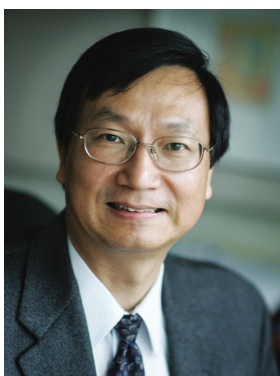


EDITORIAL

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“...while the Data Monitoring Committee plays an important role in maintaining the validity and integrity of the clinical trial, adaptive design clinical trials may trigger a greater role and increased responsibility for the Data Monitoring Committee.”

¹Center for Biologics Evaluation & Research, US FDA, 1401 Rockville Pike, HFM-215, Rockville, MD 20852, USA

²Department of Biostatistics & Bioinformatics, Duke University School of Medicine, Durham, NC, USA

*Author for correspondence:
E-mail: min.lin@fda.hhs.gov

Data Monitoring Committees in adaptive clinical trials

Min Lin^{*1} & Shein-Chung Chow²

Data Monitoring Committees (DMCs) have been widely utilized in clinical trials for study monitoring. The DMC, independent of any activities related to clinical operation of the study, is a group of individuals with pertinent expertise who review on a regular basis accumulating data from one or more ongoing clinical trials [1]. Depending on the study objectives, the primary responsibility of the DMC is to ensure the validity and integrity of the intended clinical trial by performing ongoing safety monitoring, as well as interim analysis for efficacy [2–3,101–102]. The use of DMCs in clinical trials can be traced back to the early 1960s [1]. However, the DMC did not appear in pharmaceutical trials until the early 1990s [3]. In 2006, the US FDA published a guidance on the ‘Establishment and Operation of Clinical Trial Data Monitoring Committees’ [1] to assist the sponsor in: determining the need for a DMC; establishing a DMC; and, setting up standard operation procedures for DMC’s function and activity.

Adaptive design clinical trials have received a great deal of attention in recent years due to their potential features of flexibility and efficiency. Practically, adaptive designs allow researchers to modify the trial procedures and/or statistical methods of ongoing clinical trials based on accrued data. In the FDA draft guidance, entitled ‘Adaptive Design Clinical Trials for Drugs and Biologics’, an adaptive design clinical study is defined as a study that includes a prospectively planned opportunity for modification of one or more specified aspects of the study design and hypotheses, based on analysis of data (usually interim data) from subjects in the study (fully blinded or unblinded manner) [4]. According to the FDA draft guidance [4], adaptive designs are classified into two categories: well-understood and less-well-understood designs. Well-understood design mainly refers to the study designs with planned modifications based on an interim analysis that either need no statistical correction or properly account for the analysis-related multiplicity issues, such as traditional group sequential designs. In general, regulatory agencies have extensive experiences in well-understood designs in terms of study conduct and statistical properties. Conversely, less-well-understood designs refer to the study designs with statistical properties that are not fully understood. There is relatively little regulatory experience in evaluating the validity and integrity of less-well-understood design approaches. The main concerns with any less-well-understood adaptive designs noted in the draft guidance are control of the study-wide type I error rate, minimization of the impact of any adaptation-associated statistical or operational bias on the estimates of treatment effects and the interpretability of the results.

Although a DMC is not required in clinical studies [1], the use of a DMC in pharmaceutical industry trials, especially in confirmatory studies, has become popular over the past two decades [3]. In practice, the DMC has been widely used in clinical trials with group sequential designs to reduce potential operational

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bias that may be introduced through unblinded analyses of the treatment effect at the interim looks. The DMC may recommend early study termination due to demonstrated efficacy or futility after examining the interim analyses in a secure and confidential manner. The well-established DMC operating procedures used in traditional group sequential design trials have been expanded to other adaptive design studies in recent years [4]. However, unlike the DMC in group sequential design studies, the DMCs in less-well-understood adaptive design trials are sometimes expected to implement preplanned adaptation procedures and to provide recommendations to the sponsor regarding how to adapt the trial design. Thus, members of the DMC are required to have the technical expertise to provide assurance of the scientific validity of any adaptation. Therefore, the role of the DMC is becoming more complex compared with its traditional role [4].

Does the adaptive design give too much responsibility to the DMC? There have been discussions regarding whether the additional burden should be added on the existing DMC or if a separate committee should be established in order to monitor scientific validity and integrity of the clinical trials utilizing adaptive design methods. However, separate committees could potentially result in conflicting decisions/recommendations. Another potential issue is whether there is enough expertise in the world to fill two expert committees for every adaptive clinical trial. Gallo *et al.* suggested establishing an augmented DMC to ensure additional expertise and experience relevant to the type of decisions to be made [5]. Conversely, the DMCs in adaptive design studies may be conflicted in working on both adaptations for efficacy and safety and/or futility monitoring, especially when the study primary end point is safety related (e.g., death). To address such a potential conflict, an extensive charter that clearly describes the role, responsibility, function, activities and adaptation/decision-making algorithms of the DMC is suggested to be developed before a trial starts [6]. The charter may also define who will prepare the analyses for the DMC, who may access the unblinded data, what information, and under what circumstances, is permitted to be released to the sponsor. In order to maintain the validity and integrity of the study, the DMC may only carry out the responsibilities that are described in the DMC charter and may make necessary recommendations or decisions based on the prospectively documented adaptive algorithm.

A major concern when utilizing a DMC in clinical trials is the independence of the DMC. Clearly, the independence of the DMC is designed to ensure the quality, validity, and integrity of the clinical trial.

For less-well-understood adaptive design trials, it is critical to have an independent DMC as the DMC is unblinded to interim data analysis of the treatment effect. The FDA draft guidance suggests that interim analyses prepared for the DMC review should be performed either externally to the sponsor or by a group within the sponsor that is unequivocally separated from all other parties to the study [4]. However, is a DMC ever really independent? As pointed out by the DMC guidance [1], DMCs are rarely entirely independent of the sponsor due to the fact that the sponsor selects the DMC members, the sponsor gives the DMC its charge and, perhaps most importantly, the sponsor pays for the DMC's expenses and services. In practice some sponsors may make every attempt to influence the function and activity of the DMC [6]. Issues that have been observed include, but are not limited to: the sponsor may appoint the DMC members who are closely related to the sponsor or in favor of their product; the sponsor may replace the DMC members when the DMC members have strong opinions regarding the design and analysis of the study protocol and/or charter; the sponsor usually takes the lead to assist the DMC to develop a charter and the sponsor may seek advice from individual DMC members without the knowledge of the chairman of the DMC [6].

In practice, the DMC may not be in a position to change the study design except for cases of serious safety-related concerns. In adaptive design studies, as indicated in the FDA draft guidance [4], the DMC may be charged only with providing necessary recommendations in terms of trial design on the basis of prospective adaptation algorithms. Since the DMC may be unblinded to interim study results (e.g., trials using less-well-understood adaptive designs), it might be biased to provide any subsequent recommendations to any aspect of the study design, conduct and analysis. Conversely, the sponsor may or may not accept the DMC's recommendation. One issue that has been discussed is the dilemma that occurs when the sponsor does not accept the DMC's recommendation [6]. In this case, DMC members who strongly disagree with the sponsor's decision may decide to resign from the committee or bring the issue to the attention of a regulatory agency or an institutional review board if the members have substantial safety concerns regarding the ongoing trial.

Another issue is whether it is appropriate to allow the DMC to communicate with the regulatory agency directly in the event of wrong doing in the conduct of the clinical trial [6]. From the sponsor's point of view, it may be undesirable to reveal information that could weigh against ultimate approval to the regulatory

agency, especially if the information is limited and/or has not yet been verified. From the DMC's point of view, it may be important to bring any critical concern regarding the safety and/or integrity of the trial to a regulatory agency's attention.

In summary, while the DMC plays an important role in maintaining the validity and integrity of the clinical trial, adaptive design clinical trials may trigger a greater role and increased responsibility for the DMC. For adaptive design clinical studies, in addition to safety data monitoring, DMCs may also be expected to implement the adaptation procedures based on the prospective adaptation algorithms. Controversial issues regarding the DMC of an adaptive design trial have been raised:

- Should the additional responsibility be added on the existing DMC or a separate committee?
- Is a DMC really independent?
- What if the sponsor does not accept the DMC's recommendation?

- Should the DMC be encouraged to communicate with regulatory agencies directly?

These issues have an impact on the quality, integrity and success of clinical trials conducted at various phases of clinical development, especially in late-phase studies.

Disclaimer

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