Letting bias in through the back door? *Trial Statisticians: the not-so-independent members of an Independent Data Monitoring Committee*

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Independent Data Monitoring Committees (DMCs, DSMBs, DMECs) aim to protect the interests of trial participants. The duty of care towards participants is paramount and should be untrammelled by conflicting interests.

Good Clinical Practice (GCP) provides direction on composition and operation of DMCs[1, 2]. ICH E9 states: *"All staff involved in the conduct of the trial should remain blind to the results of… [interim] analyses, because of the possibility that their attitudes to the trial will be modified and cause changes in the characteristics of patients to be recruited or biases in treatment comparisons."* The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) provided similar regulatory guidance.[3, 4] Neither *requires* the statistician performing the interim analyses to be independent or different from those involved in trial management and performing the final analyses. However the FDA[3] states: "*the integrity of the trial may be best protected when the statisticians preparing unblinded data for the DMC are external to the sponsor and uninvolved in discussions regarding potential changes in trial design while the trial is ongoing.*" Industry routinely implements this FDA guidance, but this is rarely the case in publically funded trials.

The risk of conflicts of interest in industry with the development of drugs is somewhat obvious, but conflicts may be less clear in academia. Academics do however have an interest in the success of their trials, which may lead to career advancement. Trial statisticians in UK and US government funded trials are often responsible for creating unblinded DMC reports and attending closed sections of meetings, undermining the principle of the committee being independent, with interim results from ongoing trials known by at least one of the management team. Many statisticians working on academic trials do not perceive this to be bias and some are reluctant to rescind their informed status. This is in breach of GCP.

Whether the allocations are explicit or data are analysed blind (e.g. described as groups 'A' and 'B'), the statistician knows the potential treatments. It is our experience that they or DMC members will normally deduce the randomised allocation through the adverse event or outcome profiles.[5] In a recent trial, blood concentrations were higher in one randomised group, resulting in adverse events. The DMC clinicians identified the treatment groups, unblinding the trial statistician.

When trial statisticians present interim results to the DMC, they cannot avoid contributing to the interpretation. They are party to discussions between the independent DMC members and will exert influence despite being conflicted in discussions. Further, when the trial

management group to which they belong considers changing some aspect of the trial, for example inclusion criteria or the definition of the primary outcome, the trial statistician cannot put aside their knowledge. The statistician may know from the emerging data the implications for the trial.[6] This occurred in a trial of two vasectomy techniques.[7] Although the interim analyses were presented blinded, the DMC guessed the allocations, with the trial statistician party to this information. The trial statistician noticed an interaction. This was instrumental in stopping the trial despite the DMC recommending continuation.

One of us was a member of a DMC where the trial statistician presented the interim results; however the timing of the primary outcome was not defined in the protocol or statistical analysis plan. The primary analysis would thus be specified *with knowledge of unfolding results,* a clear source of bias. The trial statistician did not address the ambiguity which was also not addressed by the Trial Management Group; the DMC member subsequently resigned.

In 2005, the DAMOCLES group published a charter for DMCs.[8] They did not give guidance on who should undertake interim analyses or present them to the DMC, merely documented what usually happened.[9] Three alternative models were presented, including one where the statistician analysing data for the DMC would be semi-independent and a little removed from trial management. This charter has been widely adopted in UK publicly funded trials despite its recommendations being out with *GCP*. This may be because authors were employed by UK academic or research councils, which are not funded as generously as industry. A completely independent statistician would increase costs. However many clinical trials units include two statisticians in their grant applications. This would allow a compromise to involve (at least) two statisticians in all trials; one attending trial management meetings and performing the final analysis and the other performing the interim analyses, attending the DMC meetings as a non-voting member and confirming the final analysis. The second statistician would forfeit any trial management responsibilities from the point of first interim analysis.[3, 10, 11] A third independent, qualified and experienced statistician from a different centre would sit on the DMC as a voting member.

Society has a duty of care towards those who participate in research. Researchers have a responsibility to ensure they provide unbiased guidance to inform future care. DMCs should be independent and use their position only to intervene with trial management when there are serious safety concerns, or where efficacy can be established unequivocally. Properly constituted, independent DMCs should be established in all but the lowest risk trials.

References

1. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. E6(R1) guideline for good clinical practice. 1996. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf

2. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH E9 statistical principles for clinical trials. 1998. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step4/E9_Guideline.pdf

3. Food and Drug Administration Guidance for Clinical Trial Sponsors Establishment and Operation of Clinical Trial Data Monitoring Committees 2006 http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127073.pdf

4. European Medicines Agency Guideline on Data Monitoring Committees 2005 http://osp.od.nih.gov/sites/default/files/resources/WC500003635.pdf

5. Gøtzsche PC. Blinding During of Manuscripts Data Analysis and Writing. Control Clin Trials 1996;17:285–90

6. Ellenberg SS, George SL. Should statisticians reporting to data monitoring committees be independent of the trial sponsor and leadership? Stat Med 2004;23:1503–5

7. Chen-Mok M, Bangdiwala SI, Dominik R, Hays M, Irsula B, Sokal DC. Termination of a randomized controlled trial of two vasectomy techniques. Control Clin Trials 2003;24:78–84

8. The DAMOCLES Study Group. A proposed charter for clinical trial data monitoring committees: helping them do their job well. Lancet 2005;365:711-22

9. Grant AM, Altman DG, Babiker AB et al. Issues in data monitoring and interim analysis of trials. Health Technol Assess 2005;**9**(7). http://www.journalslibrary.nihr.ac.uk/__data/assets/pdf_file/0003/64992/FullReport-hta9070.pdf

10 Siegel JP, O'Neill RT, Temple R, Campbell G, Foulkes MA. Independence of the statistician who analyses unblinded data Stat Med 2004;23:1527–29

11 Pocock SJ. A major trial needs three statisticians: why, how and who? Stat Med 2004;23:1535–39

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