

Guidelines for data and safety monitoring for clinical trials not requiring traditional data monitoring committees

SCT Working Group on Data Monitoring:

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This is a commissioned report by a writing committee formed by the Society for Clinical Trials. The committee was formed with the objectives of 1) reviewing data monitoring guidelines for confirmatory (phase III) trials published by the National Institutes of Health, US Food and Drug Administration, Veterans Administration, and the International Conference on Harmonisation and 2) proposing corresponding guidelines for exploratory clinical trials (ie, most phase I and phase II trials and others not requiring a fully independent data monitoring committee). These trials typically involve fewer subjects and are of shorter duration than phase III trials. Nevertheless there are safety concerns, especially because these are often the first human trials for a new intervention. Recommendations are given for appropriate elements of a data monitoring plan, decision criteria for institution of a data monitoring committee (DMC), and critical elements for a DMC to consider in exploratory trials. Review and approval of data monitoring plans are suggested to fall under Institutional Review Board purview. Forming a committee with all the characteristics of a traditional phase III trial monitoring committee may be warranted for a small fraction of exploratory trials. Such a panel could consist of both trial investigators and outside members. The paper concludes with examples of data and safety monitoring practice from the University of Wisconsin Comprehensive Cancer Center and the AIDS Clinical Trials Groups. *Clinical Trials* 2006; 3: 314–319. www.SCTjournal.com

Introduction and terminology

Data and safety monitoring in clinical trials can be defined as a planned, ongoing process of reviewing data collected in a clinical trial with the primary purpose of protecting the safety of trial participants, the credibility of the trial, and the validity of trial results [1]. Data monitoring committees have been formed for the purpose of providing independent review of clinical trial data. The National Institutes of Health (NIH) [2–4], US Food

and Drug Administration (FDA) [5], the US Department of Veterans Affairs (VA) [6] and the International Conference on Harmonisation (ICH) [7–9] have all issued guidelines for the formation and best practices for these committees. These guidelines include criteria for deciding which trials need a formal Data Monitoring Committee (DMC). With some exceptions, the criteria correspond closely to the definition of randomized controlled trials with mortality or major morbidity endpoints.

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Recent policy guidelines in the US [3,4] indicate that a data monitoring plan should exist for all clinical trials be they exploratory (phase I, II) or confirmatory (phase III).¹ A principal issue in this regard is whether independent review, such as a formal DMC is required in the exploratory trials or whether other models can better meet the needs of these early clinical studies. Complete independence of members from the investigators and sponsors and severe restrictions on access to interim trial results are defining characteristics of DMCs for phase III trials and certain other trials, so the decision to rely on a DMC has real implications. Our concern is with those trials not using a DMC, not the question of whether a particular trial should use one.

The data monitoring plans of all studies, regardless of phase, share common elements, but most attention heretofore has been on studies employing formal DMCs. We want to encourage a systematic approach for the interim monitoring of all clinical trials. Little guidance is available for organizing monitoring plans for exploratory trials, although some individual institutions have established guidelines (eg, [10,11]). In this article we attempt to provide such guidance. Hibberd and Weiner [13] recently addressed the same issue, although the perspective is somewhat different. The DAMOCLES Project has provided a comprehensive bibliography on data monitoring [14].

In November, 2003 the Publication Committee of the Society for Clinical Trials identified a need for specifying characteristics of acceptable data monitoring plans for exploratory clinical trials. The society commissioned a writing committee to propose a set of characteristics the society could support. This paper presents the committee's recommendations.

The term *data monitoring plan (committee)* herein will be considered to be equivalent to *data and safety monitoring plan (board)* as used in NIH guidelines. We use the term *sponsor* to mean the organization that provides funding for the clinical trial. It can be a government agency, foundation, pharmaceutical firm or institution conducting the trial. The term *subject* may refer to a patient or other volunteer. The term *intervention* may refer to a drug, surgical procedure, medical device or behavioral intervention.

¹ "Exploratory" clinical trial means any trial that does not require a fully independent data monitoring committee; it generally refers to phase I and II, but not always. Traditionally Data Monitoring Committees have been employed mainly for randomized controlled trials, and some phase III trials use historical or other nonrandomized controls. Our focus here is on clinical trials not deemed to require a Data Monitoring Committee under relevant regulations and policies.

The issues discussed here are relevant beyond the United States, although terminology differs in other locales. "Institutional Review Board" (IRB) is not quite equivalent to "Ethics Committee" or "Local Ethics Committee" as used elsewhere. Details of the recommendations contained herein would have to be adapted to the local regulatory or policy environment.

Prerequisites of an adequate plan

All trials must be designed to facilitate monitoring. The components of a good protocol are the topic of many guidances and are outside the scope of this paper. A well-written protocol will prevent multiple unnecessary deviations which might impact on study integrity or even safety. The following protocol and design elements should be regarded as prerequisites for a good data monitoring plan:

- Eligibility criteria must ensure enrollment of subjects with appropriate risk/benefit ratio – that is, do not put subjects at risk by enrolling those who are either unlikely to benefit and/or at inordinate risk for toxicity. Establish meaningful baseline organ dysfunction limits for entry, for example, hypertension or diabetes adequately controlled.
- On-treatment safety evaluations (examinations, adverse event monitoring, laboratory testing, ECGs, and so on) must be required at sufficient intervals to elicit emerging safety problems in the relevant subject population, and the amount of information and level of detail that is necessary for capture on case report forms is adequately specified.
- Subject registration systems must be in place to ensure that all eligibility criteria, including the signing of the informed consent document, are checked prior to treatment start. Suitable guidance is given regarding concomitant medication and procedures.
- Adequate provisions must be made for discontinuation or dose modification of the drug in an individual subject in the case of adverse event, disease progression and need for additional/alternative therapy.
- Adequate procedures must be established for discontinuing the entire trial or suspending enrollment of subjects for reasons of safety and/or efficacy.
- Directions regarding the observation, determination and reporting of adverse events are satisfactory and all sponsor contact personnel are identified.
- There must be an adequate plan for data management so that data (case report forms, laboratory reports) are submitted in a timely manner and

data are processed, summarized and monitored with appropriate frequency.

- There is a cogent analytic plan for safety and efficacy and justification of sample size.
- Ongoing data and safety review process (including to whom recommendations go) must be described.
- Definitions of potential conflicts of interest for protocol team, investigators and DMC members should be described.

Basic structure and operations

The fully independent, chartered DMC is the ultimate implementation of the data and safety monitoring principles [1]. The opposite end of the spectrum consists of the study chair or principal investigator, usually with a few staff and other close colleagues, following trial progress and making adjustments in an informal way. The historical record demonstrates that the informal approach has been effective in a large majority of trials. Those situations in which it has not been effective point to the need for models that incorporate more formality and independence, albeit short of a DMC.

In the last few years experience has been gained with monitoring structures intermediate between DMCs and those using only study chairs. The two relevant dimensions of difference are the degree of independence and of preplanning. "Independence" in this context has no absolute definition. DMC members almost always have no role whatsoever with the trial they monitor other than service on the DMC. Less restrictive interpretations would allow persons in the same institution who do not collaborate with the protocol team members or see the trial volunteers. They might even be in the same medical school department as long as there were no supervisory relationships. A particular monitoring entity could, in principle, have any fraction of its members fully independent, partially independent, or internal to the protocol team.

Each structure involves different trade-offs. Each increment of independence will add to perceived objectivity, with the fully independent DMC maximizing that perception. With regard to preplanning, DMCs normally work with interim analysis plans completely specified at the start, reviews rarely occur more than twice yearly and are scheduled well in advance, and most meetings are in person. Exploratory trials by their nature need more flexibility, in particular to respond to unexpected adverse events. It is easier to arrange meetings on short notice when members are in close proximity. When preliminary safety information is minimal, the risk of such events can be higher, as is often the case in exploratory trials, increasing the need for flexibility. Flexibility is

also a real advantage when an IRB has required that accelerated continuing review take place.

In general, most phase III trials will have DMCs, most phase II trials will have partially independent committees, and most phase I trials are monitored by the protocol team. In those instances where a formal committee is felt to be necessary for an exploratory trial, the data monitoring plan should include specifics to answer the following questions:

- What are the committee's responsibilities?
- To whom or what does the committee report?
- Who should serve on the committee?
- How are the members appointed?

To avoid confusion, we reserve "DMC" for committees having all the characteristics and methods of operation advocated by Ellenberg *et al.* [1]. We refer to other formal committees as Study (or Safety) Monitoring Committees (SMC). The SMC for an exploratory clinical trial should always consist of physicians knowledgeable as a group about the indication and expected safety issues. A biostatistician should generally be included in the SMC. At the phase I – pharmacokinetics/dosimetry level – the protocol team is typically sufficient to assume responsibilities for data monitoring. The data collected are objective and the trials are of short duration. However, if the trial is a novel therapy for which there is limited or no prior experience (such as gene therapy, nanotechnology and/or drug-eluting stents), outside reviewers with relevant expertise may be necessary.

SMC responsibilities would be similar to those of DMCs but would be scale-limited. For instance, it may be impractical to propose a group sequential early termination plan for a trial that enrolls only 20 subjects. One of the first SMC responsibilities would be to specify what data it needs to fulfill the responsibilities of its charter. The SMC would then review the protocol to ensure that the data needed are being collected in the trial and with the appropriate frequency. The SMC should have the right to recommend trial termination and/or protocol amendments for safety concerns. The reporting process of such a decision to the sponsor and IRB should be clearly documented before the trial begins. The SMC should also monitor accrual and make recommendations as to the feasibility of completing the trial as specified in the protocol.

Review and approval of a monitoring plan

Who should determine whether a data monitoring plan is acceptable? In addition to the trial sponsor, the local Institutional Review Board (IRB) must be

satisfied the plan is adequate, at least for trials supported by NIH. In reviewing a data monitoring plan an IRB would consider the scientific merits and the relative risk to subjects of the protocol and might propose enhancements or changes to the data monitoring plan. In assessing the details of a data monitoring plan the IRB would take into account whether the interventions used are already approved, safety is well understood and issues of combination therapy of approved interventions are addressed. The IRB would be expected to take the appropriate NIH, VA, ICH FDA and sponsor guidelines for data monitoring into account. These deliberations may result in a request for modification of the data monitoring plan such as requiring outside members on the SMC, or changing eligibility requirements to eliminate subjects who are not likely to benefit. The IRB will usually require reports from the SMC, no less often than annually and much more often in the case of trials that may involve significant risk.

Many institutions currently have one or more Clinical Research Committees (CRC) whose deliberations for proposed clinical trials generally precede those of the IRB. These committees usually evaluate the scientific merit of proposed clinical trials. If the IRB chooses to delegate or share responsibilities with the CRC, this division of labor should be clearly documented.

Examples of data and safety monitoring practice

The following are two examples of data and safety monitoring practice. The first example is from a typical National Cancer Institute (NCI)-designated cancer center where many early phase exploratory clinical trials are conducted and the other from two clinical trial groups in HIV/AIDS.

Comprehensive cancer center

Exploratory clinical trials are typical in oncology. A large number of cancer clinical trials in every phase are conducted at the NCI-designated cancer centers in the United States. NIH policy [2,4] requires that grantees have procedures in place for data and safety monitoring of clinical trials to ensure the safety of participants, the validity of data, and the appropriate termination of studies for which significant benefits or risks have been uncovered. Following NIH policy, every NCI-designated cancer center is expected to have in place an institutional data and safety monitoring plan that meets the NCI's specific requirements [12]. The NCI's requirements include four essential elements of data and safety monitoring: 1) monitoring the progress of

trials and the safety of participants, 2) plans for assuring compliance with requirements regarding the reporting of adverse events, 3) plans for assuring that any temporary or permanent suspension of an NCI-funded clinical trial is reported to the NCI, and 4) plans for assuring data accuracy and protocol compliance.

The University of Wisconsin Comprehensive Cancer Center (UWCCC) is a NCI-designated cancer center. It receives the Cancer Center Support Grant (CCSG) from the NCI. To receive the CCSG, it is required to have in place an approved Protocol Review and Monitoring System (PRMS). In addition to the required review by the IRB, which focuses on the protection of human subjects, PRMS reviews and monitors cancer clinical trials for scientific merit, priorities and progress.

At UWCCC, the Clinical Affairs Committee (CAC) and its subcommittee, the Clinical Trials Monitoring Committee (CTMC), make up the PRMS. The Clinical Affairs Committee is charged primarily with review of clinical trial protocols related to cancer for scientific merit and priorities, and the Clinical Trials Monitoring Committee is charged with review for scientific progress and reports to the Clinical Affairs Committee. The Clinical Affairs Committee also evaluates cancer clinical trial protocols for adequacy of the data monitoring plan. Only after approval by the Clinical Affairs Committee, protocols can be submitted to the local IRB. The UWCCC developed a template for investigator-initiated protocols, which UWCCC investigators are expected to use [11].

As NIH policy acknowledges, at the frontline of data and safety monitoring are principal investigators and project managers. The UWCCC clinical research program is organized around disease and modality groups. Each group is responsible for monitoring safety of participants in its portfolio of clinical trials, for validity of data and for appropriate termination of studies. The Clinical Trials Monitoring Committee serves as the UWCCC's data and safety monitoring board. Each group is required to submit a data and safety monitoring report for each protocol to the Clinical Trials Monitoring Committee quarterly or semi-annually. A typical report includes the summary of study status, status of enrolled participants, treatment and dose adjustments, adverse events and objective response. Cumulative adverse event rates are monitored monthly by each group. If a study exceeds a pre-specified rate of adverse events, it is immediately reported to the Clinical Trials Monitoring Committee Chair for discussion and any necessary actions are taken in consultation with the Clinical Trials Monitoring Committee. The Clinical Trials Monitoring Committee also monitors whether each group is complying with the data monitoring plan

specified in the protocol, both in terms of timely reporting of adverse events and regulatory reporting responsibilities. Data accuracy and protocol compliance are monitored by the UWCCC's internal quality control program, which includes quarterly quality assurance and response review and semi-annual internal audit.

For protocols initiated by outside sponsors such as industry or NIH, UWCCC evaluates sponsor data monitoring plans for adequacy and relies on their monitoring procedures for the study. However, the safety of participants enrolled at UWCCC, its affiliates and regional partners is monitored by the Clinical Trials Monitoring Committee regardless of the sponsorship being intramural or extramural.

AIDS Clinical Trials Groups (ACTG)

The Adult and Pediatric AIDS Clinical Trials Groups (AACTG and PACTG, ACTG will hereafter denote either AACTG or PACTG) undertake a large number of clinical trials including many phase I and II trials. All trials are multicenter involving AIDS Clinical Trials Units (ACTUs) throughout the US and increasingly internationally. Funding is primarily from the National Institute of Allergy and Infectious Diseases (NIAID) and so the monitoring of trials needs to meet National Institute of Health requirements. For phase III clinical trials, NIAID organizes a DMC entirely independent of the ACTGs, which reviews interim analyses. For earlier phase trials, the ACTGs organize monitoring of studies.

Regardless of the phase of a clinical trial, the approach to monitoring of a trial is defined in the trial protocol. This includes details of what interim results will be monitored and when analyses will be completed, who will review interim results, and what guidelines will be followed for modification or termination of a study. Standard operating procedures for monitoring are followed in both ACTGs. All protocols are reviewed internally within the ACTGs and by NIAID. Once approved, they are submitted to the local IRB(s) of each of the AIDS Clinical Trials Units who propose to enroll patients into the trial, to the FDA if the study is being done under an IND application, and also to the appropriate regulatory agencies and national ethical review committees of other countries where the study will be conducted.

Monitoring of most phase II trials and some phase I trials is undertaken using a similar approach to the monitoring of phase III trials. Specifically, the ACTG organizes a Study Monitoring Committee (SMC) that includes investigators who are not involved in the conduct of the trial, either in terms of being members of the trial's scientific team or being

involved in the enrollment and follow-up of patients in the trial. The set of investigators includes clinicians and a senior statistician from the ACTG statistical center, together with immunologists, virologists or pharmacologists, depending on the study question being addressed. Some Study Monitoring Committees may also include a community representative. In general, the Study Monitoring Committee members are ACTG investigators though for some studies, particularly the later stage phase II trials, there may be one or two members from the NIAID DSMB. Non-ACTG investigators may be included when there is need for specific expertise that cannot be obtained from within the ACTG, usually because the ACTG investigators are involved in the study. For some scientific areas, there is a standing Study Monitoring Committee which reviews all trials in those areas. For other areas, a separate Study Monitoring Committee is established for each trial. The decision about this is largely determined by the number of trials and the availability of independent investigators in the scientific area. Some IRBs require details of Study Monitoring Committee membership in order to satisfy themselves that the committee is appropriately qualified.

Study Monitoring Committees review interim results of a study at least once per year but for many trials reviews are more frequent. Additional reviews can be requested at any time if an emergent issue arises. For example, trial protocols may state that a review is to be triggered by a pre-defined number of adverse events of a particular kind or severity. This provides a "safety valve" which may be particularly important in earlier phase trials. Following a review, the Study Monitoring Committee makes written recommendations about whether to continue the study unchanged, to modify it, or to terminate it. These are advisory to the Executive Committee of the ACTG. Following each review, a letter is also sent to the local IRBs of all AIDS Clinical Trials Units involved in the study. These letters include a brief summary of the status of the study, including accrual but not follow-up data, information about when the study was reviewed, what the recommendation was, and when the study will next be reviewed.

Some trials, particularly phase I trials, may have all monitoring undertaken by the protocol teams. This is most common in trials, such as dose escalation studies, in which there is a requirement for very rapid reporting of all adverse events with real-time review by the protocol teams, eg, weekly. This follows the pre-specified criteria laid out in the protocol. The protocol team includes a representative from an ACTG scientific committee that has responsibility for oversight of all trials in a particular scientific area, including study viability. As with studies monitored by a Study Monitoring Committee, for trials that are monitored by the

protocol teams, a letter is sent to the local IRBs of all AIDS Clinical Trials Units involved in the study whenever criteria for trial modification are met (eg, if the dose of a study drug is to be changed according to criteria in the protocol) or when a trial is to be modified for other reasons. In addition, a letter is sent at least every six months confirming that the monitoring of the study is ongoing and that none of the criteria for modification have been met.

Although pharmaceutical companies occasionally collaborate with the ACTGs in conducting trials (eg, by providing drug or laboratory assay support) and have representation on protocol teams, the Executive Committee of the ACTG or NIAID is ultimately responsible for decisions about modification or termination of trials independent of the company staff.

Summary and conclusions

This paper presents procedures for the creation and enforcement of data monitoring plans for exploratory trials. Given their often limited objectives and short-term nature, exploratory trials are frequently conducted without the use of a formal DMC. In such situations, there remain minimum requirements for data monitoring plans and IRB oversight. The key elements of such plans are outlined. Furthermore, several study-specific factors must be considered in organizing the monitoring apparatus for an exploratory trial, and we have suggested items for consideration. Finally, we have outlined factors that should be considered when constituting a DMC for exploratory trials.

It is the responsibility of the IRB to take NIH, VA, ICH, FDA and sponsor guidelines into account when reviewing or developing data monitoring policies for exploratory clinical trials. However, the implementation of these directives must remain decentralized, as has always been the case with IRBs. We feel confident in specifying minimum standards but do not feel that data monitoring implementation must be the same in all locations. Differences may occur, for example, in policies of what data are to be monitored, who should do the monitoring and how frequently the monitoring should occur. Inter-institutional variability has always existed for IRBs and respects the spirit of local autonomy. Review and enforcement should be the role of the IRB but delegation of some responsibilities to other groups, such as a Clinical Research Committee, may be necessary and preferable for some institutions.

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References

1. **Ellenberg SS, Fleming TR, DeMets DL.** *Data monitoring committees in clinical trials: a practical perspective.* John Wiley & Sons, 2002.
2. **US National Institutes of Health.** NIH policy for data and safety monitoring, 10 June, 1998, <http://grants1.nih.gov/grants/guide/notice-files/not98-084.html>, accessed 15 May 2006.
3. **US National Institutes of Health.** Guidance on reporting adverse events to Institutional Review Boards for NIH multicenter trials, 11 June, 1999, <http://grants1.nih.gov/grants/guide/notice-files/not99-107.html>, accessed 15 May 2006.
4. **US National Institutes of Health.** Further guidance on data and safety monitoring for phase I and II trials, OD-00-038, 5 June, 2000, <http://grants1.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html>, accessed 15 May 2006.
5. **US Food and Drug Administration.** Guidance for clinical trial sponsors: establishment and operation of clinical trial data monitoring committees, 2006, <http://www.fda.gov/cber/gdlns/clintrialdmc.htm>, accessed 15 May 2006.
6. **US Department of Veterans Affairs.** Cooperative studies program: guidelines for the planning and conduct of cooperative studies. Office of Research and Development, January 2001.
7. **International Conference on Harmonisation.** E3-structure of clinical study reports, November 1995. www.ich.org, accessed 15 May 2006.
8. **International Conference on Harmonisation.** E6-good clinical practice: consolidated guidelines, May 1996, www.ich.org, accessed 15 May 2006.
9. **International Conference on Harmonisation.** E9-statistical principles for clinical trials, February 1998, www.ich.org, accessed 15 May 2006.
10. **University of Minnesota.** IRB home page. Data safety monitoring. www.urb.umn.edu/guidance/dsm/index.cfm, accessed 15 May 2006.
11. **University of Wisconsin Comprehensive Cancer Center.** Policy and procedures for data and safety monitoring. 30 May, 2002, www.uwccc.wisc.edu/ctro/SOPs/DSM_Plan_May30_2002.pdf, accessed 15 May 2006.
12. **National Cancer Institute Data and Safety Monitoring Guidelines.** <http://www.cancer.gov/clinicaltrials/conducting/dsm-guidelines>, accessed 15 May 2006.
13. **Hibberd PL, Weiner DL.** Monitoring participant safety in phase I and II interventional trials: Options and controversies. *Journal of Investigative Medicine* 2004; **52**: 446–52.
14. **Sydes MR, Spiegelhalter DJ, Altman DG, Babiker AB, Parmar MKB and the DAMOCLES Group.** Systematic qualitative review of the literature on data monitoring committees for randomized controlled trials. *Clin Trials* 2004; **1**: 60–79.