Report: ethical, scientific issues related to 'post-market' clinical trials

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Amid growing concerns about clinical trials for drugs that have been approved by the F.D.A. but are later linked to serious health risks, an independent committee at the Institute of Medicine led by two professors from Johns Hopkins University has developed a conceptual framework to guide the agency through the tough decision of ordering such controversial "post-market" drug-safety trials.

The recommendations of the committee, requested by the Food and Drug Administration, lay out a set of considerations that the F.D.A. can reference to ensure that clinical trials uphold ethical duties to trial participants. The committee also stresses that the agency be accountable to the public in its decision-making processes.

Presented on July 9 in a letter report to the F.D.A., the framework is organized around these recommendations:

- The F.D.A. should determine if questions about possible risks or the risk-benefit balance of a drug or vaccine already on the market are serious enough to justify a policy decision, such as whether to revise the product's label.

- A randomized, controlled trial of a drug linked to serious side effects should be conducted only when the existing scientific evidence and any evidence from new observational studies still do not supply the F.D.A. with enough data to make responsible

policy decisions.

- The agency should use "regulatory-science" principles and practices that emphasize public accountability and transparency when determining the need for a policy decision — or the need for new knowledge to support a policy decision.

- Such post-marketing trials to assess the safety and efficacy of approved drugs should be properly designed so that they minimize risk to patients and monitor risks on an ongoing basis. Any risks should first be judged as "acceptable" by appropriate oversight bodies.

- Lastly, the F.D.A. and relevant oversight agencies should ensure that such trials have a comprehensive and meaningful informed-consent process in place, and one that continues over the course of the trials. Specifically, participants should be promptly advised of developments such as new research findings or changes in clinical practice that could affect their willingness to continue to accept the risks associated with a trial.

"The letter report was designed to provide general, broad guidance about some of the ethical issues that need to be taken into account by the F.D.A. in requiring post-market safety studies," says Ruth Faden, Ph.D., M.P.H., the committee's co-chair and the director of the Johns Hopkins Berman Institute of Bioethics.

The other co-chair is Steven Goodman, M.D., Ph.D., a professor of oncology in the Division of Biostatistics at the Johns Hopkins Kimmel Cancer Center and a core member of the Berman Institute faculty as well. Goodman is editor-in-chief of Clinical Trials: Journal of the Society for Clinical Trials and serves on the society's board of directors.

"The post-marketing context poses more difficult ethical and design challenges than we could address in this letter report," says Faden, a member of the Institute of Medicine (IOM). "We plan to take on these challenges in more detail in our full report."

The more immediate report responds to one of several questions that the F.D.A. asked IOM to explore in a review of ethical and scientific issues related to studying the safety of drugs on the market. The agency requested an initial report on the ethical issues in advance of a meeting it will hold July 13 and 14 to discuss the case of the diabetes drug Avandia.

The report covers some of the issues at play in the case but does address the specific controversies surrounding a large-scale clinical trial launched by the drug's maker, GlaxoSmithKline PLC.

A more detailed analysis of the issues discussed in the report, as well as their implications and effects, will be presented in the committee's final report, which is expected to be complete in the spring of 2011.

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