

Ethical and IRB Approaches for a Successful Embedded A vs. B Pragmatic Trial

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Embedded Pragmatic Clinical Trials of Therapeutic A vs. B Interventions

NIH Collaboratory, Bethesda MD

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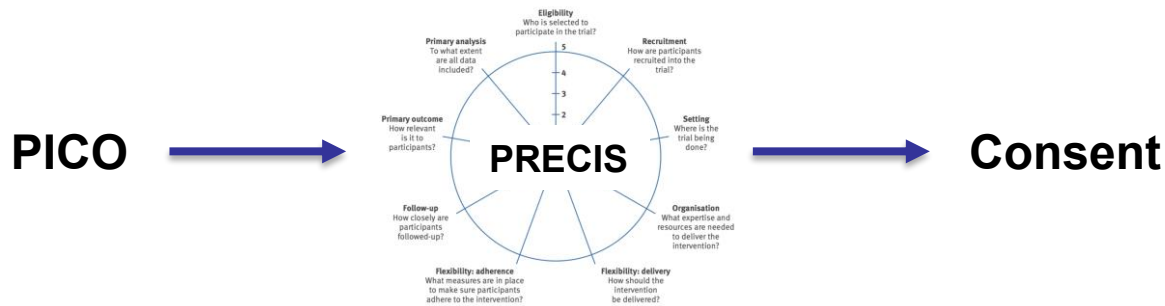
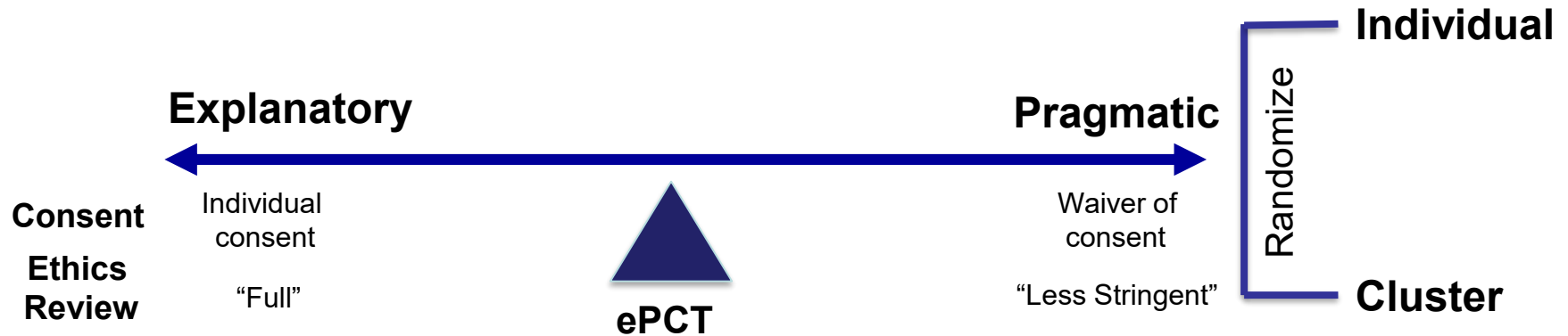


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Where is the threshold?



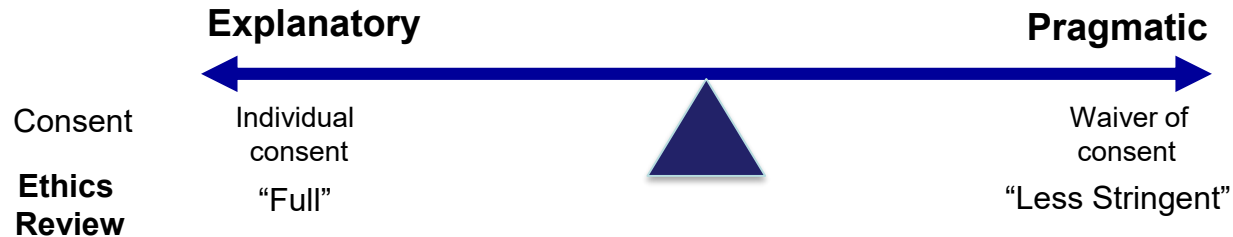
Common Rule and FDA Regulations

Assume that:

- ePCT is research, not QI or operations
- Wherein feasible (practicable) to obtain individual consent, such consent will be obtained.
- Documentation of consent is not the pivotal concern here

To discuss:

- Ethics Review and IRBs
 - IRB inefficiencies
 - Risks of Research
 - Practicability
- Randomization and Consent
 - Consent at the level of the individual
 - Cluster at the level of the institution or community
- Regulatory Uncertainty and Opportunity

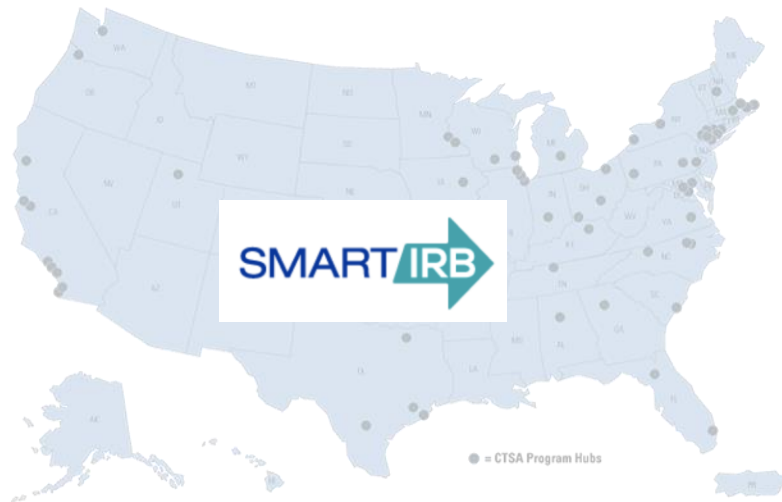


- Ethics Review in ePCT:
 - Unless intention is individual informed consent (with documentation of IC) :
no “less stringent” ethics review → Full board review
 - Independent of where that threshold is set
 - Arguably even in context of minimal risk and particularly as we explore how to advance these approaches and this field
 - Risks to institutional reputation and, importantly, to public trust
- IRB inefficiencies are not an excuse

IRB Evolution

From multiplicity of IRB reviews to

- Independent, central, and sIRB for multisite trials
- Time, and NIH and federal policy, will help



www.SMARTIRB.org

416 have joined since 2016

Including

- All CTSA hubs
- Universities
- Academic Medical Centers
- Community Hospitals
- Cancer Centers
- PPRNs
- Independent IRBs
- and others

Which is not to say that evolution of IRB education and flexibility is not necessary

Arguably, must evolve posture of IRB from paternalism to participant-centered focus

Partners:
PCORnet
Trial Innovation Network

IRB review criteria: 2 comments

- “Practicability”
- “Risks of Research”
 - Risks and effects **of the research**, over and above the risks of the necessary clinical care
 - Often IRBs evaluate the risks of the treatment itself, not the risks of the research
 - That said, often a difficult assessment

”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).” (45 CFR 46.111(a)(2))

See: <https://www.hhs.gov/ohrp/regulations-and-policy/requests-for-comments/draft-guidance-disclosing-risk-in-standards-of-care/index.html>



IRB review criteria: 2 comments

- “Practicability”
 - “**The study** could not practicably be conducted without the waiver or alteration” (45 CFR 46.116(d)(3))
 - It does not say “that obtaining consent would be impracticable”
 - The focus therefore is on the study, not consent*
 - Scientific validity would be compromised.
 - Ethical concerns would be raised if consent were required.
 - There is a scientifically and ethically justifiable rationale why the research could not be conducted with a population from whom consent can be obtained.
 - Practicability should not be determined solely by considerations of convenience, cost, or speed.
 - Generalizability of the findings, and potential impact on representativeness in recruitment, is a critical determinant here
 - Thus, practicability of individual consent only one component of practicability (and on that score, issue of clinical practice inefficiencies has not been adjudicated.)

*See: <https://www.hhs.gov/ohrp/sachrp-committee/recommendations/2008-january-31-letter/index.html>

Options for consent

- Default: Individual Informed Consent
- Minimal risk research
 - Waiver or alteration of consent
- “Minor increase over minimal risk”
 - Ensure that risks of research are evaluated
- Greater than minimal risk
 - Individual informed consent
 - Utilize regulatory flexibility:
 - Conduct research without federal funding
 - Alternative consent models
 - Alter elements of consent
 - Retain right to withdraw data at end of research (~'deception'; of limited utility)
 - Secretarial waiver
 - 5 Notices in FR, last in 2003.

Respect for persons

- For any ePCT, important to have participant/patient-engagement throughout the process, and specifically around acceptability of alternative consent models
- Insofar as possible, formal community consultation and engagement recommended
- Data minimization standard
- Important that social value of the study is clear, and clear to the individual, community, and public

Education and notification

- General education of the role of clinical research generally, and clinical trials specifically, in all patient-care encounters and community
- Notification
 - Of institutional policy at institution
 - Of approach to the community
- Whenever possible and wherein the integrity of the research will not be compromised, notification of any ongoing study to likely participants
 - Signage in appropriate clinical settings
 - Hospital video channels, with attention to translations
- Communication of any “additional pertinent information” and the results of the study, in plain language, at the end of the study.

Education and notification appropriate for all research, not just ePCT or CRT



Regulatory uncertainty

- Despite commentary during ANPRM and NPRM, regulations specific to PCT, CRT, adaptive trial designs were not part of the Revised Final Rule.
- To date, no regulatory guidance or draft guidance
- Federal regulators have the ability to apply enforcement discretion if they wish
- OHRP and FDA both willing to engage
- Specific discussion and engagement is recommended

Thank you
and
Discussion

Draft Ethical Framework for the Design and Conduct of Pragmatic Trials

Spencer Phillips Hey, Ph.D.



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The Problem (part 1)

- Increasing interest from many research stakeholders in conducting more pragmatic trials
- Pragmatic trials have great potential to fill critical knowledge gaps, but they may also raise ethical issues that are not yet well-recognized and understood
- No existing consensus or guidance to ensure appropriate ethical oversight

Canadian Institutes of Health Research (CIHR)-funded project

- Develop a comprehensive ethical framework and guidance documents that can inform ethical analysis, review, and regulation of pragmatic trials

The Problem (part 2)

- Pragmatic trials are not all the same
- Trials can be more “pragmatic” in some ways; more “explanatory” in other ways
- So is an “ethical framework for pragmatic trials” even possible?

Our approach

- Rather than focus on the trial per se (“is it pragmatic?”), focus on the research question
- Use the PICO framework to analyze the various components of the research question
- Develop guidance that elucidates the connection between the question, the appropriate design elements, and the normative implications for ethical oversight
 - What are the questions this trial is intended to answer? [PICO]
 - Is the trial appropriately designed to answer these questions? [PRECIS 2]
 - **What are the ethical implications of these design choices?**

PICO (Population, Intervention, Comparison, Outcome)

- Widely used in systematic reviews to answer health-related questions
- Recommended as a tool for study design
 - What are the populations of interest?
 - What is the intervention we want to study?
 - What is an appropriate and informative comparator?
 - What are the population- or policy-relevant outcomes?
- We hypothesize that this breakdown can also be useful to structure the ethical evaluation of a trial

PRagmatic Explanatory Continuum Indicator Summary (version 2)

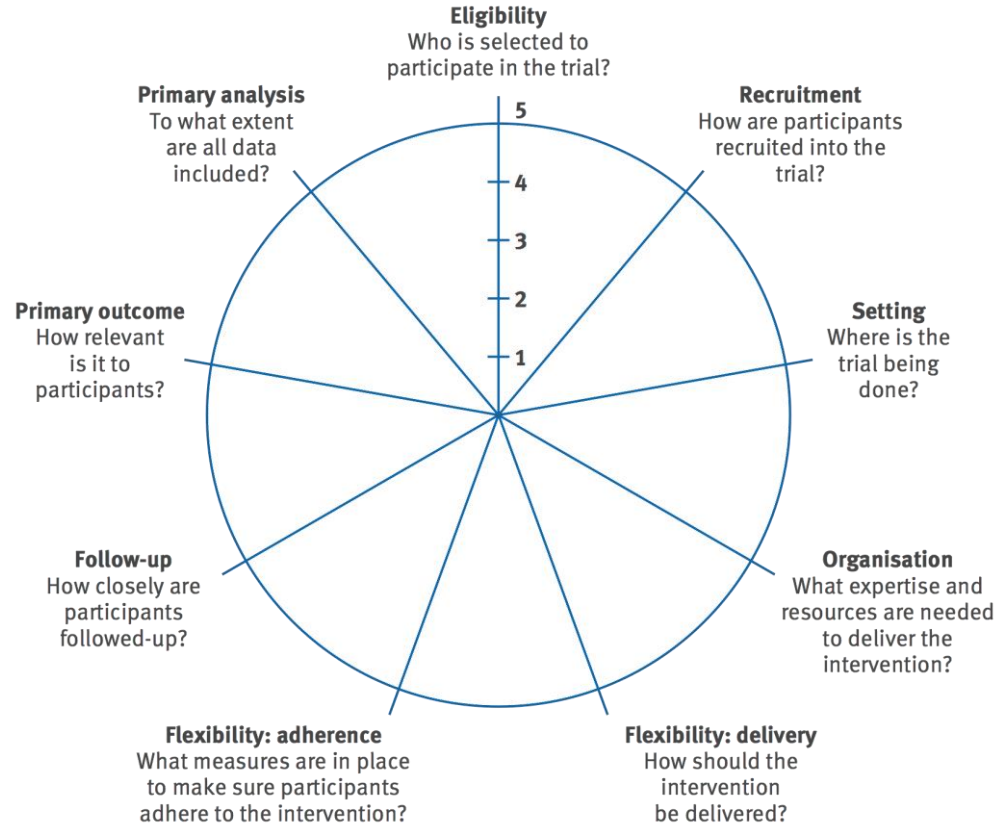


Table 1. Population

| | Very Explanatory | | Threshold(s) | Very Pragmatic | |
|---|--|--|---|--|--|
| | Descriptive | Normative | | Descriptive | Normative |
| A. What is the target population? | Homogeneous subset of a larger applicable population | Risk/benefit likely homogeneous across study sample, but may not generalize to applicable population | Sliding scale, informed by 1.C, 1.D | Full applicable population | Risk/benefit likely generalizable, but may be vulnerable subpopulation in sample |
| B. What are the units of randomization? | More likely to be individuals | Individual-focused approaches to risk/benefit should be sufficient | May include social groups | Entire health systems, nested communities | Risk/benefit analysis is multi-level and may be conflicting; engage gatekeepers |
| C. Who are the research participants? | Usually individual patients | Individual informed consent is required | Consent process is complex, informed by 1.B | Patients, providers, social groups | Consent may need to be flexible; waivers may be appropriate |
| D. How similar are the sites of recruitment? | May be highly specialized, homogeneous settings | Local EC may be sufficient; may engage local gatekeepers | Large multi-site trial (but possibly central EC review) | Multiple institutions, diverse geography and resources | Gatekeepers from each site need to be engaged in conduct of trial |

Table 2. Intervention/Comparator

| | Very Explanatory | | Threshold(s) | Very Pragmatic | |
|--|---|--|---|--|---|
| | Descriptive | Normative | | Descriptive | Normative |
| A. What is known about the risks and benefits of the interventions? | Efficacy and safety are uncertain; effectiveness unstudied | Full ethics review is required | Estimates for efficacy and safety available for subset of applicable pop. | Risks and benefits are well understood for all interventions | If risks are minimal, then less stringent ethics review may be required |
| B. Are interventions experimental or in routine use? | No interventions are in routine use | Standard protections of subjects should be applied | Sliding scale, informed by 2.A | Most or all interventions are in routine use | Equipoise may be satisfied, but risks may not be minimal |
| C. How representative is trial setting of real-world conditions? | Highly specialized, may not be representative of real-world setting | Scientific value emphasized over social value | Sliding scale, informed by 1.A, 1.D | Diverse settings, representative of the real-world | Sites may not be able to implement or have future access |
| D. Are protocols strict or flexible? | Strict, blinding, little tolerance for protocol deviation | Scientific value emphasized over generalizability | Sliding scale, informed by 2.A, 2.B, 2.C | Flexible, open-label, wide tolerance for provider judgment | Increased risks of biases and validity threats |
| E. How widely available outside the trial are the interventions? | None available outside of trial, control is placebo | Vulnerable populations may be over-represented | Some interventions are accessible, informed by 1.D, 2.B, 2.C | Study interventions widely available outside the trial | May be recruitment challenges; risks to third-parties |

Table 3. Outcome

| | Very Explanatory | | Threshold(s) | Very Pragmatic | |
|--|--|---|--|---|---|
| | Descriptive | Normative | | Descriptive | Normative |
| A. Is the primary outcome mechanistic or holistic? | More mechanistic | Emphasize scientific value over social value | Complex, multi-component interventions | More holistic | Emphasize social value over scientific value |
| B. Why are these good outcomes, given the state of evidence? | Efficacy is uncertain | Standard protections of research subjects needed | Sliding scale, informed by 2.A, 2.C, 3.A | Efficacy is known, but effectiveness or implementation is uncertain | If risks are minimal, less stringent ethics review may be required |
| C. What groups have immediate interests at stake in the research? | Researchers, scientists, or drug/device developers | Scientific value is priority and needs to be high | Sliding scale, informed by 1.A-D, 3.A | Patients, providers, communities, policymakers, general public | Engage social groups in outcome selection; groups may be obliged to participate |
| D. What types of outcome data are collected? | Newly generated data, biological and clinical test results | Subjects face additional risk exposure | Some data already exists or collection entails minimal marginal risk | Existing data, routinely collected data, health records | Marginal risk may be low; need to ensure data validation |
| E. What data is included in the primary outcome analysis? | Favor per protocol analysis | Additional burden of monitoring adherence; needs high value to offset | Sliding scale, informed by 2.C, 3.A, 3.D | Favor intent-to-treat analysis | Scientific value may be low; needs high social value |

How might this help?

- Dissolve the need to define a “pragmatic trial” for the purposes of ethical analysis and oversight
- Harmonize ethical analysis with a framework widely used for evidence synthesis and trial design, and thereby facilitate communication between stakeholders
- Provide a foundation for a unified framework for ethical analysis of trials, while highlighting the ethical consequences of particular design choices

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Consent: Ethical and Regulatory Challenges in Pragmatic Trials

Judith Carrithers, JD, MPA
Director of Regulatory Services



PCT Framework and Consent



- PCT: Evaluate the effectiveness of an intervention in a real-world clinical practice setting
- PCT: Imbed clinical trials seamlessly into everyday practice of medicine
- PCT: Trials may involve individual randomization or cluster randomization

- Consent: Full regulatory research consent requirements may disrupt clinical practice
- Consent: Costs and delays could make PCTs difficult or impossible to execute
- Consent: Unique challenges in cluster randomized trials

Ethical Framework



➤ Belmont Report

- ✓ Respect for persons
 - ✓ Beneficence
 - ✓ Justice
- Respect for persons requires that subjects, to the degree they are capable, be given the opportunity to choose what will or will not happen to them – to have the opportunity to consent or choose not to consent
- This includes three elements: information, comprehension and voluntariness



Regulatory Framework



- HHS and FDA regulations require 8 basic elements and 6 additional elements (when necessary) of consent
- Basic elements:
 - ✓ Statement that the study involves research; study description
 - ✓ Reasonably foreseeable risks and discomforts
 - ✓ Reasonably expected benefits
 - ✓ Disclosure of alternative procedure/treatments
 - ✓ Confidentiality of records
 - ✓ Compensation and treatment for injury (if more than minimal risk)
 - ✓ Contact for questions, subject's rights, injury
 - ✓ Statement that participation is voluntary and may be withdrawn at any time without penalty or loss of benefits

Regulatory Framework (Additional Elements)



> Additional elements:

- ✓ Unforeseen risk
- ✓ Investigators may terminate participation
- ✓ Any additional costs
- ✓ Consequences of withdrawal
- ✓ Significant new findings
- ✓ Approximate number of subjects

Alteration/Waiver of Consent



- **HHS allows (*under 45 CFR 46.116(d)*) & FDA will not object (*July 2017 Guidance*) to the waiver or alteration of consent if the IRB finds and documents the study is:**
 - ✓ No more than minimal risk
 - ✓ Waiver or alteration will not adversely affect the rights and welfare of the subjects
 - ✓ The study could not practicably be conducted without the waiver or alteration
 - ✓ When appropriate, subjects will be provided with additional pertinent information after participation

- **When is it not practicable to obtain consent?**
 - ✓ How does this differ for individually randomized trials and cluster randomized trials?

- **How is risk evaluated when:**
 - ✓ Two standard-of-care therapies are being evaluated?
 - ✓ Some subjects will receive standard-of-care and others will receive an experimental intervention?

Focusing on Practicable and Minimal Risk



- **Practicable:** In many pragmatic trials with individual randomization, the participant will meet with the physician. Why is it not practicable to obtain consent at that meeting?
- **Minimal Risk:**
 - ✓ Strong arguments that assignment to one of two standard-of-care treatments is minimal risk since the individuals would be receiving one of these treatments for clinical care if not in the study
 - ✓ Under OHRP draft guidance, if an individual subject will face potentially different risks than she or he would have faced without enrollment, these are considered risks of the trial
- Many pragmatic trials would not meet the standards for waiver or alternation based on impracticability or minimal risk determination



Proposed Solutions/Alternative Consent Models in Individual RCTs



> Lower standards of disclosure/alter elements of consent

- ✓ For example, in a study comparing two standard-of-care treatments which in clinical practice requires only verbal consent, integrate clinical and research consent with a brief explanation of the treatment, rationale, alternatives, risks and benefits, with the research element of randomization described (verbal or written consent documented in the electronic health record)
- ✓ Transparent
- ✓ Minimal/no disruption in clinical practice
- ✓ Minimal increased burden on physician or patient
- ✓ May not include all of the regulatory elements for consent (voluntariness, confidentiality; signed consent form)
- ✓ Requires an IRB determination that research risks are minimal
- ✓ Requires an IRB determination of impracticability

> Provide site specific broadcast notification

> Waive consent



Individual Randomization v. Cluster Randomization



> Individual RCT:

- The individual participant is the unit of randomization, intervention and outcome assessment
- Traditional research ethics and regulatory requirements assume individual consent, then randomization, intervention and data collection

> Cluster RCT:

- Unit of allocation, intervention and outcome assessment may differ (involving groups rather than individuals)
- Harder to determine who needs to consent as everyone involved in the cluster is affected



Ethical & Consent Issues in CRT



- > Threshold question: Is the project QI or research/clinical investigation?
- > If it is research/clinical investigation:
 - ✓ Who are the subjects? The potential subjects include health care providers, their patients, teachers, their students, and individuals who are the targets of the cluster randomized research activities
- > Cluster randomization affects everyone in the cluster, may not be possible to opt out
- > Clusters may be randomized before individual participants are identified (e.g., hospital-wide randomization) so consent prior to randomization is not possible
- > Cluster level randomization may preclude the right to refuse or withdraw consent, but may retain the right to refuse data collection



Proposed Solutions/Alternative Consent Models in Cluster Randomized Trials



- Provide site specific broadcast notification
- Delay consent; allow subjects to consent to use of data after intervention occurs
- Waive consent





Thank you

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