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Comments on the
FDA Draft Guidance for Clinical Trial Sponsors –
“On the Establishment and Operation of Clinical Trial DMCs”
(<http://www.fda.gov/cber/gdlns/clindatmon.htm>)
Docket Number 01D-0489

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Introduction

The FDA has provided a timely draft document that provides excellent guidance to clinical trial sponsors regarding the establishment and operation of Data Monitoring Committees (DMCs).

In this letter, recommendations for two revisions, with justification, are provided.

Recommendation #1:

Section 4.3.1.2: Meeting Structure

In the fourth sentence in the lead paragraph for this section, “aggregated safety and outcome data” should not be included among the examples of non-confidential data that may be discussed in “open” sessions.

Justification for Recommendation #1

Aggregate data on efficacy and safety outcomes—that is, pooled data giving the total number of events across all study groups—often provide suggestive information regarding the relative benefit-to-risk profiles of the treatments being compared. Hence, in most settings, these data should not be included in the Open Reports and should not be discussed in Open Sessions of the DMC meetings. Consider a clinical trial of an experimental drug in advanced cancer patients, where historical evidence indicates the control regimen should yield approximately 15% two-year survival. When one-half of the trial’s targeted number of endpoints have occurred, pooled data estimates of two-year survival of 25% or 10% could give a strong impression that the experimental regimen is effective or ineffective, respectively. Even if that impression is incorrect, resulting actions taken by trial investigators, sponsors or patients could compromise trial integrity and credibility.

It could also be inappropriate to include pooled data on secondary endpoints in an Open Report. Consider, for example, a clinical trial designed to assess the effect of a behavioral intervention in preventing transmission of HIV. Release of early data showing a substantial reduction (or no reduction) in the surrogate endpoint of self-reported risk taking behavior could lead to pre-judgment about the efficacy of the intervention, or might lead to a data-driven reformulation of trial primary or secondary endpoints.

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The proper level of access to aggregate efficacy and aggregate safety data needs to be determined on a trial-by-trial basis. Inclusion of such data in an Open Report would be appropriate if this information could broadly inform trial investigators and care-givers about how to enhance the quality of trial conduct, while not providing them clues about the relative benefit-to-risk profiles of the treatments being compared. An illustration is provided by the trial of erythropoietin in hemodialysis patients with congestive heart failure, (Besarab A, Bolton WK, Browne JK, et.al., 1998). It was clearly known that erythropoietin substantially impacted a biological marker, hematocrit level. The randomized trial was designed to determine whether benefit on a long-term clinical endpoint, patient survival, could be achieved by the intervention, where dosing would be titrated in a manner to achieve an intended level of effect on the marker. In this instance, data on changes in the biological marker provide important insights about adherence to the study regimen, without providing any new insights about efficacy and, hence, would be very appropriately included in the Open Report. A similar illustration is provided by the ongoing NIAID-sponsored ESPRIT trial, that is evaluating the ability of IL-2 to reduce the occurrence of AIDS-defining events, mediated through its previously established immunologic effects represented by changes in the biological marker, CD-4 level. Aggregate data on changes in CD-4 level could be provided in the Open Report since insights from this information would be limited to quality of adherence to the protocol-specified regimens.

Even when it is not proper for aggregate efficacy and safety data to be widely distributed through inclusion in the Open Report, such data could be provided to selected individuals who “need to know” such information to carry out their ethical or scientific responsibilities in the conduct of the trial. In studies with endpoint adjudication committees, for example, the number of endpoints submitted by sites for adjudication will be known at least to the members of that committee. The study chair and/or certain members of the steering committee may also need to have access to that information if they are responsible for monitoring the work of the adjudication committee. A trial’s medical monitor who is responsible for providing timely reporting of serious adverse events to regulatory authorities would have at least indirect access to aggregate safety data. In addition, since the determination of the need for sample size adjustments is usually based on the event rate for the primary endpoint in the pooled data, such information would need to be provided to whomever has been charged with this responsibility. In any of these settings in which individuals are provided access to aggregate efficacy and safety data on a “need to know” basis, these individuals should be required to maintain the confidentiality of this information except where it is necessary to do otherwise to carry out their ethical or scientific responsibilities in the conduct of the trial.

Recommendation #2:

Section 6.5: Sponsor Access to Interim Data for Planning Purposes

In the third bullet point, the FDA should delete the sentence, “For example, rather than viewing all outcome data and all primary endpoint data, the sponsor may just need to know whether the conditional probability of success on the primary endpoint is more or less than a specified magnitude.”

Justification for Recommendation #2

Knowing the “conditional probability of success on the primary endpoint” typically would allow one to determine the interim estimate of treatment effect on that endpoint. Hence, to achieve the confidentiality advocated by the FDA in the lead paragraph of Section 4.2 of the draft Guidance Document, information about whether the conditional probability of success on the primary endpoint is more or less than a specified magnitude should not be provided, unless the “specified magnitude” corresponds to a value that would indicate the interim results are sufficiently extreme to justify a recommendation regarding early termination.

If the FDA would wish to use a different example in this bullet point, a suggestion is provided:

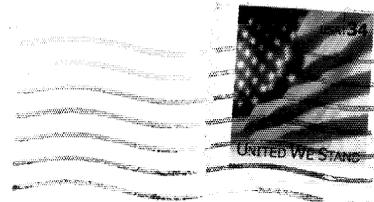
- The sponsor should determine the minimum amount of information needed, and this information should not provide direct insights about the likelihood the trial will achieve a positive result. For example, to assist in defining eligibility criteria of a subsequent trial, the sponsor might wish to know whether estimates of treatment effect in a specified subgroup are less than in the overall data set (without any indication being given about the size of the current overall estimated effect).

Reference

1. Besarab A, Bolton WK, Browne JK, et.al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *New England Journal of Medicine* 1998; 339: 584-590.



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