

Orange County
OCRA
REGULATORY AFFAIRS
Discussion Group
PMB 624

5405 Alton Parkway, Suite 5A
Irvine, CA 92604-3718

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March 5, 2002

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, room 1061
Rockville, MD 20852

Re: Docket #01D-0489 – “Guidance for Clinical Trial Sponsors on the Establishment and Operation of Clinical Trial Data Monitoring Committees”

Dear Sir or Madam:

OCRA, the Orange County Regulatory Affairs Discussion Group is pleased to provide feedback to the Agency on the draft guidance “*Guidance for Clinical Trial Sponsors on the Establishment and Operation of Clinical Trial Data Monitoring Committees (DMC)*” released this past November 2001. OCRA is a volunteer organization made up of industry representatives from the Southern California area. Our membership includes individuals from approximately 100 local companies from the pharmaceutical, medical device, biologics and IVD industries.

Please find our comments on the pages attached to this letter. If you have any questions, or would like to discuss this document further, please do not hesitate to contact me, or Judy Gordon, D.V.M., OCRA’s president-elect.

Sincerely,



Marcia Yaross, Ph.D.
President
Orange County Regulatory Affairs Discussion Group

01D-0489

C23

Docket #01D-0489 – “Guidance for Clinical Trial Sponsors on the Establishment and Operation of Clinical Trial Data Monitoring Committees”

**COMMENTS FROM ORANGE COUNTY REGULATORY AFFAIRS DISCUSSION GROUP
OVERVIEW**

OCRA supports the use of DMCs for high risk/long term studies and for studies in which FDA and the sponsor agree that a DMC could facilitate an expedited regulatory review. We believe that in these contexts, DMCs can significantly bolster scientific integrity and patient safety in clinical trials. However, we strongly urge FDA to reconsider the blanket approach taken in this guidance document. While DMCs may be appropriate to implement in drug and biologics clinical studies, they are not suitable or necessary for the majority of device studies. We strongly urge FDA to either revisit this document and revise it appropriately for device studies, or to state more clearly that there are no implied requirements for sponsors of device trials.

Similarly, OCRA is concerned that the Agency did not consider the issue of blinding separately for device trials. The document does not differentiate between device, drug and biologics studies. An assumption of blinding is stated and implied throughout the document. Blinding is neither necessary nor possible in the majority of medical device clinical trials. Devising a double-blind study is challenging, for example, when the device being studied is an implant or a surgical instrument used to deliver a therapy. Randomized double-blind, placebo-controlled trials work well when dispensing an injection, inhalation or systemic investigational product, but achieving true blinding in a device trial can add a disproportionate cost and a higher level of complexity and is simply not always possible. On this basis, we recommend that FDA consider drafting a separate guidance document for device studies.

SPECIFIC COMMENTS, CONCERNS, AND RECOMMENDATIONS

SECTION	COMMENTS
1.1	There is some confusion in the industry over terminology. DMCs have also been referred to as Safety Committees, Event Committees, and Data Safety and Monitoring Boards (DSMB). If FDA intends to unify these terms under “DMC” it may be appropriate to do so in this section. OCRA would also suggest that, in the spirit of harmonization with ICH GCP’s, it would be appropriate to use the term IDMC, Independent Data Monitoring Committee.
1.2	The second to the last statement in this section implies that all studies require DMCs. OCRA would recommend that FDA revise and / or qualify this statement appropriately.

SECTION	COMMENTS
2	<p>Section 2 contains statements that are contradictory. On the one hand, the guidance states “...DMCs should be established for controlled trials with mortality or major morbidity as a primary or secondary endpoint. They may also be helpful in settings where trial participants may be at elevated risk of such outcomes even if the study intervention addresses lesser outcomes such as relief of symptoms. Although DMCs may prove valuable in other settings as well, a DMC is not needed or advised for every clinical study.” On the other hand, the general criteria for inclusion of DMC review described in this and in other sections are so broad, that they would likely apply to most clinical research, and would leave sponsors feeling obligated to implement a DMC for the majority of studies.</p> <p>OCRA disagrees with the assertion in section 2.3 that “a DMC can help assure the scientific validity of the trial”. It is incumbent on sponsors to design scientifically valid studies that address issues of bias; and it is incumbent on FDA to review and approve these studies, ensuring the adequacy of the study design to provide either reasonable assurance of safety and effectiveness (in the case of medical device clinical trials) or evidence of safety and efficacy, for drugs and biologics . We strongly believe that in this role, a DMC is a redundancy. In fact, as pointed out in the draft guidance, formation of DMCs was initially undertaken for NIH-sponsored clinical trials, which were generally not conducted under the oversight of FDA. Given the extensive oversight provided by the FDA, and the commitment of the FDA to provide guidance to manufacturers and sponsors on designing studies intended to support either NDAs, PLAs or PMAs, we believe that the involvement of a DMC in either assessing or assuring the scientific validity of clinical trials being conducted under either IND or IDE as redundant and potentially in conflict with the objectives of the sponsor and of FDA. While FDA has an obligation to identify the least burdensome path from a regulatory perspective, DMCs have no obligation to this legislative mandate. This can result in requests from DMCs to sponsors for clinical trials that are more complex and burdensome than may be necessary for obtaining a product approval, since the intent of the DMC may be to further scientific knowledge, rather than to meet the statutory pre-market requirements.</p> <p>In addition, here, as in many other sections of this guidance document, FDA asserts that blinding is a preferred, if not a mandatory requirement for a successful trial. As mentioned above in the overview to these comments, blinding is not feasible for most device and, in some cases, raises ethical concerns. Furthermore, sponsors already have access to unblinded data from adverse events reports. These difficulties are not acknowledged in this guidance, and would result in serious compliance difficulties should this document be enforced.</p>

SECTION	COMMENTS
4	<p>The definition of the role of a DMC is excessively prescriptive, and highly reminiscent of the NIH model for DSMB's. The goal of most industry sponsored trials is to demonstrate safety and efficacy of a therapy for market clearance / approval purposes. DMCs in NIH studies are largely concerned with assuring the scientific validity of a study, and to furthering the body of scientific knowledge in a given medical area. A DMC in the context of a regulatory trial must therefore be flexible and geared towards a sponsor's regulatory objectives. Further, as discussed in section 2 above, OCRA believes that sponsors, together with FDA, already shoulder the burden for assuring scientific validity.</p>
4.2	<p>This section emphasizes FDA's position that <i>"Knowledge of unblinded interim comparisons from a clinical trial is not necessary for those conducting or those sponsoring the trial"</i>. As was discussed above, this is often very difficult to accomplish in a device trial and will present a huge compliance issue for sponsors of device studies.</p>
4.3.1.2	<p>The recommendation that FDA be allowed to attend DMC meetings is unreasonable in all, perhaps, but the case where this arrangement is agreed to upfront for expedited review. FDA's participation in the open-session of the DMC may bias FDA's review of the PMA and other submissions made by the sponsor. Furthermore, complete disclosure to FDA may negatively impact the independence and behavior of the DMC. Interactions between a DMC and FDA will seriously undermine the sponsor's role in the trial.</p>
4.3.2	<p>The draft guidance states that it has <i>"A major concern when data on group differences are assessed repeatedly as they accumulate is that the Type I error (false positive) rate may be inflated if adjustment is not made for the multiple looks at the data. Typically, procedures should specify a statistical approach in advance of the trial's initiation that permits multiple interim reviews while maintaining the Type I error rate at the desired level."</i> OCRA believes that this type of error compounding is inappropriate in the context of a safety evaluation being conducted by an independent Data Monitoring Committee in the absence of a "stopping rule" or determination of early stopping of a study for efficacy. It should not be required by the guidance.</p>
4.4.2	<p>It is OCRA's position that DMCs should be allowed to recommend early termination of a study if statistical significance for the primary endpoints was reached and this has been agreed to within the context of an IDE or IND submission.</p>

SECTION	COMMENTS
4.4.1.5	<p>OCRA disagrees with the FDA's position on retaining a DMC for studies with less serious outcomes. This is unnecessarily burdensome (increasing time, costs, and complexity) and again creates a redundancy in trial oversight. The role proposed for a DMC in these types of studies is already adequately provided by IRBs, FDA, and the sponsor.</p>
4.4.2	<p>Early studies (such as pilot, feasibility and phase I studies) are conducted by sponsors in order to gain a better understanding of the therapy, what the potential safety issues may be under "normal-use" conditions, and what the requirements may be to demonstrate efficacy in a pivotal trial.</p> <p>Further, results from early studies are often used to better design the pivotal trial. Blinding sponsors to this crucial feedback will hinder their ability to improve the therapy and better understand the product. In addition, these studies are seldom powered to demonstrate any sort of statistical significance; biasing is not an issue.</p>
4.4.3.2	<p>For the reasons previously expressed in this letter (see comments for section section 4.3.1.2), OCRA strongly believes that making DMC meeting minutes available to FDA for review may bias the way a DMC makes its decisions. FDA oversight of any sort is likely to make a DMC more conservative and more likely to terminate studies prematurely. Study information is already available to FDA on an interim basis through statutorily defined reporting requirements, including reporting of serious adverse events, unanticipated adverse device effects and annual reports to both INDs and IDEs.</p>
6	<p>OCRA does not believe that an independent statistician (one external to the sponsor) should be required to perform interim analyses. Hiring a statistician unfamiliar with the nuances of the study design, the medical condition or outcomes data will likely result in increased costs, time delays and possible misinterpretation of the data. Furthermore, this implies that a study sponsor must engage two statisticians for every clinical trial being conducted, i.e., one for the analysis of the study results intended for use in the PMA or NDA or PLA, and another, independent statistician solely for purposes of reporting to the DMC.</p>

OCRA has appreciated this opportunity to give FDA feedback on its proposed future policy for clinical trial monitoring and oversight. We would like to reiterate that, while we support use of DMCs for long term/high risk studies and for certain expedited review

studies, we believe that the decision to employ a DMC for all other studies rests solely with the sponsor. Also, we would like to emphasize here again that blinding is inappropriate / not feasible for most device trials. We would again like to urge the Agency to consider separating the requirements for drugs and biologics from devices, and to create independent documents. Also, because the document is written so prescriptively, OCRA recommends that the document be used as a reference document only, and that FDA clearly state that compliance with this document is voluntary.

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