

COMMENTARIES

Managing risk in healthy subjects participating in clinical research

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In this issue of the Journal, two letters discuss the observation that rifabutin can cause severe neutropenia in healthy subjects.^{1,2} This correspondence serves two major purposes. First, it makes us more aware of a potentially serious adverse reaction that can occur in such individuals taking rifabutin; second, and perhaps more importantly, it raises the implicit questions, what degree of risk is acceptable in research studies performed in healthy subjects and how do we assess and manage such risks?

These questions are not theoretical because serious side effects have been described with virtually every drug and, therefore, potentially could occur in any study that involves drug administration. Serious adverse effects in healthy volunteers appear to be uncom-

mon, but they can be difficult to identify in computer literature searches and may not always have been published. The most serious adverse event, the death of a healthy volunteer, is a tragedy; such deaths are rare,³⁻⁷ perhaps an indication that the systems in place to protect subjects, though imperfect, have had an effect. The protection of healthy subjects, a group who obtains no direct medical benefit by participating in a study, and of patients depends on a set of complementary elements identified and discussed in a recent Institute of Medicine report.⁸ These are as follows:

1. The investigators carrying out the research.
2. The institutional review boards (IRBs) responsible for evaluating scientific and ethical integrity.
3. Bodies other than IRBs that ensure regulatory compliance and responsible research.
4. Research sponsors.
5. Monitoring bodies such as data safety monitoring boards and committees.

Each of these components is important but has potential limitations. The investigator carrying out the research has the responsibility for decisions regarding the study, but he or she usually has a vested interest in performing the study and may have scientific, financial, or other conflicts of interest. IRBs provide oversight to ensure responsible conduct of research, but they have been faced with increased demands and accountability

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and an increase in the number and complexity of protocols with resources that have not always been adequate to meet this expanded need.^{9,10} Research sponsors responsible for funding research have a responsibility for the safety of the studies, but they may have a vested interest and a financial conflict of interest. Data safety monitoring boards in large randomized clinical trials operate independently under well-defined guidelines with statistical and other expertise represented on the board. The board is usually reimbursed for this activity, and its major functions are to monitor the progress of a study, to recommend alterations to the protocol to improve safety, and to stop a trial prematurely if groups differ with regard to prespecified efficacy or futility end points or if toxicity in one group is deemed unacceptable. Data safety monitoring boards or committees are now being constituted for many much smaller studies that are not randomized clinical trials but involve the administration of a drug. Such boards and committees absorb some of the workload and responsibility for processing reports of adverse events and reassessing the risk-benefit ratio from IRBs and also provide an additional level of oversight, but they pose unique challenges. Extreme variability in approval decisions and regulatory interpretation among IRBs has been identified as a weakness in the current protection system.⁸ The variability in decisions made by smaller committees is likely to be even greater. The expertise required on such committees and their composition, roles, powers, responsibilities, reimbursement, and oversight have not yet been well defined and will vary according to the risk and design of a study. The logistics are daunting when one considers the number of protocols at large institutions performing research that will require monitoring by such committees, as well as the fact that the members likely to be best qualified—clinical researchers and clinical pharmacologists—are in short supply and face many other career demands.^{2,11-13}

How will such a committee deal with the occurrence of an uncommon but potentially serious adverse event in a healthy individual in a small study? This same question faces all researchers who perform studies and those who oversee the safety of subjects participating in research: What degree of risk is acceptable and how do we deal with it? With this in mind, I asked Dr Franklin Miller, a bioethicist, to write the accompanying Commentary¹⁴; this appropriately emphasizes the importance of the assessment of risk and benefit in making ethical decisions regarding research. In clinical pharmacology studies the probability, magnitude, and potential duration of harm, as well as the potential benefits, are sometimes known. More often, however, given the exploratory role of clinical pharmacology in drug

development and therapeutics, these are difficult or even impossible to quantify. Nevertheless, there is risk associated with the performance of research, and a challenge that faces all clinical pharmacologists is recognition and management of this risk, often with imprecise information to guide decisions. Weighing risk against benefit, re-evaluating this assessment as new information becomes available, acting to minimize or avoid risk, and participating in the multilevel systems that protect subjects are all contributions that clinical pharmacologists can make that will facilitate both the protection of research subjects and scientific progress.

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