RESEARCH ETHICS

Rethinking Research Ethics: The Case of Postmarketing Trials

Human subjects research ethics needs to directly address threats to the evidence base of the medical information economy.

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From the Nuremberg Code onward, the core mission of human subjects research ethics has been to protect study participants from infringements motivated by a zeal for medical progress. However, with individuals, clinicians, and policymakers increasingly dependent on scientific information for decision-making and with vast social resources invested in developing and utilizing the fruits of research, actors have powerful incentives to coopt research for narrow ends. Contemplated revisions to human subjects research ethics policies in the United States (*1*) and existing policy in Canada (*2*) and the United Kingdom (*3*) fail to capture harms that, although they may not threaten participants, nonetheless undermine the social value of research. This is illustrated by postmarketing (phase IV) research. As a corrective, research ethics should focus on safeguarding the integrity of research as a critical component of an evidence-driven, health information economy.

Postmarketing Research as a Case Study

Phase IV studies investigate drugs, devices, or biologics that have already received regulatory licensure. Generally, they are funded by drug companies and provide a means of testing findings from fastidiously designed trials in less stylized settings. They also provide greater statistical power for safety assessment. Initiatives like the U.S. Patient-Centered Outcomes Research Institute (PCORI) in the 2010 Affordable Care Act signal a renewed commitment to harnessing phase IV studies to address evidentiary gaps in comparative effectiveness, drug safety, and real-world utility (*4*). Yet studies often fall short of these ambitions. In contrast with premarketing trials, drug regulators have very limited influence over the production of phase IV evidence (*5*). This removes a critical check on design and reporting quality.

To their harshest critics, postmarketing trials are a backwater in which pharmaceutical companies use the simulacrum of scientific investigation to hawk their products. Studies sometimes enlist hundreds of physicians to recruit only a few patients each, thereby exposing more prescribers to the product; other studies are alleged to pay investigators extravagant fees (*6*). Sponsors sometimes obscure the nature of their interest in phase IV studies from volunteers and investigators. Using research in this way allows drug and device companies to circumvent rules against directly remunerating physicians for prescriptions (*7*). Recruiting physician-investigators with the promise of peer-reviewed publication confers an aura of scientific authenticity to the enterprise.

In 1996, several postmarketing studies of the antiseizure medication gabapentin were exposed as "seeding" use of the drug for unapproved indications (*8*). The prominently published ADVANTAGE trial of the anti-inflammatory drug rofecoxib also was revealed to be a seeding study (*6*). Postmarketing studies instigated over safety concerns surrounding two recently withdrawn drugs were found unsuited to the goal of pharmacovigilance (*9*, *10*). More systematic analysis shows that many other phase IV studies suffer various deficiencies, including statistical underpowering, absence of comparator arms, and publication bias (*11*).

The Current Research Ethics Framework

Because few, if any, of these branding practices violate laws and because institutional review boards (IRBs) may be the only venue where phase IV protocols receive formalized prospective review, critics have turned to research ethics to mount objections. These take two forms. First, policies stipulate that risks to volunteers must be reasonable in light of benefits to volunteers, if any, and society. Some critics charge that marketing objectives cannot justify risks to study participants (*6*, *12*). Second, some argue that phase IV studies' hidden marketing agenda compromises informed consent (*13*). If volunteers are unaware that a trial is a branding exercise, they may not be adequately informed about the ends to which they are contributing.

These criticisms accord well with the reigning model of research ethics, which locates the moral tension in clinical research at the interface between subjects—who may be unable to adequately safeguard their own welfare—and investigators. However, by shoehorning the problems of phase IV studies into the familiar categories of risk and informed consent, they miss much of what makes these practices objectionable.

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Concerning the first objection, many postmarketing studies have little impact on participant welfare and involve no more than a chart review or inclusion in a registry. Studies that go beyond this often enroll patients only after they have opted for an intervention in a clinical setting or entail little departure from standard of care. Current ethical guidelines evaluate social value only insofar as it justifies risk to volunteers: the less the risk, the less the need to substantiate social value. Thus, they provide inadequate bases for challenging studies that pose little risk but that generate biased evidence. These difficulties would be exacerbated by proportionate review, a central plank in many policies governing human subjects research, including proposals to amend those in the United States (*1*–*3*). This approach, which calibrates depth of protocol scrutiny to the level of volunteer risk, is motivated by the sensible observation that low-risk studies can divert review resources from riskier ones. Yet many problematic phase IV practices pose little threat to volunteers and thus escape review.

As for the second objection, disclosure of marketing aims would defuse concerns about deception, but do little to improve the value of such studies or diminish the social harms caused by production of biased evidence and the cooptation of research systems.

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The Integrity of the Research System

A more robust ethical framework should focus on preserving the integrity of research as the foundation of an evidence-driven, health information economy. By a health information economy, we mean a system in which various parties collaborate in producing health-related information that is then consumed by others. Sometimes information is used to produce interventions, improve health services, or set policy. Other times it is an input into further inquiry. The ability of the parties who use this information to advance care, improve knowledge, and increase efficiency depends critically on its validity, relevance, credibility, and accessibility to stakeholders. Although studies are often financed and performed by private actors, they have public repercussions. How research is conducted not only affects the quality of the information that others consume, but also patient expectations, provider practices, the expenditure of scarce resources, and the efficiency of health-care systems.

Deficiencies in phase IV studies like those above are not always detectable for editors, policy-makers, or other evidence users. Adverse events might be withheld, primary end points altered, and provider practices or patient expectations influenced by engaging with a trial rather than its results. These threaten the integrity of research as the foundation of an evidence-driven health information economy in three ways.

First, policy-makers, clinicians, and third-party payers who base treatment decisions, guidelines, or reimbursement on biased studies harm patients and misallocate resources. As the social resources dedicated to the health sector balloon, so, too, do the stakes of ensuring that resources are used efficiently.

Second, the "bench-to-bedside" process of translating basic research into clinical treatments is a series of investigations in which many different actors both produce and consume scientific information. Just as unreliable preclinical research can derail promising therapeutic avenues (*14*), the cumulative human and capital investment in inquiry and development can be squandered where biased phase IV evidence promotes inappropriate application of interventions.

Third, confidence in scientific medicine and the social influence associated with it is eroded when the outward signs of scientific merit are used solely as a vehicle for marketing. To ensure that confidence in medical information is warranted for those who rely on it, the system of knowledge production and utilization must be designed to either leverage or limit the influence of parochial motives on evidence production.

Those who fund, conduct, take part in, and ultimately benefit from the results of scientific inquiry participate in research to advance a diverse mix of personal or social goals. Whether this is antithetical to the efficient production of reliable medical evidence depends on whether ethical and policy frameworks bring individual interests into alignment with the social goals of research. When demand is driven by high-quality evidence of superiority on clinically relevant comparisons, expanding an intervention's market share advances both parochial and social ends. Influencing clinician practice and increasing stakeholder familiarity with such treatments advances social ends when it reduces unwarranted variation and expense, and improves patient outcomes. Profit seeking advances social interests when incentives channel human ingenuity toward bridging knowledge gaps about best practices.

Preserving the integrity of the research system also requires protecting the rights and welfare of participants, because knowledge cannot be produced within a liberal democracy without the participation of volunteers who are confident that their basic interests will be safeguarded. But subject protections should be seen as one important facet of a broader effort to ensure that, as contributors to the health information economy advance their individual agendas, they are also helping to produce important social benefits.

Ethics Should Inform Oversight

A framework that highlights the ethical significance of threats to the health information economy should facilitate a search for mechanisms that empower actors and institutions to promote more informative and valuable forms of inquiry.

One strategy would be to rectify discontinuities between pre- and postmarketing oversight by granting regulators greater authority over postmarketing research (*15*). Creating a centralized entity for certifying phase IV trial protocols or expanding the purview of existing institutions, such as the U.S. Food and Drug Administration or the PCORI, could provide incentives for conducting higher-quality studies (*16*). At least, registration and reporting requirements should be expanded to include phase IV observational studies (*17*).

Absent these ambitious institution-making proposals, the burdens of promoting high standards of design and clinical relevance would fall to three actors that presently have some—albeit limited—role in shaping incentives in this arena. First, if IRBs are to play a role in strengthening such studies, their mandate will have to be expanded to permit greater scrutiny of study quality, reporting plans, and clinical relevance. This might also require strengthening their membership to ensure the relevant scientific and statistical expertise. Nevertheless, such changes would have limited impact on deficient trial reporting.

Second, medical journals could adopt phase IV–specific review and reporting criteria. These might include expanded requirements for review; submission (e.g., provision of an approved protocol); and disclosure of data. Even if studies are not published, the clear articulation of quality benchmarks and registration obligations can impact the upstream conduct of sponsors and investigators.

Finally, there should be a broad-based discussion of the responsibilities of medical societies for articulating and implementing standards for member participation in post-marketing studies (*18*).

Unlike private transactions in many other spheres, research transactions serve crucial social ends. Because those ends can be frustrated without putting study participants at risk, research ethics and policies need to adopt a broader focus—one that directly addresses threats to the evidence base of the medical information economy.

References and Notes

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