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Regulatory Perspectives on Data Safety Monitoring Boards

Protecting the Integrity of Data

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Abstract

The use of interim analyses and data safety monitoring boards (DSMBs) can assist greatly in the timely determination of whether or not a medicine has an acceptable benefit-risk profile. Regulatory authorities regard the appropriate use of interim analyses favourably, but will consider the extent to which the conduct of interim analyses and the involvement of DSMBs may have compromised the evidence of efficacy and safety from a clinical trial. Issues of particular concern, which may potentially introduce bias, include the dissemination of interim data and the rules by which a trial might be terminated early. If data from trials which employ a DSMB are to be considered reliable and scientifically valid, it is the responsibility of the trial sponsor to demonstrate that the DSMB is set up and run appropriately and to verify that any bias introduced has had no important effect on the conclusions.

The potential impact of interim analyses on the reliability of trial results is well recognised.[1-3] In this paper, the phrase 'data safety monitoring board' (DSMB) is used as a general term for a body that reviews interim trial data and which has the potential to influence the future conduct of a trial. Another popular name for such a body is simply 'data monitoring committee'; other similar terms are also used. DSMBs have different functions to those of ethics committees and their function is generally different to that of routine trial monitoring for which all sponsors have a responsibility. A DSMB can assist in the timely determination of whether new medicines are safe and efficacious. They may be important from an ethical point of view, as randomisation may become unethical if equipoise is compromised. An external body helping to maintain the relevance and scientific validity of the trial might also be beneficial.

DSMBs are not required in most clinical trials and interim analyses should not, in general, be used simply to provide comfort to an anxious sponsor that the trial will ultimately be a success. DSMBs are more appropriately used in phase III trials of life-threatening or other serious diseases and 'mega-trials', where establishing an unequivocal benefit of a particular treatment might render further randomisation unethical. Such trials might be conducted either by pharmaceutical companies or by not-for-profit governmental or academic organisations. One can argue that the financial pressures for success differ between these types of organisations but the principles behind the good conduct of interim analyses and use of DSMBs are similar for each. The different organisations will not be discussed separately here.

Using interim analyses and DSMBs can compromise the integrity of trial data if they are not set up

and managed appropriately. Their use has, therefore, become a focal point of assessment by regulatory authorities. Statistical and medical assessors concern themselves particularly with the reliability of trial data and would carefully consider the potential impact of using a DSMB.

This paper considers some of the issues involved with using a DSMB in a trial to be used to support evidence of efficacy in a regulatory submission. We do not distinguish between interim efficacy and interim safety data although it is accepted that, in some serious conditions, unblinded summaries of interim safety data might be necessary for optimal patient management. Such data summaries are preferred to individual patient listings in blinded trials as they do not reveal the treatment code for any given patient.

1. Equipoise, Multiplicity and Bias

To understand why regulatory authorities may be concerned over the use of DSMBs we briefly consider the following three concepts.

Equipoise in a clinical trial exists when there is a lack of evidence for choosing one treatment strategy over another.[4] This is important so that it is ethical to randomise patients between two (or more) treatment regimens.

Multiplicity is a general term that, in this context, relates to repeated hypothesis testing.[5] It is well understood that a trial with a single hypothesis test (a single endpoint tested at a single time point) is not affected by multiplicity. However, particularly in long-term trials, it is possible, and often desirable, to analyse the data on more than one occasion. It is in these situations, where there is more than one opportunity to declare a trial a success, that multiplicity arises. Regulatory authorities and good clinical practice require that this multiple testing should be accounted for.

Bias is a systematic deviation of results or inferences from the truth or processes leading to such systematic deviation.[6] Bias may arise from a number of sources including the actions of trial investigators and the chosen method of statistical analysis. The most important features of trial design used to avoid bias are blinding, randomisation, and the prespecification of important features of the statistical analysis.

2. Influences on Data Integrity

2.1 Dissemination of Interim Data

In general, the most reliable clinical trial data come from adequately powered, randomised, double-blind trials. Whilst interim assessment of efficacy and/or safety data can be desirable, even necessary, for trials in some indications, care must be taken that interim analyses and involvement of a DSMB do not introduce bias. A key issue relating to the influence of interim analyses is the dissemination of the interim results, which may result in an impact on future trial conduct.

A possible consequence of disseminating interim data to persons involved in running a trial, or with a vested interest in its outcome (financial or otherwise), is the introduction of bias. It is possible that the extent of any bias will render the trial results difficult to interpret and unacceptable for regulatory purposes.[1]

Trial investigators are in a unique position to introduce bias in numerous ways, intentionally and unintentionally. The knowledge of interim results might, for example, influence protocol amendments or the pattern of recruitment, the use of concomitant treatments or the assessment of subjective endpoint data. Sponsor personnel (including employees of clinical research organisations [CROs]) may similarly be compromised because of their direct involvement with the study and access to trial investigators. The involvement, therefore, of trial investigators and sponsor personnel in the consideration of interim data is preferably limited to, at most, knowledge of aggregate data (that is, data that are presented without separation by treatment group). Data, for example, on recruitment, overall demography, overall event rates or variability might help verify the external validity of the trial or identify current weaknesses in trial conduct or recruitment. The forum for discussion of such aggregate data is often termed the 'open' session of the DSMB meeting.

Access for trial investigators and sponsor personnel to unblinded, comparative data will increase the likelihood that regulatory authorities will be concerned about the possibility of bias and, therefore, that the conclusions may be unreliable. Without evidence to the contrary, a regulator might make the conservative (from their point of view) assumption that all trial investigators and relevant sponsor personnel are fully aware of interim results even if only one trial investigator or member of the sponsor personnel has had access to unblinded data. Therefore, it is recommended that sponsor personnel do not sit on the DSMB and are not privy to unblinded interim data.

Adherence to strict standard operating procedures to control the conduct of interim analyses can help and providing the details of these procedures can assist in the regulator's determination of whether or not the conduct of the interim analysis was acceptable. It is the process as much as the technical statistical aspects that will be scrutinised.[7] The information most useful to the regulator is that concerning the management of interim data (the data flow) and the composition of the DSMB. Minutes of DSMB meetings and a list of personnel (sponsor employees, CRO staff or trial investigators) who had access to either treatment allocations or interim data separated by treatment group should also be supplied. Information on when these persons had access to such data in relation to any major changes in trial conduct is also important.

Despite the concerns outlined above, it is understandable, not least for planning future studies, that a sponsor may wish to be aware of interim results and to be involved with interim amendments to the trial protocol. A compromise is for the sponsor to be represented on a second committee, often called the steering committee. The steering committee commonly controls the future direction of the study. For example, they may have the final say on whether the trial continues as per protocol, continues but with amendments to the protocol, or is stopped. The steering committee would not usually have unblinded access to the interim data, thus avoiding some of the concerns outlined above, instead they would consider the conclusions and recommendations made by the DSMB. It is crucial that the relationship between the two committees be well defined in advance of the trial. In particular, as for the DSMB, regulatory authorities will wish to know the composition of the steering committee and precisely which members, if any, have access to unblinded interim data. Arguments on why these steering committee members required knowledge of interim data will be closely scrutinised.

A common exception to the guidance of excluding sponsor personnel from involvement with the DSMB is the participation of a statistician, whose role is to prepare the interim analyses and data summaries. The statistician may work for the sponsor or for a sponsor-retained CRO, but they are still often termed as 'independent'. It might be considered that the involvement of a statistician closely associated with the trial may greatly facilitate the conduct of the interim analysis. However, it must be recognised that such personnel are unlikely to be completely dispassionate about the trial outcome and are almost always compromised in the same fashion as other sponsor personnel, in that they have a vested interest in the trial being successful. If such an 'independent' statistician is involved, it is preferable that they have no involvement in the trial conduct, although they may have been involved with early discussions on trial design. A statistician from a CRO not otherwise involved in the trial, or from academia, may well give the impression of being even further detached from trial investigators and sponsor personnel, and might therefore be a preferred choice for the regulator. However, it is important that the statistician conducting the interim analysis is trained to be fully aware of the trial design, and the protocolled statistical methods and data presentations.

One further safeguard sometimes used in blinded trials is that this statistician may, where possible, analyse and present comparative interim data in a 'partially blinded' fashion, where treatment groups are simply labelled as A and B and the exact identification of the groups remains blinded. In this model, only the DSMB statistician or chair would have

access to the true treatment allocations, as members of the DSMB do generally require fully unblinded data. This process is seen by some to be helpful, although it certainly cannot be seen to be a full guarantee of eliminating bias.[8] In many circumstances, even this level of information can lead to unblinding (e.g. through information seen relating to efficacy data, laboratory data or adverse effects). Therefore, even partially blinded interim data should not be available outside the DSMB and the independent statistician should only partially unblind that portion of the randomisation scheme required for the interim analysis. The criticism of this model is that it is only usually suitable for simple interim analyses that can be interpreted symmetrically. If, for example, a negative trend in the data might warrant further analyses to explore the nature of the risk, whilst a positive trend would warrant no additional analyses. In this example the question is not symmetric and partial blinding might not be appropriate.

Regardless of whether or not the statistician is unblinded at the interim analysis, it is crucial that they do not discuss the interim data or future trial conduct with anyone. Protection from such contact with persons involved with study conduct is often termed a 'firewall'. The lengths to which a sponsor goes to construct this firewall can be described to regulators and is an important part of the sponsor's justification that the trial could not have been compromised.

2.2 Composition and Remit

In preference to trial investigators and sponsor personnel, DSMBs should ideally comprise (at least) medical and statistical experts with no vested interest in the outcome of the trial. The broad remit of the DSMB is to monitor the trial conduct and interim results in an independent fashion. These persons should have access to all relevant data in an unblinded fashion in order to make informed decisions over the future of the trial. Unblinded data are commonly discussed in the 'closed' session of the DSMB. This part of the meeting would usually involve only the DSMB members themselves, although the statistician who prepared the interim analysis might be available to answer questions about the trial data or statistical analysis. What constitutes 'all relevant data' may be debated and will vary on a case by case basis. Effort should be made prior to the start of the trial to determine the content and format of the interim data presentations. However, it may be necessary to provide additional data at the time of the DSMB meeting to fully understand the emerging trial data. In some situations a single measure of efficacy or safety data may be sufficient. Other situations will warrant a full spectrum of data to facilitate a judgement on risk-benefit.

Pre-specifying a remit for the DSMB is critical. As a minimum, the remit would outline the roles and responsibilities of the DSMB members and the options available to the DSMB at each interim analysis. The sponsor and DSMB should agree in advance of the trial whether it can be stopped prematurely on grounds of efficacy or safety, or both. Concerning efficacy, it should be clear whether the trial can be stopped following a clear demonstration of positive efficacy and whether it can be stopped for futility. Statistical guidelines employed to assist the DSMB recommendations should be pre-specified in detail in the trial protocol.[9,10]

2.3 Early Termination

Regulatory authorities are particularly concerned over trials that are stopped prematurely and declared 'successful' as these are the ones that are more likely to be used in support of efficacy and safety in a regulatory submission. Of particular concern is the level of evidence for efficacy on which the trial was terminated. It is important that the overall type I error of the trial is controlled, conventionally using a level of $p = 0.05$. Because of multiplicity, the p-value required to declare a trial successful at the interim analysis will need to be considerably more extreme.[9,10] Similarly, the final analysis of a trial will also require adjustment for multiplicity if interim analyses have taken place. Also of concern is whether the trial should be stopped outright or whether a protocol amendment might be implement-

ed that could be useful in answering further questions on the efficacy and safety of the treatments. Examples include looking at efficacy in subgroups or in long-term use. Regulators may remain unconvinced on efficacy unless the trial is stopped only when the totality of evidence is unequivocal.

Stopping a trial prematurely because of lack of efficacy presents just as many scientific challenges but since these trials are rarely submitted for regulatory assessment there may be fewer regulatory concerns.

3. Further Considerations

The issues outlined above concerning whether or not the integrity of trial data might be compromised by its interim assessment are somewhat intangible. Even if sponsors or regulatory authorities can identify the direction of any bias, they cannot usually quantify its magnitude. Therefore, it is often difficult to categorically establish that the bias has had no important effect on the trial results. There are some situations where the potential for bias is increased. Open-label trials, in particular those with subjective (e.g. investigators' global assessment of efficacy) rather than objective endpoints (e.g. death) run a much greater risk of being influenced, either consciously, or perhaps more likely, unconsciously, by knowledge of interim results. Results from such trials are, therefore, likely to be viewed with some scepticism by regulators and the sponsor may find it difficult to justify that the magnitude of any bias introduced is unimportant.

A further methodological concern relates to protocol amendments that may impinge on the trial conclusions. This was reflected in an editorial in the *International Journal of Cardiology* that concluded: "… matters of statistical plans do matter and steering committees should think very carefully before changing the primary endpoints of major trials".[11] Changing the status of an endpoint (e.g. from secondary to primary or vice-a-versa) or changing an analysis method once interim data are known cause concern. This is particularly relevant if endpoints or analyses previously declared primary do not reliably demonstrate efficacy or safety.

There are many ways in which regulatory authorities might view interim analyses and the involvement of DSMBs as introducing bias. However, they will also consider the levels of statistical and clinical significance of the final results. The magnitude of any bias can rarely be accurately assessed. Any flaws in trial conduct will necessarily be weighed against the strength of evidence from the trial to arrive at a final judgement on benefit-risk.

4. Conclusions

Regulatory authorities regard the appropriate use of interim analyses favourably, but will consider the extent to which the conduct of interim analyses and the involvement of DSMBs may have compromised the evidence of efficacy and safety from the trial. Interim data from clinical trials should not generally be disseminated beyond the DSMB and, in particular, not to trial investigators or sponsor personnel. Regulatory authorities will always be concerned over the potential introduction of bias, particularly in open-label trials. Sponsors are cautioned that implementing major protocol amendments in the knowledge of interim data may damage the integrity of the trial. It is the responsibility of the sponsor to convince the regulatory authority that, following an interim analysis and the involvement of a DSMB, the trial remains scientifically valid and the data form a sufficiently reliable basis for an assessment of benefit-risk.

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