Clinical Trials and Learning Healthcare Systems Research

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Rules of Engagement

This is a discussion, not a lectureship. Insight is not necessarily predicated on knowledge. Share your thoughts!

"In all affairs it's a healthy thing now and then to hang a question mark on the things you have long taken for granted." (Bertrand Russell)

Question your own dogma….and mine. Keep an open-mind.

"Do not fear to be eccentric in opinion, for every opinion now accepted was once eccentric." (Bertrand Russell)

Speak up! Both now, and as you pursue your work and ideas moving forward. Embrace the discourse.

Learning Objectives

1) Understand the definition of a clinical trial according to the NIH, and its implications.

2) Define and discuss pragmatic clinical trials and their particular relevance to LHS research.

3) Define and discuss the strengths and limitations of adaptive trial designs and their suitability to LHS research.

LO #1: What is a Clinical Trial

NIH Definition

"*A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on the health-related biomedical or behavioral outcomes.*"

- What did you think would be in this definition that is not there?
- Decision Tool: What did you learn? What surprises you?
- If our QI project is considered to be a clinical trial by the NIH decision tool, what does that imply in terms of implementing and operationalizing your study?
- How does this compare/contrast to your institutional policies?
- What is the purpose of the institutional IRB?
  - The Tuskegee Syphilis Experiment

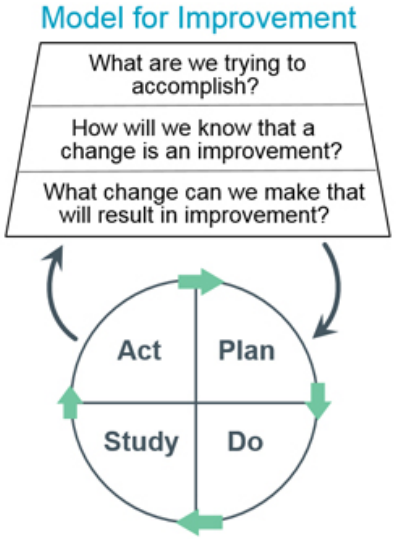
OHRP
OFFICE FOR HUMAN RESEARCH PROTECTIONS

Jeopardy: What is…..?

The framework to systematically improve how care is delivered to patients. Processes have characteristics that can be measured, analyzed, improved, and controlled. [This] entails continuous efforts to achieve stable and predictable process results, that is, to reduce process variation and improve the outcomes of these processes both for patients and the health care organization and system.

AHRQ Agency for Healthcare Research and Quality

Institute for Healthcare Improvement



Langley GL, Nolan KM, Nolan TW, et al. The improvement guide: a practical approach to enhancing organizational performance. San Francisco: Jossey-Bass; 1996.

The Plan-Do-Study-Act cycle was developed by W. Edwards Deming. [Deming WE. The new economics for industry, government, education. Cambridge: Massachusetts Institute of Technology; 1994.]

LO #1: What is a Clinical Trial

Clinical Trial

"*A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on the health-related biomedical or behavioral outcomes."*

Quality Improvement

"The framework to systematically improve how care is delivered to patients. Processes have characteristics that can be measured, analyzed, improved, and controlled. [This] entails continuous efforts to achieve stable and predictable process results, that is, to reduce process variation and improve the outcomes of these processes both for patients and the health care organization and system."

Quality Improvement or Clinical Trial- A Case Study in Appendicitis

LO #1: What is a Clinical Trial

QI or Clinical Trial - A Case Study in Appendicitis

Clinical Question: Can we decrease disability in children with appendicitis if we treat them non-operatively with antibiotics alone?

- How should we approach this question? Trial or QI and why?
  - What information do you want to answer this question?
  - What are your thoughts around informed consent for this study?
  - How would a SAE be handled in these methodologies?
- Has this process brought you clarity or confusion in characterizing a study as a trial or a QI initiative?

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LO #2: What is a Pragmatic Clinical Trial

Trials designed with an emphasis on using a treatment in clinical practice. They investigate a treatment strategy that can be implemented into usual care in a diverse patient population. They incorporate the perspective of stakeholders including patients, clinicians, and healthcare systems and are designed to generate actionable and relevant results that can be used for clinical decision-making.

LO #2: What is a Pragmatic Clinical Trial

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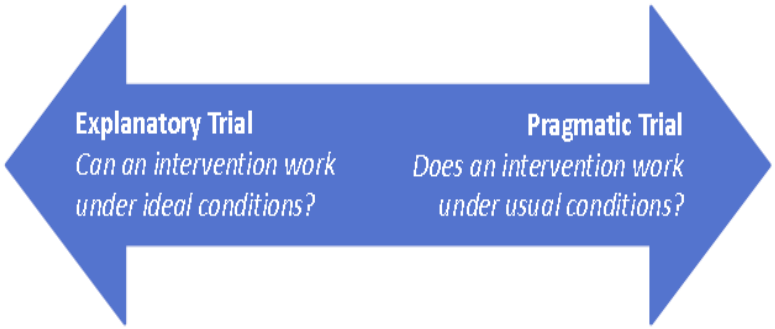


LO #2: What is a Pragmatic Clinical Trial

"Designed for the primary purpose of informing decision-makers regarding the comparative balance of benefits, burdens and risks of a biomedical or behavioral health intervention at the individual or population level." PRECIS -2

- Occur in usual care locations
- Utilize existing clinical infrastructure, operations, and personnel
- Minimal eligibility criteria to maximize recruitment and generalizability
- Delivery, follow-up, and adherence are aligned with current practice
- Occur along a spectrum, with some trials being more pragmatic than others

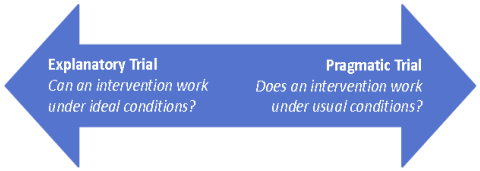
Thorpe KE, et al. 2009. A pragmatic-explanatory continuum indicator summary (PRECIS): a tool to help trial designers. *J Clin Epidemiol*. 62:464–475.

Califf RM, Sugarman J. 2015. Exploring the ethical and regulatory issues in pragmatic clinical trials. Clin Trials. 12:436–441.

LO #2: What is a Pragmatic Clinical Trial

- What do you think are the perceived advantages of the pragmatic trial design? What are the challenges of the pragmatic study design?

Increased control
Internal validity
Safety monitoring
Less complicated statistical approach



Decreased control
External validity
Research protocol compliance and adherence challenges

- Which of these features do you think is most important and why?

LO #2: ADAPTABLE

- Describe the trial *(Charles Varnell, CCHMC)*
- What were the "Innovative Operative Approaches" that the investigators deployed? *(Suchita Rao, Children's Colorado)*
- If successful, how could these approaches change the current paradigm of conducting clinical trials? (*Melissa Smith Parrish, BCH and Erica Sood, Nemours*)
  - MSB: how do you see this as applicable to your work with NC3?
  - ES: How do you see this study informing the types of recruitment strategies for clinical trials in complex CHD patients….prenatally?

LO #2: ADAPTABLE

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- Describe the trial
- What were the “Innovative Operative Approaches” that the investigators deployed?
- If successful, how could these approaches change the current paradigm of conducting clinical trials?
- How do you envision PEDSnet contributing to the design or conduct of a pragmatic trial in your field?
  - Pediatric healthcare QI networks
  - Acute care or critical care
  - Chronic conditions
  - Shared decision-making; health education
  - Mitigating disparities to access

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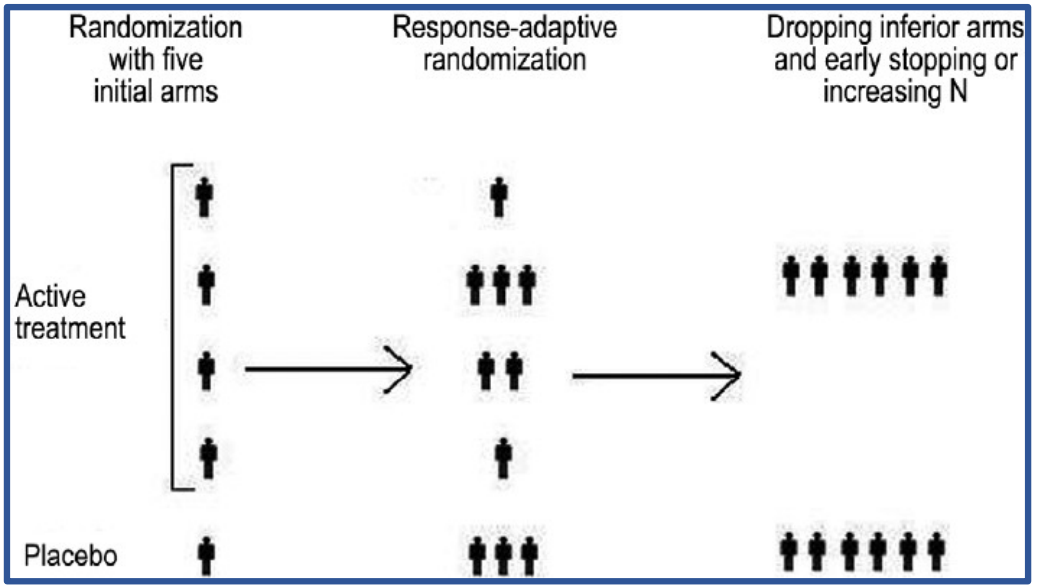
LO #3: What is an Adaptive Trial Design?

- Design that allows for modifications to the trial or statistical procedures during the course of the trial without undermining the validity or integrity of the trial design
  - Adaptive features, criteria, and time points are pre-specified
    - Eligibility
    - Treatment dose, duration, or group (treatment switching design)
    - Endpoints
    - Study procedures
    - Criteria to evaluate clinical response
    - Statistical procedures: randomization blocks (adaptive randomization design), interim analyses timing (group sequential design; drop-the-loser)

	Conventional Trial	Adaptive Design
Design	Rigid	Flexible
Treatment Arms	2-3	Many
Hypothesis	Hypothesis testing	Fit data to hypothesis
Modifications	Discouraged	Pre-specified and allowed
Statistical approach	Frequency methods	Bayesian Approach
Interim Analysis	Usually 1-2	Possibly many
Role of DSMC	Occasional	Frequent
Regulatory view	Well endorsed	?Speculative

Response-Adaptive Randomization combined with Drop-the-Loser Design



LO #3: What is an Adaptive Trial Design?

- Bayesian approach for analyses
  - Developed to account for new data in updating the probabilities that are under investigation
  - Instead of determining the likelihood of a treatment effect occurring by chance (Frequentist method) with fixed input, a Bayesian approach provides the probability of the treatment being effective as data changes.

Standards for Design and Reporting: PCORI and FDA

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