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Case Commentaries

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Blinds and Research Risks

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This case raises several ethical issues related to the communication and management of research risk. The ethical resolution of many of those issues will depend on matters of expert clinical judgment. We bracket regulatory issues, assuming that reporting requirements are fulfilled and that the data monitoring committee (DMC), investigators, and relevant bodies comply with their various mandates. Our focus is on the general ethical considerations they confront as they do so.

The case report describes the sudden appearance, and management of an unanticipated adverse event. The first and most dramatic question posed is whether this ethically demands stopping the study altogether. If so, many other questions about the trial are rendered moot. To be clear, our understanding is that the affected patient was successfully treated and at no ongoing risk, so the relevant risks are just those to participants going forward. Do those risks require stopping the trial?

Begin with the most unfavorable assumption: Assume the patient who experienced the adverse event was known by the DMC to have been previously enrolled in the active arm of the drug trial. Thus, the DMC knows that the study drug may have caused the adverse event, a theory supported by reasonable hypotheses about the drug's mechanism of action—that is, that it might lead to exuberant reconstitution of the immune system upon cessation.

But even if the patient is assumed to be on the study drug, that fact alone would not guarantee that the study drug was actually the cause of the event. Thus, the DMC would still have to go on to make its best assessment as to the likelihood of that relationship. In making a judgment here, the DMC would need to draw on its understanding of the underlying disease course, the pharmacological properties of the study drug, and the full weight of its data about other subjects' outcomes.

In addition to assessing its likelihood, the DMC would also need to assess the seriousness of the risk. This would involve attention to the monitoring and treatments plans of the study in terms of how well they can catch and mitigate future events of the same character.

Depending on how both the likelihood and seriousness judgments are filled in, they could result in a wide range of ultimate risk assessments. Once such a risk assessment is made, how might the DMC proceed? In general, bodies regulating research risk must consider absolute risk thresholds, risk–benefit ratios, and the overall minimization of risk, and we discuss these in order.

Within research ethics, many believe that once the risks to participants exceed a certain absolute threshold they render a trial impermissible, although there is a lack of consensus on what precisely that threshold is or what justifies it; points of comparison in establishing such a threshold have included socially tolerated but risky altruistic activities like organ donation or volunteer firefighting (London 2006; Miller and Joffe 2009). If the DMC came to believe on the basis of this new information that the trial exceeds a threshold of this kind, it could not be allowed to proceed. But we suspect, and will assume for the sake of further analysis, that a sufficiently close monitoring plan could bring the absolute risks of participation within reasonable limits. We similarly assume that the trial's social value is sufficient to produce an adequate risk–benefit ratio.

This brings us to the question of risk minimization. For research to be ethical, it must minimize the risk to enrolled subjects. But this injunction is not absolute. Research will often involve additional risks that one would not face in clinical care; this is part of what differentiates the two enterprises. Rather, researchers must minimize risk insofar as is consistent with the scientific value of the research, and this may involve difficult trade-offs.

In this case, it is fortunate that the clinical care necessary for addressing this adverse event was independent of whether the participant had been on the active or

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control arms. It was not the case, for instance, that there was any potential interaction between the clinical care and the study drug, nor did the participant require a specific antidote. This substantially reduces the tension between the scientific value of maintaining the blind and the imperative to minimize risks to enrolled subjects.

We can underline this point by considering a poignant story of an unblinding event in Spain (Eduardo and MacKillop 2001). A doctor, in a panic upon finding the participant he's treating entering a hypotensive crisis, calls the sponsor to demand that it break the blind. The sponsor initially resists, but, upon repeated demands, eventually relents and supplies the unblinding code. The patient is successfully treated. But the treatment did not depend on the patient's study enrollment arm—it was completely standard treatment for hypotension, which resolved in a completely standard way. And in this particular case, not only were the participant's own data compromised, but worse yet the study was arranged in blocks such that the unblinding of one participant de facto unblinded several others.

Insofar as risks can be acceptably mitigated by close monitoring and a readiness to provide treatment that doesn't depend on whether participants are in the active or control arms, this allows researchers an attractive way to protect both the blind and the participants. Still, even when such a proposal is a feasible way of managing newly discovered risks, it is imperative that the consent process be updated to include any salient new information. Informed consent must always reflect the researchers' best current understanding. In any case, these are the sorts of ethical issues that investigators and regulators will have to confront.

All of the preceding discussion has proceeded under the assumption that the DMC knows that the patient who experienced the adverse event had been previously enrolled in the active arm. Suppose finally that this is not so. In one respect, this greatly simplifies the case. If the patient was not in the active arm, then the patient's experience cannot indicate the possibility of a formerly unknown risk with the drug. Nonetheless, the DMC must still make a decision about disclosure. If for no other reason than peace of mind, the patient and investigator are likely both concerned to know whether the adverse event could be drug related. But even the benign disclosure that because the patient never received the study drug, and so could not have been harmed by it, will itself have to take place in consideration of the impact that disclosure has on the data and the value of the research as a whole. ■

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