external data. For example, if external reports indicate that use of the study drug in a different indication raised serious, unexpected safety concerns, a decision about continuing the ongoing trial may depend on whether the interim data suggest important benefits that may make the newly found risks acceptable, or the extent to which the newly identified concerns are evident in the ongoing study. In some circumstances, DMCs of separate but closely related trials (e.g., trials of the same product in different patient populations) may consider sharing confidential interim data when unexpected safety issues arise in one trial and information from the two trials together may improve decision-making in both trials. Because such sharing limits the extent to which the trials can be considered independent, it should be pursued only in the rare situations when early stopping might be considered, but the issues leading to this consideration are ambiguous, for example, when a safety concern arises that appears biologically implausible. Both DMCs would typically require the express consent of the respective sponsors prior to sharing such information.

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

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

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

4.4.1.5. Studies of Less Serious Outcomes

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

DMCs have not been commonly established for short-term studies of interventions to relieve symptoms. The need for an outside group to monitor data regularly to consider questions of early stopping for efficacy or protocol modification is usually not compelling in this situation. Such a group is probably warranted only when termination of the trial for efficacy, even at the expense of obtaining more complete safety information, would be indicated for ethical reasons.

For products intended solely to relieve symptoms, as opposed to curing or delaying progress of a serious disease or medical condition, an expert group to oversee all studies at all stages of development, monitor the developing safety database and make recommendations for design of successive studies based on early results may be useful. The sponsor or investigator could refer an unusual safety concern arising in any study to this type of external group for review, while maintaining its own primary role in monitoring the accumulating results. Such a group may be particularly valuable when the patient population is at relatively high risk of serious events; for example, in studies of drugs to control symptoms of angina, congestive heart failure, or chronic obstructive lung disease. The external group would independently evaluate individual events and overall event rates in ongoing studies and advise the sponsor about emerging concerns. Clearly, monitoring considerations of this type are more clinical than statistical. Sponsors frequently constitute internal groups to monitor these types of studies, and these may be satisfactory in most cases. Nevertheless, external advisors, who will be less committed to the existing development plan, may identify some problems more readily than internal reviewers. Thus, sponsors may find it valuable to augment such internal groups with one or more external advisors.

4.4.2. Early Studies

DMCs are not usually warranted in early studies such as Phase 1 or early Phase 2 studies, or pilot/feasibility studies, but formal monitoring groups may be useful for certain types of early clinical studies. While these formal monitoring groups will often consist of individuals internal to the sponsor and/or investigators, a DMC overseeing safety may be considered when risk to participants appears unusually high, e.g., with particularly novel approaches to treating a disease or condition. When the investigator is also the product manufacturer or IND/IDE sponsor, and thereby subject to potentially strong influences related to financial and/or intellectual incentives, a DMC could provide additional, independent oversight that would enhance safety of study participants and the credibility of the product development. Sponsors may therefore wish to consider establishing DMCs in such settings.

A DMC's role in early phase studies would be different from that in late Phase 2 or Phase 3 studies. Early studies are often exploratory in nature; they are frequently not randomized or controlled and therefore accumulating results are known to the investigators and sponsor. Issues regarding statistical interpretation of interim data, or confidentiality of interim data, are therefore generally less relevant in this setting. Nevertheless, for difficult situations in which the potential scientific gain from continuing a study must be evaluated in the context of ethical considerations for ensuring subjects' rights and welfare, particularly in settings such as those described above, DMCs may be helpful to investigators, sponsors and IRBs by providing independent, objective expert counsel. We expect,

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

4.4.3. Other Responsibilities

4.4.3.1. Making Recommendations

A fundamental responsibility of a DMC is to make recommendations to the sponsor (and/or, as noted in the Introduction, a steering committee or other group delegated by the sponsor to make decisions about the trial) concerning the continuation of the study. Most frequently, a DMC's recommendation after an interim review is for the study to continue as designed. Other recommendations that might be made include study termination, study continuation with major or minor modifications, or temporary suspension of enrollment and/or study intervention until some uncertainty is resolved.

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

4.4.3.2. Maintaining Meeting Records

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

We also recommend that after each meeting, the DMC issue a written report to the sponsor based on the meeting minutes. This report does not have to be extremely detailed, but should include sufficient information to explain the rationale for any recommended changes. Sponsors should establish procedures to minimize the potential for bias, such as requiring that reports to the sponsor include only those data generally available to the sponsor (e.g., number screened, number enrolled at each site) (see 21 CFR 314.126(b)(5) (drugs) and 21 CFR 860.7(f)(1) (devices)). If no changes are recommended, the report may be as simple as "The DMC recommends that the study continue as designed." We further recommend that the report to the sponsor include a summary of the discussion in any open session of the meeting and document any information provided orally to the sponsor that was not included in the written report. The sponsor may convey the relevant information in this report to other interested parties such as the study investigators, who should provide any such information, as appropriate, to participating IRBs. Of course, sponsors and/or investigators must report to participating IRBs, as well as to FDA, applicable changes in the protocol or study procedures made as a result of DMC recommendations (see 21 CFR 56.108(a)(3) and (4) and 312.30 and 312.66 for drugs and 21 CFR 812.40 for devices).

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

5. DMC RECOMMENDATIONS AND REGULATORY REPORTING REQUIREMENTS

All clinical trials conducted under an IND or IDE are subject to regulatory safety reporting requirements. These requirements include prompt reporting to FDA of certain serious and unexpected adverse events (see 21 CFR 312.32(c), 21 CFR 312.52, 21 CFR 812.46(b), 21 CFR 812.150(b)(1)). In general, for an event that is individually recognizable as a serious event potentially related to administration of a medical product (e.g., agranulocytosis, hepatotoxicity for drug studies), the sponsor (sometimes through a CRO managing that aspect of the trial, see 21 CFR 312.52) is responsible for notifying FDA (21 CFR 312.32, 21 CFR 812.150(b)(1)). The sponsor may make this notification with or without unblinding the individual case, as appropriate.

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

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

Findings conveyed to a sponsor by a DMC as part of a recommendation to modify the trial could therefore mean that serious and unexpected events were occurring, and the sponsor would consequently be required to report an analysis of these events to FDA and to all study investigators according to 21 CFR 312.32(c)(1)(B)(ii) (drug trials) and 21 CFR 812.150(b)(1) (device trials). Study investigators are generally responsible for reporting such findings to their IRBs, according to 21 CFR 312.66 (drug trials) and 21 CFR 812.150(a)(1) and 21 CFR 812.40 (device trials), although direct reporting from sponsors to responsible IRBs may be arranged and may be preferable in some situations; for example, when a central IRB has been established. For a device trial, however, the sponsor is responsible for notifying all participating IRBs when an evaluation of an unanticipated adverse event is conducted (21 CFR 812.150(b)(1)).

The requirement to report DMC recommendations related to serious adverse events in an expedited manner in clinical trials of new drugs (21 CFR 312.32(c)) would not apply when the DMC recommendation is related to an excess of events not classifiable as serious. Nevertheless, we recommend that sponsors inform FDA about all recommendations related to the safety of the investigational product whether or not the adverse event in question meets the definition of "serious." Examples might be recommendations to lower the dose of a study agent because of excess toxicity, or to inform current and future trial participants of an emerging safety concern that had not been recognized at the start of the trial.

6. INDEPENDENCE OF THE DMC

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

Independence is defined on a continuum. DMCs are rarely, if ever, entirely independent of the sponsor, as the sponsor generally selects the members, gives the committee its charge, and pays committee members for their expenses and services. Aside from being compensated for their duties as DMC members, however, we recommend that these members generally have no