Ethical & Regulatory Oversight Considerations
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Learning goals
- Learn about the regulatory and ethical challenges of conducting ePCTs (and resources for addressing them!)
- Discuss unique needs of historically underrepresented and mistreated groups
Important things to know

- Ethical analysis for ePCTs is a work in progress
- Federal and local policies and/or their operationalization regarding the oversight of ePCTs are in flux
- There is often confusion and misunderstanding about ePCTs on the part of patient-subjects, providers, IRBs, and DSMBs

ePCTs are motivated by ethical imperatives

ePCTs also raise interesting ethical and regulatory questions
Evolving understanding of ethical/regulatory issues for ePCTs

- Informed consent
- Data monitoring
- Defining minimal risk
- Research/quality improvement distinction
- Vulnerable subjects
- IRB harmonization
- Data sharing
- Identifying direct and indirect subjects
- Gatekeepers
- FDA-regulated products
- Nature of ePCT interventions
- Privacy
- Management of collateral findings

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, and policy-makers is well documented. However, serious shortcomings in evidence persist. Pragmatic clinical trials that use novel techniques including 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 pragmatic clinical trials 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 pragmatic clinical trials to improve this 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-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 pragmatic clinical trials. In the series of articles commissioned on this topic published in this issue of Clinical Trials, each of these aspects is addressed in a dedicated article, with a special focus on the interplay between ethical and regulatory considerations and pragmatic clinical research aimed at informing "real-world" choices about health and health care.

Keyword

Clinical trials, cluster-randomized trial, ethics, evidence-based medicine, learning health-care system, patient-centered outcomes research, pragmatic clinical trial
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Informed Consent, Waivers, and Alterations
Approaches to notification & authorization

- Informed consent
- Nondisclosure

**Alterations**

- Broad notification
- Opt-out
- Opt-in

True or false: The same regulatory criteria apply for both waivers and alterations of consent.
Which of the following is NOT an acceptable justification for waiving or altering informed consent?

Criteria for waiver/alteration of consent

- Research involves no more than minimal risk
- Research could not practicably be carried out without the waiver or alteration
- If research involves using identifiable private information or identifiable biospecimens, it could not practicably be carried out without using such information or biospecimens in an identifiable format
- Waiver or alteration will not adversely affect the rights and welfare of the subject
- Where appropriate, subjects will be provided with additional information about their participation

(Common Rule: 45 CFR 46.116(f))
Criteria for waiver/alteration of informed consent

- Research involves no more than minimal risk

"Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests." §46.102

Distinguishing research risks

- “Minimal risk” refers only to the additional risk of the research (not the underlying risk of the disease)
Regulatory permissible ≠ ethically optimal

- Regulatory criteria for waivers and alterations identical…but they are ethically distinct
  - Aim for alterations to consent to be the “minimum necessary”
  - Consider options to demonstrate respect for persons, beyond consent processes

Examples: information sheets or flyers
Discussion:

- Why might a study team notify patients about a PCT, even if the study meets the regulatory criteria for a waiver of consent?
Why monitor for changes to risk-benefit balance and data integrity?

- Protect the welfare of research participants
- Inform decision making for patients with the same clinical condition outside the trial
- Ensure trial results will be informative

Data monitoring committee

Group of experts that review the ongoing conduct of a clinical trial to ensure continuing patient-subject safety as well as the validity and scientific merit of the trial
Unique considerations for monitoring ePCTs

- Poor adherence to intervention: problem or finding?
- Limited or delayed access to study outcomes during study conduct & implications for early termination
- Differential data collection/contact by study arm

Adapted from Greg Simon, PCT Grand Rounds, December 8, 2017

Unique considerations for monitoring ePCTs

- Nature of the study interventions (and evidence base regarding their safety)
- Level of data needed to change practice, especially when studying treatments in wide use?
- Differential obligations for trials using waivers/alterations of consent?

Adapted from Greg Simon, PCT Grand Rounds, December 8, 2017
Data Sharing & PCTs

Increasing expectation for sharing clinical trials data
Challenges for Sharing PCT Data

Often conducted with waivers or alterations of informed consent

Use of extant data (e.g., EHR, claims)

If PCT uses a waiver/alteration of consent…

- Cannot assume sharing data is consistent with preferences of patient-subjects
- Cannot rely on informed consent to fulfill ethical obligation of respect

What does it mean to respect patient-subjects in the context of (not) sharing data from a PCT conducted under a waiver/alteration of informed consent?
Implications of Embeddedness for PCT Data Sharing

- Data may be “about” those beyond patient-subjects
- Increased risk of privacy violations
- Increased risk of biased/misleading analyses
- Data may be controlled by a third party (e.g., CMS)

PCTs and Underrepresented Groups
PCTs, equity, and underrepresented groups

- Traditional explanatory research often lacks representativeness
- Yet embedded nature of PCTs may similarly reinforce research inequities

Promoting equity and representativeness

- Selection of health system partners
- Prospective engagement of stakeholders to identify and mitigate barriers to recruitment and implementation
Justice and equity in pragmatic clinical trials: Considerations for pain research within integrated health systems

Joseph Ali1,2 | Alison F. Davis3 | Diana J. Burgess4,5 | Daniel I. Rhon6
Robert Vining7 | Stacey Young-McCaughan8,9 | Sean Green3 | Robert D. Kerns10,11

Achieving Health Equity in Embedded Pragmatic Trials for People Living with Dementia and Their Family Caregivers

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Important things to do

- Designate someone to track local and federal regulatory developments and serve as liaison with regulatory/oversight bodies
- Budget sufficient time for proactive education and negotiations with relevant regulatory/oversight bodies
- Identify all parties who might be affected by the study and its findings; consider protections and processes
Resource: The Living Textbook

Visit the Living Textbook of Pragmatic Clinical Trials at

www.rethinkingclinicaltrials.org

Question & Answer