

Topic 5: Regulatory and Ethical Challenges of ePCTs

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Overview

1

Introduction

2

Whose rights/welfare need to be protected?

3

What are different approaches for notification and authorization?

4

Working with human subjects oversight bodies

5

A plea



Introduction

ePCTs are motivated by ethical imperatives



ePCTs also raise interesting ethical and regulatory questions

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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 Devereaux 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**

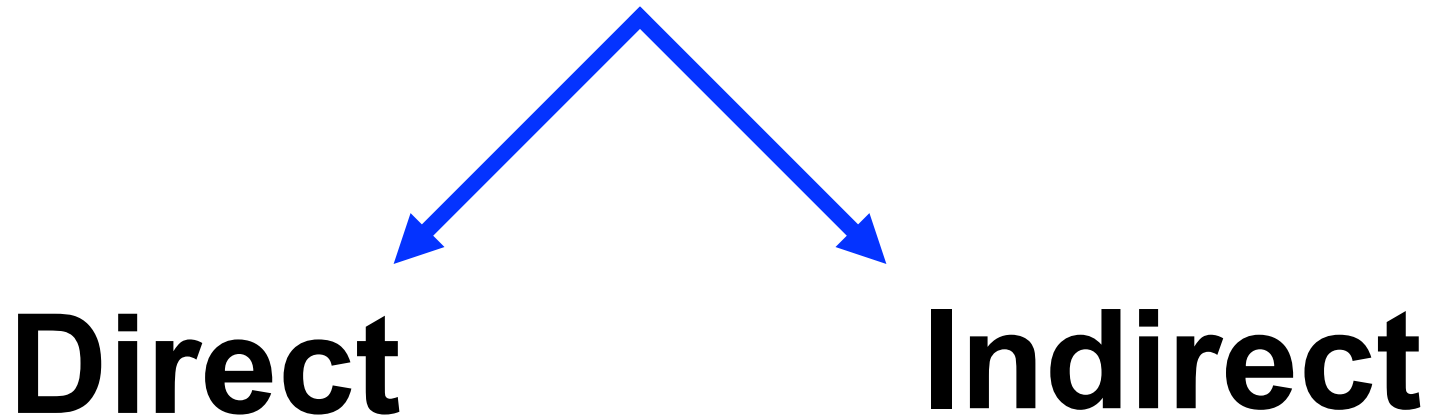


2

Whose rights/welfare need
to be protected?

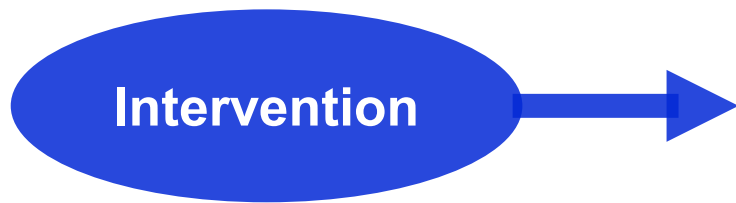
(Ethical, not regulatory question)

Types of participants in an ePCT

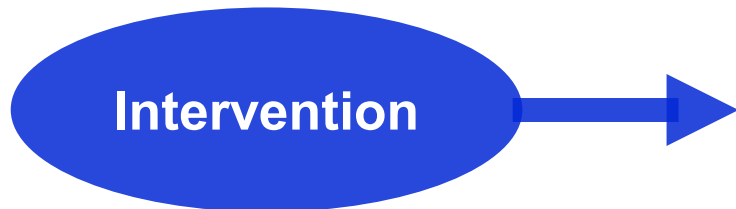


Direct participant

Immediate and/or mediated target of the intervention



Patients



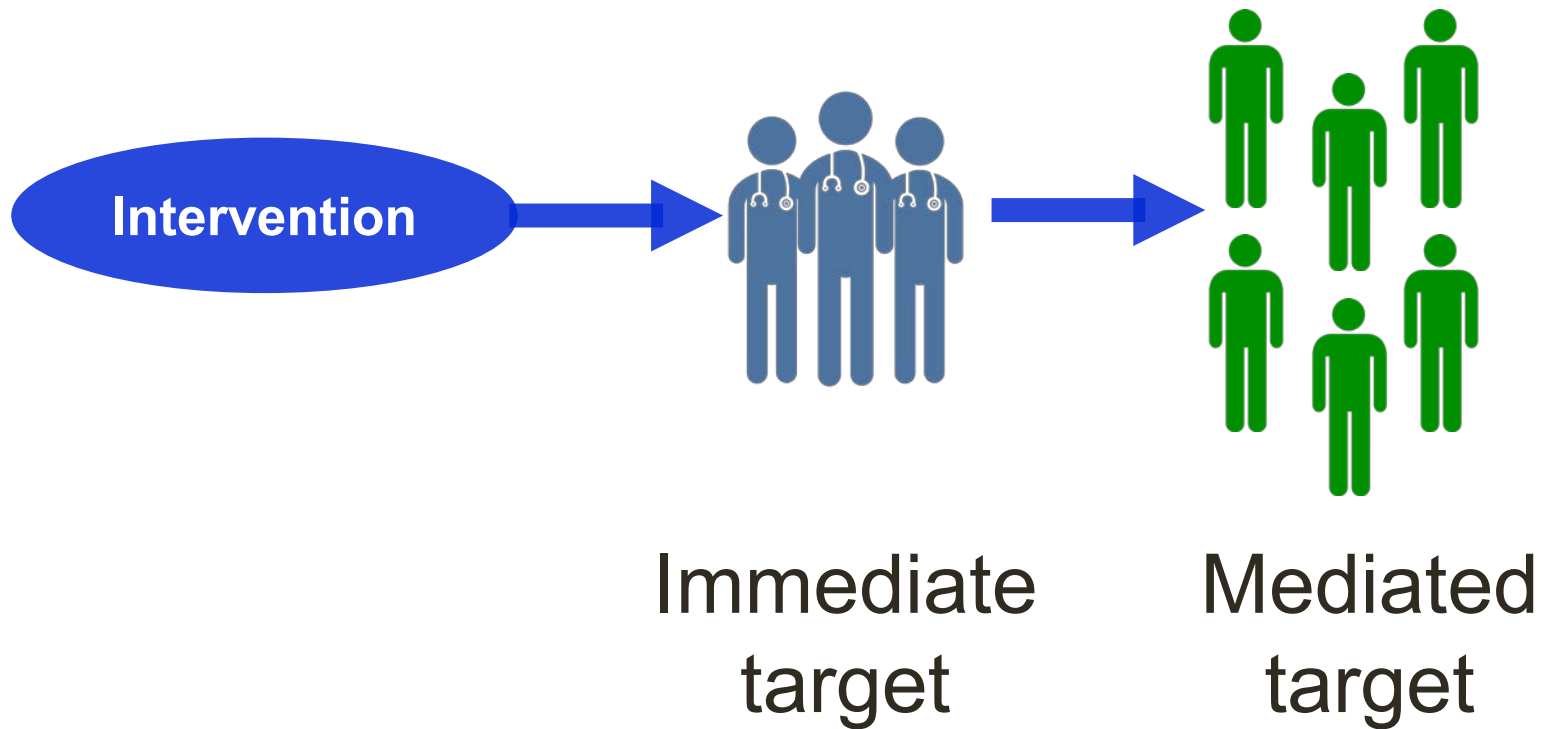
Providers



Clinics

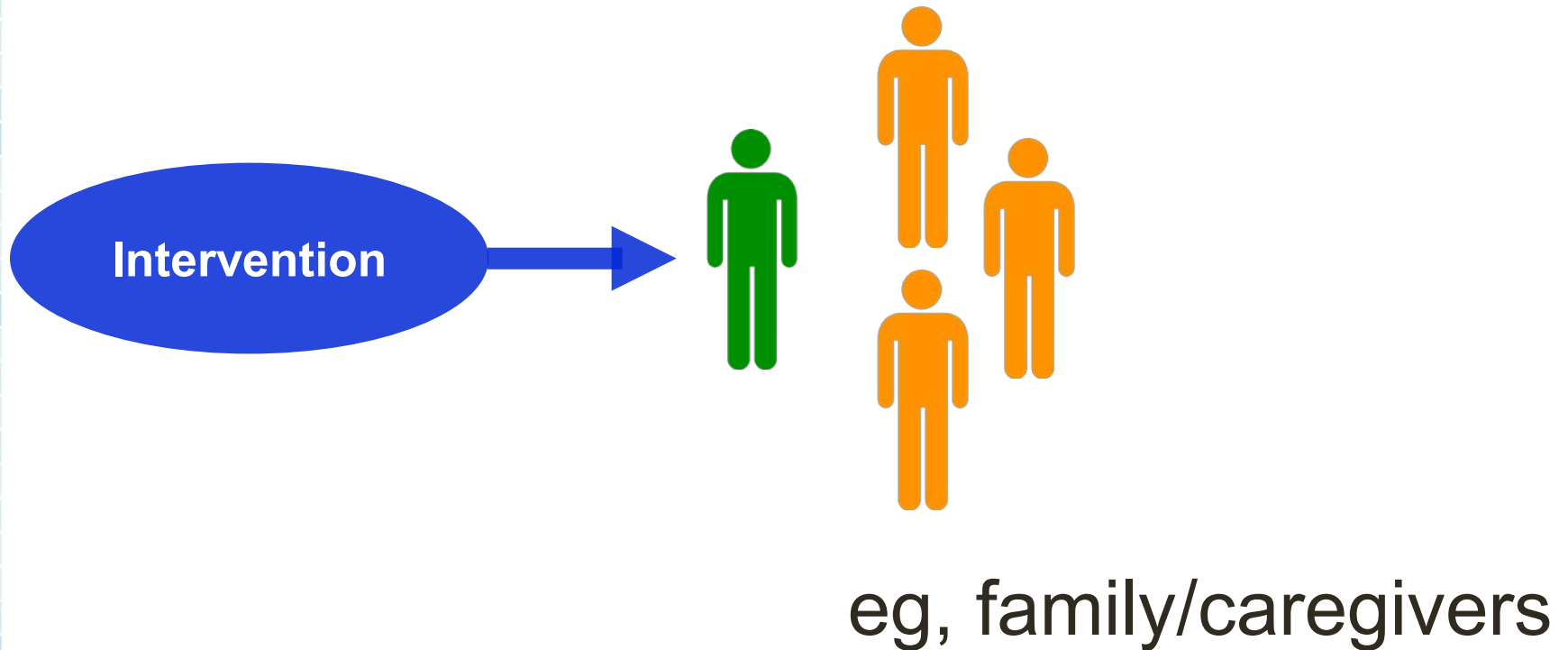
Direct participant

Immediate and/or mediated target of the intervention

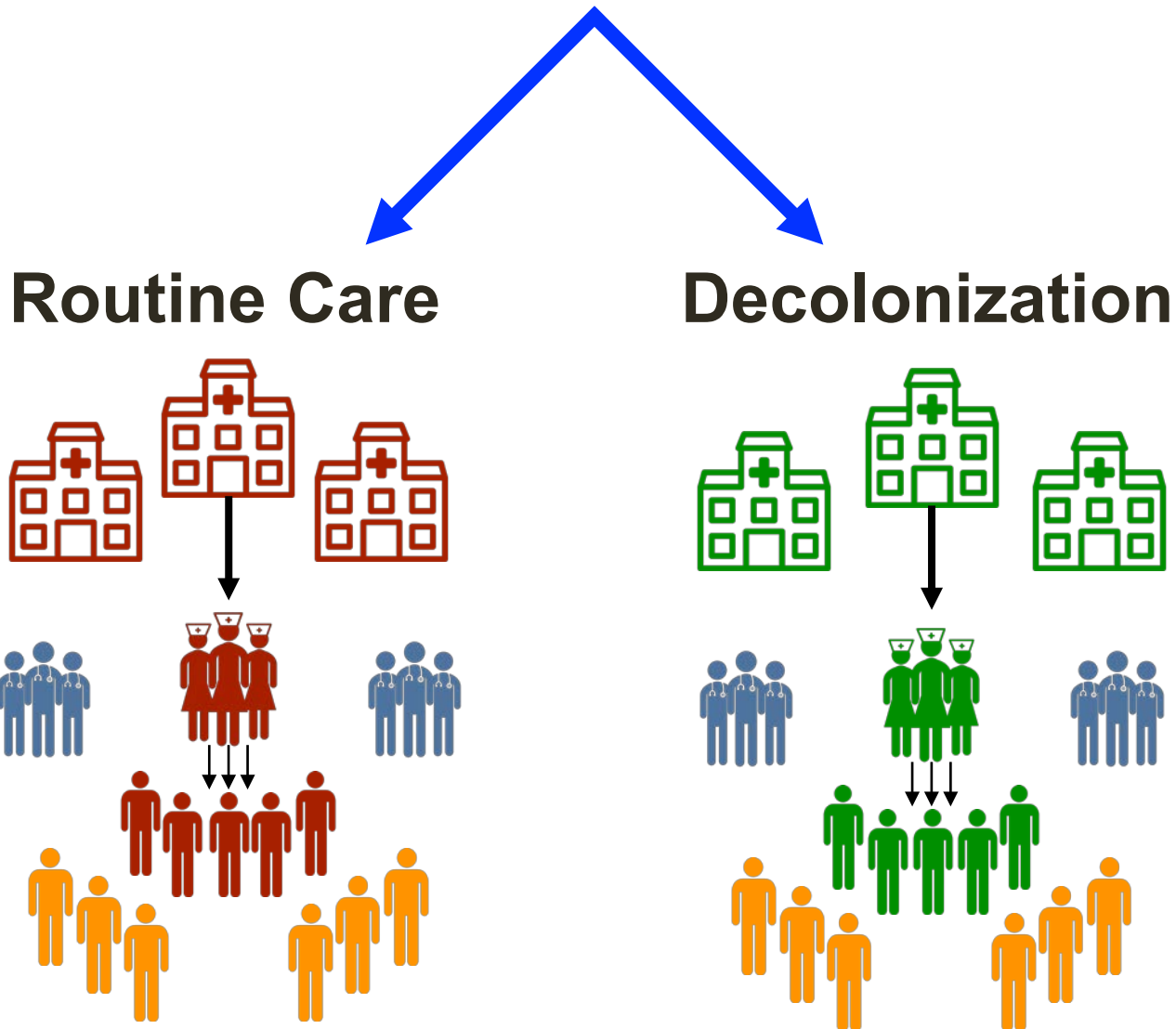


Indirect participant

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



Example: Active Bathing to Eliminate Infection (ABATE) trial



Types of participants in an ePCT

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graph TD; A[Types of participants in an ePCT] --> B[Direct]; A --> C[Indirect];
```

Direct

Rights and welfare
reviewed by IRB

Indirect

Rights and welfare
reviewed by
gatekeepers

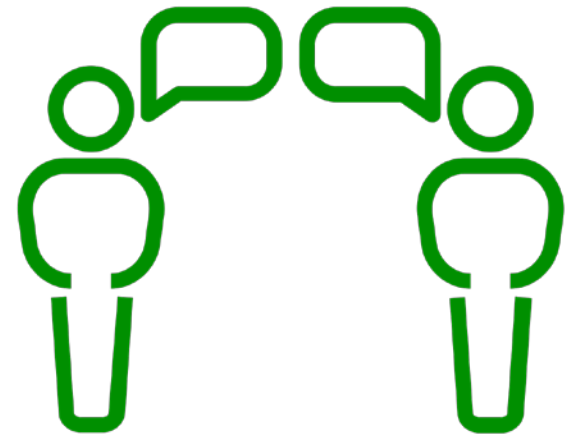
Who are the direct and indirect participants for your study?

What are the potential risks and benefits for each?

1 min



4 min

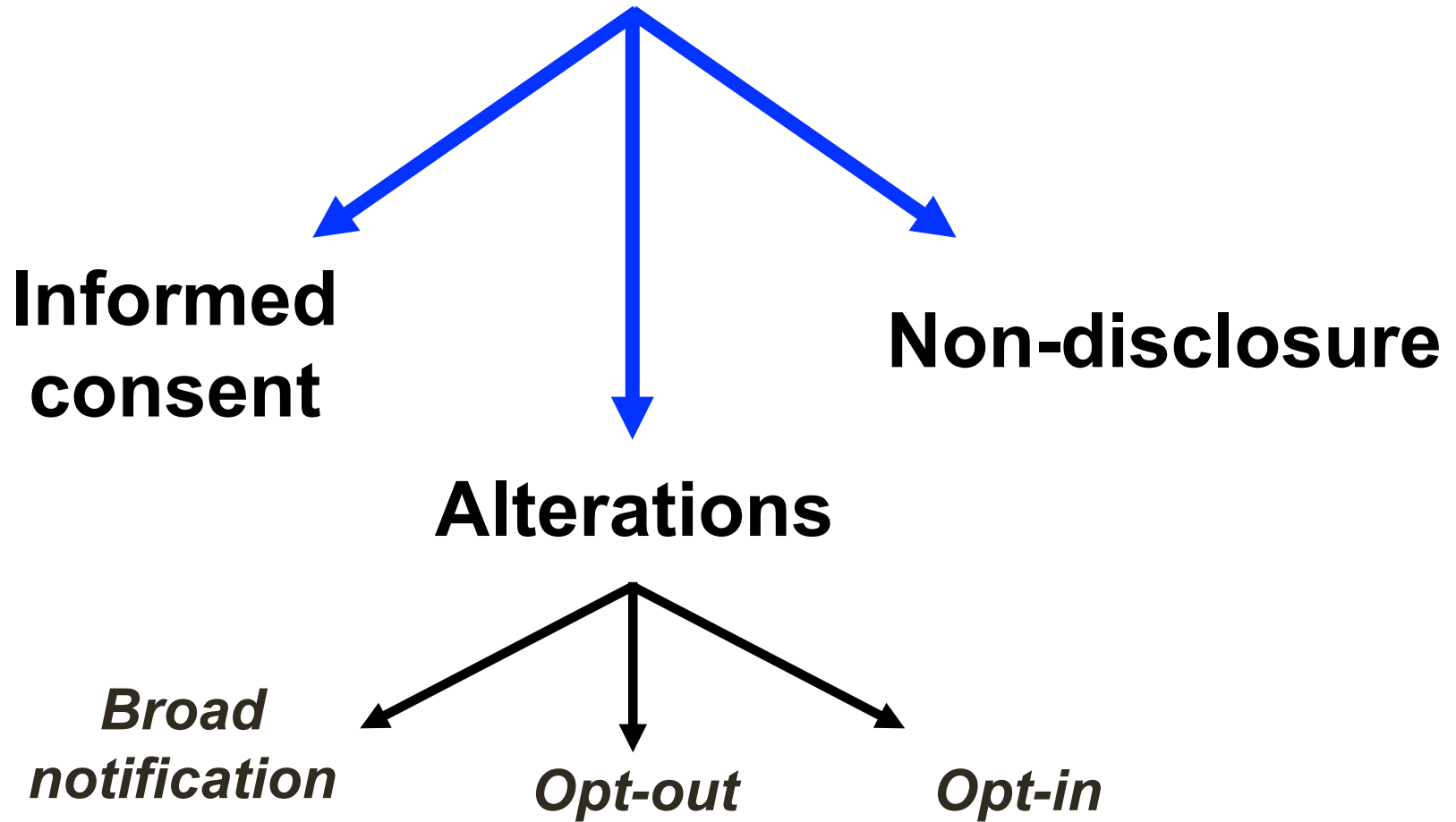




3

What are different approaches for notification and authorization?

Approaches



Approaches

Informed
Consent

Non-disclosure

Alterations

**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).”

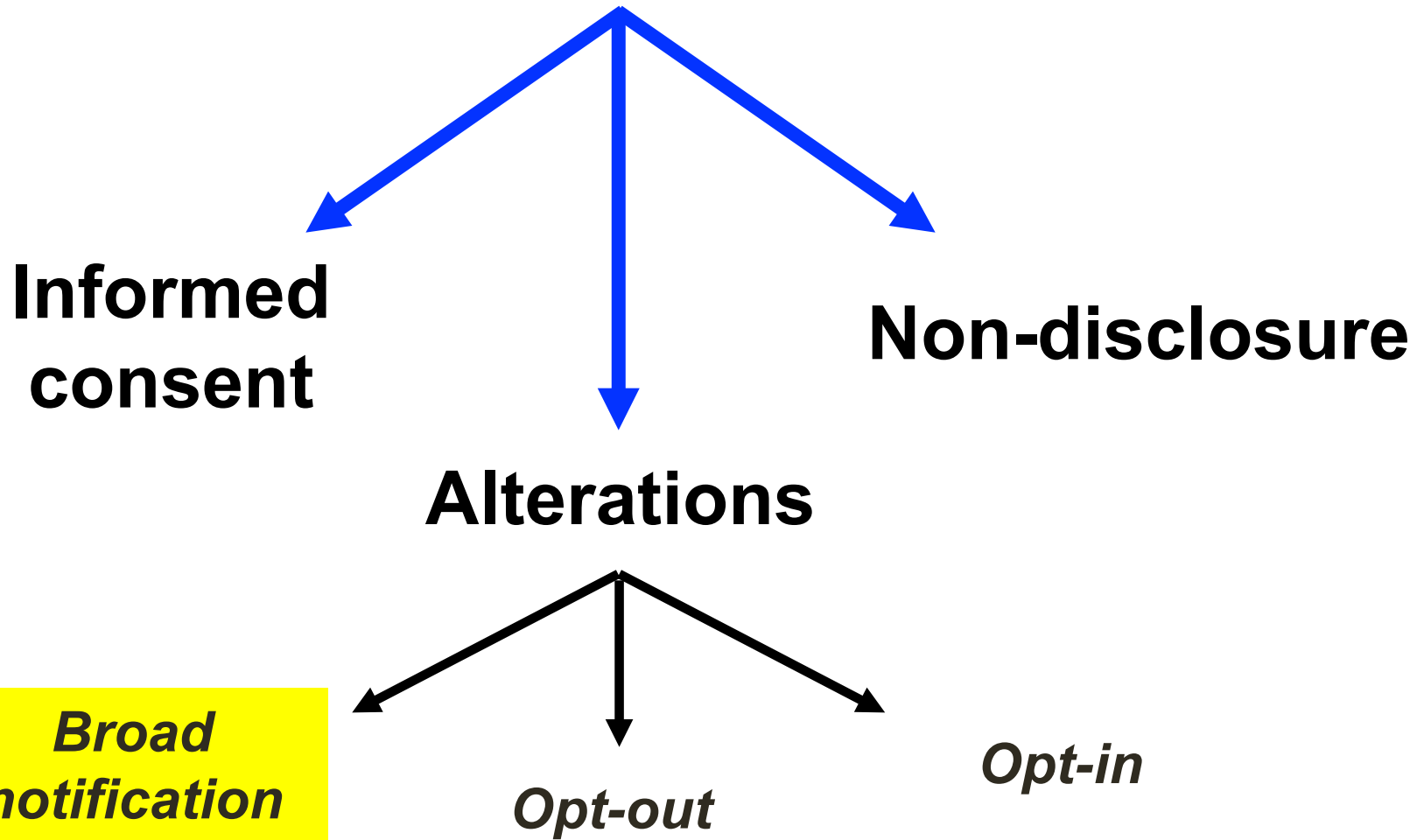
Common Rule: CFR 46.111 (a)(2)

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

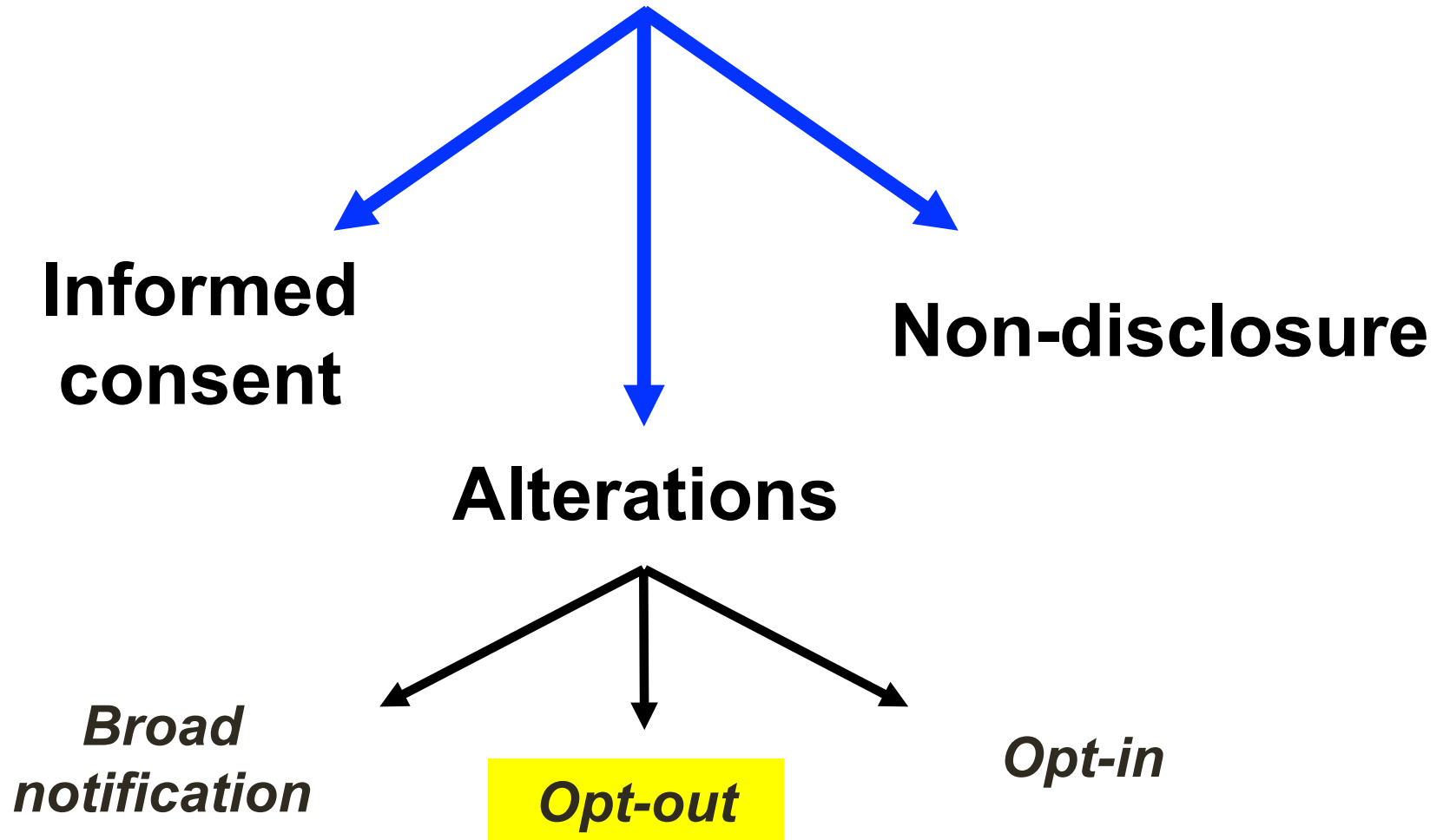
From the OHRP Draft Guidance

**Some debate
here!!!**

Approaches



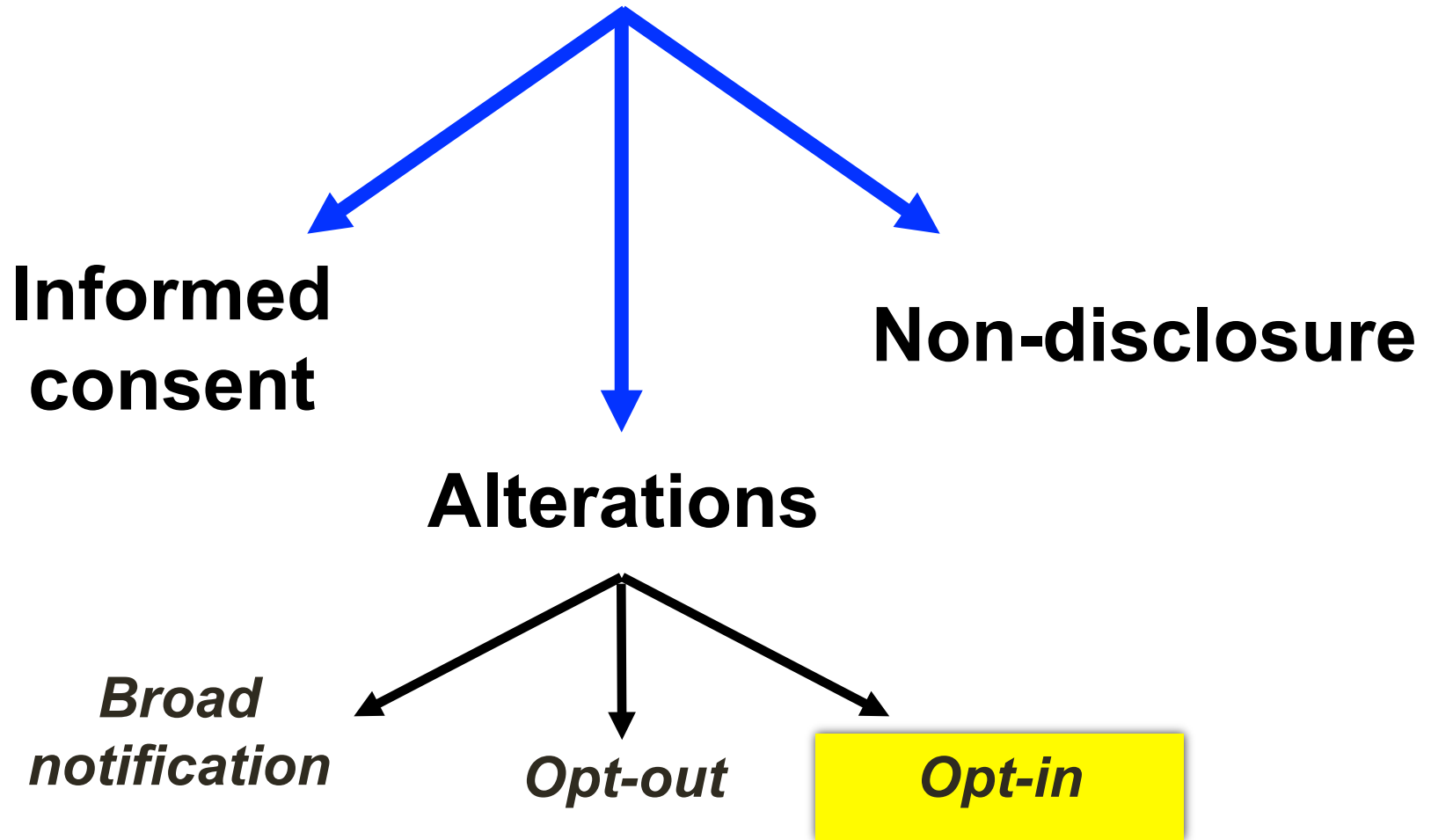
Approaches



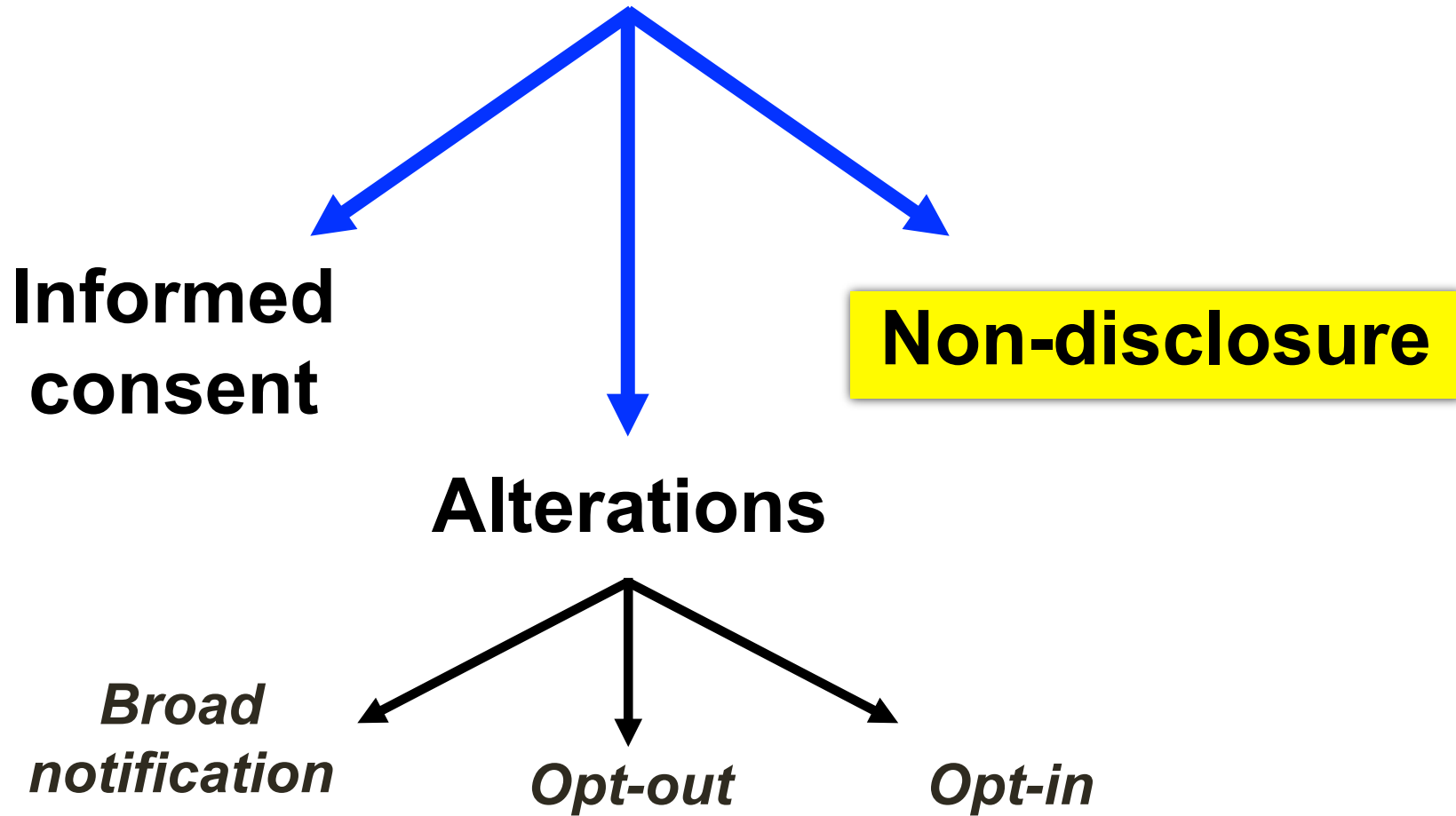
TiME consent process

- 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



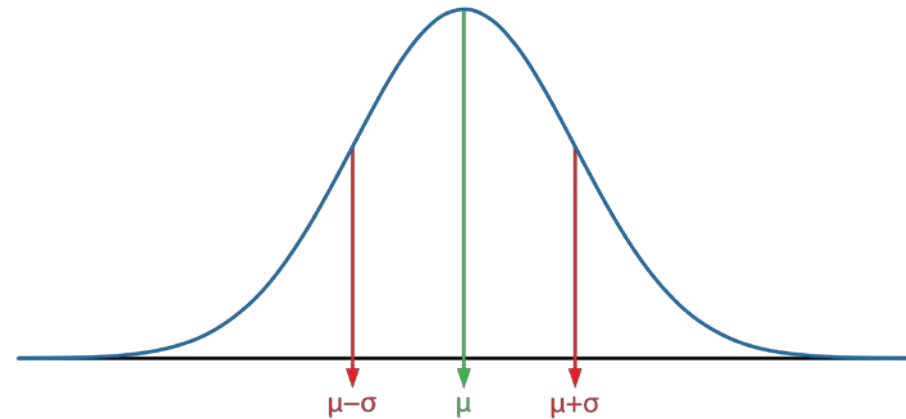
Approaches



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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Martina Bresciani, BA,* Zachary Lampron, MPH,* Li Lin, MS,* Rachel J. Topazian, BA, †
and Jeremy Sugarman, MA, MPH, MD ‡ § ||*

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 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)

C 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

1

Difficulty understanding aspects of pragmatic trials of accepted medical practices

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.
- 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.

which
type works
better

will
This
same

“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+
- WC-MR

Medical Records – UTI

- GN
- O
- O+
- WC-MR

Individual Randomization – Blood Clot

- GN
- O
- O+
- WC(I)
- WC(C)

Individual Randomization – UTI

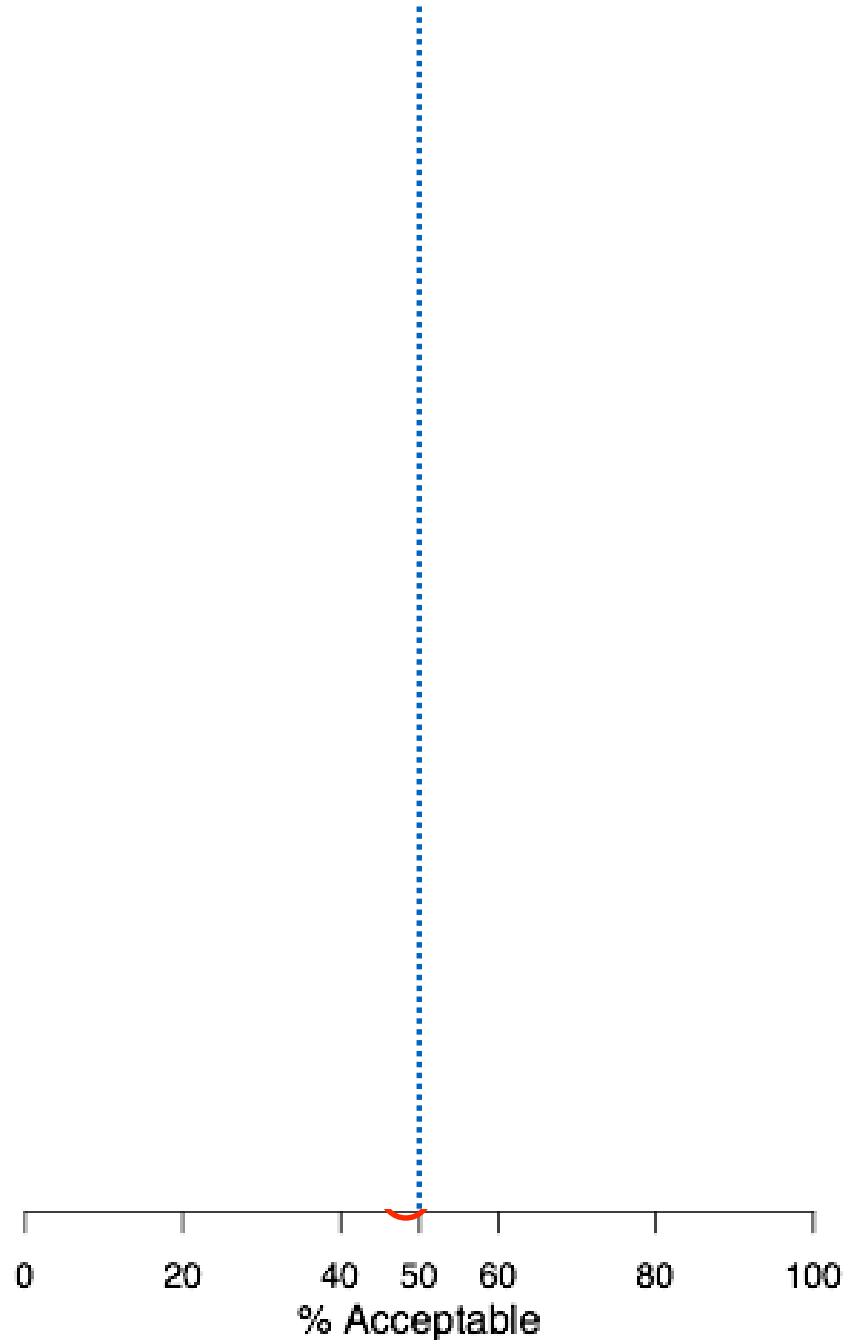
- GN
- O
- O+
- WC(I)
- WC(C)

Cluster Randomization – Surgical Rods

- POST
- GN
- GN – OO

Cluster Randomization – Needles

- POST
- GN
- GN – OO



1

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

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Including descriptions of background clinical risks increased length of form, but did not change any outcome

5

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.

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Active alternatives to written consent—such as oral consent—may not be expected to compromise consent quality



4

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

```
graph TD; A[Major Issues] --> B[Single IRB review]; A --> C[Lack of experience reviewing/monitoring ePCTs];
```

**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

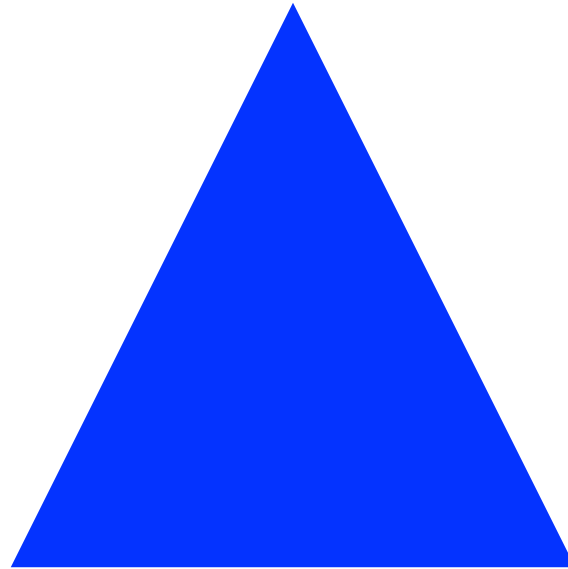
- Poor adherence to intervention: problem or finding?
- Inference about adverse events
 - Availability of clinical data to assess relatedness
 - Should AEs still be monitored?
- Limited/delayed access to study outcomes during study conduct
- Are interim analyses actionable?



5

A plea

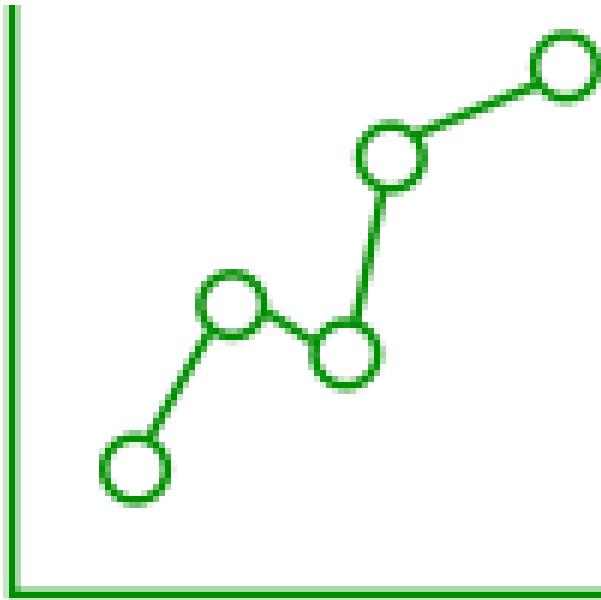
Ethics/morality



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