DMC. This role is distinct from the DMC statistician (or statisticians), who is a voting member. The independent statistician or statistical group, as well as an adaptation committee (should one exist), should have access to unblinded data and ensure they are familiar with the design, setting, and objectives of the trial and should have sufficient time and access to the data to provide insightful analyses responsive to the needs of the DMC.

2. Conflict of Interest

Conflicts of interest should be evaluated when choosing individuals to serve on a DMC. One potential conflict is a financial interest that could be substantially affected by the outcome of the trial.[23] Aside from being compensated for their duties on the committee, DMC members should have no ongoing financial relationship with a trial's commercial sponsor (or its direct

[23] See section VIII of this guidance for further discussion. See also the HHS Guidance on Financial Conflicts of Interest (2004), available at https://www.hhs.gov/ohrp/regulations-and-policy/guidance/financial-conflict-of-interest/index.html, which provides points to consider in determining whether specific financial interests in research affect the rights and welfare of human subjects and what actions could be considered to protect those subjects.

competitors[24]) and should not be involved in the conduct of the trial in any role other than that of a DMC member.

Persons known to have strong views on the relative merits of the intervention(s) under evaluation in the clinical trial may have an *intellectual* conflict of interest or bias and may not be able to review the data in a fully objective manner; such individuals are therefore usually not appropriate DMC members. Each potential DMC candidate should be well vetted by sponsors for financial as well as intellectual conflicts of interest.

3. Training Considerations

Adequate preparation for the role as a DMC member is integral to the DMC's mission. DMC members should understand that the roles and responsibilities of DMC membership differ from participation in a clinical trial as an investigator. Sponsors are therefore strongly encouraged to consider the learning and training requisites of members selected to serve on a DMC before involvement in their first DMC meeting[25] and perhaps again later, if needed.

B. Establishing a Charter Describing DMC Obligations, Responsibilities, and Standard Operating Procedures

All DMCs should operate under a written charter that clearly states the purpose of the DMC, the specific questions it is expected to address, and the possible recommendations it can make to the sponsor during the trial. DMC charters should prespecify the meeting schedule and the types of data that will be available for review so that all members have a good understanding of responsibilities associated with their DMC membership. The charter should outline the operating procedures governing the DMC deliberations to reduce concerns that changes made with knowledge of interim unblinded data might bias the trial results and interpretation. The charter should note that DMCs should not have a role in redesigning the trial after reviewing unblinded data. It is critical that during DMC deliberations there is no introduction of bias by investigators or sponsors and that all proceedings involving data analysis and availability, and/or any potential changes to the protocol during the trial[26] be carried out with appropriate attention to maintenance of confidentiality of unblinded interim results in order to maintain trial credibility. To maintain confidentiality of unblinded information, DMC members should be aware of all stipulations under the charter related to meeting formats (i.e., who should be present during sessions), confidentiality, and data handling. The charter can be prepared by the sponsor and presented to the DMC for discussion and agreement or be prepared by the DMC itself with presentation to the sponsor for concurrence.

[24] For the purposes of this guidance, *direct competitor* refers to the commercial sponsor of a trial for a product that is or would be competitive with that being evaluated.

[25] See the guidance for industry *Adaptive Designs for Clinical Trials of Drugs and Biologics* and the guidance for industry and Food and Drug Administration staff *Adaptive Designs for Medical Device Clinical Studies.*

[26] Potential changes in protocol may include those involving safety, such as restricting eligibility or dropping a trial arm.

The DMC charter and documented concurrence with the charter by all DMC members should be in place in advance of performing any interim analyses and ideally before the initiation of the trial and any subject enrollment. 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); 312.41(a); 812.150(b)(10)). In such cases, FDA would usually consider the charter when FDA reviews the study protocol. At a minimum, we recommend that the DMC charter include the following elements.

1. Composition of Committee:

    - Criteria and rationale for selection of committee members
    - Outline and clarification of roles of committee members including voting and nonvoting members
    - Procedures for assessing financial and intellectual conflict of interests for potential DMC members, including procedures for identifying and considering concurrent service of any DMC member on other DMCs for trials of the same, related, or competing product
    - Procedures for adding or removing members when appropriate or for disbanding the DMC, including procedures for informing FDA and disclosing to FDA the rationale for these changes

2. Meeting Information, Schedule, and Format:

    - Planned frequency of meetings, when additional meetings might be scheduled, and preferred platform (e.g., email, video, phone, in person) for communications and conditions for convening ad hoc meetings
    - Who may attend open and closed portions[27] of DMC meetings and whether any members will not attend full meetings
    - Who will create specific reports and have access to them, where reports will be stored, what reports will be generated in the course of the clinical trial (e.g., prespecified statistical monitoring plan, statistical analysis plan) and how they will be transmitted within and outside of the DMC
    - Handling of meeting minutes for open and closed portions
    - Definition of a quorum of DMC members, including representation of scientific and other disciplines

[27] See section VI.D.1 of this guidance.

3. Planned Analyses by Committee and Protection of Data, if applicable, including:

    - Schedule and basis of planned interim analyses identified in the protocol and/or statistical analysis plan

    - Analyses associated with prespecified safety considerations

4. Maintaining Confidentiality of Data:

    - How unblinded analyses will be prepared (e.g., by an independent statistician) for the DMC and at what frequency

    - How blinding of the trial will be maintained for sponsors, investigators, and subjects

    - What procedures will be followed to maintain confidentiality of interim comparative data in communications between the DMC, the sponsor, and outside parties

    - What strategies will be used for maintaining blinding and confidentiality when preparing reports for the DMC open sessions

    - Who, besides the DMC and the independent unblinded statistician, will have access to interim data and reports to the DMC chair

C. DMC Responsibilities

1. Monitoring of Trial Conduct

The DMC considers various matters related to trial conduct. The sponsor, the trial leadership (such as a steering committee), and to some extent IRBs also have responsibilities for ongoing assessment of data regarding the trial conduct. Such matters related to trial conduct can include:

- Rates of recruitment, ineligibility, noncompliance, protocol violations, and dropouts—overall and by trial site

- Completeness and timeliness of data

- Degree of concordance between site evaluation of events and centralized review

- Balance between trial arms on important prognostic variables

- Accrual within important trial subject subsets

2. Monitoring of Results of Interim Analysis of Trial Data

Interim analyses are generally conducted for one or more of the following purposes:

- Safety — to determine if there is a credibly increased risk of a serious adverse outcome in subjects receiving the investigational product, indicating that enrollment should be stopped. To determine a safety risk, review of unblinded efficacy data should also be conducted by the DMC as they evaluate a benefit-risk assessment.

- Implementing a predefined adaptive feature:[28]

  - Efficacy — to determine if there is statistically strong evidence of efficacy such that enrollment should be stopped.[29]

  - Futility — to determine if there is no longer a reasonable likelihood that the trial will reach a conclusion of effectiveness, so that enrollment should be stopped to protect subjects from further exposure to a potentially ineffective investigational product and to conserve resources.

  - Other adaptations — a DMC or a separate adaptation committee should determine if a prespecified adaptive aspect of the trial design is to be implemented. This can include modifying the sample size, changing a randomization ratio, or restricting future enrollment to a prespecified subgroup (adaptive enrichment).

a. Monitoring for Safety

The most common and most recognized purpose of a DMC is to monitor clinical trials for safety. First, in studies where the investigational product is intended to prevent significant morbidity or mortality, the effect on the primary effectiveness endpoint itself would almost always have safety implications if the group receiving the investigational product had a lower response than the control. If subjects given the investigational product are found to be at higher risk for mortality, disease progression, or loss of organ function than those given the control, the DMC may recommend early termination on safety grounds. However, such assessments carry the risk of falsely concluding that there is an adverse effect, just as repeated assessments of effectiveness endpoints 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 usually less rigorous (i.e., have a lower threshold for stopping the investigational product) than those applied to early stopping for benefit, because it is usually appropriate to demand less

[28] ClinicalTrials.gov is a database of privately and publicly funded clinical studies conducted around the world and is a resource provided by the U.S. National Library of Medicine. Listing a study does not mean it has been evaluated by the U.S. Federal Government; not all listed studies are regulated and/or evaluated by FDA. Information on whether a DMC has been appointed for a registered trial can be provided on ClinicalTrials.gov using the optional Data Monitoring Committee data element (Y/N) (https://www.clinicaltrials.gov/prs-info/protocol-definitions#study-oversight).

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 effectiveness endpoint appears to be emerging, a precise assessment of a negative trend on a potentially important safety endpoint may be appropriate for benefit-risk considerations.

For trials that are terminated because of safety concerns, timely communication with FDA is required (see, e.g., 21 CFR 312.56(d) (drugs); 21 CFR 812.40, 812.46(b)(2), and 812.150(b) (devices)). For trials where there is a potential safety concern, the sponsor should take immediate action, as warranted, in the interest of patient safety and initiate discussion with FDA as soon as possible about the appropriate course of action, both for the trial in question and any other use of the investigational product, before suspending or terminating a trial.

A second important aspect of safety monitoring is comparison of adverse event rates (other than trial endpoints) 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 (Wittes et al. 2007). The DMC should generally be provided with interim summaries of serious adverse events by treatment arm. This approach is particularly important to identify and distinguish serious events that typically occur in the disease being treated, as well as the intervention itself, or for events that can be anticipated to occur at an observable background rate in the population under investigation. An effect of the investigational product on these events can only be detected by comparing the rates of the events in treatment and control groups.

A third aspect of safety monitoring is consideration of serious individual events. Although a DMC typically reviews adverse event data, as discussed previously, the committee may elect to review all or just certain serious adverse events. It is recommended that DMCs not routinely review all adverse events individually.[30] If the DMC sees trends or identifies an unanticipated serious safety concern, it should provide feedback to the sponsor or trial steering committee so that the sponsor can take appropriate action to address potential safety concerns.

Concerns about the extent and type of adverse events observed can lead to early termination of the trial when the DMC decides that the potential benefits of the intervention are unlikely to outweigh the risks. In other cases, a DMC should recommend measures short of termination that may reduce the risk of adverse events. For example, the DMC may recommend:

- Changing the eligibility criteria or screening procedures 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. This alteration could entail dropping a particular arm in studies with more than two arms.

[30] See 21 CFR 312.32(c).

- Informing current and future trial subjects of newly identified risks through changes in the consent form, and in some cases reconsenting current subjects for continued trial participation.

It is important to note that trial monitoring of interim data for safety purposes does not imply that only safety data should be reviewed by a DMC. In determining whether the potential for safety risks is such that trial modification or early termination is warranted, a DMC should consider the potential for benefit in its deliberations. For this reason, sponsors should plan to provide to DMCs the data and analyses sufficient for benefit-risk determinations while taking the appropriate steps to ensure integrity of trial results (see section VI.D.3 of this guidance).

b. Monitoring for Effectiveness

Another common purpose of a DMC is to monitor trial data for effectiveness. Particularly in trials of investigational products where effectiveness would have important implications for treating a serious condition, including for subjects in the trial, it is desirable that clear evidence of effectiveness be identified as soon as possible. In these instances, it is imperative to consider the importance for prespecification and appropriate methods to avoid inflating the chance of obtaining an erroneous result by repeated looks at the accruing comparative data. Estimates of treatment effect should be unstable at early points in a trial, and there is a substantial chance of observing a nominally statistically significant but false benefit at one of multiple interim analyses during a trial of an ineffective product (Pocock and Hughes 1989) (see section VI.D.2 of this guidance). A DMC, guided by a prespecified statistical monitoring plan acceptable to both the DMC and the trial leadership, will generally be charged with recommending early termination on the basis of a positive result only when the data are compelling and the risk of a false positive conclusion is acceptably low. The statistical monitoring plan should describe the criteria for early termination and should be included in the DMC charter, as well as the statistical analysis plan, and should describe the criteria for early termination.

c. Monitoring for Futility

A related purpose of a DMC is to determine trial futility. If the interim data suggest that the new product is of no benefit, a DMC may consider whether continuation of the trial would be futile (that is, the trial is highly unlikely to be successful if run to completion) and may recommend early termination on this basis. In this case, false negative conclusions are of concern; available statistical procedures should be used to guide such determinations (see section VI.D.3 of this guidance).

d. Monitoring to Make Other Types of Adaptations to the Trial Design

An adaptive design is defined as a clinical trial design that allows for *prospectively planned* modifications to one or more aspects of the design based on accumulating data from subjects in the trial.[31] This may include interim analyses with prespecified criteria for stopping the trial for

[31] See the guidance for industry *Adaptive Designs for Clinical Trials of Drugs and Biologics* and the guidance for industry and Food and Drug Administration staff *Adaptive Designs for Medical Device Clinical Studies.*

efficacy or futility (see sections VI.C.2.b and c above). Other aspects of the design that might be modified include the sample size, study arms (e.g., elimination of a particular dose or doses), randomization ratio, and trial population. Some adaptations can be based on blinded or noncomparative data accumulated in the trial. For example, if the overall event rate in a trial is low, a decision could be reached to increase trial size or to introduce prognostic enrichment. Such adaptations should either be prespecified in the protocol or done by an entity without access to comparative data; they do not threaten trial integrity because they do not involve unblinding of interim results. These adaptations could reasonably be made by a steering committee or the sponsor, assuming they are blinded to the comparative data.[32] If the adaptations are unblinded (including those instances in which the treatment arms are labeled as A and B rather than as treatment and control), it is particularly important that the opportunities for adapting not only be prespecified but that they also be conducted in a manner designed to preserve trial integrity.

A DMC could have the responsibility of recommending to the sponsor that a specific adaptive design element be implemented. If so, this responsibility should be explicitly stated in the DMC charter, recognizing that the main priority of a DMC is both to ensure subject safety and to preserve trial integrity.

3. Consideration of External Data

The DMC, the sponsor, or the trial steering committee may consider the impact of external information on the trial being monitored when appropriate. In these instances, protocol changes based on consideration of external data should be proposed by the sponsor or steering committee to minimize influence/bias from knowledge of internal comparative results. The release of results of a related trial (e.g., a trial of a pharmacologically related drug or comparable device) may have implications for the design of the ongoing trial, or even its continuation. In some cases, particularly when unexpected safety issues arise in related trials, 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 a wide range of recommendations, such as (1) termination of the trial, (2) termination of one or more trial arms, (3) changes in target population, dose, and/or duration of the intervention, (4) changes in monitoring, or (5) use of concomitant treatments. The DMC may also recommend changes to the consent form, investigator's brochure, and/or letters from the sponsor to trial subjects describing the external results.

When FDA has critical safety information regarding another trial of the investigational product or a trial of a related product from the same sponsor that is relevant and important for a DMC to consider, FDA may request that the sponsor confirm that the DMC for the ongoing trial is aware of the existing safety data and is taking that data into consideration in evaluating the interim safety data from the ongoing trial. An example would be a situation in which FDA is considering a marketing application in which a safety issue is of concern and the sponsor has a second, ongoing trial of the investigational product. In such situations and as appropriate, FDA may request that the sponsor arrange for FDA to communicate with, or even meet with, the DMC.

[32] Ibid.

In some circumstances, program-wide DMCs could be helpful. These are DMCs of separate but closely related trials (e.g., trials of the same product in different subject populations) that 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 for both trials. Sharing the results of trials of related investigational products poses potential confidentiality problems, and the DMC charter should address how information can be shared when the DMC members are not exactly the same across trials within the program. From an ethical perspective, it is important to consider safety-related issues in both trials when considering appropriate trial changes and to institute similar safety changes in both trials.

The role of the DMC in considering interim changes to a trial protocol or other aspects of trial conduct in response to external information raises additional issues that merit consideration. In many cases, a DMC's knowledge of both the interim trial results and external data can have undesirable consequences. For instance, various types of trial modifications (e.g., changing endpoints, changing or adding to prespecified analysis subgroups) could have significant effects on statistical inferences (e.g., Type I error probability) if made with knowledge of interim results. If it is perceived that emerging results could influence these types of interim protocol changes, the credibility of the trial can be severely damaged. It should be understood that an unplanned change in trial design that may have been informed by unblinded interim analyses is discouraged without first discussing with FDA.

4. Recommendations and Documentation

a. Making Recommendations

A fundamental responsibility of a DMC is to make recommendations to the sponsor concerning the continuation of the trial. Most frequently, a DMC's recommendation after an interim review is for the trial to continue as designed. Other less frequent but possible recommendations, however, as discussed previously, include trial termination, trial continuation with major or minor modifications (such as implementation of prespecified adaptive elements), or temporary suspension of enrollment and/or trial intervention until an identified uncertainty is resolved.

A DMC should express its recommendations clearly to the sponsor because a DMC's actions potentially affect the safety of trial subjects. Both a written recommendation and an oral communication, with opportunity for questions and discussion, can be valuable. Recommendations for modifications are best accompanied by the minimum amount of data critical for the sponsor to make a reasonable 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 and until a decision is made regarding acceptance or rejection of the recommendation in order to help maintain confidentiality of the interim results should the trial continue. We recommend that a DMC document its recommendations and rationale in a manner that can be reviewed by the sponsor and then circulated, as appropriate, to IRBs, FDA, and/or other interested parties, when based on interim data. Major trial changes—such as early trial termination, change in population or entry criteria, or change in trial endpoints—can have

substantial impact on the validity of the trial and/or its ability to support the desired regulatory decision. Sponsors should discuss with FDA any proposed protocol changes based on review of interim data that were not planned for, before implementation, and submit such changes to FDA in accordance with 21 CFR 312.30 and 812.35. However, if the sponsor learns of information that presents an imminent safety hazard to trial participants, sponsors should implement the necessary changes as quickly as possible to ensure the safety and welfare of study subjects (see 21 CFR 312.30(b)(2)(ii) and 812.35(a)(2)).

b. Maintaining Meeting Records

FDA recommends that the DMC keep minutes of all meetings but use separate minutes for open and closed sessions.[33] We also recommend that after each meeting the DMC issue a written report to the sponsor based on the meeting minutes. This report should include sufficient information to explain the rationale for any recommended changes. Sponsors, as discussed previously in this section, should establish procedures to minimize 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) and 21 CFR 860.7(f)(1)). If no changes are recommended, the report may be as simple as "The DMC recommends that the trial continue as designed." We further recommend that the report to the sponsor include a summary of discussions in any open session of the meeting. The sponsor may convey the relevant information in this report to other interested parties, such as the trial investigators or, as appropriate, to reviewing IRBs. Sponsors and/or investigators must report to and obtain prior approval from reviewing IRBs and/or FDA, as appropriate, for protocol changes made as a result of DMC recommendations, in accordance with applicable FDA regulations (see 21 CFR 56.108(a)(3) and (4); 21 CFR 312.30 and 312.66 (for drugs); 21 CFR 812.35 and 812.40 (for devices)).

FDA recommends that the DMC or the group preparing the confidential interim reports to the DMC maintain all meeting records to promote continued confidentiality of interim data. FDA may request copies of these records when the trial is completed (21 CFR 312.58; 21 CFR 812.150(b)(10)), and we may also request access to the electronic data sets used for each set of interim analysis. FDA therefore recommends that sponsors arrange for archiving such electronic data sets.

D. Interim Data and Analyses

As described in 21 CFR 314.126(b)(5) and 21 CFR 860.7(f)(1), sponsors of controlled studies should take appropriate measures to minimize bias.[34] Knowledge of unblinded interim

[33] See section 5.5.2 in the ICH guidance for industry *ICH E6(R2) Good Clinical Practice: Integrated Addendum to E6(R1)*. See Guidelines for establishing and operating a Data and Safety Monitoring Board (DSMB) at https://www.niaaa.nih.gov/research/guidelines-and-resources/guidelines-establishing-and-operating-data-and-safety-monitoring.

[34] 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 investigations for devices (as described in 21 CFR 860.7(f)).

comparisons from a clinical trial is rarely critical for those conducting or sponsoring the trial. Such knowledge can bias the outcome of the trial by inappropriately influencing trial conduct or the approach to 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 statisticians performing these analyses and presenting them to the DMC. Consistent with 21 CFR 314.126(b)(5) (drugs) and 21 CFR 860.7(f)(1) (devices), sponsors should establish written procedures, which should be included in the DMC charter, to ensure minimization of the potential for bias, such as maintaining confidentiality of the interim data (see section VI.C.1.d of this guidance). Before initiation of the clinical trial, sponsors should consider addressing such confidentiality issues in written agreements between the sponsor and members of the DMC, as well as written agreements between the sponsor and investigators. Trial design modifications that involve examination of comparative analyses include discontinuation of treatment arms or adjustments to sample-size based on estimated treatment effects observed during a trial. A DMC can be involved in making recommendations about planned (prespecified) adaptations based on their review of interim results.

Even for trials not conducted in a double-blind fashion, where investigators and subjects 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 or the independent statistician performing the analyses.

1. Confidentiality of Interim Data

As emphasized, access to the accumulating comparative effectiveness data should be limited to the DMC and any statistical personnel involved in generating the interim analysis results for DMC review. Broader access unblinds the trial and could lead to bias. Of note, FDA considers the data to be unblinded when they are reviewed by treatment group (e.g., A versus B), whether or not the groups are identifiable. As with the review of any unblinded safety and effectiveness data, this function should be reserved for the DMC. However, an entity that reviews safety reporting may review unblinded data—usually data only for particular adverse events of interest and subjects with those events—with the awareness that confidentiality regarding unblinded data should be maintained to preserve trial integrity. One helpful approach that could be considered is maintaining appropriate firewalls between such safety review entities and those directly involved in the conduct of the trial, especially if the safety review entity is also tasked with performing aggregate analyses of adverse events across treatment arms.

As noted, the DMC will usually be provided with unblinded data to make its assessments. It is usual to have an independent statistician perform those analyses and for that statistician to be clearly *firewalled* and have no role in modifications of the trial conduct. Trial integrity will be best protected when the statisticians preparing unblinded data are external and independent from the sponsor and DMC and are uninvolved in discussions regarding potential changes in trial design while the trial is ongoing. Balanced against this concern, however, is the importance for the statisticians reporting to the DMC to be very familiar with details of the trial and to have ample opportunity to assess the interim data.

Attendance at meetings raises the same confidentiality issues as does access to interim reports provided to the DMC. FDA fully expects confidentiality of the interim data during interactions with clinical trial stakeholders, including the sponsor and/or trial investigators. To facilitate this interaction without compromising confidentiality, many DMC meetings include an open session where non-confidential data are discussed, such as 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 trial being monitored. Open session discussions might include representatives of the sponsor, steering committee, trial investigators, FDA representatives, or others with trial responsibilities, and benefits exist to having a wider attendance at these sessions. These subjects provide an opportunity for those with relevant knowledge of the trial to share their insights with the DMC and raise issues for the DMC to consider.

The DMC should discuss the comparative interim data in a closed session attended only by the DMC members and the statistician who prepared the data 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.

2. Interim Reports to the DMC

In many cases, the DMC receives reports in two parts: (1) 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 (2) a closed section, in which the comparative outcome data are presented. The open section of these reports should be provided to sponsors, who should convey any relevant information in this section to investigators, IRBs, and other interested parties, because the data presented in the open section should not bias the future conduct of the trial and are often important for improving trial management.

3. Analysis Used by the DMC

The typical statistical analysis plan (SAP) submitted to FDA focuses on defining the principal features of the statistical analyses of the primary and secondary variables associated with the trial objectives. DMCs may review additional exploratory analyses that are distinct from those in the formal SAP submitted to FDA. The SAP details the (pre-specified) statistical methods and also provides a basis for the sample sizes anticipated for the trial. It should also provide for pre-specified interim analyses to determine early success or to stop for futility (i.e., the overall trial appears unlikely to succeed). However, the DMC may perform or request additional statistical analyses outside the SAP that look at the accumulated data to date and decide, for example, that the chances for meeting the success criteria at the end of the trial are low. They may also consider sensitivity analyses that can be used to challenge that decision. The DMC would then convey their recommendation to the trial sponsor or steering committee. A DMC may also conduct or request unblinded analyses by considering both the primary endpoint of interest and imbalances in serious adverse events among the trial arms. Therefore, these statistical analyses may also differ from those in the SAP.

For those trials in which another group makes decisions that impact trial design and/or conduct, it is important to convey those changes to the DMC when they occur. For example, an adaptation committee may recommend adding or dropping an arm, or an entity that reviews safety reporting may identify a new safety concern. These decisions may affect the statistical considerations of the DMC.

Finally, as noted earlier, the DMC may serve as the entity that reviews safety data for recommending when an IND or IDE safety report should be sent to FDA[35] or may serve as a program-wide safety assessment group involving multiple trials. The statistical analyses used to review safety data may vary accordingly but are unlikely to be part of the SAP submitted to FDA.

VII. INDEPENDENCE OF THE DMC

The independence of a DMC depends on the relationships of its members to those sponsoring, organizing, conducting, and regulating the trial (Ellenberg 2012). Independence is established when members have no involvement in the design or conduct of the trial or in the endpoint determination except through their role on the DMC or the adjudication committee. In addition, no significant financial or other important connections should exist between the DMC members and the sponsor (other than their compensation for serving on the DMC), or other trial organizers, nor should there be other professional or financial relationships that could influence or be perceived to influence the members' objectivity in evaluating trial data (see section VI.A.2 of this guidance).

A critical issue in planning and managing the 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 objectives, design, and conduct. Defining *independence* too narrowly and rigidly may eliminate 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. Moreover, although sponsors should not examine unblinded comparative data of an ongoing trial, sponsor representatives, trial statisticians, and trial 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 VI.C.1.b of this guidance. The involvement of such persons with the DMC should 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.

Independence of the DMC from the sponsor is critical, because it (1) ensures that sponsor interests do not influence the DMC, (2) enhances the DMC's objectivity and reduces the possibilities for bias, increasing the validity of the trial's conclusions, (3) preserves the ability of

[35] See section V.D of this guidance and see the draft guidance for industry *Safety Assessment for IND Safety Reporting*.

the sponsor to make appropriate modifications to a trial in response to new external information on trial conduct problems without introducing bias, and (4) may shield the sponsor (and thus the trial) from conflict of interest by maintaining the sponsor in a fully blinded state.

VIII. FDA RECOMMENDATIONS AND REGULATORY REPORTING REQUIREMENTS

As discussed in section VI.C.1.a. of this guidance, evidence of a possible relationship between many serious adverse events, especially those that occur spontaneously in the population, and an investigational product may be detectable only by comparison of rates in the two arms of a controlled trial and not by review of individual cases. Consistent with 21 CFR 312.32(d)(1), the sponsor must investigate a DMC's recommendation relating to such safety events as potentially reportable to FDA under 21 CFR 312.32. If the sponsor concludes that there is a *reasonable possibility* that the increased rate of serious unanticipated adverse events was associated with use of the drug, the finding, and support for it (which could include the DMC report, any analyses, and pertinent data) must be submitted to FDA as a serious unexpected suspected adverse reaction. Similar considerations would also apply if the sponsor concludes that an increased rate of adverse events constitutes an unanticipated adverse device effect under 21 CFR 812.46(b) and 812.150(b)(1).

Findings conveyed to a sponsor by a DMC as part of a recommendation to modify the trial could be based on a finding that there was an increased rate of serious and unexpected adverse events in the investigational product arm, and the sponsor may accordingly be required to report an analysis or evaluation of these events to FDA and to all trial investigators according to 21 CFR 312.32(c)(1)(i)(B)(ii) (drug trials) and 21 CFR 812.150(b)(1) (device trials). In clinical trials for investigational products, the requirement to expediently report unexpected serious adverse events for which there is a reasonable possibility that the drug caused the adverse event (21 CFR 312.32(c)) or unanticipated serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device (21 CFR 812.3 and 812.150(b)(1)) 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 DMC recommendations related to the safety of the investigational product, whether or not the adverse events that led to the recommendation meet the definition of *serious*. Examples include recommendations to lower the dose of an investigational drug because of excess toxicity or to inform current and future trial subjects of an emerging safety concern with the investigational product that had not been recognized at the start of the trial.[36]

A DMC recommends to the sponsor whether to continue, modify, or stop a trial or trials; the sponsor decides whether to accept recommendations to discontinue a trial. The final decision on

[36] A noncomparative analysis is an examination of accumulating trial data in which the treatment group assignments of subjects are not used in any manner in the analysis. A comparative analysis is an examination of accumulating trial data in which treatment groups are identified, either with the actual assigned treatments or with codes (e.g., labeled as A and B, without divulging which treatment is investigational). For more information about comparative and noncomparative analysis, see the guidance for industry *Adaptive Designs for Clinical Trials of Drugs and Biologic*s. It should be noted, reporting data with codes can be informative and should be best treated as unblinded.

whether to discontinue the trial based on a DMC's recommendation is the sponsor's. For trials that may be terminated early because a substantial benefit has been observed, DMCs and sponsors should consider the adequacy of data with regard to other issues such as safety, duration of benefit, outcomes in important subgroups, and important secondary endpoints. Sponsors may discuss with FDA the DMC's recommendations for early termination based on evidence of effectiveness, because the regulatory implications of early termination should be considered.

Note that for trials that fall under the jurisdiction of more than one regulatory body, reporting requirements during a trial may vary.[37] It is important for sponsors and DMC members to be aware of and comply with relevant jurisdictional reporting requirements.

[37] For the purposes of this guidance, the term aggregate refers to data within a treatment arm or across treatment arms.

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APPENDIX

Data Monitoring Committees (DMCs) were initially used 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 United States (and similar bodies abroad)—that targeted improved survival or reduced risk of major morbidity (e.g., acute myocardial infarction) as the primary objective. In a set of recommendations to the National Heart Institute in 1967,[1] an NIH external advisory group first introduced the concept of a formal committee charged with reviewing the accumulating data as the trial progressed in order to monitor safety, effectiveness, and trial conduct issues.

The recommendation for the establishment of such committees was based on the recognition that interim monitoring of accumulating trial data was essential to ensure the ongoing safety of trial subjects but that individuals closely involved with the design and conduct of a trial could not be expected to be fully objective in reviewing the interim data for any emerging concerns and should not see unblinded data. The involvement of expert advisors external to the trial organizers, sponsors, and investigators was intended to ensure that issues would be addressed in an unbiased way. The operational and functional aspects of these committees, based on experience over several decades, were discussed in a 1992 NIH workshop.[2]

[1] Heart Special Project Committee, 1988, 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, 9(2):137–148.

[2] Ellenberg, S, N Geller, R Simon, and S Yusuf, editors, 1993, Proceedings of Practical Issues in Data Monitoring of Clinical Trials, Bethesda, MD, January 27–28, 1992, Statistics in Medicine, 12:415–616.