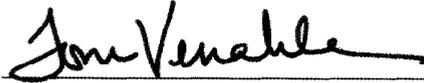


Comments - Docket # 01D-0489
Draft Guidance - Data Monitoring Committees (DMCs)

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Section 4.3 - Establishing Standard Operating Procedures

This section seems to blur two separate documents -- an SOP in which a sponsor could specific its approach to DMCs *in general*, and another document which is *specific* for a particular DMC, describing the objectives, roles and responsibilities, scope, schedule of meetings, etc. It may be worthwhile for a sponsor to develop its own SOP for DMCs, but I believe Section 4.3 is DMC-specific.

A statement of scope as to an DMC's "scope" is also remarkably important, in what some DMCs are focused on safety-alone (eg, serious AEs, select AEs, select labs), whereas some DMCs are also responsible for recommendations given interim efficacy results. In addition, ICH-E9 invites a sponsor to constantly review accumulating data in a blinded manner to assess enrollment patterns, protocol compliance, and the validity of various assumptions (eg, variability of the primary efficacy parameter). A sponsor may not want to duplicate (and pay for) these efforts within the DMC.

Recommendations

1. Consider using the term *Charter* to represent this DMC-specific document. Such a term would then be unique and not overlap with the names of other common documents used in the industry.
2. Expand the content of that charter to include objectives, the scope of the DMC, the roles and responsibilities of the DMC-members, its chair, and the sponsor, general operating plans, and so on. Notice here that "operating plans" can be introduced without using the term "SOP". That Charter should be approved by the sponsor's core team and the DMC members.
3. Develop another paragraph that describes other beneficial documents, eg, Analysis Plan, table shells, specific operating plans.

Section 4.3.1.4 - Format of Interim Reports and Use of Treatment Codes

Page 9 - The "independent-statistician preparing all DMC reports" as *ideal* was very controversial at the public hearing. Statisticians do not work in a vacuum. SAS

programmers prepare many of DMC reports. Programs require some degree of validation. A statistician's manager should approve the interim analysis and report. In turn, several people would "touch" the unblinded data. The guideline recommends "sponsor independence" as ideal. This necessitates CROs. I've seen two CRO budgets in the past months with price tags of \$100,000 and \$140,000. It does seem expensive.

The independent-statistician recommendation means that for any study with a DMC, we have a project-statistician and a DMC-statistician. Each statistician is expected to develop an understanding of the protocol, the analysis plan, and the data as it accumulates. Plainly speaking, we may not have that many statisticians, nor other support staff.

The guideline needs other alternatives.

Recommendations:

1. Position sponsor-independent-statistical-services (not just singular statistician) as ideal, but offer other alternatives, e.g., say a steering-committee-independent-but-within-the-sponsor option, plus a least desirable option, namely sponsor-dependent.
2. Insist that the people providing the service be identified in the Charter. In addition, the Charter should specify how these people channel the information so that any potential bias is minimized. Alas, all Charters should be provided to the agency.

Page 10 - In general, the DMC data should be unblinded. I agree with that, but realize that many DMC members don't. They prefer "masked treatments", e.g., treatments A, B, C given access to an sealed envelop containing the actual treatment identity of A, B, and C. Such an envelop is opened only if warranted during DMC proceedings.

Recommendation - In the guideline, say that "in general, DMCs should have access to the actual treatment assignment", but acknowledge the level of blinding and measures to ensure confidentiality should be agreed to in the Charter.

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