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Exploring the ethical and regulatory issues in pragmatic clinical trials

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Abstract

The need for high-quality evidence to support decision-making about health and health care by patients, physicians, care providers, policymakers is well documented. However, serious shortcomings in evidence persist. Pragmatic clinical trials (PCTs) that use novel techniques and emerging information and communication technologies to explore important research questions rapidly and at a fraction of the cost incurred by more “traditional” research methods promise to help close this gap. Nevertheless, while PCTs can bridge clinical practice and research, they may also raise difficult ethical and regulatory challenges. In this article, the authors briefly survey the current state of evidence that is available to inform clinical care and other health-related decisions and discuss the potential for PCTs to improve the current state of affairs. They then propose a new working definition for pragmatic research that centers upon fitness for informing decisions about health and health care. Finally, they introduce a project, jointly undertaken by the National Institutes of Health (NIH) Health Care Systems Research Collaboratory and the National Patient-Centered Clinical Research Network (PCORnet), which addresses 11 key aspects of current systems for regulatory and ethical oversight of clinical research that pose challenges to conducting PCTs. In the series of articles commissioned on this topic in the current issue of *Clinical Trials,* each of these aspects receives its own dedicated article, with a special focus on the interplay between ethical and regulatory considerations and pragmatic clinical research that leverages

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innovative designs and new technologies and networks to inform “real-world” choices about health and health care.

Keywords

Pragmatic clinical trial; Cluster randomized trial; Ethics; Learning healthcare system; Evidence-based medicine; Clinical trials; Patient-centered outcomes research

Choices about health and health care are best made when patients, clinicians, and policymakers have access to convincing scientific evidence to inform and guide their decisions. Unfortunately, the choice of a diagnostic strategy or therapy may represent no more than an educated guess as to which approach will yield the best outcome for a patient or population. Even professional guidelines for delivering health care may lack reliable, high-quality evidence upon which to base treatment recommendations.[1] As a result, healthcare decisions, some with profound consequences, are all too often based on subjective impressions or indirect comparisons from studies that were not designed to inform decision-making with a level of evidence that is now considered to be “high quality.”[1–6]

Although a large volume of clinical research is currently being conducted, relatively few trials are designed to yield the kind of data that can actually support informed decision-making. Of the more than 350 clinical trials registered with ClinicalTrials.gov each week, the vast majority are small pilot studies, or are oriented toward exploring biological mechanisms.[7]

However, there is another path for obtaining useful evidence. Health care is being revolutionized by the progressive implementation of evolving healthcare systems and data analytics that many hope will lead to a data-intensive “learning healthcare system”[8] in which continuous learning takes place in the context of routine patient care, ultimately yielding definitive answers to clinical questions. Almost every American now has an electronic health record (EHR), and insurance claims data used for billing purposes are increasingly standardized at a national level. Integrated health systems, which encompass hospitals, medical practices, and other health services within single corporate entities, are developing enterprise data warehouses that combine structured information from these and other sources in ways that enable the distillation of high-quality data from healthcare transactions.[9,10] Furthermore, information on diagnoses, medical procedures, medications, and adverse events from a majority of the U.S. population are becoming available without any need for additional data collection.[11] At the same time, the capacity for storing and analyzing very large quantities of data has advanced to the point that the huge amount of accessible data is no longer itself a limiting factor for research.

Significant progress is also being made toward the collection of patient-reported outcomes, which can supplement already available data to shape more robust assessments of different interventions. Growing and increasingly sophisticated toolsets for collecting patient-reported outcomes,[12] widely available Internet access that now reaches 87% of American adults,[13] and wearable networked devices and mobile phones together will allow for efficient

automated collection of information and mutual communication between patients and healthcare providers. Already, this new “data fabric,” stitched together from multiple systems with different primary purposes, has the potential to support continuous learning through observational analysis of data collected as part of routine clinical practice. It could also enable the rapid implementation of prospective clinical trials when the research question at hand would best be answered with the prospective assignment of a potential therapy by randomization or some other method.

Physicians and healthcare systems that are motivated to provide the highest-quality care naturally seek to reduce the uncertainty surrounding decision-making processes affecting health and healthcare delivery. Ideally, each of their recommendations and actions should be based in high-quality evidence and reflect an informed understanding of the optimal balance of benefit and risk for their patients. Although the gold standard for such decisions has been (and remains) data from randomized clinical trials, there is increasing recognition that results from experiments done in specialized, highly controlled research settings may not be uniformly generalizable to “real-world” practice.[14]

In other words, there is a gap between efficacy and effectiveness that the analysis of existing data can bridge. Experience suggests that the best way to accelerate improvement in clinical outcomes is to conduct efficient clinical trials that enjoy broad support from patients and providers, and then implement those findings within quality health systems. This approach —itself fundamental to the learning health system concept—has yielded a number of notable successes. For example, it has likely contributed to a significant reduction in the rate of death from myocardial infarction at U.S. hospitals,[15] increased life expectancy in cystic fibrosis patients by more than a decade,[16] and led to enormous improvements in survival for children with cancer.[17] One shared aspect of these systematic efforts to improve care and medical outcomes is a transformation of traditional roles, in which patients and their families become the strongest advocates for research and seek out physicians, care teams, and practices with a commitment to research and learning in practice. In such settings, patients may band together to volunteer relevant data in order to enhance understanding of their medical and social issues and accelerate development of new diagnostic strategies and therapies.

Because medical therapies that are known to be effective usually have relatively modest effects,[18–21] establishing whether one such therapy is better than another necessitates the use of an appropriate research design. Two core elements tend to be critical: (1) sample sizes large enough to detect those effects and (2) the use of randomization to control for potential biases. Broad recognition of the importance of these factors has led to major efforts both within the United States and abroad. In 2008, the U.S. Food and Drug Administration created the Sentinel Initiative to analyze medical data from over 100 million Americans in order to illuminate issues related to the safety of medical products following their approval for marketing.[22] This system now incorporates medical insurance claims data from over 150 million Americans, as well as a growing body of data gathered from EHRs. Sentinel projects are exempt from federal requirements to obtain individual informed consent and review by institutional review boards (IRBs).[23]

Fostering clinical research on a wider scale

Two other recent initiatives are working to leverage data from clinical care for research. The National Institutes of Health (NIH) Healthcare Systems Research Collaboratory (https://www.nihcollaboratory.org/) was created in 2012 to foster innovative approaches to research in which multiple health systems use data from EHRs to conduct pragmatic clinical trials at a fraction of the cost usually associated with conventional clinical research. Shortly after the creation of the Collaboratory, the Patient-Centered Outcomes Research Institute funded the National Patient-Centered Clinical Trials Network (PCORnet; http://www.pcornet.org/) to link multiple integrated health systems and "patient-powered" networks into a national consortium for patient-centered outcomes research. Both the Collaboratory and PCORnet are focused on transforming clinical research to take advantage of new structures in healthcare systems and data analytics to conduct scientific investigations that will improve health outcomes.

Toward a working definition of pragmatic clinical trials

The types of research being undertaken by the Collaboratory and PCORnet can be described by the term *pragmatic* (or practical) *clinical trials* (PCTs). These terms have been used by different experts to denote various concepts, resulting in ambiguity that can lead to miscommunication. For this reason, we briefly explore the background of this concept and propose a definition that encompasses the entire spectrum of the types of clinical trials of interest.

The concept of the PCT emerged decades ago from the general division of randomized controlled trials into groups classified as either *mechanistic* or *pragmatic.* The former were defined by their intent to evaluate a biological or mechanistic hypothesis, while the latter were defined as trials aimed at answering questions that inform decision-makers about health and healthcare. This fundamental division according to a trial's purpose remains a critical distinction.

Schwarz and Lellouch were among the first to explore this topic. In a 1967 publication, they identified an "explanatory" approach "aimed at understanding," and a "pragmatic approach" that posed the following question: "which of the two treatments should we prefer?"[24] Nearly 2 decades later, Yusuf, Collins, and Peto published a seminal paper that proposed streamlining and simplifying trial designs to enable larger sample sizes and more reliable estimates of the modest treatment effects usually observed in unbiased assessments of therapies.[25] In 2003, Tunis, Stryer, and Clancy defined PCTs as "trials for which the hypothesis and study design are formulated based on information needed to make a decision."[26] This definition was in contrast to "explanatory trials" aimed at "better understand(ing) how and why an intervention works." According to the definition offered by Tunis and colleagues, a PCT must: "(1) select clinically relevant alternative interventions to compare, (2) include a diverse population of study participants, (3) recruit participants from heterogeneous practice settings, and (4) collect data on a broad range of health outcomes."[26]

More recently, a group of investigators developed a construct for PCTs known as PRECIS,[27] which defines "pragmatic" trials in contrast to "explanatory" trials. Based on work by a consortium of clinical trialists and methodologists, the PRECIS tool incorporates a 10-spoke "wheel" to provide a visual representation that allows investigators to assess the degree to which a trial incorporates "pragmatic" principles.[27] The purpose of this tool is not to prescribe a particular trial design strategy, but rather to provoke careful consideration of these factors as they relate to the specific purpose of each trial. In this sense, the concept of explanatory versus pragmatic trials is represented as a spectrum or continuum, in which a trial design may need to be more or less pragmatic in each dimension, given the specific exigencies of a given study.

Although each of the preceding definitions of PCTs have merit, for the purposes of this series of articles, we propose three key attributes of PCTs: (1) an intent to inform decision-makers (patients, clinicians, administrators, and policy makers), as opposed to elucidating a biological or social mechanism; (2) an intent to enroll a population relevant to the decision in practice and representative of the patients/populations and clinical settings for whom the decision is relevant; and (3) either an intent to (a) streamline procedures and data collection so that the trial can focus on adequate power for informing the clinical and policy decisions targeted by the trial or (b) measure a broad range of outcomes.

Given these attributes, a common-sense definition for a PCT would thus be: *Designed for the primary purpose of informing decision-makers regarding the comparative balance of benefits, burdens and risks of a biomedical or behavioral health intervention at the individual or population level*.

Ethical and regulatory challenges

Although the technical and analytical elements needed to support a learning health system are now emerging, another key issue has arisen that is inherent to PCTs: namely, whether existing regulatory and ethical frameworks governing medical practice and research are capable of protecting the rights and interests of patients and research participants while remaining sufficiently flexible to accommodate new research methods that could ultimately help reduce death and disability.

The ethical principles articulated in the Belmont Report[28] and the regulatory structures for research based on those principles have served society well by establishing an effective system for research oversight. Importantly, a central assumption of this system is that medical practice should be distinguished from research. In the former, the physician is viewed as a professional with a primary fiduciary relationship to the patient who integrates available knowledge and experience for the patient's direct and individual benefit. In contrast, a researcher's primary interest is the creation of generalizable knowledge, in pursuit of which the researcher must adhere to explicit protocols and procedures.[29]

Although much of this construct remains relevant, the context has changed since the publication of the Belmont Report. The typical physician is now likely to be part of a healthcare team that includes many other responsible clinicians, all of whom work for a

corporation or health system subject to intense pressure on financial margins and performance metrics—and such systems increasingly emphasize the use of data to measure quality and guide a standardized approach to clinical care. Further, as the field of clinical research has matured and the tools at its disposal have grown increasingly sophisticated, the frailty of the existing body of medical knowledge used to support practice has been revealed. It is increasingly clear that a potential solution lies in a data-rich integration of research and practice, but such integration poses challenging questions about appropriate ethical and regulatory oversight.

The Collaboratory/PCORnet experience: adapting to a novel research landscape

Relatively early in their respective efforts, members of both the Collaboratory and PCORnet encountered challenges arising from current ethical and regulatory frameworks. For example, early trials in the Collaboratory confronted difficult questions about the acceptability of modifying consent process and ensuring that mechanisms were in place to address safety monitoring.[30] Ultimately, many of these issues were solved through deliberations that convened multiple stakeholders who were facilitated by the Collaboratory's Ethics and Regulatory Core.[31] In PCORnet, privacy was a chief concern, necessitating the formation of a special Task Force to supplement the expertise of an Ethics and Regulatory Task Force.[32] Nevertheless, it became apparent that long-term success in implementing new clinical research methods (which include designs such as randomized comparative-effectiveness trials, cluster-randomized trials, and rapidly conducted observational studies) would also require a reexamination of existing ethical and regulatory approaches to oversight of medical practice and research.

An expert meeting held in Bethesda, Maryland in 2013 focused on pragmatic cluster-randomized trials, followed by publications describing and expanding upon the deliberations of that meeting, articulated key ethical and regulatory issues facing pragmatic clinical research.[33,34] This special series of articles in *Clinical Trials* builds upon this work to address 11 prominent ethics and regulatory challenges specifically in the setting of PCTs. These include the following: (1) the role of gatekeepers;[35] (2) harmonization of institutional review boards;[36] (3) distinctions between research and quality-improvement activities;[37] (4) the nature of interventions in PCTs;[38] (5) identifying direct and indirect subjects;[39] (6) determining what constitutes "no more than minimal risk" research in PCTs;[40] (7) the use of waiver or modification of informed consent;[41] (8) engaging vulnerable subjects in PCTs;[42] (9) investigations involving the use of FDA-regulated products;[43] (10) privacy;[44] and (11) the role of data monitoring.[45]

Work on these papers was coordinated by the Collaboratory with funding from the National Institutes of Health. In order to address these issues, we assembled multidisciplinary teams with expertise in each of the areas. Team members were recruited through the Collaboratory, PCORnet, and elsewhere. The teams initially met by teleconference and created draft manuscripts. An in-person meeting including each writing group was convened in Baltimore, Maryland in January 2015 to review and refine the respective papers, which were subsequently sent for independent blinded peer review, and in most cases, further revision.

Pragmatic clinical trials are not in themselves novel, and issues arising from methods commonly used in PCTs have already prompted serious engagement.[46] However, an increasingly information-intensive practice environment and the corresponding opportunity to mitigate or prevent the harm done when important research questions continue to go unanswered present an urgent case for reexamining the ethical and regulatory matrix in which pragmatic research takes place. But at the same time, proposed systemic improvements to existing oversight systems must be carefully examined to ensure that the rights and interests of patients and research participants are appropriately protected as important pragmatic research is implemented.

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