

**Comments on
CHMP Guideline on Data Monitoring Committees
(CHMP/EWP/5872/03, Draft, 18 November 2004)**

German Region of the International Biometric Society

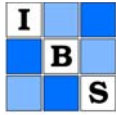
General comments:

1. The scope of the guideline should be given, e.g. to which phases of clinical development it (mainly) applies.
2. The term 'independent' is not defined precisely. This may be interpreted as 'independent of the sponsor' or 'external to a study but still employees of the sponsor'.
3. The term 'unblinded study information' is mentioned in several chapters. In general, several degrees of unblinding are possible: 1) unblinding with regard to individual patients, 2) inspection of results on different endpoints by treatment group, 3) inspection of results on different endpoints by treatment group labelled as A and B. It would be desirable to have a more precise statement on which degree of unblinding is considered.

Major comments:

1. page 2, Introduction, 1st paragraph, 3rd sentence

'On the other hand it is also important to ensure that a trial continues for an adequate period of time and is not stopped too early in order to answer its scientific questions.'



That depends on the reason for stopping the trial. In case of futility or safety issues, the most scientific questions are obsolete. In case of stopping early for efficacy, it is important to ensure that the questions with regard to safety and other secondary endpoints are addressed adequately. The context of this statement should be rendered more precisely.

2. page 4, II. 6th paragraph, 1st sentence

‘There are (rare) situations where besides indication and patient population the study design might give reason for setting up a DMC.’

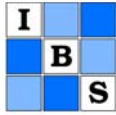
It is not clear what is meant by ‘indication and patient population’ as reasons for setting up a DMC. Most of the discussion to this point has been regarding safety reasons for needing DMCs. But there are many studies which create a DMC to conduct futility assessments of efficacy, as well as early stopping due to positive efficacy. DMCs are also needed when interim analyses occur to make decisions regarding a future study, such as dose selection or endpoint selection for a follow-up trial.

In our opinion, a DMC is required whenever unblinded interim analyses are planned, since the study team should not have access to unblinded data during study conduct. This refers to every type of unblinded interim analysis and not only to situations where a possible design modification is intended.

3. page 4, III. 3rd paragraph, 5th sentence

‘It is also a responsibility of a DMC to apply appropriate statistical methods.’

In our opinion, these methods should be described in the study protocol and/or the statistical analysis plan usually prepared by the study statistician. Procedures should be in place to make sure that the DMC approves the methods to be applied.



4. page 5, III. 5th paragraph, 5th sentence

‘If changes in the study conduct are recommended by a DMC, sufficient information should be provided to allow the sponsor to decide whether and how to implement these recommendations.’

The DMC should make known to the sponsor the reasons for their recommendations. But they should not necessarily submit sufficient information in order for the sponsor to make an informed decision on whether to accept the DMC recommendation. The process should include a provision, that when the DMC recommendation is significant (e.g. stop the study for safety reasons), that the sponsor have the ability to convene an Internal Review Group, who are unblinded to the same data that the DMC evaluated, in order to make an informed decision. This restricts the unblinding that occurs within the sponsor to a small group, and does not include anyone who is involved with the study.

5. page 5, IV. 3rd paragraph

‘Biostatistical expertise should also form part of a DMC’.

A stronger statement is suggested: ‘Biostatistical expertise must form part of a DMC’.

6. page 7, VI. 3rd paragraph

The situation described in this chapter is rather difficult. Only prospectively planned interim analyses of the primary analysis parameter should be performed. Thus, as a consequence, during study planning it should be considered whether the DMC will require access to efficacy data during safety monitoring. If this is the case, interim analyses of the efficacy endpoint should be planned accordingly.

It may be added that if no decision is to be made based on the review of efficacy data and/or no penalty is paid, then the need for review of efficacy data by the DMC may be questioned.



Minor comments:

1. page 4, II. Last paragraph, 2nd sentence

‘... (up to a few weeks) ...’

This seems to be a lower limit for the preparation in some cases. The text in brackets should be deleted.

2. page 4, II. Last paragraph, Last sentence

‘where’ instead of ‘were’ (2x)

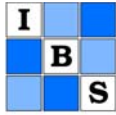
3. page 5, III. 6th paragraph, 2nd sentence

We do not agree that it is the DMC's ‘responsibility’ to ensure policies are in place. Nor is it their responsibility to create the DMC Charter. It is the sponsor's responsibility. The DMC does, however, sign off on the charter, thereby signifying their approval of its contents.

4. page 5, IV. 1st paragraph

‘In general the preparations for setting up a DMC should be finalised prior to finalising the study protocol for several reasons: ...’

In our opinion it should be possible to appoint DMC members even after finalisation of the study protocol, if they agree to the procedures laid down in due time before their first access to trial data. In addition, the first reason listed for setting up the DMC prior to finalize the protocol, implies that the protocol is final. That is a contradiction.



5. page 5, IV. 5th paragraph, 1st sentence

‘While a DMC completely independent ..., this is may not ...’

Is or may?

6. page 6, IV. Last paragraph

With regard to the financial interests, it should be specified that the expenses for the DMC have to be appropriate, since there is a financial relationship by nature. With regard to the example of authorship of publication as non-financial interest, it is hard to understand why these are serious conflicts, since there are interests concerning authorship also for other persons involved. This is relevant also in studies without a DMC.

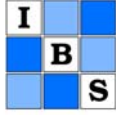
7. page 6, V. 1st paragraph, 4th sentence

‘Clear operating procedures ... should be in place prior to the start of the trial’.

This requirement is too strict. Clear operating procedures ... should be in place in due time before the first access to trial data is granted to the DMC.

8. page 6, V. 2nd paragraph, 6th bullet, and page 7, 4th paragraph

The guideline says that ‘... format (e.g. templates) for analyses to be assessed by the DMC, including methodological aspects’ should be covered in the working procedures of the DMC. This is usually covered in the Statistical Analysis Plan of the interim analysis and reference to this document should be sufficient.



9. page 6, V. 3rd paragraph, 1st sentence

We suggest rewording this sentence to state that the DMC charter should clearly describe who performs these interim analyses.

10. page 7, VI. 5th paragraph

The impact of futility analyses on the type II error is of concern to the sponsor and not to the regulator. Therefore, the guideline should not require that this problem is considered in the study protocol. We do not regard the decrease of participation chance as a problem.