Sounding Board

Masked Monitoring in Clinical Trials — Blind Stupidity?

In randomized clinical trials of treatment, information about which subjects are receiving the new treatment and which are receiving the standard treatment is often withheld from both the researchers and the subjects. Such masking is a reasonable precaution to prevent bias. However, many trials have a special monitoring committee to decide when to stop or modify a trial, and this committee is also often asked to review masked data. Monitoring committees review interim results to make certain continued randomization does not expose one group of subjects to inferior treatment.[1-4] When a significant difference emerges, enrollment is stopped or the design of the trial is altered appropriately. Does it make sense to keep the nature of the treatment from monitoring committees, as well as researchers and subjects?

Masked monitoring grows out of a general dictum in treatment trials: mask when possible. This dictum is born of the fear of treatment-related bias, and withholding information about treatment is seen as a way to maintain objectivity. The desire for the objectivity made possible by masking has even led to the suggestion that it should be extended to the process of writing the results of trials for publication.[5]

Masked monitoring is thought to increase the objectivity of monitors by making them less prone to bias. What is overlooked is what masking does to degrade the competency of the monitors.

The requirement of competency takes precedence over the desire for objectivity when research involves human subjects — a principle evident in the Nuremberg Code[6] and subsequent codes for research on human beings. Masking should not be imposed if it entails avoidable risks for patients.[7] Masked monitoring denies the monitors the key information they need to perform in a competent fashion, and incompetent monitoring poses a risk to research subjects.

Masked monitoring is achieved by coding the treatments (e.g., with the use of letter or number codes) and summarizing the results according to the coded treatment. The monitors thus have access to the results according to the treatment group, but because of the coding, they do not know whether the results are for the treatment being tested or the treatment being used for comparison. The monitors compare the treatment groups by subtracting the results in one group from the results in the other group, but because of the masking, they do not know whether the difference favors the test treatment or the control treatment.

The assumption underlying masked monitoring is that recommendations for a change in the study protocol can be made independently of the direction of a treatment difference, but this assumption is false. Usually, more evidence is required to stop a trial because of a benefit than because of harm. Trials are performed to assess safety and efficacy, not to "prove" harm. Therefore, it is unreasonable to make the monitors behave as if they were indifferent to the direction of a treatment difference.

Another weakness of masked monitoring is the stifling effect it has on the analytic processes needed to probe emerging treatment differences. A prudent monitoring committee will not act on a treatment difference without first performing a series of exploratory analyses to see whether the difference can be explained away and whether the results are consistent with what is already known about the treatment in question. Under conditions of masking, these analyses are unfocused and inefficient. Two sets of analyses must be performed: one set deemed reasonable if the difference is in favor of the test treatment and another set deemed reasonable if the difference favors the control treatment.

Once masking has been imposed, even with the understanding that it can be lifted on request, it tends to become permanent. There is a reluctance to request that the masking be removed, because the request itself comes to be seen as heralding recommendations for changing the protocol. The debate about whether to remove the masking can extend over several meetings of the monitoring committee, diverting attention from the more important task of thoughtful and informed monitoring.

There are also more prosaic reasons for being wary of masked monitoring. Masking complicates the preparation of interim reports submitted to monitoring committees and increases the chance of errors in the reports. Information likely to interfere with masking (e.g., treatment-specific side effects or certain laboratory determinations) has to be censored or presented separately from the coded data.

Furthermore, masking is rarely foolproof, even when the necessary precautions are taken. Sophisticated monitors can break the code on the basis of telltale side effects of treatments. Monitors tend to start speculating as soon as treatment differences emerge. The various degrees of certainty among committee members make for contorted dialogue because of the need to behave as if none of the members have broken the code. The nature of the dialogue and interaction required by the masking is at odds with the need for informed, competent monitoring.

If masked monitoring has so little to recommend it, as I have suggested, why is it practiced? One rea-

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son concerns the value placed on objectivity in reducing the possibility of treatment-related bias in trials. Masked monitoring has an aura of impartiality. The urge to maintain objectivity in trials is reflected by efforts to mask the processes of treatment administration and data collection for the purpose of preventing treatment-related bias and by the constraints imposed on monitoring to make it more objective (e.g., stopping rules based on P values and restrictions on what the monitors examine and the number of examinations they perform). Another reason, perhaps, is that the route to objectivity is straightforward, through the imposition of rules, whereas the route to competency is much more complicated.

It is imperative that someone be aware of the nature and trend of the results as randomized treatment trials proceed. If the desire to ensure objectivity keeps the investigators from assuming this role, then it should be assumed by fully informed monitoring committees that perform in accordance with ethical principles and to the satisfaction of institutional review boards. The committee members should have the necessary skills and expertise to perform their job and should be free to act without constraint or the prospect of interdiction by the sponsors of the research.

We need to make sure that the drive for objectivity does not lead to trials with triple masking, in which neither the patients, nor the investigators, nor the monitors know what is going on. Institutional review boards and investigators must ensure that the monitoring process is sufficient to protect human subjects.

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