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Ethics and Regulatory Challenges and Opportunities in Patient-Centered Comparative Effectiveness Research

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Abstract

The Affordable Care Act includes provisions for the conduct of large-scale, patient-centered comparative effectiveness research. Such efforts aim towards the laudable moral goal of having evidence to improve health care decision making. Nevertheless, these pragmatic clinical research efforts that typically pose minimal incremental risk and are enmeshed in routine care settings perhaps surprisingly encounter an array of ethics and regulatory challenges and opportunities for academic health centers. An emphasis on patient-centeredness forces an examination of the appropriateness of traditional methods used to protect the rights, interests, and welfare of participants. At the same time, meaningful collaboration with patients throughout the research process also necessitates ensuring that novel approaches to research (including recruitment and consent) entail necessary protections regarding such issues as privacy. As the scientific and logistical aspects of this research are being developed, substantial attention is being focused on the accompanying ethics and regulatory issues that have emerged, which should help to facilitate ethically appropriate research in a variety of contexts.

The confluence of advances in health information technologies and clinical research operations along with increased acknowledgement of the need to have patients meaningfully engaged in research makes it possible to address some of the critical information gaps

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regarding routine health care. Accordingly, the Affordable Care Act includes provisions for the conduct of patient-centered comparative clinical effectiveness research through the Patient-Centered Outcomes Research Institute (PCORI).[1] While such “pragmatic” or “practical” clinical trials that are intended to inform decision makers about health-related decisions, rather than address a mechanistic hypothesis as in the case of conventional clinical research, are not new, the current scope is unprecedented.

To fulfill its mandate, PCORI is taking a variety of approaches to conducting research. Of particular relevance for academic health centers is the National Patient-Centered Clinical Research Network (PCORnet), which is essentially a network of networks that is designed to serve as a platform for this research. PCORnet includes both Clinical Data Research Networks (CDRNs) and Patient-Powered Research Networks (PPRNs).[2] CRDNs involve hospitals and health systems. PPRNs consist of groups of patients focused on particular diseases or conditions. Together these networks provide crucial perspectives and expertise to conduct patient-centered outcomes research. However, these promising research efforts can encounter an array of ethics and regulatory challenges for academic health centers. Addressing these issues will be fundamental to achieving the laudable goal of helping to meet the broad moral claim to obtain evidence to improve clinical practice.

The early experience of the National Institutes of Health's (NIH's) Health Care Systems Research Collaboratory offers insight not only into the types of issues that will be faced by those conducting patient-centered clinical research, but also how to navigate some of them. The Collaboratory is conducting a series of demonstration projects, each of which involves a pragmatic research design, is performed across different health systems, and uses the electronic health record as the primary means of data collection. These demonstration projects typically pose minimal incremental risk and burdens to participants, yet they have raised some perhaps surprisingly complex ethics and regulatory issues.[3] These include questions related to consent, risk determination, the nature of interventions, identifying research participants, regulated products, Institutional Review Boards, research and quality improvement, vulnerable subjects, data monitoring, and gatekeepers.[4] Further, pragmatic trials that employ cluster randomization face additional issues.[5]

As PCORnet was being formed, to better understand the potential ethical and regulatory barriers to research and needs regarding them, the CDRNs and PPRNs were surveyed.[6] The most prevalent ethics concerns overall were related to informed consent, patient engagement, privacy and confidentiality, and data sharing. The most prevalent regulatory concerns overall were related to Institutional Review Boards, privacy and confidentiality, and informed consent. These concerns reveal an uncomfortable fit between the usual practices of research oversight, and measures designed to ensure the ethical conduct of pragmatic clinical research where there is also a set of somewhat different protections in place that are based in clinical practice. While it is of primary importance to ensure that research is ethically sound, it is also important to consider how our current approaches to doing so might be inappropriately hindering research without actually offering protection.[7]

The results of the survey of PCORnet CDRNs and PPRNs demonstrated considerable overlap in the anticipated ethics and regulatory challenges with those faced in the NIH

Collaboratory. However, in PCORnet, substantial attention also rightly focused on privacy given that its proposed approach is dependent upon information sharing.[8] In addition, PCORnet's non-negotiable commitment to robust patient engagement has been accompanied by other challenges as well as opportunities. Consistent with the history and spirit of disease-based activism, PPRNs voiced concern over the delays that can be associated with research oversight. Although at first glance such concerns seem similar to those articulated by researchers frustrated by the bureaucratic delays that may accompany research oversight, the fact that they were coming from those who were supposed to be "protected" by the oversight process underscores the need to identify and implement appropriate efficiencies. Accordingly, PPRNs are devoting substantial attention to developing alternative models for securing consent (such as web-based platforms and mobile applications) and information sharing. Although such approaches are welcome, it will be important to ensure that well-intentioned efforts provide sufficient protections for the rights, interests, and welfare of participants.

At the same time, collaborating on patient-centered research requires CDRNs to develop ways of engaging patients as true research partners while also ensuring adherence to other ethical and regulatory requirements. For example, what are the implications of having a patient advocate as a full member of a research team within an academic medical center? What is the appropriate training regarding research ethics? What are the implications under the privacy rule of the Health Insurance Portability and Accountability Act?

To begin to more fully address the sorts of ethics and regulatory issues faced in large-scale pragmatic clinical trials, including patient-centered comparative effectiveness research, the NIH Collaboratory, with additional support from PCORI, assembled a series of multi-stakeholder teams to develop in-depth academic manuscripts on a selected set of these issues. Following several months of writing and an in-person meeting, manuscripts on each issue underwent peer-review and were published as a special series in *Clinical Trials*.[9] Now that these articles are available in the literature, there is a hope of disseminating the information through several channels such as an online Living Textbook and a series of web-based "Grand Rounds" sessions to prompt discussion and debate about ethics and regulatory issues faced in pragmatic clinical research. In addition, there is a plan to develop a set of derivative products that would be useful to those designing, conducting, overseeing, or participating in such research. For instance, a possible derivate product would be a draft charter for Data Safety and Monitoring Boards charged with oversight of pragmatic clinical trials.

Nevertheless, for major patient-centered pragmatic clinical trials and comparative effectiveness research initiatives to ethically meet the strong moral claim of providing the data needed to inform health care decision-making, additional efforts will need to focus on the ethics and regulatory aspects of the research. This arguably includes the imperative to gather data regarding these issues. First, of substantial importance will be information about the attitudes of the general public toward this type of research and the related ethics and regulatory issues. Fortunately, there are several such projects sponsored by the NIH and PCORI ongoing with some initial published reports. Second, investigators conducting this research should be encouraged to actively evaluate the approaches they develop to address

specific ethics and regulatory challenges, such as electronic consent that is deployed across multiple clinical settings. Third, as PPRNs and CDRNs tackle the ethics and regulatory issues they face, they should be encouraged to describe their efforts so that they can be evaluated by others and further adopted if appropriate. In aggregate, these data should be helpful as policies and practices are being shaped, which should help to facilitate ethically appropriate research in a variety of contexts.

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