Ethical and Regulatory Oversight Considerations

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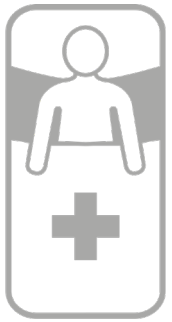
Learning goals

- Learn about the regulatory and ethical challenges associated with ePCTs
- Understand considerations for distinguishing quality improvement versus research

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 patients, providers, IRBs, and DSMBs

ePCTs are motivated by ethical imperatives



ePCTs also raise interesting ethical and regulatory questions

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Evolving understanding of unique 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

Article

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Exploring the ethical and regulatory issues in pragmatic clinical trials

Robert M Califf[1,2,*] and Jeremy Sugarman[3,4]

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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Current ethics/regulatory in flux

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Determining if the Common Rule applies

- ✓ The activity is conducted or supported by HHS
- ✓ The activity is non-exempt human subjects research

To determine whether the activity is non-exempt human subjects research, **ask these questions:**

1) Does the activity involve **research**?
2) Does the research involve **human subjects**?
3) Is the human subjects research **exempt**?

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Does the ePCT involve a research intervention?

Definition of research:

Research means a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge

Common Rule: 45 CFR 46.102(l)

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Distinguishing QI versus research

- Quality improvement activities
  - Are not subject to the Common Rule
  - Are intended to improve the quality of a healthcare delivery locally
  - Are not intended to contribute to generalizable knowledge

Regulatory perspective:
Who are the subjects in ePCTs?

Definition of human subject:

Human subject means a living individual about whom an investigator conducting research:

- obtains **information or biospecimens** through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or

- obtains, uses, studies, analyzes, or generates **identifiable private information or identifiable biospecimens**

Common Rule: 45 CFR 46.102(e)(1)

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Regulatory perspective:
Who are the subjects in ePCTs?

- **Test Case:**
  - Nursing homes randomized to receive a training intervention for staff
  - Post-training, investigators use data from medical records to assess patient health outcomes and staff behaviors

Largent et al. Ethical & Regulatory Issues for Embedded Pragmatic Trials Involving People Living with Dementia. JGAS 2020.

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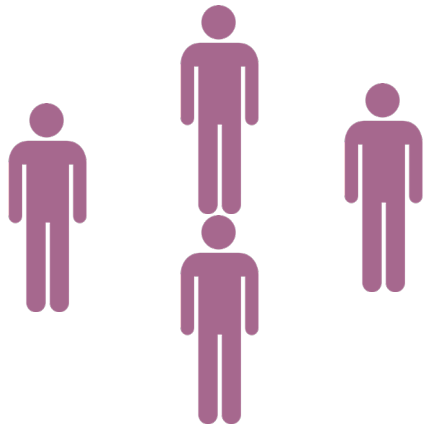
Regulatory & ethical challenges of ePCTs



Ethical, not regulatory, question:

Whose rights and welfare need to be protected?

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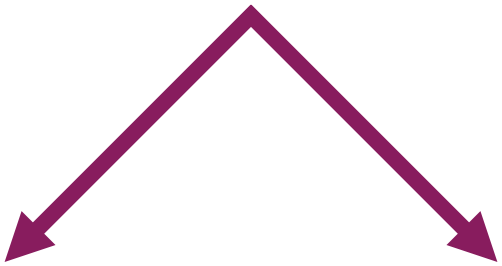
Types of participants in an ePCT



Direct

Indirect

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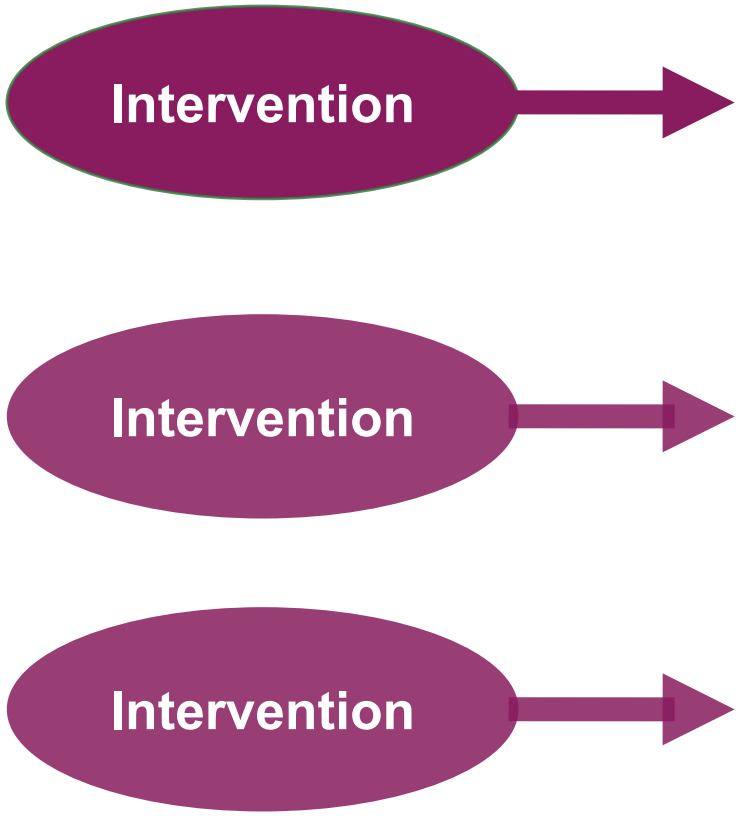
Direct participants

Immediate or mediated targets of the intervention



Patients

Providers

Clinics

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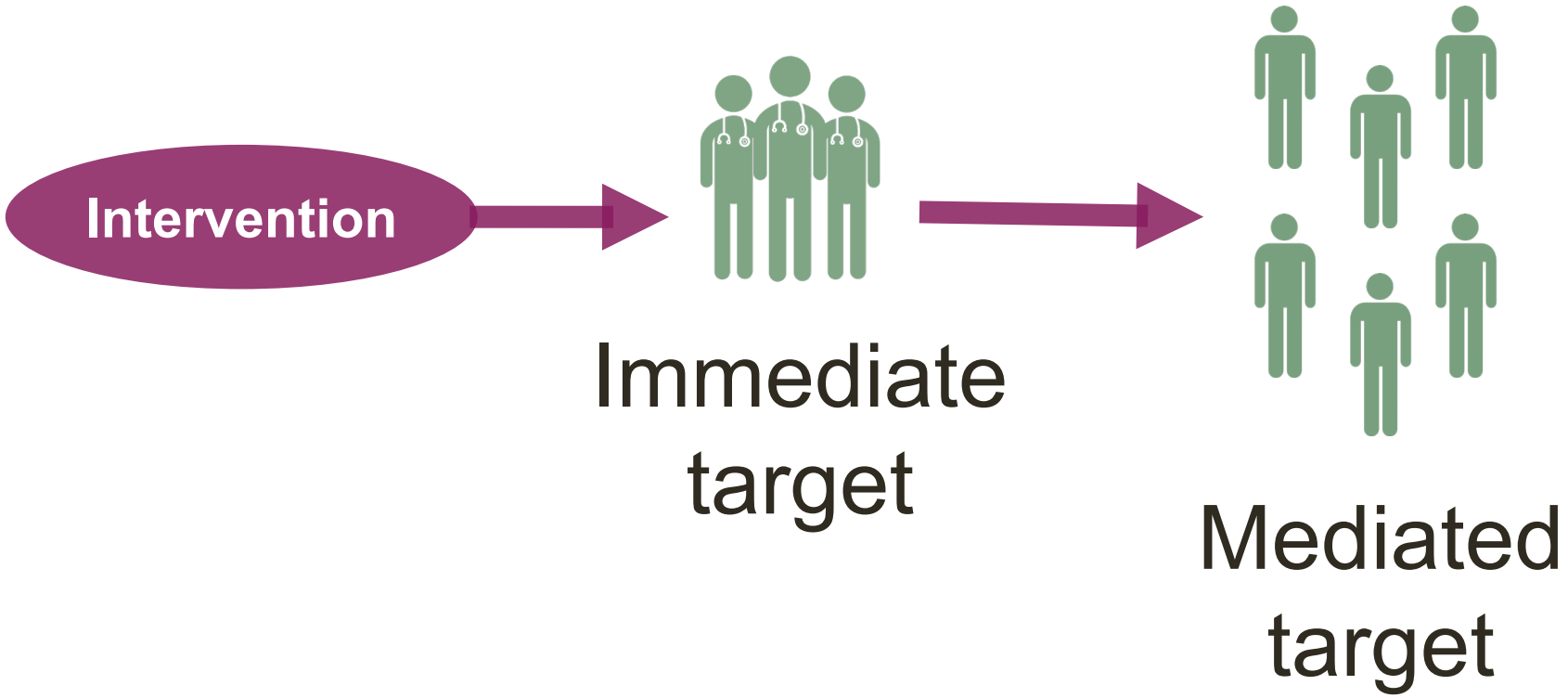
Direct participant



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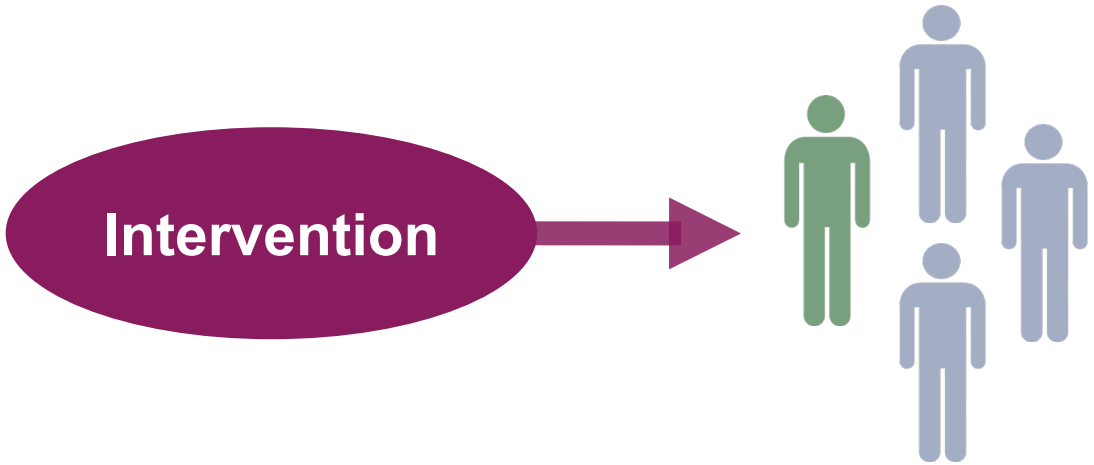
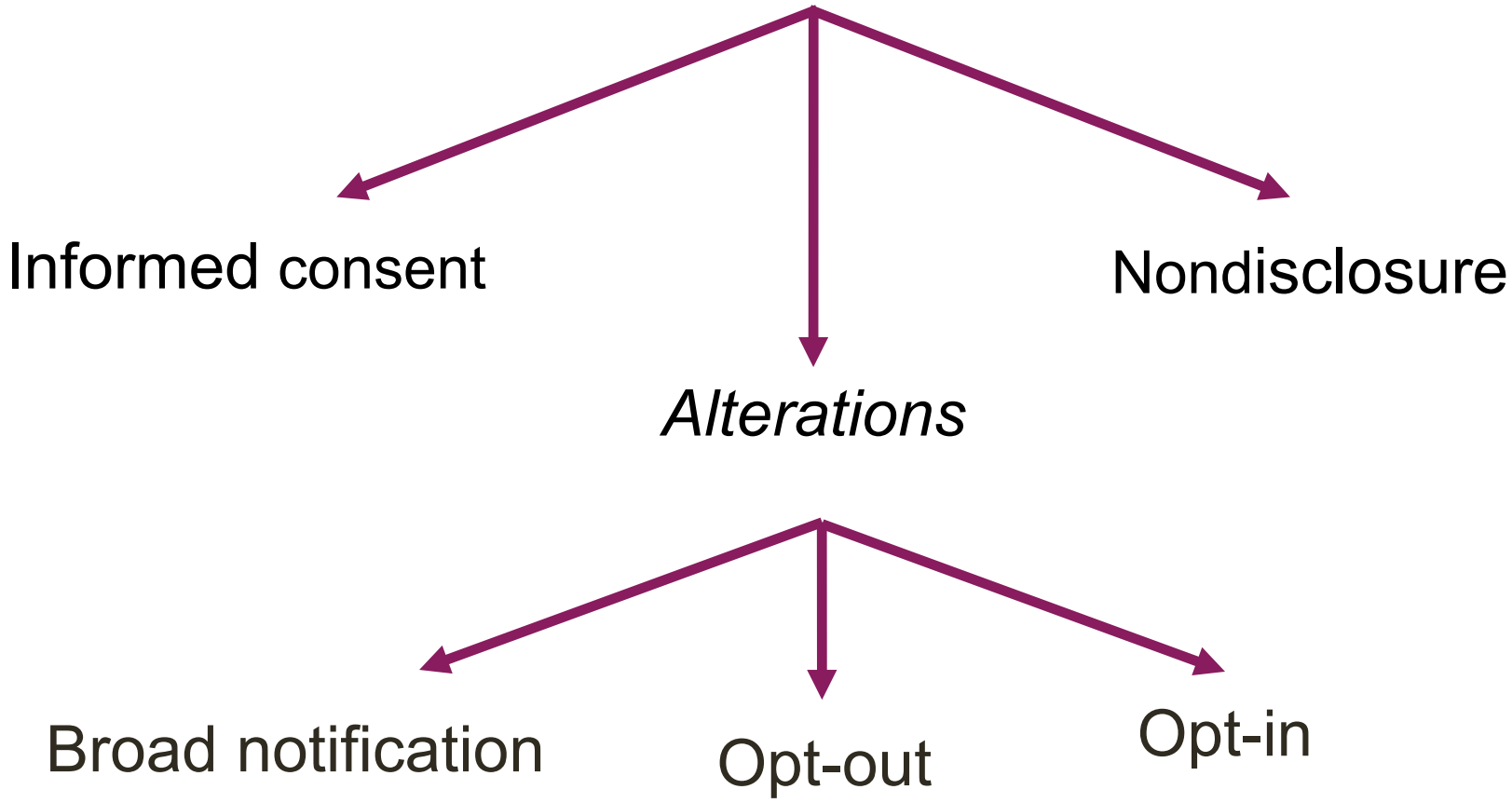
Indirect participants

People affected by routine exposure to the environment (e.g., family/caregivers)



Approaches to notification & authorization



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Criteria for waiver/alteration of informed consent

- The research involves no more than minimal risk
- The research could not be carried out practicably without the waiver or alteration
- The waiver or alteration will not adversely affect the rights & welfare of the subject, and
- Where appropriate, the subjects will be provided with additional information about their participation

Common Rule: 45 CFR 46.116(f)

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Working with human subjects oversight bodies

- Institutional review boards (IRBs)
- Data monitoring committees (DMCs) or data and safety monitoring boards (DSMBs)

Requirement for single IRB review

- Applicability
  - US institutions engaged in cooperative research for the portion of the research conducted in the United States
- Does not apply:
  - When more than single IRB review is required by law (including tribal law)
  - Whenever any Federal department or agency supporting or conducting the research determines and documents that the use of a single IRB is not appropriate for the particular context

Data monitoring committee

Group of experts that review the ongoing conduct of a clinical trial to ensure continuing patient safety as well as the validity and scientific merit of the trial

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Unique considerations for monitoring ePCTs

- Poor adherence to intervention: problem or finding?
- Limited or delayed access to study outcomes during study conduct
- Differential data collection/contact by study arm
- Level of data needed to change practice, especially when studying treatments in wide use?
- Are interim analyses actionable?

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

Important things to do

- Designate someone to track local and federal regulatory developments and serve as liaison with regulatory/oversight bodies
- You can contact OHRP for guidance
- 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

Resource: OHRP contacts and resources

- Submit your questions to OHRP@hhs.gov
- Visit OHRP website at www.hhs.gov/ohrp
- Bookmark this page for quick reference to OHRP resources on the revised Common Rule: www.hhs.gov/ohrp/education-and-outreach/revised-common-rule/index.html

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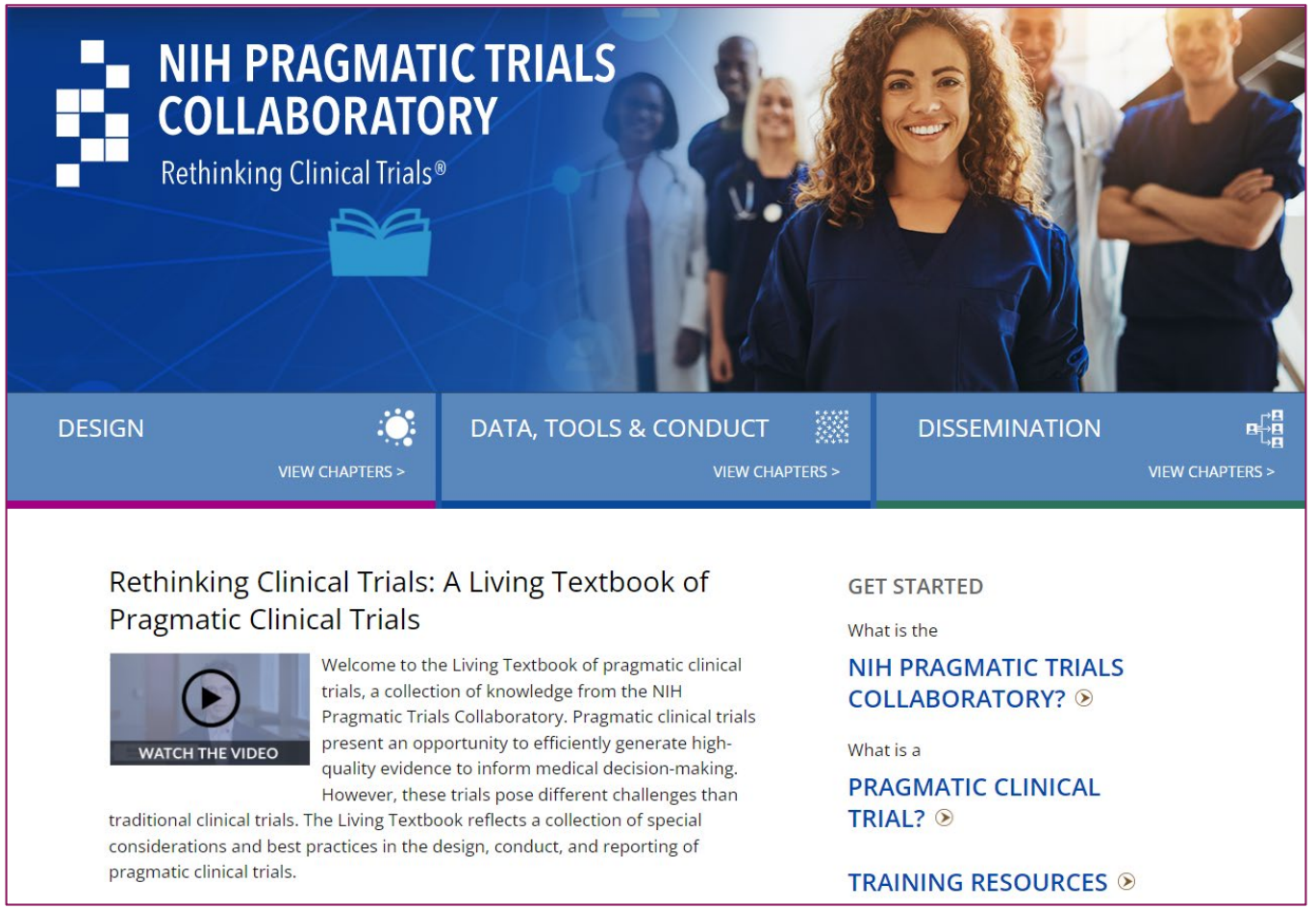
Resource: The Living Textbook

Visit the Living Textbook of Pragmatic Clinical Trials at

www.rethinkingclinicaltrials.org



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