Ethical Issues in Studying the Safety of Approved Drugs: A Letter Report

Committee on Ethical and Scientific Issues in Studying the Safety of Approved Drugs; Institute of Medicine

ISBN: 0-309-15779-X, 26 pages, 8 1/2 x 11, (2010)

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Board on Population Health and Public Health Practice

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

THE NATIONAL ACADEMIES PRESS
Washington, D.C.
www.nap.edu

THE NATIONAL ACADEMIES PRESS 500 Fifth Street NW Washington, DC 20001

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This study was supported by Contract HHSF223200810020I between the National Academy of Sciences and the Food and Drug Administration. Any opinions, findings, conclusions, or recommendations expressed in this publication are those of the authors and do not necessarily reflect the view of the organizations or agencies that provided support for this project.

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Printed in the United States of America

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Suggested citation: IOM (Institute of Medicine). 2010. *Ethical Issues in Studying the Safety of Approved Drugs: A Letter Report*. Washington, DC: The National Academies Press.

"Knowing is not enough; we must apply.
Willing is not enough; we must do."
—Goethe

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COMMITTEE ON ETHICAL AND SCIENTIFIC ISSUES IN STUDYING THE SAFETY OF APPROVED DRUGS

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This report has been reviewed in draft form by persons chosen for their diverse perspectives and technical expertise in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards of objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We thank the following for their review of this report:

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Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations, nor did they see the final draft of the report before its release. The review of the report was overseen by **Brian L. Strom, MD, MPH,** University of Pennsylvania School of Medicine and **Elaine L. Larson, PhD, RN,** Columbia University. Appointed by the National Research Council and the Institute of Medicine, they were responsible for making certain that an independent examination of the report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of the report rests with the author committee and the institution.

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Margaret Hamburg, MD
Commissioner
US Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Dear Dr. Hamburg,

In April 2010, the US Food and Drug Administration (FDA) asked the Institute of Medicine (IOM) to respond to five questions about ethical and scientific issues in studying the safety of approved drugs. FDA requested a final report on the five questions in 2011. In light of the scheduling of a joint meeting of FDA's Endocrinologic and Metabolic Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee on July 13–14, 2010, FDA further requested a letter report addressing question 1 of the charge—"What are the ethical and informed consent issues that must be considered when designing randomized clinical trials to evaluate potential safety risks?"—by July 2010. The attached letter report, which has been reviewed in accordance with IOM review procedures, addresses that question.

Sincerely,
Ruth R. Faden
Steven N. Goodman
Cochairs, Committee on Ethical and Scientific Issues in Studying the Safety of Approved Drugs

CONTEXT OF THE INSTITUTE OF MEDICINE STUDY AND CHARGE TO THE COMMITTEE

Public Law 110-85, the Food and Drug Administration Amendments Act of 2007 (FDAAA 2007; PL 110-85) expanded the US Food and Drug Administration (FDA) authorities and responsibilities over drugs[1] during the postmarketing period (that is, after a drug is approved to enter the US market). The expanded authorities, many of which were recommended in *The Future of Drug Safety: Promoting and Protecting the Health of the Public* (IOM, 2007), provide FDA with additional regulatory tools, such as requiring clinical trials or other studies after a drug has been approved, to protect the health of the public. With the expanded postmarketing authorities comes the recognition that critical decisions regarding the study of drugs after approval raise new challenges and questions, both ethical and scientific, for the agency to consider. FDA therefore asked the Institute of Medicine (IOM) to "convene a committee to evaluate the scientific and ethical issues involved in conducting studies of the safety of approved drugs." The specific questions that the committee was asked to evaluate are presented in Box 1. In light of the scheduling of a joint meeting of FDA's Endocrinologic and Metabolic Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee on July 13–14, 2010, FDA requested a letter report addressing question 1 of the charge—"What are the ethical and informed consent issues that must be considered when designing randomized clinical trials to evaluate potential safety risks?"—by July 2010.

BOX 1 Charge to the Committee

The Food and Drug Administration (FDA) has requested that the Institute of Medicine convene a committee to evaluate the scientific and ethical issues involved in conducting studies of the safety of approved drugs. Questions to be explored by a committee include:

1. What are the ethical and informed consent issues that must be considered when designing randomized clinical trials to evaluate potential safety risks?
2. What are the strengths and weaknesses of various approaches, including observational studies, including patient registries, meta-analyses, including patient-level data meta-analyses, and randomized controlled trials, to generate evidence about safety questions?
3. Considering the speed, cost, and value of studies, what types of follow-up studies are appropriate to investigate different kinds of signals (detected pre-approval or post-marketing) and in what temporal order?
4. Under what circumstances should head-to-head randomized clinical trials for safety be required?
5. How should FDA factor in different kinds of safety evidence in considering different kinds of regulatory actions?

COMMITTEE'S APPROACH TO ITS CHARGE

In response to FDA's request, IOM convened a committee of persons who had expertise in clinical trials, epidemiology, pharmacoepidemiology, bioethics, law, patient safety,

[1]For simplicity, the committee uses the term *drugs* throughout this report, but similar considerations would apply to biologics.

biostatistics, public health, and health policy. Those experts agreed to prepare both this letter report, which focuses on question 1 of the charge, by July 2010 and a final report that addresses all the questions in the charge by 2011.

For the present letter report, the committee held one meeting, which included an open session in which it heard from representatives of FDA and representatives of the Agency for Healthcare Research and Quality (AHRQ) and the National Institutes of Health (NIH), which funded this report with FDA. The committee provided an opportunity for other stakeholders to present their perspectives and concerns at the meeting. The committee conducted searches of the literature on the ethics of clinical trials and informed consent relevant to postmarketing clinical trials. This letter report does not, however, present a comprehensive literature review of the subject.

Given the short period available for preparing this letter report, the committee focused on identifying a conceptual framework to guide its analysis of the ethics of the design and conduct of postmarketing safety research required by FDA, including key issues that need to be taken into account in assessing ethics and informed consent in randomized controlled trials. In developing this framework, and in its explication in this letter report, the committee relied on the extensive body of codes, regulations and guidance on the ethics of research involving human participants, much of which is built around a commitment to several basic moral principles, including beneficence, respect for persons and their autonomy, and justice. The committee did not enumerate all the ways in which the issues raised in this letter report can affect the ethics of a study, did not detail how the various issues should be weighed against one another, and did not explore in depth issues related to the ethical and scientific justifications of randomized controlled trials. A more detailed analysis of those issues and their implications and effects will be included in the committee's final report.

The committee's conceptual framework consists of four classes of considerations, as shown in Box 2. In accordance with the framework, the remainder of this letter report is organized in four major sections: the public health context of drug safety, regulatory science and public accountability, design considerations, and additional ethical obligations to research participants.

THE PUBLIC HEALTH CONTEXT OF DRUG SAFETY

The ethics of any postmarketing study required by FDA, including randomized controlled trials, should be assessed in the context of FDA's mission to promote and protect public health. The safety of the US drug supply contributes to the nation's health, and FDA is the agency responsible for ensuring this safety. As stated by the FDA commissioner and deputy commissioner, "to be healthy, people need access to . . . innovative, safe, and effective medical products" and "FDA's job is to support this access and, in doing so, to promote health, prevent illness, and prolong life" (Hamburg and Sharfstein, 2009). With specific reference to drugs, FDA's job includes (FDA, 2010a)

- "Protecting the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products"
- "Advancing the public health by helping to speed product innovations"

- "Helping the public get the accurate, science-based information they need to use medicines and foods to improve their health"

The committee believes that FDA, to fulfill its public health mission, should allow a drug to enter and remain on the market only if the balance of the risk to the benefit is appropriate for its intended use. The committee also believes that it is critical to FDA's public health mission that the agency: provide information needed by clinicians to prescribe a drug responsibly and needed by patients to take it appropriately; foster innovation and drug development by using decision-making processes that are predictable, clear, and timely; and conduct its responsibilities in a way that fosters public trust in the drug oversight system.

BOX 2 Conceptual Framework for Analyzing the Ethics of Postmarketing Randomized Clinical Trials Required by the Food and Drug Administration: Four Central Classes of Considerations and Recommendations

I. The Public Health Context. The Food and Drug Administration (FDA) should determine that there is a substantial public health question about the nature or acceptability of the risks, or the risk–benefit profile, of a marketed drug—a question that requires a policy decision from FDA.

II. Regulatory Science and Public Accountability. FDA should use regulatory-science principles and practices that include processes of public accountability and transparency to determine the need for a policy decision, the need for new knowledge to support a policy decision, and the policy decision based on the new knowledge.

III. Design Considerations. It is appropriate for FDA to require that a randomized controlled trial be conducted to provide additional evidence about an approved drug's efficacy and safety only when (i) uncertainty about the risk-benefit balance is such that a responsible policy decision cannot be made based either on the existing evidence or on evidence from new observational studies, and (ii) the trial is properly designed and implemented to reduce uncertainty about the risk-benefit balance sufficiently for a responsible policy decision to be made.

IV. Additional Ethical Obligations to Trial Participants. FDA should ensure that the trial will answer the public health question with a design that minimizes risks to trial participants and involves ongoing monitoring of risks. The risks should be judged to be acceptable by appropriate oversight bodies before and during the trial and by trial participants at enrollment and as appropriate during the trial. Specifically, FDA and appropriate oversight bodies should ensure that the trial includes a comprehensive and meaningful informed consent process that continues during the trial and that takes into account any substantial changes in clinical practice and professional standards and any new research findings relevant to a participant's willingness to accept the risks associated with the trial. The FDA and appropriate oversight bodies should ensure that those conducting the trial convey such changes to participants in a timely and understandable fashion.

Ensuring the acceptability of the risk–benefit profile of a drug after it is approved for the US market is no less central to FDA's public health mission than ensuring the acceptability of the profile before it is permitted to enter the market. As discussed later in this letter report, because of the infrequency and delayed occurrence of some adverse events, there is often more uncertainty about the risks posed by a new drug at the time of approval than there is about its efficacy. In addition, when an agent is approved on the basis of surrogate end points, the estimated degree of benefit may change when the effect on clinical end points is studied. Postmarketing research may be important for examining such clinical end points. Therefore, the committee agrees with a previous IOM committee that a drug-safety system "has at its core a lifecycle approach to drug risk and benefit" and that such a system "would require continuous

availability of new data and ongoing, active reassessment of risk and benefit to drive regulatory action (responsive to the accumulating information about a given drug), and regulatory authority that is strong both before and after approval" (IOM, 2007).

The new authorities and regulatory tools provided in FDAAA 2007 (PL 110-85) expanded the possibilities for FDA to adopt a comprehensive life-cycle approach to the assessment of the risks and benefits associated with marketed drugs. FDAAA 2007 mandated that FDA establish an active surveillance system for monitoring drugs by using electronic data from health-care information holders and gave FDA new authorities that include the ability to require revisions to a product label, to require further study of a drug, to restrict the use of a treatment to specified populations, and to require a formal Risk Evaluation and Mitigation Strategy (REMS). Those authorities provide new regulatory opportunities that are short of the pre-existing option of drug withdrawal. Under FDAAA 2007, FDA can require postmarketing studies and clinical trials under the following circumstances (PL 110-85):

> "To assess a known serious risk related to the use of the drug involved."
> "To assess signals of serious risk related to the use of the drug."
> "To identify an unexpected serious risk when available data indicates the potential for a serious risk."

The ability to require further study of a drug is a powerful tool for FDA to use in acquiring additional information to make informed, science-based decisions as part of its public health mission. In making a decision whether to require a postmarketing study, however, FDA not only should consider the ethical issues that arise in obtaining information to clarify a policy decision[2] but should bear in mind that such issues vary among types of studies.

The committee concludes that for FDA-required postmarketing research to be ethical, a critical first step is the determination by FDA that it is facing a policy decision of importance to public health that cannot satisfactorily be resolved with existing evidence.[3,4]

REGULATORY SCIENCE AND PUBLIC ACCOUNTABILITY

As noted above, FDA can require a postmarketing trial "to assess signals of serious risk" (PL 110-85). The key to the ethics of a postmarketing safety trial is a determination that a safety signal, if it represents a true risk, would warrant a policy decision and that new knowledge is needed to determine the existence and magnitude of the risk and thereby inform the nature of the decision. If, for example, the existing information about a safety risk is sufficient to warrant the removal of a drug from the market, then it would be unethical to conduct a trial. On the other

[2]When referring to a policy decision the committee means choosing among the range of responses available to the FDA when safety signals emerge—including the decision to continue a drug's monitoring plan without modification, the decision to add a warning to a drug's label, the decision to require a postmarketing trial, and the decision to remove a drug from the market—some of which are not mutually exclusive.

[3]The committee's conclusion is consistent with that of a previous committee of the National Research Council that was related to Environmental Protection Agency consideration of research involving human subjects (NRC, 2004).

[4]This conclusion, and this entire letter report, is specific to research on postmarketed products required by FDA. In this regulatory and public health context, it is critical from an ethics standpoint that existing evidence be insufficient to make an appropriate policy determination. Scientific studies of approved and marketed medical products outside this FDA context are an increasing component of biomedical and health services research and also can contribute significantly to population health.

hand, existing evidence about a new safety signal may be sufficient to warrant a change in labeling but not sufficient to warrant removal from the market, a policy decision that may be appropriate once the risks, or risks in relation to potential benefits, are better characterized. In such a context, it may be possible to design and implement an ethically acceptable trial. The same reasoning applies to judgments about whether a current trial should be stopped. If new evidence from any source, including the trial itself, is determined to be sufficiently compelling to ground a policy decision without waiting for additional new information, allowing the trial to continue would be unethical.

The ethics of postmarketing studies requires that the kinds of determinations outlined above be based on the best principles and practices for making policy decisions under conditions of uncertainty, including appropriate processes for transparency in decision making and public accountability. Those principles and practices, sometimes referred to as the emerging field of regulatory science,[5] require that policy decisions reflect the best available scientific evidence and analytic techniques drawn from a wide array of disciplines and technical expertise, including decision sciences, behavioral economics, and cognitive psychology. Public accountability and transparency increase the likelihood that the perspectives of stakeholders,[6] who have kinds of knowledge different from those of technical experts, are included in the making of policy decisions. Transparency and other public accountability processes also may increase the likelihood that the public will view regulatory and policy decisions, including the conduct of a trial and a decision to continue or discontinue a clinical trial, as fair and acceptable.[7]

Accurately assessing the risks posed by and the potential benefits of a drug requires the use of a wide variety of scientific data, including findings from animal studies of toxicology, basic research (for example, mechanistic studies and structure–activity relationships), clinical trials, high-quality epidemiologic and health-services research (such as observational studies and meta-analyses), and postmarketing surveillance systems that detect and analyze adverse events. FDA and those advising FDA therefore should be able to consider all data, and the design and analyses that led to those data, that are relevant to a given public health question, whether or not they are deemed proprietary information or trade secrets.

Judgments about the adequacy of available evidence for FDA decisions require input from a multidisciplinary team acting through a process that can integrate and take advantage of the different kinds of knowledge and perspectives that reside in clinical practice, biologic science, ethics, biostatistics, epidemiology, and research design. The decision-making process should also minimize and correct for potential cognitive and intellectual biases that arise from previous policy decisions or strongly held opinions—for example, the human tendency to focus on evidence that confirms a pre-existing belief or decision and to discount evidence that contradicts it.

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[5]FDA defines regulatory science as "the development and use of new tools, standards and approaches to more efficiently develop products and to more effectively evaluate product safety, efficacy and quality" (FDA, 2010b).

[6]Relevant government stakeholders include FDA, NIH, AHRQ, and the Centers for Disease Control and Prevention. Relevant nongovernment stakeholders include industry, academe, health-care providers, payers, patients, and other members of the public.

[7]As the committee has already noted, FDA and those advising FDA therefore should have access to all information relevant to a given public health question, whether or not the information is deemed proprietary information or trade secrets. One tension in meeting acceptable standards of transparency with stakeholders is managing public access to such information.

Modern tools for risk communication and public engagement should be used to ensure that all stakeholders—including physicians, other health professionals, interested patients and their families, and members of the public—understand the decision problem facing the agency, including what is known about the benefits and risks associated with the therapy in question and the pertinent uncertainties. Uncertainties could pertain to the quantity and quality of evidence, the risk–benefit profile, or the effect of policy decisions on future risks. Engagement with stakeholders is required to explain the types of uncertainties at issue and how the agency is dealing with the uncertainties in making its policy decision and to permit the agency to understand how those affected by its actions weigh risks and benefits.[8]

In using best practices to determine whether additional research is required, the agency should also keep in mind that one aspect of its mission to advance public health involves accelerating the evolution of effective new therapies from bench to bedside by encouraging product innovation (FDA, 2010a). That is most likely to occur when FDA's regulatory regime facilitates industry's ability to make informed research-and-development decisions—for example, by applying consistent requirements and criteria for assessing risks and possible benefits, by making decisions in accord with a clear and understandable framework, and by responding in predictable ways to different kinds of information, including new information about risk.

DESIGN CONSIDERATIONS

It is never ethical to involve research participants in an inappropriately designed or inappropriately conducted study or any study that does not have a reasonable prospect of answering the research question under study. Without a reasonable prospect of contributing to scientific knowledge, the exposure of research participants to even minimal risk or inconvenience can never be justified. In the case of postmarketing clinical trials required by FDA, that ethical precept requires further specification and strengthening. In particular, before a clinical trial is selected as the design of choice, it should be determined that no other research or information gathering effort—including a new observational study—can reduce the uncertainty about a drug's risk–benefit profile sufficiently to support a responsible policy decision.[9] It is also critical that the clinical trial be designed to provide precisely the data needed to facilitate the policy decision that needs to be made. Finally, there should be sufficient continuing monitoring of the trial to ensure that the associated risks (if any) continue to be acceptable.[10]

A comprehensive assessment of risks associated with a drug is often impossible in the premarketing-study phases because of small samples, short followup, and the selected nature of the populations included in preapproval trials. In addition, across the lifespan of a drug, the benefit profile and consequently the acceptability of risks in relation to benefits can change with the development of alternative treatment or prevention methods or even with the evolution of the

[8]The committee acknowledges that there are significant challenges to implementing policy making and regulatory processes that appropriately balance scientific evidence and stakeholder input (Lomas et al., 2005).
[9]This observation is again specific to the FDA context under consideration in this letter report.
[10]Continuing monitoring of a trial is essential to ensure that risks (if any) to participants continue to be acceptable. How monitoring should be conducted is also an essential feature of a properly designed trial. In this letter report, we have elected to discuss monitoring in the section on design considerations. It would fit equally well in the section on other obligations to trial participants.

disease or causative agent, such as the development of resistance to a given antibiotic. The assessment of benefits and risks is a dynamic process that requires continual revisiting and monitoring, and changes in evidence about risks should be considered against evidence about benefits at the time of the reassessment. Postmarketing safety studies constitute an important part of understanding the dynamics of the risk–benefit balance.

The most important features of any research are that the research question is properly conceived and that the proposed study is designed appropriately to address the question that has been specified. In the postmarketing context all such questions pertain to the risk–benefit profile of an approved treatment. However, not all changes in the risk–benefit balance are policy concerns, although they might merit alterations in medical practice. For example, the introduction of lower-risk therapies of similar or greater efficacy would justify changes in medical practice; without a new safety concern about the old agent, however, this situation might not require action by FDA.

A number of questions of policy relevance can remain or arise after approval. They include:

- Whether treatments approved on the basis of surrogate end points or biomarkers—such as lipid concentrations, blood pressure, or glycated hemoglobin—show improvement in clinical end points.
- Whether benefits seen in preapproval studies are not experienced by identifiable patient groups, in which case the acceptability of risks in these groups might be altered.
- Whether additional safety concerns that affect the risk–benefit profile arise from
  - Newly identified serious adverse events.
  - More serious or more frequent harms than expected in the intended population or in identifiable patient groups that may be defined by co-treatments, patient characteristics or co-morbidities, or disease or treatment-delivery characteristics.

New safety signals may arise from various sources: spontaneous reports of adverse events, safety-surveillance systems, observational studies, meta-analyses, and randomized trials. FDA can require new research to address key safety questions if the existing evidence is insufficient to infer causality or to characterize the frequency and severity of observed harms with adequate confidence or if such evidence is not complete enough to judge the acceptability of the risk–benefit profile for a drug's intended use.

The first step in deciding whether new research is needed is to assess the strength of the existing evidence related to new safety or risk–benefit concerns. The traditional hierarchies of evidence based on study design, which are regularly used in determinations of efficacy (Barton et al., 2007; Owens et al., 2010), might not apply in a straightforward manner to safety evidence. Randomized controlled trials are optimal for efficacy determinations because the randomization of large numbers of patients creates groups that have similar average risks of the outcome of interest. Observational studies designed to evaluate the efficacy or anticipated effects of treatment, either intended benefits or expected harms, are often liable to confounding by indication (Vandenbroucke and Psaty, 2008). That is, the reasons that physicians treat patients differently or that patients prefer particular treatment options are often related to factors that themselves affect outcomes. For example, if sicker patients choose medical care more often and avoid surgery, observational studies of surgical vs medical care could provide false evidence that surgery has more favorable results than medical care. Similarly, if an adverse effect of a drug is known, physicians may avoid prescribing it for patients who are at higher risk for the effect. Thus, in observational studies of the anticipated effects of treatment, it may be difficult to

determine whether differences in outcomes are due to the treatments themselves or to the other factors that led to the treatment choices. Although such differences due to other factors can often be minimized through design and analysis, they cannot be eliminated with the same confidence as one would attach to a high-quality randomized trial.

In the evaluation of unintended or previously unsuspected effects of drugs, however, observational safety studies are less likely than studies of known effects to be influenced by confounding by indication. Under specific circumstances, observational studies may be adequate not only to identify the presence of an important safety issue but, if the findings are replicated, to provide convincing evidence that an association is causal. For instance, a well-designed and well-conducted observational comparison of two similar drugs that came onto the market at the same time, that are used for the same condition at the same stage, and that have similar side-effect profiles could provide useful and valid estimates of the risk associated with a safety signal (Vandenbroucke and Psaty, 2008). In addition, some observational studies of safety may have distinct advantages over trials. They can often be much larger than randomized controlled trials, involve longer patient followup, include a broader diversity of patients and care settings, and be completed more quickly. Because of those features, observational studies evaluating infrequent outcomes that occur long after exposure and in which confounding by indication is unlikely can sometimes provide higher-quality safety evidence than randomized controlled trials, if the trials were not optimally designed to capture such safety outcomes.

The relative strength of other research designs may be different between safety and efficacy determinations. Meta-analysis of randomized controlled trials can increase the ability to detect rare events, but if the trials encompassed by the meta-analysis were not well designed or well conducted to capture safety outcomes or reported them inconsistently (Ioannidis and Lau, 2001), the meta-analysis may produce misleading results. An unexpectedly low incidence in the control group of a randomized trial may signal a problem with the conduct of the study.

All observational studies and meta-analyses of randomized trials may be affected by confounding or bias. If the estimated relative risks are small, selection bias, confounding, and measurement error may be alternative explanations for associations found in an observational study. But small relative risks of serious outcomes associated with widely used agents can have substantial public health consequences. Under such circumstances, if there is substantial uncertainty about a safety signal, a well-designed and well-conducted postmarketing randomized clinical trial is the best approach for characterizing the risk–benefit profile. The opportunity to evaluate both risks and benefits in the same study is an important advantage of randomized trials.

In evaluating or proposing a postmarketing randomized trial, the design and conduct should be closely scrutinized for quality and relevance to the US context. Findings from trials conducted in countries where medical care differs substantially from that in the United States may be less relevant to US populations (HHS, 2010).

Non-inferiority studies—designed with the one-sided intent to show that a therapy is not worse than another by some predetermined margin—pose some special challenges compared with the superiority trials traditionally used to evaluate efficacy (Fleming, 2008; Kaul and Diamond, 2006, 2007). The implications of poor quality in the design or conduct of a non-inferiority study are often the opposite of those in a superiority trial (Temple and Ellenberg, 2000). Low-quality study conduct, such as poor compliance with treatment regimens, usually biases a superiority trial toward a finding of no difference between treatments but often biases a

non-inferiority trial toward a finding of "equivalence" or "non-inferiority" between treatments. Thus, the findings of a poorly conducted non-inferiority trial may inappropriately support a conclusion that the treatments under study are "equally" efficacious or "equally" safe. Non-inferiority trials may therefore require special oversight and scrutiny by FDA, as well as appropriate adjustment for poor compliance, to ensure valid inferences.

Another critical, and perhaps underappreciated, aspect of non-inferiority designs that makes them problematic for safety assessments is the rationale for the choice of the non-inferiority margin. The selection of a margin that is too large can result in a finding that the two treatments are "equally safe" even if their risks are substantially different. Regardless of the hypothesis-test verdict in such a trial, FDA should look carefully at the estimated difference and its confidence interval in deciding whether meaningful differences in safety have truly been ruled out (Kaul and Diamond, 2006).

All those considerations also apply to the assessment of existing evidence and to a determination of what kind of research design is needed to generate new evidence. Because observational designs usually generate fewer ethical concerns than randomized controlled trials, a decision to require a randomized controlled trial to resolve safety questions should be based on the determination that neither the existing evidence nor new, prospectively conducted observational studies can provide safety evidence sufficiently reliable for FDA to make a sound policy decision.

If a randomized controlled trial is deemed necessary for an FDA-policy decision, its characteristics should include the following:

1. The evidence gap should be clearly present and specifically identified, and the research question and study design should be precisely crafted to address the gap.

This effort involves not only the review of the quantity, quality, and consistency of the existing evidence but careful selection of a study population, end points, treatments, comparators, and setting.

2. The trial should be adequately powered, and the trial procedures and the pre-specified analytic plans should be appropriate to provide answers to the study questions.

If a study addresses more than one question or end point, it should be powered so that all major outcomes of interest can be adequately studied. If the proposed trial uses a non-inferiority design, the non-inferiority margin should confidently exclude small risks of serious events, especially for widely used drugs. The analytic plan should be laid out in detail at the time the study protocol is approved by the sponsor and institutional review boards (IRBs). The data-management and quality-assurance plans should be fully described and adequate both for the protection of research participants and for the trial to achieve its aims.

3. The inclusion and exclusion criteria should reflect the best available knowledge about risks and potential benefits in the population.

From a public health perspective, it is desirable to test the effectiveness and safety of a drug for its intended use in a sample that is representative of the population receiving

the drug. However, the ethical obligation to minimize risks to research participants may require excluding some who are at a high risk of adverse events. It is never ethically justified to include in a postmarketing trial participants for whom the drug is contraindicated by the currently approved product label unless their involvement is necessary to answer a specific question and the risks to them posed by participation are acceptable.[11] The exclusion of participants for whom more moderate safety warnings or precautions have been issued presents a more difficult case and involves a tradeoff among several considerations: the prevention of possible harm to participants, the generalizability of the trial's findings to patient populations in which the drug is being used, and the ability to reach an answer to the study's safety questions more quickly (if the participants are likely to experience the outcome of interest at a higher rate).[12]

4. A comprehensive and robust safety-monitoring plan should be in place.

Every postmarketing clinical trial should have a properly qualified data-safety monitoring board (DSMB) in place with a written charter and a pre-specified data-monitoring plan, which includes statistical guidelines for stopping the trial early (Ellenberg et al., 2003; Grant et al., 2005). The frequency and intensity of DSMB review should be determined on the basis of the seriousness, incidence, and timing of known or possible harms. The DSMB should meet before trial onset to review and approve the charter, protocol, and monitoring procedures and then at regular intervals to review not just outcomes and adverse events but the various aspects of trial conduct and data quality.

A critical issue for trial monitoring is the standard of evidence required to halt a trial on the basis of harm. Typically, differences that cross pre-specified boundaries of statistical significance are required to halt trials for efficacy. However, depending on the type and degree of benefit, boundaries for harm may vary. The criteria for stopping a trial if the efficacy end point veers in the direction of harm are typically less stringent than the criteria for stopping for efficacy differences in the direction of benefit. Modest evidence of an adverse effect on an efficacy end point may be sufficient to rule out a clinically meaningful benefit even if the point estimate does not exclude a null effect. On the other hand, if benefit on one end point is established (for example, cardiovascular health), but the trial is being done to assess a suspected harm on a different end point (for example, hepatic failure), a higher standard of proof of the harm signal might be required. The Women's Health Initiative trial, for example, stopped its estrogen–progestin arm because the breast-cancer outcome crossed the pre-specified safety boundary and because the global index outcome just trended in the direction of harm, effectively ruling out a substantive net benefit (Wittes et al., 2007).

Other issues that affect the evidence threshold for stopping for harm are whether and how external information is used. This matter is not a settled methodologic issue, but if an emerging signal of harm is similar to that seen in external studies, it is ethically justified and may be ethically required to halt a trial earlier than if such evidence did not exist (Pocock, 1996).

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[11]If new information raises substantial uncertainty about the appropriateness of the current product warning, suggesting that it may be in the interest of patients to have the warning removed, it may be ethically acceptable to mount a trial that involves patients who are the subject of the warning to resolve this question.

[12]If such a trial is otherwise determined to be ethically justifiable, the consent process should emphasize to potential participants the existence of safety warnings or precautions.

Although vigorous safety monitoring is crucial for minimizing risks to participants in postmarketing trials, it is but one of multiple ethical considerations that must be addressed and satisfied if ethical obligations to research participants are to be fully honored.

ADDITIONAL ETHICAL OBLIGATIONS TO RESEARCH PARTICIPANTS

In the context of FDA-required randomized controlled trials, the need for a well-designed randomized controlled trial to determine the proper policy decision in response to a new drug-safety concern is a necessary but not sufficient condition for a trial to be ethically acceptable. Obligations to protect the rights and welfare of participants in a trial—to whom special duties of care and compassion may be owed because of illness, disability, or threat of illness—should be respected.

The general ethical principles governing research that involves human participants are well established and apply to the postmarketing context as they do to all human research (Council for International Organizations of Medical Sciences, 2002; DHEW, 1979). In the present letter report, the committee specifies aspects of those principles that have particular relevance to postmarketing research. In a postmarketing study, the risks to participants should be kept to the minimum that can be achieved while the trial is still able to answer the motivating policy question. The risk–benefit balance should be judged to be acceptable by FDA, participating IRBs, and the DSMB before initiation and throughout the course of the trial. That balance should also be acceptable to trial participants. To ensure that patients view the risks as acceptable in relation to any potential benefits, the trial should include a meaningful informed consent process that continues over the course of the trial and that includes prompt communication to participants of relevant new evidence or developments in clinical practice or professional standards that might affect their evaluation of the risks and benefits associated with continued participation.

Although the risks to research participants in randomized controlled trials are expected to be reasonable in relation to anticipated benefits, there is substantial consensus in both domestic regulatory and other guidance documents that different ways of balancing risk and benefit can be ethically justified. For example, both FDA regulations (21 CFR 50/56) and the Common Rule (45 CFR 46 Subpart A) distinguish among research that does not present greater than minimal risk, research that involves greater than minimal risk but offers the prospect of direct benefit to individual subjects, and research that involves greater than minimal risk and no prospect of direct benefit to individual subjects but is likely to yield scientific knowledge about the subjects' disorder or condition. A trial in which the risks to participants are not outweighed by the prospect of direct medical benefits to participants may be justifiable if a question of pressing public health importance cannot be properly answered without the conduct of the trial and if other conditions intended to safeguard the rights and interests of participants are satisfied. Those conditions include but are not limited to determination by appropriately constituted review committees that the risks are small enough to make it ethically acceptable to ask people whether they are willing to be exposed to the risks in the service of contributing to the public good, minimization of the risks through careful study design and a robust monitoring plan that is in place throughout the course of the trial, and implementation of a thorough informed consent process that adheres to the highest standards of respect for participants.

The informed consent process should provide an accurate, comprehensible explanation of the available knowledge about the risks and benefits associated with being assigned to the treatment and control groups. It is a bedrock principle of research ethics that participants who put themselves at risk in human research should receive an understandable, unbiased, accurate, and comprehensive disclosure of the potential benefits and risks attached to study participation (DHEW, 1979; ICH, 1996). A comprehensive disclosure is important to fulfill the substantive moral requirement of informed consent that participants have a meaningful *understanding* of what is being asked of them, including the risks and benefits (if any), not merely that information is provided to them (Faden and Beauchamp, 1986).

When a substantial amount of information indicating that a drug to be studied may involve serious safety risks has already accumulated, there are heightened obligations to ensure that potential participants understand the risks posed by study enrollment. Those obligations may include special efforts to communicate complex risk information clearly and to establish that participants have sufficient understanding of what the risks mean to them.

The emphasis given to risk information in the consent process should increase with the severity of risk and the level of certainty about the causal association between the drug and the adverse outcome. At a minimum, risks that should be disclosed should include any black-box warnings, the "major statement" currently listed in television advertisements, any adverse-event findings of an FDA advisory committee, and a summary of evidence from published peer-reviewed studies.

Communicating complicated risk information and research findings to participants poses challenges. It is critical that the information be conveyed in a manner that can be understood and weighed by participants. A "kitchen sink" approach to consent-form drafting, in which voluminous information is included with little attempt to distill it into a short format that is useful to participants, is unfortunately increasingly common in clinical trials and should be avoided. Participants are likely to be overwhelmed by a long and complex form and unable to weigh conflicting study findings or findings about different types of risk.

Verbal disclosures and written consent documents (both consent forms and information sheets) should help potential participants to understand how experts weigh the available evidence about the safety profile of the drug being studied. Moreover, there is a growing set of additional resources (for example, decision aids, videos, and interactive electronic presentations) to supplement written materials that may enhance participants' understanding of complex clinical information. Although evidence about the effectiveness of techniques designed to improve and document understanding among potential research participants is mixed (Kass and Taylor, 2008), such interventions as engaging in additional interpersonal conversations with potential participants and asking them to explain the study to a friend have been shown to be helpful (Flory and Emanuel, 2004; Kass and Taylor, 2008; Lindegger et al., 2006). Whatever efforts are employed to communicate with potential participants, it is key that they include information that is useful to participants about where the weight of the evidence falls with regard to serious risks and the level of confidence that experts have in drawing conclusions about the risks. A statement that "Some studies have found that the drug causes X, whereas others have not" may be true but misleading if nearly all well-designed studies have reached the same conclusion and there is little or no reliable evidence on the other side.

In addition to safety risks, people who are considering participation in research need to know how the care that they will receive in a protocol may differ from the care that they would ordinarily receive. Thus, information about "Alternatives to Participation" should convey the current standard of care for the health condition that the study drug targets. That is particularly crucial in cases in which medical practice has shifted away from prescribing the study drug because accumulating evidence from passive surveillance, observational studies, and small trials or meta-analyses suggests that another therapy is as effective and has a more favorable safety profile. A statement that if a potential participant does not enroll in the trial, he or she is more likely to have a different drug prescribed should be communicated in this situation. If clinical practice continues to shift during the trial period, the statement should be strengthened; researchers have an ethical obligation to disclose all new developments that may affect a person's willingness to continue to participate in a research study.

Comprehensive informed consent processes can help ensure that trial participants understand the potential consequences of study participation in addition to what they are contributing to the advancement of public health in the regulatory arena. They cannot, however, serve as an exclusive or sufficient ethical justification for conducting a postmarketing trial. The other ethical bases for initiating a trial should be independently satisfied. People should not be asked to assume risks that are not justified in light of the benefits of the trial to participants or society. Particularly in research settings in which participants have low literacy, low income, and poor access to modern health care and medicines, even a robust consent process may do little to countervail the pressures that lead people to participate in research. Regulators, IRBs, and DSMBs should serve as particularly strong bulwarks against unethical experimentation in such settings.

RECOMMENDATIONS

The committee recommends that the ethical and informed consent issues related to FDA-required postmarketing clinical trials should be evaluated according to the considerations identified in the conceptual framework summarized in Box 2 as explicated in this letter report.

Given the timeframe of this letter report, the committee does not detail all the issues within the framework or discuss how various considerations should be weighed. The committee plans to provide further details in its full report in 2011.

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