Topic 5: Regulatory and Ethical Challenges of ePCTs

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Introduction
ePCTs are motivated by ethical imperatives

ePCTs also raise interesting ethical and regulatory questions
CLINICAL TRIALS
Journal of the Society for Clinical Trials

EXPLORING THE ETHICAL AND REGULATORY ISSUES IN PRAGMATIC CLINICAL TRIALS
LEADING A SERIES OF 12 ARTICLES ON DIFFERENT ASPECTS OF THIS TOPIC

COLUMN
Clinician Trialist Rounds 28: When RCT Participants are Lost to Follow-Up,
Part I: Why Even a Few Can Matter
M Walsh, PJ Dewaneaux and DL Sackett

TRIBUTE
An Interview with David Sackett
RB Haynes and SN Goodman
Evolving understanding of unique ethical/regulatory issues for ePCTs

- Informed consent
- Data monitoring
- Defining minimal risk
- Research/quality improvement distinction
- Vulnerable subjects
- IRB harmonization
- Identifying direct and indirect subjects
- Gatekeepers
- FDA-regulated products
- Nature of ePCT interventions
- Privacy
Current ethics/reg environment is in flux

1/19/2017
Revised Common Rule published
Current ethics/reg environment is in flux

1/19/2018
Original compliance date
Current ethics/reg environment is in flux

7/19/2018

Delayed compliance date

Further delay is possible (likely?)
Current ethics/reg environment is in flux

And more . . .
(Certificates of Confidentiality, single IRB review of multisite trials, etc.)
Your dedicated ethics/regulatory liaison
Whose rights/welfare need to be protected?

(Ethical, not regulatory question)
Types of participants in an ePCT

Direct

Indirect
Direct participant

*Immediate and/or mediated target of the intervention*

- **Intervention** → **Patients**
- **Intervention** → **Providers**
- **Intervention** → **Clinics**
Direct participant

*Immediate and/or mediated target of the intervention*
Indirect participant

PCTs may affect people by way of routine exposure to the environment

eg, family/caregivers
Example: **Active Bathing to Eliminate Infection (ABATE) trial**

Routine Care  
Decolonization
Types of participants in an ePCT

Direct
- Rights and welfare reviewed by IRB

Indirect
- Rights and welfare reviewed by gatekeepers
Who are the direct and indirect participants for your study?

What are the potential risks and benefits for each?

1 min

4 min
What are different approaches for notification and authorization?
Approaches

Informed consent

Non-disclosure

Alterations

Broad notification

Opt-out

Opt-in
Approaches

Informed Consent

Alterations

Non-disclosure

Require a waiver

Broad notification

Opt-out

Opt-in
Conditions for waiver of consent

An IRB may waive or alter the requirements of informed consent if all of the below are deemed true:

• “The research involves no more than minimal risk to the subjects;
• The waiver or alteration will not adversely affect the rights and welfare of the subjects;
• The research could not practicably be carried out without the waiver or alteration; and
• Whenever appropriate, the subjects will be provided with additional pertinent information after participation.” §46.116
Minimal risk

“In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research).”

*Common Rule: CFR 46.111 (a)(2)*

“The reasonably foreseeable risks of research include already identified risks of the standards of care being evaluated as a purpose of the research.”

*From the OHRP Draft Guidance*
Approaches

- Informed consent
- Non-disclosure

Alterations

- Broad notification
- Opt-out
- Opt-in
Approaches

- Informed consent
- Non-disclosure

Alterations

- Broad notification
- Opt-out
- Opt-in
TiME consent process

• Time to Reduce Mortality in End-stage renal (TiME) disease hypotheses: Facility implementation of ≥4.25-hour dialysis session duration improves outcomes compared with usual care

• Patients starting dialysis at participating facilities are given a brief information document with:
  • Purpose of the trial
  • How session duration will be affected by the trial
  • Toll-free telephone number to obtain additional information from the research team and to opt-out of participation

• Informational posters in participating dialysis facilities throughout the duration of the trial
Approaches

Informed consent

Non-disclosure

Alterations

Broad notification

Opt-out

Opt-in
LIRE trial

• Tests whether inserting epidemiological evidence in lumbar spine imaging reports will reduce subsequent diagnostic and therapeutic interventions

• Waiver of consent was granted
  • Risk of contacting subjects deemed greater than the risk of study procedures
  • By informing primary care providers and patients, they risk invalidating the results
What do data suggest about different approaches?
Comparison of Approaches for Notification and Authorization in Pragmatic Clinical Research Evaluating Commonly Used Medical Practices

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Background: For pragmatic clinical research comparing commonly used treatments, questions exist about if and how to notify participants about it and secure their authorization for participation.

Objective: To determine how patients react when they seek clinical care and encounter one of several different pragmatic clinical research studies.

Research Design: In an online survey using a between-subjects experimental design, respondents read and responded to 1 of 24 hypothetical research scenarios reflecting different types of studies and approaches to notification and authorization (eg, general notification, oral consent, written consent).

Subjects: English-speaking US adults 18 years and older.

Most respondents (77%–94%) felt that participation in the hypothetical study posed no risks of harm to their health or privacy.

Conclusions: Current attitudes about notification and authorization approaches and difficulties understanding pragmatic clinical research pose significant challenges for pragmatic clinical research. Data from this study provide a starting point to developing solutions to these surprisingly complex issues.

Key Words: comparative effectiveness research, ethics, informed consent

(Med Care 2017;00: 000–000)

Substantial efforts are now being directed at improving the
Approaches to Notification & Authorization

Written consent (with clinical risks included)

Written consent

Oral consent + info sheet

Oral consent

General notification (with opt-out)

Post-notification after study done
Difficulty understanding aspects of pragmatic trials of accepted medical practices

1

2

3

4

5
SCENARIO 29

You go to the local clinic for a routine checkup. There is a sign on the waiting room wall describing a research study in which the clinic is participating.

- Our clinic, along with other clinics around the country, is taking part in a research study.
- Researchers want to find out the best method for taking blood for routine tests. Clinics typically collect blood using one of two different types of needles. Researchers want to know if one type of needle is better than the other in terms of the number of attempts (times patients need to be stuck with a needle) needed to get enough blood.
- As part of the study, different clinics have been randomly selected to use one type of needle or the other. This means that some clinics were selected to use the first type of needle, and all the doctors and nurses there are using that type, while other clinics were selected to use the second type of needle, so all the doctors and nurses there are using that type.
- Later on, to see if one type works better than the other, researchers will look at specific parts of patients’ medical records to see how many attempts were needed to get enough blood to draw enough blood.
- Researchers have to follow the same rules that are already in place to protect health information and keep it secure.
- There will be no extra follow-up calls or visits that patients need to do related to the study.
- If you have any questions, please contact Dr. Smith at 123-4567.

“There will be no extra follow-up calls or visits that patients need to do related to the study.”
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Experimental Therapeutic Misconception ?
1. Difficulty understanding aspects of pragmatic trials of accepted medical practices

2. Nontrivial consent bias, but it’s the same for all approaches for N&A

3. Less active approaches to N&A viewed as unacceptable for some types of pragmatic research

4. 

5. 
Medical Records – Blood Clot
- GN
- O
- O+I
- WC–MR

Medical Records – UTI
- GN
- O
- O+I
- WC–MR

Individual Randomization – Blood Clot
- GN
- O
- O+I
- WC(I)
- WC(C)

Individual Randomization – UTI
- GN
- O
- O+I
- WC(I)
- WC(C)

Cluster Randomization – Surgical Rods
- POST
- GN
- GN – OO

Cluster Randomization – Needles
- POST
- GN
- GN – OO
Difficulty understanding aspects of pragmatic trials of accepted medical practices

Nontrivial consent bias, but it’s the same for all approaches for N&A

Less active approaches to N&A viewed as unacceptable for some types of pragmatic research

Including descriptions of background clinical risks increased length of form, but did not change any outcome
WHAT ARE THE RISKS OF THE STUDY?

In this study, researchers must follow laws to protect health information and keep it secure. However, there is a very small chance that information about you might become known to people outside of the study.

Federal Privacy Regulations provide safeguards for privacy, security, and authorized access. Except when required by law, you will not be identified by name, social security number, address, telephone number, or any other direct personal identifier in study records disclosed outside of City Medical Center.
Difficulty understanding aspects of pragmatic trials of accepted medical practices

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Active alternatives to written consent—such as oral consent—may not be expected to compromise consent quality
Working with human subjects oversight bodies: IRBs and Data Safety and Monitoring Committees
Major Issues

- Single IRB review
- Lack of experience reviewing/monitoring ePCTs
Single IRB review

- NIH policy on sIRB review, effective January 25, 2018
- Revised Common Rule requires U.S.-based institutions engaged in cooperative research to use a single IRB for regulatory review
- The sites involved in research that uses a single IRB need to
  - Sign a reliance agreement, which outlines who is responsible for what (usually for each protocol)
  - Develop systems for fulfilling institutional responsibilities
  - Develop mechanisms for reporting relevant institutional information to reviewing IRB
TSOS “single” IRB experience

- University of Washington IRB does not have capacity for “centralization”
- Western IRB (WIRB) serves as the centralized IRB
- No single administrative contact
- Only 4 sites “cede” to centralized WIRB review
- 20 individual site IRB submissions (out of 24 sites)
Major Issues

- Single IRB review
- Lack of experience reviewing/monitoring ePCTs
Budget sufficient time for initial and continuing education/negotiation
Data monitoring committee

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

- Poor adherence to intervention: problem or finding?
- Inference about adverse events
  - Availability of clinical data to assess relatedness
  - Should AEs still be monitored?
- Limited/delayed access to study outcomes during study conduct
- Are interim analyses actionable?

Adapted from Greg Simon, MD, Collaboratory Grand Rounds, December 8, 2017
A plea
Ethics/morality

Regulations

Empirical research
Collect data to contribute to the learning!

- Describe current practices and beliefs
- Test assumptions of an ethical argument
- Measure potential impact of different regulatory policies
Important things to know

• Ethical analysis for ePCTs is a work in progress

• Federal and local policies regarding the oversight of ePCTs are in flux

• There is often confusion and misunderstanding about ePCTs on part of patients, providers, IRBs, and DSMBs
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

• Look for opportunities to contribute to evolving empirical data on different approaches