Rethinking Research Ethics: The Case of Postmarketing Trials

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Abstract

Phase IV studies are often criticized for poor scientific standards. Yet they provide an important resource for addressing evidence shortfalls in drug safety, comparative effectiveness, and real-world utility. Current research ethics policies, and contemplated revisions to them, do not provide an adequate framework for preventing social harms that result from poor post-marketing research practice. Rather than focus exclusively on the welfare and interests of human volunteers, research policies and ethics should also safeguard the integrity of the research enterprise as a system for producing reliable medical evidence. We close by briefly describing how an integrity framework might be implemented for phase IV studies.

Phase IV and other post-marketing studies have a checkered reputation. To their harshest critics, the post-marketing trial arena is a backwater in which pharmaceutical companies use the simulacrum of scientific investigation to hawk their products. To their defenders, post-marketing studies are a vital tool for addressing numerous evidentiary gaps in comparative effectiveness, drug safety, and real-world utility. With the creation of the Patient Centered Outcomes Research Institute in the 2010 Affordable Care Act,⁽¹⁾ the Obama administration has signaled its commitment to harnessing phase IV studies to advance the latter set of priorities.

However, recent proposals to amend the Common Rule (and finalized policies elsewhere)⁽²⁾ may be on a collision course with these aims. Central to proposed revisions is the concept of proportionate review-⁽³⁾ the notion that depth of protocol scrutiny should be calibrated to the level of volunteer risk.⁽⁴⁾ Proportionate review is motivated by the sensible observation that low risk studies can divert review resources from riskier ones. Yet many of the most reviled practices in post-marketing research pose little threat to volunteers. Phase IV studies thus provide an occasion to ask whether current paradigms of research oversight adequately capture the full range of ethical issues at stake in clinical investigation.

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The Standard Framework

Phase IV studies investigate drugs, devices, or biologics that have already received regulatory licensure. In theory, they provide a means of testing findings from fastidiously designed trials in less stylized settings. They also provide greater statistical powering for detecting adverse drug reactions.(5)

Yet post-marketing studies often fall short of these ambitions. In 1996, litigation exposed several post-marketing studies of the anti-seizure medication gabapentin as “seeding” use of the drug for unapproved indications.(6) Another suit, brought against the makers of rofecoxib, revealed its prominently published ADVANTAGE trial to be a seeding study. In the case of two recently withdrawn drugs, post-marketing studies instigated over safety concerns were found unsuited to the goal of pharmacovigilance.(7–8) More systematic analysis shows that many other post-marketing studies suffer various deficiencies, including statistical underpowering, absence of comparator arms, inadequate outcome assessment, and publication bias.(9)

Post-marketing studies are commonly viewed as using the trappings of scientific investigation to disguise advertising objectives. 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 physician-investigators extravagant fees for their contributions.(10) Sponsors often obscure the nature of their interest in phase IV studies from volunteers and physician-investigators. Using research in this way allows drug companies to circumvent rules against directly remunerating physicians for prescription.(11) Recruiting physician-investigators with the promise of peer-reviewed publication confers an aura of scientific authenticity to the enterprise.

Because few if any of these practices violate laws, critics have naturally turned to research ethics to mount objections. These usually 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 under the cover of research exposes participants to risks that go unredeemed. This view is prominent in criticisms of ADVANTAGE;(10) it is also a theme in criticisms of CAFÉ, a phase IV study involving the psychiatric drug quetiapine.(12) One way studies might expose patient-volunteers to unredeemed risk is if financial and professional blandishments induce investigators to offer enrolment or adhere to protocols against better medical judgment.(13)

Second, policies require that competent volunteers provide valid informed consent before enrolment. However, some critics of phase IV studies argue that their hidden marketing agenda(10, 14–15) compromises informed consent. If patient-volunteers are not aware 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 oversight, which locates the moral tension in clinical research at the interface between subjects—who may be unable to adequately safeguard their own welfare—and physician-investigators. Proportionate review cements this focus. However, by shoehorning the problems of phase IV studies into

the familiar categories of risk and informed consent, they miss much of what makes common post-marketing practices so objectionable.

Concerning the first objection, many post-marketing 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. When studies do affect treatment allocation, they often entail little departure from standard of care. Because current policies evaluate social value only insofar as it justifies risk to volunteers, they have no grounds for challenging studies that pose little or no risk but that generate biased medical evidence.

As for the second objection, if sponsors disclosed to participants their hope that a trial will familiarize practitioners with new methods or interventions, they would defuse the objections about the hidden nature of their marketing agenda. However, this would do little to improve the social value of such studies, or to diminish the social harms caused by poor phase IV study practices.

The Integrity Framework

The inability of research ethics to capture problems in the conduct of post-marketing studies reflects the historical origin of prevailing frameworks. Predicated on the assumption that research ceaselessly strives to advance the common good, from the Nuremberg Code onwards, the core mission of research ethics has been to protect participants from moral infringements motivated by a zeal for medical progress. The exponential growth in biomedical research, the vast amounts of money invested in developing and then utilizing interventions, and the importance of scientific information for clinical and policy decision-making has generated powerful incentives for actors to coopt research for narrow goals like fostering brand loyalty.

What we call the “integrity framework” provides a corrective to this restrictive focus on risk and informed consent. It holds that research ethics must preserve the integrity of research as a critical component of an evidence-driven, health information economy. By the latter we mean a system of health promotion, including public health and clinical medicine, in which the assessment and development of interventions, policies and practices is driven by evidence about key variables like safety, efficacy, effectiveness and value. Protecting the rights and welfare of subjects is a necessary component of the integrity framework, since research cannot function without the participation of patient-volunteers who are confident that their basic interests will be safeguarded. Subject protection, however, is insufficient to meet the broader imperatives of securing the evidence base of the medical information economy.

Deficiencies in phase IV studies like those surveyed above threaten the integrity of the research enterprise in three ways. First, the research process from bench to bedside is a series of investigations in which many different actors both produce and consume scientific information. Ensuring that research employs rigorous methods to answer questions that are relevant to clinical practice is essential to the success of the research enterprise. Just as poor

quality preclinical research can derail promising therapeutic avenues,(16) the cumulative human and capital investment in inquiry and drug development can be squandered where poor phase IV study evidence leads to inappropriate application of interventions.

Second, policy-makers, clinicians, and third-party payers who base treatment decisions, practice guidelines, or reimbursement schedules on biased studies harm patients and misallocate resources. As the social resources dedicated to the health sector balloon, so too does the imperative to ensure resources are used effectively and efficiently.

Third, confidence in scientific medicine and the social influence associated with it is jeopardized when the outward signs of scientific merit are used solely as a vehicle for advertisement. To preserve the confidence of those who rely on medical information, whether to advance research or to better meet patient needs, there must be widespread recognition that the system of knowledge production and utilization is designed either to harness or constrain the influence of parochial motives on evidence production.

The integrity framework provides clear reasons for establishing mechanisms that prospectively evaluate the quality of phase IV study design independent of volunteer risk. It also departs significantly from two, somewhat contradictory assumptions embedded in standard accounts of research ethics-first, that research that protects the personal interests of volunteers will inexorably generate socially valuable information, and second, that motivational purity among research actors is a moral prerequisite for ethical human research. Our contention is that the pursuit of differing and sometimes conflicting interests on the part of actors is not antithetical to a system of knowledge production and consumption that efficiently advances the social goal of producing reliable medical evidence. Rather, the system of research funding, oversight, and publishing should be configured in ways that foster the production of socially valuable evidence and penalize methodologically flawed inquiry. In this way, all stakeholders can be confident that, although different parties may participate in research to advance various private and public interests, the integrity of the evidence generation process will remain intact and the goal of ensuring an evidence-driven health information economy will be advanced.

Conclusion

In contrast with premarketing trials, limited mechanisms are in place to compel the production and dissemination of high-quality evidence in post-marketing research.(17) The key to correcting deficiencies in post-marketing research lies in empowering institutions to promote scientific quality and deter bias. Though our goal in this article has been to underscore the moral imperative to adopt such a focus, we offer several options that might be implemented at the level of institutional design.

First, laws might be modified to grant regulators greater authority over post-marketing research,(18) or to incentivize higher quality post-marketing studies.(19) This could involve expanding the purview of existing institutions, such as the FDA, the Patient Centered Outcomes Research Institute, or creating a centralized entity for certifying post-marketing trial protocols. In any event, the goal of these regulatory mechanisms would be to enforce

high standards for design, to ensure clinical relevance, and to promote studies that help advance the standard of care. They should also require prospective registration and reporting of all post-marketing studies (current FDA registration policies do not extend to post-marketing observational studies).(20)

Absent these ambitious institution-making proposals, the burdens of righting the post-marketing research enterprise are likely to fall on IRBs and other actors with existing authority. IRBs could be tasked to oversee the quality of phase IV research and their mandate and membership requirements changed to effectuate this goal. This would require increased scrutiny of phase 4 studies, regardless of risk to participants. Medical journals could adopt strict and explicit review and reporting criteria, and medical societies might articulate standards for member participation in post-marketing studies.(21–22)

Unlike private transactions in other spheres, research transactions serve crucial social ends—namely, providing the evidence base for the medical information economy. As the case of phase IV studies shows, these ends are easily subverted without necessarily putting patient volunteers in harm's way.

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References

1. Office of the Legislative Counsel. Patient Protection and Affordable Care Act. Public Law 111–148 (2010).
2. Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, Social Sciences and Humanities Research Council of Canada. Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans. Dec. 2010
3. Department of Health and Human Services, Food and Drug Administration, Advance Notice: Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators. *45 CFR 46, 45 CFR 160, 45 CFR 164, 21 CFR 50, 21 CFR 56*. (2011).
4. Federman, DD.Hanna, KE., Rodriguez, LL., editors. Responsible Research: A Systems Approach to Protecting Research Participants. National Academics Press; Washington, DC: 2002.
5. Eichler HG, Pignatti F, Flamion B, Leufkens H, Breckenridge A. Balancing early market access to new drugs with the need for benefit/risk data: a mounting dilemma. *Nat Rev Drug Discov*. Oct.2008 7:818. [PubMed: 18787530]
6. Steinman MA, Bero LA, Chren MM, Landefeld CS. Narrative review: the promotion of gabapentin: an analysis of internal industry documents. *Ann Intern Med*. Aug 15.2006 145:284. [PubMed: 16908919]
7. Psaty BM, Furberg CD, Ray WA, Weiss NS. Potential for conflict of interest in the evaluation of suspected adverse drug reactions: use of cerivastatin and risk of rhabdomyolysis. *JAMA*. Dec 1.2004 292:2622. [PubMed: 15572720]
8. Nissen SE. The rise and fall of rosiglitazone. *Eur Heart J*. Apr.2010 31:773. [PubMed: 20154334]
9. Hasford J, Lamprecht T. Company observational post-marketing studies: drug risk assessment and drug research in special populations--a study-based analysis. *Eur J Clin Pharmacol*. Jan.1998 53:369. [PubMed: 9516039]
10. Sox HC, Rennie D. Seeding trials: just say “no”. *Ann Intern Med*. Aug 19.2008 149:279. [PubMed: 18711161]

11. Psaty BM, Rennie D. Clinical trial investigators and their prescribing patterns: another dimension to the relationship between physician investigators and the pharmaceutical industry. *JAMA*. Jun 21.2006 295:2787. [PubMed: 16788134]
12. Elliott, C. Mother Jones. Foundation for National Progress; San Francisco, CA: 2010. The Deadly Corruption of Clinical Trials.
13. Christensen JA, Orlowski JP. Bounty-hunting and finder's fees. *IRB*. May-Jun;2005 27:16. [PubMed: 16021797]
14. Rao JN, Cassia LJ. Ethics of undisclosed payments to doctors recruiting patients in clinical trials. *BMJ*. Jul 6.2002 325:36. [PubMed: 12098730]
15. Hill KP, Ross JS, Egilman DS, Krumholz HM. The ADVANTAGE seeding trial: a review of internal documents. *Ann Intern Med*. Aug 19.2008 149:251. [PubMed: 18711155]
16. London AJ, Kimmelman J, Emborg ME. Research ethics. Beyond access vs. protection in trials of innovative therapies. *Science*. May 14.2010 328:829. [PubMed: 20466907]
17. Carpenter D. Policy Forum: Reputation, gatekeeping and the politics of post-marketing drug regulation. *Ethics Journal of the American Medical Association*. 2006; 8:403.
18. Carpenter D. A proposal for financing postmarketing drug safety studies by augmenting FDA user fees. *Health Aff (Millwood)*. Jul-Dec;2005 :W5. Suppl Web Exclusives.
19. Falit BP. Curbing industry sponsor's incentive to design post-approval trials that are suboptimal for informing prescribers but more likely than optimal designs to yield favorable results. *Seton Hall Law Rev*. 2007; 37:969. [PubMed: 18363220]
20. Zarin DA, Tse T. Medicine. Moving toward transparency of clinical trials. *Science*. Mar 7.2008 319:1340. [PubMed: 18323436]
21. Teehan M. Guidelines for phase IV clinical trials. Joint Committee on Phase IV Clinical Trial Guidelines. *Can J Psychiatry*. Dec.1994 39:629. [PubMed: 7828115]
22. Linden M, et al. Guidelines for the implementation of drug utilization observation (DUO) studies in psychopharmacological therapy. The "Phase IV Research" Task-Force of the Association for Neuropsychopharmacology and Pharmacopsychiatry (AGNP). *Pharmacopsychiatry*. Jan.1997 30:65. [PubMed: 9035231]