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Memorandum

To: Trialists

Fr: Curtis Meinert

Re: On masked data monitoring committees

Introduction

A key question in formulating monitoring plans has to do with whether to mask the monitors. Operationally, the masking is accomplished by coding the treatment groups and then by using those codes to identify treatment groups in monitoring reports. Rather than use the actual treatment to label columns in tables in monitoring reports, arbitrary letter codes are used instead. The masking may be imposed or voluntary. ***Imposed masking*** *is where the masking remains in force until the monitoring body votes to lift it.* ***Voluntary masking*** *is where reports are distributed to members along with sealed envelopes containing the codes identifying the treatments and where individual members are free to open the envelope at will; typically announced when a member opens the envelope so others know the person is no longer masked.*

A side benefit of the masking lies in safeguards against "leaks" if reports come into the hands of people not authorized to see them. The desire to have that protection without the other downsides of masking leads some groups to practice ***revealed masking****, i.e., where results in reports are coded as above, but where the codes are announced at the outset of each review.*

The coding within and across reports may be fixed or varied. The most common form is where the code designations are invariant within and across reports. That is, the letter designation for a treatment is used for all comparisons within and across reports. A less common variety is one where the coding is invariant within a report, but allowed to change across reports. For example, the letter designation A may denote the test treatment in one report and the control treatment in the next report. A more extreme form is varied coding within a report but invariant across reports (e.g., one set of letter designations for tables relating to the primary outcome measure and different letter codes for secondary outcomes, but where that coding is maintained across reports). The most extreme form of masking is where the coding is varied within and across reports (i.e., like the form above, but where there is no ability to compare across reports because the coding differs).

There are lots of reasons to be skeptical of masking in relation to treatment effects monitoring. The primary difficulty with any form of masking, aside from the logistical difficulties posed by accomplishing it, is that it serves to reduce the competency of monitors. Even the revealed form of masking is questionable to the extent that it makes reports less reader friendly and increases the probability of error in creating and reading tables.

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The appeal of masking lies in the aura of objectivity it provides and in the expectation that it renders the analysis and recommending processes of monitoring bodies less prone to treatment-related bias. Usually, masking in monitoring bodies, however, applies only so long as there are no treatment differences and, hence, where the risk of "bias" is least. Typically, the mask is lifted if differences emerge. (Clinical Trials: Design, conduct, and analysis (2nd edition; 2012; Oxford University Press; pg 266)

Reasons for masking

1 Intuitively appealing
Comment: Objectivity is like motherhood. Who can be opposed to it? Why not mask the committee? What harm can there be in doing so?

2 Creates an aura of respectability
Comment: No doubt one of the reasons for masking is the cachet it provides. After all, is it not better to be able to say the monitoring committee was masked than not masked when results are published?

3 Protects against leaks
Comment: If results are masked they cannot be leaked even if the report falls into wrong hands. The information in reports is not helpful in the absence of treatment codes.

4 Politically appealing
Comment: Usually easier to justify than unmasked monitoring; especially appealing to sponsors who may be called to account for the trial and its operating procedures.

Reasons against masking

1 Predicated on fallacious assumption
Comment: The implication with masking is that decision making is independent of the sign of the difference but the assumption is false. Usually investigators need more evidence to conclude a test treatment is beneficial than to conclude it is ineffective or harmful.

2 Masking unlikely to be effective
Comment: Almost any test treatment will produce effects that set the treatment apart from the control treatment. The masking will be nothing more than a charade if data on outcomes and side effects are presented masked with the same coding.

The fix is to limit the masking to outcome data. That is, produce a report with outcome data masked but with side effects data unmasked.

But even with the fix, the masking is usually evident from telltale differences.

3 Two part report reduces utility
Comment: Dividing the report as suggested in item 2 makes it difficult to understand the results to the extent that safety and efficacy exist on a continuum, not as separate issues.

4 Increases the chance of mislabelling
Comment: Anyone who has produced a monitoring report lives in fear of mislabeling treatment groups. The more complicated the masking scheme, the greater the chance of error.

5 Increases the time and cost of producing monitoring reports
Comment: Though monitoring committees are largely insensitive to the time and effort involved in producing monitoring reports, the reality is that the more time and effort involved in masking reports, the less time there is for other worthwhile activities in the coordinating center.

6 Makes exploratory analyses time consuming and difficult
Comment: It is common for monitoring committees to ask for additional analyses to explore observed differences. When the results are masked the coordinating center has to

perform two sets of analyses. One set if the difference is in favor of the test treatment and another set if the difference favors the control treatment.

7 Bogus objective

Comment: The responsibility of monitoring committees is to assess the safety and efficacy of study treatments. Masking is at odds with their duty. Concern with regard to bias is secondary to the requirement of competency in monitoring.

In any case, the usual practice is to lift the mask when treatment differences arise. It is easy to be objective when there are no differences. The worries regarding biases come when differences arise.

8 Decreases competency

Comment: Competency is being possessed of the necessary skills, expertise, and knowledge to perform in a responsible fashion. Masking the monitoring body to treatment diminishes their ability to so perform.

9 Stultifies discussion

Comment: Any form of masking has a stultifying effect on discussion and interpretation of results. As long as the masking is in place, members of the monitoring committee have to behave as if they are masked, even if they are not. One of the problems with voluntary masking is that an individual who elects to unmask still has to behave as if masked in discussions out of respect for others who choose to remain masked.

Data are easiest to understand when identified by treatment group. Any coding, even if revealed when results are reviewed, reduces the utility of reports and increases the chance of people mixing up the codes.

10 Isolates investigators

Comment: The masking can have the effect of creating two classes of monitors: Those who know or think they know the treatment assignment and those who do not. Those not in the know will be less likely to enter into discussions than those who think they know the coding.

11 Reduces ability to compare across reports

Comment: Typically, members of the monitoring committee compare results from previous reports with those in the current report to gauge changes. The desire to do so is reduced by the masking, even if the coding is the same across reports.

12 Debate as to lifting the mask can be divisive and distracting

Comment: The normal practice in masked monitoring is to lift the mask on a majority vote of the committee. Typically, those discussions extend over meetings before a vote is taken. The discussion and debate syphons away energy better spent monitoring and understanding the results.

13 The fact of the lift telegraphs information regarding the trial

Comment: If the committee is masked and then the mask is lifted, that fact must be reported to IRBs and investigators and consent updated to inform patients of the change.

14 Firewalls to preserve masks debilitating and stultifying

Comment: A sometime practice, especially with masked monitoring, is to impose firewalls in the coordinating center to keep the director of the center in the dark as to treatment results. The practice is ill-advised (see a posting to trialsmeinertsway.com; http://www.jhuccs1.us/clm/PDFs/BLACKOUT.pdf entitled *My yellow brick road for blackouts, shielding, firewalls, and access to study results in multicenter trials*) because the director's duty to ensure the accuracy and quality of analyses performed for monitoring is encumbered by virtue of being firewalled.

15 Encumbers the consent process

Comment: Consent forms should contain details as to safety and efficacy monitoring. If the monitoring body is masked to treatment differences, that should be indicated in the consent

forms persons are expected to sign. Likewise, if there are firewalls to keep people responsible for the trial from knowing results, that should be revealed in consent forms.

16 Complicates IRB approvals and communications

Comment: The supposition of IRBs is that there will be a duly constituted body responsible for safety and efficacy monitoring. If a mask is imposed, IRB applications should so indicate. If the mask is subsequently lifted, the application must be amended to indicate the change.

Discussion

Some years back I wrote a piece entitled *Masked monitoring in clinical trials – Blind stupidity?* (NEJM 338: 1381-82; 1998). The purpose, obvious from the title, was to question the wisdom of masking data monitoring committees in trials.

I do not know anyone in coordinating centers who believes masking data monitoring is a good idea, yet masking is commonly practiced. (The frequency is difficult to determine because details in publications are usually not sufficient to indicate whether masks were imposed; see Kiri A, Tonascia S, Meinert CL: *Treatment effects monitoring committees and early stopping in large clinical trials*. Clin Trials 1:40-47,2004).

So how do we end up with masked monitoring?

The primary reason is because the issue often is left to the monitoring body and/or study sponsor. That being so, if it is you, as director of the coordinating center, versus the monitoring committee or sponsor and they want to mask, chances are you lose. You have a chance of winning in investigator-initiated trials by establishing policy against masked monitoring, vetted by study investigators, before the monitoring committee is appointed.

The battle against masking will be difficult if the monitoring body is appointed before the investigator group is formed. The best you can do then is to outline the downsides of masking as listed above and hope they are sufficient to dissuade.

Perhaps the most compelling argument at your disposal will be those alluded to in Items 13 and 16. The proponents of masking should be reminded of the likelihood of the mask being lifted before the trial is finished and then of the need to inform study patients and investigators of the change, thereby unwittingly telegraphing information to patients, investigators, and the world at large that something is going on in regard to study results.