

SPECIAL ARTICLE

Role of Independent Data-Monitoring Committees in Randomized Clinical Trials Sponsored by the National Cancer Institute

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Purpose: To describe the rationale for independent data monitoring committees (DMCs) for National Cancer Institute (NCI)-sponsored phase III cooperative group clinical trials.

Design: We review the necessity for interim monitoring of outcome data during the course of randomized clinical trials and summarize the reasons for establishing DMCs with requisite expertise and with appropriate independence from study investigators.

Results: The important components of the policy for cooperative group DMCs are described with a focus on the makeup of these bodies and on the complementary roles of study committee leadership and DMCs in pro-

tecting patient safety during the conduct of randomized clinical trials.

Conclusion: The cooperative group DMCs that are independent of the study committees and that have the requisite expertise to examine accumulating data and to base decisions on monitoring guidelines that are specified in advance by the study committee provide a body able to protect patient safety, to protect the integrity of the clinical experiments on which patients have consented to participate, and to assure the public that conflicts of interest do not compromise either patient safety or trial integrity.

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OVER THE PAST DECADE, there has been increasing emphasis on the importance of protecting patient-subjects from potential research risks associated with participation in clinical trials. Various aspects of patient protection have received scrutiny, including the informed consent process by which patients are advised before enrollment about the risks associated with participation in a particular clinical trial. Another important aspect of patient protection during a randomized clinical trial is monitoring efficacy outcome data, so that the trial can be modified or stopped when there is compelling evidence that one treatment is superior to the alternative treatment(s). The purpose of this report is to describe the rationale for having independent data monitoring committees (DMCs) for National Cancer Institute (NCI)-sponsored phase III cooperative group clinical trials. The policy that requires DMCs independent of study investigators for cooperative group phase III trials was established in January 1994 and has undergone several minor revisions based on experience gained upon implementation. The

text of the *NCI Cooperative Group Data Monitoring Committee Policy* (current as of submission) is included as an appendix, and the latest version can be obtained from the authors or from the Cancer Therapy Evaluation Program Web site (<http://ctep.info.nih.gov>). We do not discuss issues of the statistical methods applied to interim monitoring, since these have been addressed in recent reviews.¹

UNDERLYING PREMISE—THE NECESSITY OF RANDOMIZED CLINICAL TRIALS AND THE IMPLICATIONS FOR CLINICAL INVESTIGATORS

Before describing the rationale for the DMC structure that has been developed for cooperative group phase III trials, it is important to review the underlying premises that led to this structure. The most central premise is that randomized clinical trials are necessary in many instances to provide reliable answers to important clinical questions. The data obtained from randomized clinical trials protect the universe of future patients from treatments that are justified only by hunches and enthusiasms, and that may have little or no true benefit beyond that achievable with standard treatments. In the absence of reliable data from randomized clinical trials, treatment decisions will often be based on uncontrolled studies or observations in which apparent improved outcome for a new treatment may have resulted from patient selection, rather than from treatment effect. Examples of improved outcome related to patient selection rather than treatment delivered include bone marrow transplantation for multiple myeloma,² brachytherapy and radiosurgery for high-

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grade gliomas,¹⁴ and interleukin-2 therapy for renal cell carcinoma.⁵

A necessary condition for beginning a comparison of two or more treatments in a randomized clinical trial is that of clinical equipoise, ie, the state that exists when there is genuine uncertainty within the expert medical community—not necessarily on the part of the individual investigator—about the preferred treatment.⁶ It is important to emphasize that clinical equipoise can exist at a time when specific individual physicians favor one treatment over another based on personal experience or data from uncontrolled clinical trials. The experienced investigator will recognize that these hunches and enthusiasms for one treatment over another are often proven to be misplaced when the favored treatment is subjected to the test of a randomized clinical trial. Two recent examples of this from the oncology literature are the failure of more intensive regimens to improve outcome for patients with high-grade non-Hodgkin's lymphoma when compared with standard cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) therapy,⁷ and the failure of autologous bone marrow transplantation to improve outcome for children with acute myeloid leukemia.^{8,9} From the cardiology literature, the demonstration that class I antiarrhythmic drugs actually increase mortality when given to patients with ventricular ectopy is particularly noteworthy.^{10,11} In each of these examples, advocates for the newer therapies could cite compelling preclinical rationale and promising clinical experience that suggested superiority for the newer treatment, and yet in all of these examples the newer treatments were no better (and sometimes were worse) than the standard treatment. Thus, the experienced investigator recognizes the limitations of hunches based on inadequate data and can often accept the need to subject new treatments to definitive randomized trials, despite advocates for one or the other treatments feeling strongly that their favored therapy is superior.

The necessity in many clinical situations to conduct randomized clinical trials to identify superior treatments reliably creates the need to monitor interim efficacy data that accumulate while the trial is ongoing. As noted earlier, the primary objective of these trials is to provide reliable evidence that will convince the expert medical community of the relative efficacy of the treatments being compared. At any point during the conduct of the study, adequate data may accumulate that are sufficiently definitive to allow declaration of one treatment as superior to the other(s), and thereby destroy the clinical equipoise that was present when the trial began. From this time

forward, all patients should have the benefit of receiving this preferred treatment and should be spared the inferior treatment. The immediate question is what body should be authorized to review interim outcome data and to then make decisions about whether continuation of the trial is warranted.

One possibility for interim monitoring would be to allow treating physicians who enter patients onto the study to review interim efficacy data. This option is untenable, in large part because interim analyses may show trends that are unreliable indicators of true efficacy and that may reverse with time. Since the treating physician's first obligation is to his/her patient, the physician may feel ethically compelled to discontinue participation in the study when interim data indicate a small probability that one treatment is superior to the other, even while recognizing that these interim data are unreliable. For example, if a physician were aware that the first five treatment failures on a randomized clinical trial all occurred among patients who received one regimen, he/she may feel unable to advise a candidate patient to participate in the trial, even though there was a high likelihood that the imbalance in adverse outcomes between the regimens would eventually disappear or even reverse. In essence, physicians and patients who participate in randomized clinical trials enter into a contract in which the underlying assumption is that obtaining a reliable answer to a question of therapy is an outcome to be so valued that knowledge of interim trends is relinquished.¹² As noted by Walters,¹² "the system has to be set up in this way to have science move forward. Both the patients and the clinical investigators involved voluntarily accept temporary ignorance and rely on an independent body to make judgments on their behalf."

Before we examine further the question of what body should have responsibility for monitoring interim results, we provide graphic illustrations of the frequent unreliability of interim results and the possible dangers of acting on these results. The first involves a simulation experiment reported by Fleming et al,^{13,14} in which the simulation model had the following characteristics: "patients" were entered uniformly during a 3-year period; the final analysis was planned for 1 year after completion of accrual; and the two treatments to which "patients" were randomized had true equal efficacy. The point of the simulation was to consider the consequences of conducting multiple analyses of the outcome. When four annual analyses were performed, 17 of 100 simulated studies had a false-positive *P* value less than .05 in at least one of the tests. When 16 quarterly analyses were

performed. 26 of the 100 studies had false-positive P value less than .05 at some point. Of course, the objective of using a significance level of .05 is to restrict the false-positive rate to 5%.

The following actual example further illustrates that multiple analyses of ongoing randomized trials create the potential for early closure of a trial based on misleading early trends. It comes from the Coronary Drug Project, a randomized, placebo-controlled trial of cholesterol-lowering agents in men who had experienced a heart attack.¹⁵ After 7 years of follow-up evaluation at the planned final analysis, there was no difference in mortality between patients who received clofibrate versus placebo. However, at three times during the course of the study, the differences in mortality between the two groups of patients reached a nominal critical value (analogous to $P < .05$). If a decision to stop the trial had been made at any one of these points, then a conclusion different from the ultimate one would have been reached. Continuation of the study was allowed because of the appropriate use of more stringent criteria for significance for interim analyses.

The preceding examples illustrate the complexities associated with interim monitoring of outcome data that relate to the problem of multiple looks at accruing data. Other issues that complicate interpretation of interim data include evaluation of the relative toxicities of treatments being compared, consideration of the impact of new data from other clinical trials on continued conduct of the monitored trial, evaluation of the adequacy of accrual to the study,¹⁶ and evaluation of the adequacy of compliance with prescribed treatment. These complexities imply the need for a diversity of experience and expertise within the membership of DMCs. Furthermore, while randomized clinical trials are often necessary to provide reliable results for important clinical treatment questions, their conduct implies the need for a suitably constituted decision-making body external to physicians who enter patients onto the trial to monitor interim outcome data. The following section focuses on the appropriate composition of DMCs for randomized trials conducted by the NCI-supported cooperative groups.

COMPOSITION OF INDEPENDENT DMCs FOR COOPERATIVE GROUP PHASE III TRIALS

Having established that patients and their physicians must necessarily forego knowledge of interim outcome data, what should the membership be for the DMC charged with this responsibility? One option would be to have a subset of the persons involved in planning, conducting, and collecting research data for the trial serve

as the DMC (eg, the study chair, study statistician, and other study committee members). This was the practice commonly used in the past for cooperative group phase III trials. Typically, each randomized clinical trial had its own DMC, whose membership was largely drawn from the leadership of the study committee (including the study statistician) and its associated disease committee.¹⁷ Arguments in favor of this approach focused predominantly on the complexity of cancer clinical trials and on the consequent need to have those most informed about the trials involved in decisions about interim monitoring of outcome data.¹⁸

An important argument in favor of DMCs that are independent of study investigators is that this process allows study leadership to maintain equipoise as they continue to encourage their colleagues to enter patients onto a clinical trial.⁶ In much the same way as the treating physician abstains from accepting information about interim outcome data to present a genuine situation of clinical equipoise to patients, so the study leadership can more vigorously encourage their colleagues to participate in the clinical trial if they are unaware of trends observed in interim analyses. Additionally, as noted by Walters,¹² it is difficult for a study chair who is aware of outcome data not to disclose information about this knowledge, whether by an inadvertent statement or by a subtle inflection while discussing the study. Such inadvertent disclosure of interim data may seriously jeopardize completion of the study.

Another important reason for not having study leadership serve as the primary decision makers responding to interim outcome data is that they have a stake in the outcome of the clinical experiment and their decision-making may be influenced by this perspective. The study leaders have invested considerable time and effort in developing and implementing the study, and their future professional opportunities may be related to a successful outcome from the study. Similarly, the likelihood of funding for the sponsoring group may be enhanced by the results obtained from the study. While it is important to emphasize that the individual and group interests do not necessarily imply conflict with patient interests, it is equally important to emphasize that these interests create a perspective about the clinical trial that is distinct from the perspective of the patient. As one example, study leadership for a cooperative group clinical trial may wish to continue accrual to a study beyond its accrual target when there is no successor clinical trial in place because of the benefit to the group and its member institutions of having an open study. This perspective, which favors

keeping a clinical trial open (even though the additional accrual may not significantly enhance the ultimate reliability of the trial's conclusions), is not shared by candidate patients, who might unnecessarily experience additional inconvenience and/or toxicity by participation in the trial.

While recognizing that study investigators can and will focus on patient interests appropriately in the vast majority of cases, there remains the public perception that investigators are sufficiently interested in protecting their own research interests that this creates a potential conflict with protecting the interests of patients. This public perception is shaped in large measure by reports of situations in which there was an unfortunate separation between the interests of the investigators who conduct clinical experiments and the interests of patients.¹⁹ The public has, in the past year, been informed that government-supported investigators in the 1950s administered hallucinogens to healthy subjects without their full knowledge or consent and injected ill patients with plutonium and uranium without expectation that these patient-subjects would benefit medically from the injections.²⁰ Descriptions of the Tuskegee experiment continue to be referenced in news articles and books,²¹ and episodes of scientific misconduct in the medical community are widely reported by the popular press.²² While one could correctly argue that these examples generally represent ethical lapses of a bygone era or rare instances of a dishonest investigator, it is unlikely that the public will accept this sort of reassurance as adequate protection. This public skepticism might lead the study leadership to overcompensate and inappropriately close or alter a study when the scientific rationale was not compelling. For this reason and for the others cited, interim efficacy end points are best analyzed by independent DMCs composed of qualified persons who do not have a stake in the outcome of the clinical experiment.

The National Institutes of Health (NIH) has promulgated guidelines for the conduct of NIH-sponsored clinical trials that include specific requirements for establishing DMCs to review interim outcome data from NIH-sponsored randomized clinical trials.²³ The NIH report states that the majority of voting DMC members "should be external to the study leadership and other individuals involved with the trial at hand." Other institutes within the NIH have considerable experience with DMCs that are totally independent of the study committees that conduct the randomized clinical trials. For example, clinical studies sponsored by the National Heart, Lung, and Blood Institute (NHLBI) and clinical trials

involving AIDS patients sponsored by the National Institute of Allergy and Infectious Diseases (NIAID) use independent DMCs, as described in recent publications.^{24,25} On the other hand, a group of statisticians favored cooperative group DMCs composed predominantly of group members, in which a balance could be established between informed, expert scientists committed to the central questions of the trials and patient advocates.¹⁸ The final NCI guidelines reflect a compromise between these two extremes and recognize that the relatively large number of clinical trials conducted by each group and the complexity of many of these trials made it unfeasible to exclude group members totally. However, for objectivity, a majority of DMC members must be from outside of the group. The NCI policy statement on DMCs cautions group members who are members of the DMC to consider themselves as representing patient interests, and not group or investigator interests. Additionally, the policy requires that each DMC include at least one patient representative. Cooperative group DMCs constituted according to the NCI policy allow physicians who lead and participate in group trials to maintain equipoise during the course of each randomized trial. These DMCs, independent of study investigators, should provide the public with assurance that patient interests are protected.

WHAT IS THE ROLE OF THE STUDY COMMITTEE IN PROTECTING PATIENTS DURING A RANDOMIZED CLINICAL TRIAL?

If the DMC has responsibility for monitoring interim outcome data, does this mean that the study committee has relinquished all responsibilities for study monitoring? This is not at all the case because the study committee plays a central role in protecting patient safety throughout the course of the trial. This role begins even before the trial starts accruing patients, since the study committee develops the interim monitoring plan (as detailed in the statistical considerations section of the protocol) that defines the parameters which the DMC uses to monitor the trial.

Second, study committee members are critical to assure patient safety during the conduct of a trial, since the most relevant data (particularly in the early stages of a trial) are the toxicities experienced by patients. The body primarily responsible for monitoring toxicity is the study committee, which is empowered to propose changes in the protocol based on its concerns about unacceptable levels of toxicity. Toxicity data, unlike efficacy data, are generally not blinded by treatment arm and are usually available to

all investigators so that participating physicians can provide more appropriate care to patients entered onto the study. The study committee may at any time convey a concern regarding patient safety to the DMC, and they need not wait for the DMC to request this type of information. Additionally, the study chair is encouraged to prepare a report regarding the conduct of his/her study for each DMC meeting. This report is central to the ability of the DMC to make informed decisions, and the report should at a minimum summarize the toxicity observed among patients entered onto the study and should convey any particular concern about the ongoing conduct of the study that the study chair and study committee may have.

A final area of interaction that may occur between a cooperative group DMC and a study committee is when a study committee that is planning a new clinical trial requests outcome data for planning purposes from a study that is being monitored by the DMC. The DMC's first priorities are to assure that patients who have entered randomized trials are protected and to assure that the integrity of the monitored studies is protected. Allowing a planning committee access to outcome data from a randomized trial while patients are still receiving therapy prescribed by the randomization could jeopardize completion of the study and could increase the risk that the study will not obtain a reliable answer. Thus, release of outcome data during this period is generally avoided. The situation is somewhat different when accrual is completed and when all patients have finished the randomized portion of their therapy, since issues of patient safety and protection of the study are reduced. In this case, there is less risk of compromising the monitored study by release of outcome data to a committee that is planning a new study. This situation illustrates the conflicting interests

that the DMC must deal with in its decision-making, since all parties wish to make available outcome data as early as appropriate to investigators designing future trials. In making this decision, the DMC must first protect patients entered onto randomized trials and protect the integrity of these trials, while at the same time, it must not overlook the interests of future patients who will benefit by having the best information available for trial planning.

In closing, there is a clear tension that exists during the conduct of a randomized clinical trial between responding to trends and assuring that reliable answers are obtained. The cooperative group DMCs are charged with assuring that the balance between protecting patients entered onto phase III randomized trials and obtaining reliable answers is appropriate. To allow treating physicians and the study committee open access to interim data from randomized trials is not a viable option for two reasons: (1) their participation in and supervision of the trial may be compromised by premature responses to trends in the data; and (2) their own professional interests in the continuation of the trial may come into conflict with patient safety concerns, either in fact or in the perception of the public. DMCs that are independent of the study committees and that have the requisite expertise to examine accumulating data and to base decisions on monitoring guidelines that are specified in advance by the study committee provide a body able to protect patient safety, to protect the integrity of the clinical experiments on which patients have consented to participate, and to assure the public that conflicts of interest do not compromise either patient safety or trial integrity.

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APPENDIX

NCI Cooperative Group DMC Policy

Studies to be Monitored

One or more DMCs will be established to monitor all phase III therapeutic clinical trials of the cooperative group. Whereas a single DMC per group is acceptable and may provide the most feasible way of maximizing independence of the DMC, separate DMCs could be considered for single large trials, especially those that involve substantial risk/benefit oversight.

Responsibilities

1. The primary responsibility of the DMC is to review interim analyses of outcome data (prepared by the study statistician) and to recommend whether the study needs to be changed or terminated based on these analyses. The committee also determines whether and to whom outcome results should be released prior to the reporting of study results at the time specified in the protocol.
2. The DMC reviews reports of related studies performed by the Groups or other organizations to determine, considering information and recommendations supplied by the study committee, whether the group study needs to be changed or terminated.

3. The DMC reviews interim toxicity data although that is primarily the responsibility of the study committee.
4. The DMC reviews major modifications to the study proposed by the study committee prior to their implementation (eg, termination, dropping an arm based on toxicity results or other trials reported, increasing target sample size).

Membership

DMC members will be appointed for a fixed term by the Group Chair or his/her designee with the approval of the CTEP Associate Director or his/her designee. The nominees should be reviewed and approved by CTEP prior to their appointment. The committee will include physicians and statisticians from within and outside the Group selected based on their experience, reputation for objectivity, absence of conflicts of interest (or the appearance of same), and knowledge of good clinical trial methodology. The committee should include a consumer representative and a voting statistician from outside the group. A CTEP physician and a CTEP statistician will be non-voting members and must be free to attend all sessions of the DMC, including closed and executive sessions. The Group Statistician will not be a voting member of the DMC. A majority of the voting DMC members will not be affiliated with the Cooperative Group. Group members who are members of the DMC should see themselves as primarily representing patient interests, and not Group or Group chair interests. Members of a study committee or leadership of the disease committee (eg, chair or vice-chair of the disease committee) conducting a study will excuse themselves from all DMC discussions concerning that study and will not receive DMC reports concerning that study. Additionally, the study statistician will not be a voting member of the DMC for his/her trial. The size of the DMC should be limited, and it is unlikely that more than 10 people would be required to constitute a DMC.

The Group Chair will not attend meetings of the DMC, with the exception of a DMC that has no voting members belonging to that Cooperative Group. In this case, the Group Chair or his/her designee may attend the meetings as a nonparticipating observer.

Meetings

DMC meetings will be held at least once every six months. Each randomized clinical trial should have specified interim analysis times, although the DMC should be apprised at each meeting of the status of all trials for which it is responsible, e.g., accrual, toxicity concerns, and the next formal monitoring date as specified in the protocol.

It is recommended that a written report outlining the current status of each trial to be monitored be sent to the DMC members by the study statistician at least three weeks prior to the DMC meeting. The Study Chair may prepare a report addressing specific toxicity concerns or other concerns about the conduct of the study. The statistician's report may contain recommendations on whether to close the study, whether to report the results, whether to continue accrual or follow-up and whether DMC discussion is needed. In the event a study will be considered for closure due to slow accrual, the CTEP members of the DMC may discuss with other CTEP staff the possibility of early closure due to slow accrual. Although no confidential information would be disclosed, this would allow the CTEP members of the DMC to bring to the DMC meeting any information from CTEP concerning early closure that might be useful in the DMC deliberations.

The review of each trial may include three parts. The first part will be an open session in which members of the study team and disease committee may be present at the request of the DMC to answer questions. In this part, the focus is on accrual, compliance and toxicity issues, and no outcome results may be presented. Following the open session, there will be a closed session limited to DMC members and possibly the study statistician in which outcome results will be presented either by a member of the DMC, the Group Statistician, or the study statistician. Following this closed session, there will be a fully closed, executive session in which the DMC discusses outcome results, and then votes. At the executive session, those present are limited to DMC members.

Recommendations

DMC recommendations should be based upon results for the current study being monitored as well as upon data available to the DMC from other related studies. The study committees and DMC members will assure that the DMC is advised about relevant nonconfidential results from other related studies that become available. It will be the responsibility of the DMC, with advice from the study committee, to determine the extent to which this information is relevant to decisions to continue or modify the current study.

The DMC will provide recommendations to the Group Chair to change a study or to continue a study unchanged. The study statistician may send his/her written report prepared prior to the DMC meeting to the Group Chair at this time. In the event a change is recommended by the DMC, the Group Chair may seek the advice, in a confidential manner, of the Study Chair, Disease Committee Chair, and/or Group Statistician.

- a. In the event that the DMC recommends a study change for patient safety reasons (including early stopping of inferior therapy), the Group Chair will act to implement the change as expeditiously as possible. In the unlikely situation that the Group Chair does not concur with the DMC recommendation, then the CTEP Associate Director must be informed of the recommendation of the DMC and of the Chair's reasons for disagreeing with the recommendation. The CTEP Associate Director and the Group Chair, in consultation with the DMC Chair, will be responsible for reaching a mutually acceptable decision about the study. Confidentiality will be maintained during these discussions, but relevant data will be shared with the Group Chair, CTEP Associate Director, and other parties whom they wish to involve in reaching a decision.
- b. In the event that the DMC recommends a study be closed early due to slow accrual, provided that the CTEP members of the DMC have been previously informed of this possibility, then the recommendation of the DMC would be processed as in (a).
- c. In the event that the DMC recommends a change in a study for reasons other than either patient safety (eg, to extend accrual because of an event rate lower than expected) or study closure due to slow accrual, the DMC will provide to the Group Chair an adequate

rationale. In the absence of disagreement, the Chair will be responsible for having an amendment prepared and submitted to CTEP reflecting the recommendations of the DMC and providing the rationale for the changes. CTEP approval of the amendment will be required prior to implementation of the change, although it is anticipated that a decision to override the DMC's recommendation will be made only in the most exceptional circumstances.

Confidentiality Procedures

No communication of the deliberations or recommendations of the committee, either written or oral, should be made outside of the committee except as provided for in these policies and procedures. Statements of confidentiality should be signed by all DMC members. Outcome (efficacy) results are strictly confidential and must not be divulged to any nonmember of the DMC (excepting the Group Chair and CTEP Associate Director as described above) without the approval of the DMC until the recommendation to report the results are accepted and implemented.

Release of Results

Any planned release of outcome data (either internal to the group, to NCI personnel not members of the committee, or external (eg, paper presented at professional society meetings, seminars, papers, etc) prior to the final approval of general dissemination of results must be reviewed and approved by the DMC. In general, outcome data would not be routinely made available to individuals outside of the DMC until accrual has ceased and all patients have concluded their randomized treatment. After this timepoint, the DMC may approve the release of outcome data on a confidential basis to the Study Chair for planning the preparation of manuscripts, and/or to a small group of individuals for purposes of planning future trials. The DMC will consider special requests for information from the disease committee chair prior to that timepoint. The DMC should be made aware of any communication of analysis results outside of the statistical center at any time.

Conflict of Interest

Individuals invited to serve on the DMC (voting and nonvoting) will disclose to the Group Chair any potential, real or perceived conflicts of interest. These will include professional interest, proprietary interest and miscellaneous interest considerations as described in the attached conflict of interest policy (available by request from the Authors). The Group Chair, with the advice of an ad-hoc committee, will review possible conflicts and determine whether there is sufficient basis to exclude the individual from serving on the DMC. Potential conflicts which develop during the conduct of a trial should also be disclosed to the Group Chair.

Intergroup Trials

These guidelines apply also to intergroup trials. The DMC of the Group whose statistical center is coordinating the trial will monitor the trial. The term "Group Chair" in this document will apply to the Chair of the coordinating Group.

CTEP Oversight

In order to satisfy its objectives of protecting patients, ensuring study integrity and assuring public confidence in the conduct of clinical trials, it is essential that the DMC function in a manner that demonstrates competence, experience and independence of Group, career or financial interests. If CTEP determines that a DMC for a group is not functioning in this manner, it will discuss with the Group Chair what changes are needed to the composition or structure of the DMC.

July 9, 1996

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