RESEARCH ETHICS

Beyond Access vs. Protection in Trials of Innovative Therapies

Review of first-in-human trials should safeguard the integrity of the scientific enterprise through a focus on preclinical and clinical study quality.

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Over the past decade, researchers have initiated innovative, early-phase, clinical trials, including the first-ever testing in humans of cell therapies for myocardial infarction (*1*), as well as transplantation of embryo-derived tissues for spinal cord repair (*2*). The next decade promises more initiatives involving first-in-human trials of innovative therapeutic strategies (*3*).

Such studies frequently inspire ethical debates that revolve around the rights and welfare of research participants. However, neither "protection" nor "access" (discussed below) adequately addresses issues relating to the methodological quality of preclinical (i.e., nonhuman) studies, the design and review of early-phase clinical studies, and the continuity between preclinical studies and first-in-human trials. These issues bear crucially on the value of a translational trial as a critical stage in a larger, collaborative endeavor with a unique social mission: transforming hard-won advances in basic science into practical applications that improve care at the bedside. Before the welfare and autonomy of participants comes into view, issues relating to the ability of science to fulfill this social mission—what we hereafter refer to as the integrity of the scientific enterprise—must be adequately addressed.

Protection and Access

The autonomy and welfare of study participants is, and ought to remain, a central concern for research ethics. Scientists and reviewers charged with protecting subjects dwell on uncertainties and risk. They urge cautious study designs and extended preclinical testing, often warning that volunteer patients who have exhausted standard care options are prone to overestimating therapeutic benefit ("protection") (*4*). However, patient advocates and clinical investigators often argue that requests for additional preclinical studies—which, if conducted, delay translational trials (small trials of therapies emerging from laboratory studies)—do not advance the interests of people with untreatable diseases ("access") (*5*). If we respect people by allowing them to choose in accordance with their values and to shepherd their interests as they see fit, then preventing patients from pursuing what they may regard as their best therapeutic option disadvantages participants and slows scientific progress.

Continuity and quality. Innovative clinical research requires the sustained cooperation of diverse stakeholders, including patients and physician-researchers (as seen here), as well as scientists, sponsors, and institutions.

However, exclusive focus on personal interests of subjects fails to assign proper weight to a range of ethical issues that arise in clinical research. Medical research is primarily directed toward producing a common, rather than a private, good: It serves an inherently social purpose of generating knowledge requisite for institutions to better address unmet health needs of community members (*6*). It is also a deeply social activity (*7*) in that new knowledge and interventions are produced from a long chain of investigations, each building on the last. Yet each link in this chain is also a discrete interaction between specific stakeholders with their own individual interests (see figure, above). Because uncoordinated activities of individuals pursuing personal interests can have deleterious effects on attainment and preservation of social goods, research ethics must place more emphasis on norms that preserve relationships and institutions necessary to sustain this social good.

Individual Transactions and Social Goods

Although individual trials, each a transaction between investigators and trial participants, are regulated by ethics committees and drug regulatory authorities, there are at least three ways they can inadvertently undermine forms of broader, longer-term collaboration that sustain the production of socially valuable medical knowledge. First, studies can misallocate resources. Practically every clinical trial makes demands on social and material resources beyond those provided by study sponsors, investigators, and human subjects. For example, clinical trials deplete the pool of eligible volunteers for other meritorious trials. About 20% of trials initiated in National Cancer Institute (NCI)–designated Comprehensive Cancer Centers fail to accrue a single study volunteer (*8*), and fewer than 60% of NCI-funded clinical trials are able to meet minimal recruitment goals (*9*). Also, many early-phase trials are pursued at research centers that are heavily subsidized by public funding agencies and private philanthropies, and their management and oversight draw heavily on limited administrative resources. Poorly justified trials may also compete with better ones for highly specialized expertise and equipment. Finally, because they generally do not indemnify patients in the event of trial-related injuries, studies exact demands on third-party payers. The determination of whether a research protocol has sufficient prospect of returning social value to warrant such use of human and material resources has to be made in light of factors beyond the personal interests of researchers and potential trial participants (*10*).

Second, adversities encountered in isolated trials can have cascading effects, undermining institutional and social supports for new initiatives. Research programs are joined or abandoned on the basis of perceived beliefs of others (*11*). Unsuccessful or poorly conceived trials can dampen interest in promising therapies. Repeated failures can diminish the standing of a research program, interrupting recruitment of talent, investment, and

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institutional support. Major adverse events can undermine support for an entire field. For example, the unexpected death of a volunteer in a gene-transfer study seriously eroded confidence in the field's ability to self-regulate; many suggest that this led to a withdrawal of investment and institutional support (*12*–*14*).

Third, oversight or review procedures that allow the preferences of researchers and participants to dominate the design and conduct of translational trials can create incentives that reward low-quality trials and penalize well-designed protocols. For example, deficiencies in a trial that affect the value of the information it generates may not discourage fully informed volunteer patients having few other care options. However, clinical trial protocols are examples of what economists call "credence goods": Products whose quality is difficult to judge by consumers. Unless well-regulated, markets for credence goods are prone to low-quality products, because consumers lack the capacity to reward producers of high-quality products and to punish producers of mediocre ones (*15*, *16*). Oversight structures that establish baseline quality for translational trials ensure that participants, physicians, researchers, and investors can pursue their individual interests without compromising the social mission of the research enterprise. Volunteer subjects can be confident that the trial is based on promising, well-designed protocols; all other stakeholders have greater assurance that the program represents an efficient means of producing a social good.

The Need for Quality Preclinical Data

Elsewhere, we have argued that rigorously designed preclinical studies greatly enhance the interpretability of translational trials (e.g., because they enable researchers to troubleshoot interventions when clinical outcomes are discordant with those in animal models) (*13*, *17*). But there is a growing literature documenting quality deficiencies in preclinical research used to support phase 1 trials (*18*). In contrast with clinical research, preclinical research has only sporadically taken up measures to control bias, including a priori statement of hypothesis, random treatment allocation, blinded outcome assessment, and accounting for missing data (*19*, *20*). The preclinical literature shows evidence of publication bias (*19*, *21*), and not infrequently, first-in-human trials are initiated before preclinical studies have been subjected to peer review. Even when preclinical studies are rigorously designed and executed, first-in-human clinical studies may deviate in significant ways from the methods or procedures evaluated in preclinical studies.

Safeguarding the integrity of the scientific enterprise by ensuring that decisions about clinical trials are based on high-quality preclinical information thus entails resolving four key questions at the inception of a translational trial. First, do preclinical experiments provide a credible measure of effect? Are studies internally valid and have they been replicated independently? Second, do preclinical studies have reasonable external validity? Have investigators demonstrated that their preclinical findings are robust and generalizable and that their choice of animal models and outcome measures are justified? Third, to what extent have researchers justified the assumption that observations in a preclinical system will be reproduced in human patients? Have they presented data showing that causal preconditions of effect in animals are also present in human beings, and have they made a thorough search of the evidence? Last, when all the previous issues are addressed, do conditions used in preclinical studies correspond with those in a proposed human trial? Are delivery strategies, targets, doses, and materials in the human study identical or substantially equivalent to those validated in animals?

Ensuring the Integrity of the Enterprise

The primary responsibility for addressing these questions lies with preclinical and clinical investigators pursuing translational research. These questions should also be a focus of the various levels of ethical and scientific review that occur at each stage of the translational research process. This includes oversight by an Institutional Review Board (IRB) and committees that provide centralized review of protocols, such as the Recombinant DNA Advisory Committee and Data Monitoring Committees. These questions may also help to sensitize sponsors of translational trials to the ethical aspects of basic and preclinical research, not only when evaluating funding requests, but in ensuring that sufficient resources are in place to address them. Finally, these issues should be central in peer review and editorial scrutiny of translational studies.

IRBs may be reluctant to address these questions because such methodological issues may seem beyond their purview. But the primary value of first-in-human trials lies in the information they are expected to generate. IRBs must evaluate the quality of that information and its potential social value as part of the process of ensuring that risks are reasonable. It might be objected that these concerns run afoul of the statement in U.S. federal regulations that IRBs "should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy)" (*22*). But this is meant to prevent scientifically valuable research from being stifled because of how sensitive or controversial findings might be used at a social level. It does not prohibit IRBs from scrutinizing the quality of the science that is likely to emerge from an investigation.

The dichotomy of subject protection versus access is insufficiently sensitive to ways in which clinical trials contribute to, and depend crucially upon, the quality of other scientific investigations. This is most vividly illustrated by first-in-human trials that involve members of a disease population. However, such issues arise in any form of research that draws heavily on sustained collaboration and coordination across time of diverse stakeholders. A focus on the integrity of the research enterprise draws attention to methodological and social requirements that medical science must satisfy if it is to maintain the support of those whose cooperation makes it possible and whose interests it is supposed to serve.

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