NIH Collaboratory Rethinking Clinical Trials®

Health Care Systems Research Collaboratory

Ethical and Regulatory Issues in Pragmatic Clinical Trials: Special Issue of *Clinical Trials*

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This document, developed in 2015, provides background and links to a series of 12 articles on the ethics and regulatory challenges in pragmatic clinical trials. Each article in the special issue of *Clinical Trials* describes a topic in detail (e.g., privacy, informed consent) and, where possible, attempts to provide guidance for future pragmatic clinical trials. The project was supported by the NIH Collaboratory, with additional support from the Patient-Centered Outcomes Research Institute.

Background

There is historical and ongoing controversy regarding the ethical conduct of research involving human subjects. Throughout the 20th century, several studies designed to gain medical knowledge were carried out at the cost of harm to marginalized or vulnerable populations [1]. Recognition of these abuses led to the articulation of ethical principles for clinical research and development of regulations to ensure the protection of human subjects. The Belmont Report outlines three fundamental ethical principles for human subjects research: respect for persons, beneficence, and justice [2]. These principles serve as the foundation for federal research regulations, which are codified as 21 CFR 50 (FDA regulations on the protection of human subjects) and 45 CFR 46 (the Common Rule). Though these policies set in place important protections, they viewed clinical research as a highly controlled system somewhat separate from medical practice. This divide has resulted in a failure to provide decision-makers with high-quality evidence to make the best choices in medical practice [3-5]. As the field of clinical research has evolved to address this gap, it has become challenging to apply the current regulatory and ethical paradigms. This is evident among an increasing number of pragmatic clinical trials, which study clinically relevant alternatives (often approved or accepted treatments) in representative populations at the point of clinical care [5,6].

In contrast to traditional clinical trials that study new therapies in highly controlled settings, pragmatic clinical trials rely on streamlined processes to measure outcomes in heterogeneous populations in real-world clinical settings [6]. Some pragmatic trials use cluster randomization, in which groups (e.g., clinics, hospitals, cities) are randomized rather than individuals. Because of these differences, the application of ethical principles and regulations to pragmatic clinical trials is complex [7,8]. Questions include, what constitutes research versus a quality improvement initiative under current regulatory guidelines; how should the criteria for determining what is minimal risk research be appropriately applied; and when is a waiver or alteration of informed consent ethical and justified. As observed in the Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial (SUPPORT), there can be risks and ethical controversy even in studies comparing standard or accepted treatment options.

Attempts have been made to respond to some of the ethical and regulatory challenges faced in the conduct of pragmatic clinical trials, and more broadly, in a healthcare system that integrates research with clinical care. For example, the Ottawa Ethics of Cluster Randomized Trials Consensus Group issued a statement with recommendations for the ethical design and conduct of cluster randomized trials [9]. Issues specific to pragmatic cluster randomized trials were discussed in a subsequent workshop convened by the NIH Health Care Systems Research Collaboratory [7]. Kass and colleagues have argued that the distinction between clinical practice and research is increasingly blurred as our healthcare system advances toward a learning healthcare system [10], and current regulations and ethical principles do not account for this changing landscape. They proposed a new ethics framework for the learning healthcare system [11,12], which has been discussed and debated [13,14].

Part of the changing research environment involves a shift toward patient-centeredness [15]. Patient-centered outcomes research engages patients throughout the research process in determining what research questions are important, providing input during study design and conduct, and planning the dissemination and implementation of results [16,17]. In keeping with patient-centered research principles, engaging patients in shaping ethical and regulatory guidelines for clinical research would promote autonomy and show respect for persons [18].

NIH Collaboratory and PCORnet Writing Project

Recognizing that there are unresolved ethical and regulatory issues critical to the conduct of pragmatic clinical trials [7,8], the NIH Health Care Systems Research Collaboratory and the National Patient-Centered Clinical Research Network (PCORnet) invited a group of stakeholders, including ethicists, clinical trialists, institutional review board professionals, and patient representatives, to address a set of priority issues. The goal was to produce academic manuscripts that would thoroughly review the topics; identify best practices and provide guidance for future pragmatic clinical trials where possible; and describe issues that remain to be resolved. Work groups initiated discussions over teleconferences and then convened a day-and-a-half of face-to-face meetings with time for cross-group discussions; 78 attendees from 50 organizations were in attendance. The culmination of this effort was a special issue in *Clinical Trials*, described below.

Special Issue Articles

The table contains brief descriptions of each article in the issue with links to the open access publication and related PCT Grand Rounds webinars, presented by the authors. The entire special issue of the journal is available online.

***Clinical Trials* Special Issue**	
Citation	**Description**
Exploring the ethical and regulatory issues in pragmatic clinical trials Califf RM, Sugarman J. Clin Trials 2015;12:436-441. doi: 10.1177/1740774515598334.	This introductory article describes changes in clinical research methods that are occurring to address shortcomings in high-quality evidence available for making healthcare decisions. The authors propose a new working definition for pragmatic clinical trials and review ongoing national efforts to conduct such trials. Finally, they describe the 11 ethics and regulatory topics faced in the conduct of pragmatic research addressed by articles throughout the special issue.

***Clinical Trials* Special Issue**	
Citation	**Description**
Gatekeepers for pragmatic clinical trials Whicher DM, Miller JE, Dunham KM, Joffe S. Clin Trials 2015;12:442-448. doi: 10.1177/1740774515597699. Grand Rounds, November 20, 2015	Gatekeepers in clinical research have traditionally been considered individuals or entities who allow or deny access to potential research participants. In discussing gatekeepers for pragmatic clinical trials, the authors recognize that gatekeepers control access to a variety of resources necessary to implement a trial, such as financial support, institutional infrastructure, and patient data, in addition to the patients themselves. Gatekeepers may include research sponsors, regulatory agencies, payers, health system and other organizational leadership, research team leadership, human research protection programs, advocacy and community groups, and clinicians. These individuals and entities can have conflicting obligations or interests that influence their decisions. This article outlines a set of criteria to help guide ethical decision-making when gatekeepers are determining whether to allow access to resources for a pragmatic clinical trial.
Harmonization and streamlining of research oversight for pragmatic clinical trials O'Rourke PP, Carrithers J, Patrick-Lake B, Rice TW, Corsmo J, Hart R, Drezner MK, Lantos JD. Clin Trials 2015;12:449-456. doi: 10.1177/1740774515597685. Grand Rounds, January 15, 2016	In contrast to much literature that has focused on centralizing institutional review board (IRB) processes for multisite research, this article describes potential opportunities for harmonization and streamlining throughout the overall research oversight process. The authors draw distinctions between IRB and institutional responsibilities and then describe approaches for coordination under various models. Modifications to research oversight processes for pragmatic clinical trials are intended to promote more efficient and consistent review while maintaining review quality and the protection of research participants. The topics discussed are also relevant to traditional multisite trials.

***Clinical Trials* Special Issue**	
Citation	**Description**
Oversight on the borderline: quality improvement and pragmatic research Finkelstein JA, Brickman AL, Capron A, Ford DE, Gombosev A, Greene S, Iafrate RP, Kolaczkowski L, Pallin S, Pletcher MJ, Staman KL, Vazquez MA, Sugarman J. Clin Trials 2015;12:457-466. doi: 10.1177/1740774515597682. Grand Rounds, June 17, 2016	Classification of activities as quality improvement (QI) or research has regulatory and ethical implications. Research, according to federal regulations, is intended to create generalizable knowledge, whereas QI is designed to bring about immediate improvements in healthcare delivery in particular settings. This distinction has been challenging to apply in pragmatic research, where learning occurs within healthcare delivery settings. This article defines three types of QI: routine QI, non-routine QI, and research QI. The authors then provide recommendations for ethical oversight appropriate to each category.
Harms, benefits, and the nature of interventions in pragmatic clinical trials Ali J, Andrews JE Jr, Somkin CP, Rabinovich CE. Clin Trials 2015;12:467-475. doi: 10.1177/1740774515597686. Grand Rounds, February 19, 2016	Pragmatic clinical trials can have a variety of types of interventions (medical, behavioral, and/or technological) and targets for those interventions (patients, clinicians, and/or healthcare system processes). Further, a single trial can have a multiple overlapping intervention types and targets, with some involved more directly than others. This diversity in design influences the regulatory and ethical considerations for these trials. The authors describe a comprehensive approach to assessing net risks and benefits of pragmatic clinical trials, taking into account the nature of interventions and all potentially affected individuals or entities.
Ethical responsibilities toward indirect and collateral participants in pragmatic clinical trials Smalley JB, Merritt MW, Al-Khatib SM, McCall D, Staman KL, Stepnowsky C. Clin Trials 2015;12:476-484. doi: 10.1177/1740774515597698. Grand Rounds, March 18, 2016	Features of pragmatic clinical trials require new thinking about what it means to be a research participant. For example, because they are conducted in real-world settings, pragmatic clinical trials may affect individuals by way of routine exposure to an environment (e.g., a hospital). The authors define three categories of research participants for pragmatic clinical trials: direct participants, indirect participants, and collateral participants. Recognition of the different individuals and manner in which they are affected by pragmatic research can help to ensure their rights and welfare are protected.

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Citation	**Description**
Considerations for the determination of minimal risk in pragmatic clinical trials Lantos JD, Wendler D, Septimus E, Wahba S, Madigan R, Bliss G. Clin Trials 2015;12:485-493. doi: 10.1177/1740774515597687. Grand Rounds, April 15, 2016	A determination of whether a trial can be considered minimal risk under federal regulations has important implications for how it is conducted. For pragmatic clinical trials, which typically compare widely used therapies in routine clinical practice settings, minimal risk determinations have been variable and confusing. The authors examine factors involved in the determination of minimal risk for pragmatic clinical trials and advocate for an assessment based on incremental risk. The implications for informed consent are explored.
Use of altered informed consent in pragmatic clinical research McKinney RE Jr, Beskow LM, Ford DE, Lantos JD, McCall J, Patrick-Lake B, Pletcher MJ, Rath B, Schmidt H, Weinfurt K. Clin Trials 2015;12:494-502. doi: 10.1177/1740774515597688. Grand Rounds, May 20, 2016	Conventional informed consent processes can render some pragmatic clinical trials difficult or impossible to conduct. These trials rely on streamlined processes to collect data in clinical care settings with minimal interruptions in workflow. Under current federal regulations, all criteria for waiver of informed consent must be met before an alternative consent approach can be considered. There is also variability in how these criteria are applied. The authors argue that new standards for waiver and modification of informed consent are needed that will allow pragmatic clinical trials to be conducted while protecting participants' rights and welfare. The ethical and regulatory implications, as well as various forms of altered informed consent, are described.
The ethics and regulatory landscape of including vulnerable populations in pragmatic clinical trials Welch MJ, Lally R, Miller JE, Pittman S, Brodsky L, Caplan AL, Uhlenbrauck G, Louzao DM, Fischer JH, Wilfond B. Clin Trials 2015;12:503-510. doi: 10.1177/1740774515597701. Grand Rounds, December 18, 2015	Research policies and regulations mandate special protections for certain populations considered vulnerable, including pregnant women, fetuses, neonates, children, prisoners, persons with physical handicaps or mental disabilities, and disadvantaged persons. This article describes the regulatory and ethical considerations for including vulnerable populations in pragmatic clinical trials. The authors assert that while protection from harm remains important, there is also an ethical obligation to allow research participation in order to better inform healthcare for vulnerable populations. Recommendations are made for how

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	to balance protection with inclusion according to the risk of the study and the specific regulations that apply.
The Food and Drug Administration and pragmatic clinical trials of marketed medical products Anderson ML, Griffin J, Goldkind SF, Zeitler EP, Wing L, Al-Khatib SM, Sherman RE. Clin Trials 2015;12:511-519. doi: 10.1177/1740774515597700. Grand Rounds, July 15, 2016	The US Food and Drug Administration (FDA) has jurisdiction over almost all clinical investigations involving drugs and devices, even those already approved for marketing. This article explains that pragmatic clinical trials exempt from investigational new drug (IND) and investigational device exemption (IDE) requirements remain subject to the FDA requirements for informed consent and institutional review board review. Obtaining individual informed consent can be overly burdensome for pragmatic clinical trials, many of which can be considered low risk. The authors propose that the FDA adopt a risk-based approach to determining the need for informed consent, similar to its process for determining IND and IDE exemption.
Privacy and confidentiality in pragmatic clinical trials McGraw D, Greene SM, Miner CS, Staman KL, Welch MJ, Rubel A. Clin Trials 2015;12:520-529. doi: 10.1177/1740774515597677. Grand Rounds, August 19, 2016	In this article, the authors assert that privacy protections must be balanced with an imperative to learn from data collected during routine clinical care. The ethical principles and regulatory framework influencing the use of medical data for research are discussed. The authors then examine novel approaches to consent and authorization and their potential to address privacy concerns in pragmatic clinical trials. Patients' perspectives on the use of routine medical data for research are also considered.
Data monitoring committees for pragmatic clinical trials Ellenberg SS, Culbertson R, Gillen DL, Goodman S, Schrandt S, Zirkle M. Clin Trials 2015;12:530-536. doi: 10.1177/1740774515597697. Grand Rounds, October 16, 2015	Certain features of pragmatic clinical trials may warrant special attention when establishing data monitoring committees and developing plans for interim data monitoring. The authors describe which pragmatic clinical trials may need an independent data monitoring committee. They then use the Pragmatic-Explanatory Continuum Indicator Summary (PRECIS) tool, which contrasts pragmatic and explanatory clinical trials, to review characteristics of pragmatic clinical trials that may have implications for data monitoring. These

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	include broad eligibility criteria, less attention to protocol adherence, and increased focus on subjective patient-reported outcomes. Analytical issues such as early termination and cluster designs are also discussed. Finally, the authors examine the expertise needed for data monitoring committees of pragmatic clinical trials, including the role of patient representatives.

Bibliography

1. Kahn JP, Mastroianni AC, Sugarman J. Beyond consent: seeking justice in research. New York: Oxford University Press, 1998.

2. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research. April, 1979. Available at: http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html. Accessed December 9, 2014.

3. Kessler R, Glasgow RE. A proposal to speed translation of healthcare research into practice: dramatic change is needed. Am J Prev Med 2011;40:637-644. PMID: 21565657. doi: 10.1016/j.amepre.2011.02.023.

4. Rothwell PM. External validity of randomised controlled trials: "to whom do the results of this trial apply?". Lancet 2005;365:82-93. PMID: 15639683. doi: 10.1016/S0140-6736(04)17670-8.

5. Tunis SR, Stryer DB, Clancy CM. Practical clinical trials: increasing the value of clinical research for decision making in clinical and health policy. JAMA 2003;290:1624-1632. PMID: 14506122. doi: 10.1001/jama.290.12.1624.

6. Califf RM, Sugarman J. Exploring the ethical and regulatory issues in pragmatic clinical trials. Clin Trials 2015;12:436-441. doi: 10.1177/1740774515598334.

7. Anderson ML, Califf RM, Sugarman J. Ethical and regulatory issues of pragmatic cluster randomized trials in contemporary health systems. Clin Trials 2015;12:276-286. PMID: 25733677. doi: 10.1177/1740774515571140.

8. Sugarman J, Califf RM. Ethics and regulatory complexities for pragmatic clinical trials. JAMA 2014;311:2381-2382. PMID: 24810723. doi: 10.1001/jama.2014.4164.

9. Weijer C, Grimshaw JM, Eccles MP, et al. The Ottawa Statement on the ethical design and conduct of cluster randomized trials. PLoS Med 2012;9:e1001346. PMID: 23185138. doi: 10.1371/journal.pmed.1001346.

10. Kass NE, Faden RR, Goodman SN, et al. The research-treatment distinction: a problematic approach for determining which activities should have ethical oversight. Hastings Cent Rep 2013;43:S4-S15. doi: 10.1002/hast.133.

11. Faden RR, Beauchamp TL, Kass NE. Informed consent, comparative effectiveness, and learning health care. N Engl J Med 2014;370:766-768. doi: 10.1056/NEJMhle1313674.

12. Faden RR, Kass NE, Goodman SN, et al. An ethics framework for a learning health care system: a departure from traditional research ethics and clinical ethics. Hastings Cent Rep 2013;43:S16-S27. doi: 10.1002/hast.134.

13. Kim SY, Miller FG. Informed consent for pragmatic trials—the integrated consent model. N Engl J Med 2014;370:769-772. PMID: 24552326. doi: 10.1056/NEJMhle1312508.

14. The Hastings Center. Ethical Oversight of Learning Health Care Systems. Available at: http://www.thehastingscenter.org/LearningHealthCareSystems/. Accessed August 5, 2015.

15. Sacristan JA. Clinical research and medical care: towards effective and complete integration. BMC Med Res Methodol 2015;15:4. PMID: 25575454. doi: 10.1186/1471-2288-15-4.

16. Frank L, Basch E, Selby JV, et al. The PCORI perspective on patient-centered outcomes research. JAMA 2014;312:1513-1514. PMID: 25167382. doi: 10.1001/jama.2014.11100.

17. Gabriel SE, Normand SL. Getting the methods right—the foundation of patient-centered outcomes research. N Engl J Med 2012;367:787-790. PMID: 22830434. doi: 10.1056/NEJMp1207437.

18. Lantos JD. U.S. Research Regulations: Do They Reflect the Views of the People They Claim to Protect? Ann Intern Med 2015;162:731-732. doi: 10.7326/M15-0632.