



# Ethical Issues in Pragmatic RCTs

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# Goals of this talk

- Briefly describe what pragmatic clinical trials (PCT) are and why they are important
- Describe the central ethical tensions in PCTs.
- **Explore several examples of PCTs and discuss them together**
- Conclude with a very brief framework for assessing ethical issues in PCTs

# The importance of pragmatic randomized controlled trials (PCTs)

# The Pragmatic Ideal

- **Pragmatic:** ‘Real world’ effectiveness data for clinical and policy decisions (e.g., PRECIS-2 Tool)
  - **Recruitment of subjects** in a setting/method that mimics ‘real world’ use of the interventions
  - **Intervention used** in ‘real world’ way (flexibility, monitoring, etc)
  - **Outcomes** that are **clinically relevant**, measured in ‘real world’ manner (e.g., EHR)
- Involves **research procedures** that closely mimic the ‘usual’ **clinical** operations of the clinic/hospital (or at least as much as possible)

## PCTs usually compare 2 or more interventions

- Interventions can be drugs, procedures, policies
- They are often 'standard of care' or 'usual' or 'acceptable' practices

# Comparing two ‘standard’ practices A and B can be valuable for various reasons....

- B is new & it is 100x more expensive.
- B is more burdensome to use, but there is some limited data suggesting it *might* also be more effective.
- B has much more rigorous data supporting its use; yet A (a very similar drug) dominates the market.
- A and B are commonly used procedures (i.e., not regulated—unless a device is involved) and unknown which is better.
- A and B are two health system level policies or practices (institutions or health professionals).
- B has evolved as the standard based on one old study, or on theoretical grounds, but never been tested against alternative A.

## When A and B are compared in a pragmatic RCT, what is the ‘research risk’ to subjects?

- Pragmatic trials use little or no research-specific measures or procedures (e.g, use EMR, claims data, or public records as source of data)
- Sometimes, only ‘research’ procedure is randomization
- So the only source of research risk would be, if any, from the therapeutic interventions being tested
- But every subject receives an accepted level of treatment



So what's the problem?

# So what's the problem?

- The pragmatic imperative to ‘mimic’ real world practice seems incompatible with an ethics oversight model that assumes PCTs have significant *research* risks.
  - The vision: “learning healthcare system” (LHS) where research and clinical care are closely integrated (IOM 2007).
  - LHS may involve a programmatic and continuous integration of pragmatic RCTs with usual clinical operations.
  - But how to obtain *traditional IC* from every patient-subject for every pragmatic trial in, for example, busy primary care clinics?

## PCTs seem so different that some propose an entirely new ethics framework

“The framework we propose.. rejects the assumption that clinical research and clinical practice are, from an ethics standpoint, fundamentally different enterprises.” (Faden et al, HCR, 2013)[underline added]

“Drawing a sharp distinction between research and therapy can be appealing, but a growing number of activities in health care cannot be comfortably classified as either research or therapy, the one excluding the other.” (Kass et al, HCR 2013)[underline added]

## Some argue that PCTs are indeed ethically special: Forgoing informed consent

- For some pragmatic RCTs, “no express informed consent” necessary.(Faden et al 2013)
- “Obtaining conventional written informed consent may be not only ethically unnecessary but may render such research impracticable...”(Sugarman & Califf 2014)
- Change in regulations needed to “broaden situations in which informed consent is not required or could be waived.”(Platt, Kass, McGraw 2014)

A common view about PCTs that compare ‘standard of care’ interventions and practices: there is no or minimal research risk

For example, some authors argue, in regard to the SUPPORT trial:

“...since all the study [participants] would receive [treatments] within the prevailing standard of care, there was no additional risk to being enrolled in the trial.”

“...there was no basis for claiming an increase in risk from enrolling in the trial versus receiving standard clinical care”

(Magnus & Caplan 2013)—underline added

## Even for FDA regulated products, a proposal for identifying minimal risk PCTs (Anderson et al, Clinical Trials 2015)

The following two categories are to be deemed minimal risk so that they are eligible for alteration/waiver of consent. PCTs that are testing:

1. One or more regulated products according to approved or labeled uses.
2. One or more regulated products not according to label but according to standard of care.

In short: If standard of care PCT, then minimal risk → eligible for alteration/waivers of consent

OK, enough background.  
Let's look at some real  
examples...

# MI FREEE trial (Choudhry, NEJM 2011)

- Q: Does eliminating copayments for Rx drugs improve medication adherence and outcomes?
- Patients with recent myocardial infarctions
- Cluster randomization by insurance plan sponsor:
  - Full coverage (no copayment) for all cardiac drugs
  - vs.
  - Usual coverage
- Primary outcome: composite of readmit/revascularization
- **What was the study's 'research risk'?**
- **Is informed consent needed?**



cont'd (Choudhry et al, NEJM 2011)

- The intervention has no burdens on subjects.
- What was the research risk to subjects?
  - In copay group: no difference between usual vs research
  - In no copay group: no reasonable view that research intervention could result in net loss of welfare
- Research risk of harm seems remote while research benefit seems possible → 'no or minimal research risks'

# Increasing colon cancer screening

(Hypothetical trial from: Asch et al NEJM 2017)

- QRS Health System wants to see if two interventions will increase adherence to colonoscopies.
- RCT with three arms:
  - A: Whimsical card on 50<sup>th</sup> birthday reminding person of colonoscopy screening, with some ‘cleansing’ supplies
  - B: A card with a default appt for colonoscopy but with options for changing time of appt.
  - C: Usual (boring form letter, say....)
- Primary outcome: screening rate
- **What is the research risk?**
- **Is informed consent ethically necessary from all in 3 arms?**

# HeadPoST study (Anderson et al, NEJM 2017)

- Does lying flat after acute ischemic stroke improve outcomes? Meta-analysis in 2014 suggested better blood flow in affected hemisphere when supine/near supine. But **both** sitting and supine are still widely used.
- Cluster randomized by hospital, but individual intervention
  - Supine vs. Sit up 30 degrees
  - For 24 hours
- Same position for eating, drinking, toileting.
- Primary outcome: 90 day disability
- **Is this study minimal risk?**
- **Is a waiver of consent OK?**

# HeadPoST study consent procedures

- “The protocol was approved by all regulatory authorities and ethics committees at the participating centers.
- A **senior executive officer at each hospital acted as a “guardian”** (as part of the cluster-randomized trial design) and provided consent at an institutional level for head positioning to be implemented as a **low-risk intervention to clusters of patients as part of routine care;**
- written **informed consent** was **subsequently** obtained from the patients or their approved surrogates **for the collection of medical data and participation in the follow-up assessments.”**

# HeadPoST investigators rationale for why the study was low risk

(NEJM, in response to letter to editor 9/14/2017)

- “the insufficient amount of level 1 evidence specifying the benefits and harms of head positioning for patients with acute stroke;
- The fact that people change their head position within the ranges being tested during routine hospital care and in daily life, as they shift from activity during the day to rest and sleep at night;
- and the view that patient care would not be compromised by either of the interventions.”

# HEAT-PPCI (Shahzad et al, Lancet 2014)

- Which is better in acute MI—heparin or bivalirudin (new, \$\$\$) for antithrombosis?
- Acute MI patients randomized
  - Heparin
  - Bivalirudin
- Primary outcome: composite of several factors (inc mortality); also bleeding as primary safety endpoint.

# HEAT-PPCI consent procedures

- “Full ethical approval was granted for the use of delayed consent.
- Patients were randomly allocated treatment and underwent angiography in an emergency setting and **no attempt was made to discuss the trial or to seek consent during this phase.**
- Surviving patients or their appropriate representatives (in 15 cases) were **subsequently approached for formal consent to continue** as trial participants, to use their data and to allow contact for the 28 day follow-up.”

# HEAT-PPCI, accompanying ethics commentary (Shaw D, Lancet 2014)

- “Far from being unethical, the study sets a high standard for consent in pragmatic trials.”
- “Despite the tradition of obtaining informed consent for almost all research, some debate surrounds whether patient consent should be sought when both treatments are licensed, consensus is present regarding equipoise, and randomisation does not pose any added risk.”(my italics)
- (For an alternative perspective on HEAT PPCI, see: Dickert and Miller, BMJ 2015)



# Delivery room management of apparently vigorous meconium-stained neonate (Wiswell et al Pediatrics 2000)

- Is endotracheal suctioning prior to resuscitation better than supportive care in reducing meconium aspiration syndrome (MAS)?
- Randomized vigorous full term neonates with meconium in amniotic fluid.
  - Intubation and suctioning
  - vs.
  - Expectant management
- Primary outcomes: MAS and complications
- **What is the risk of this study?**
- **Is informed consent required?**

# Meconium study: No informed consent

- “This was a **no informed consent** protocol. The rationale for this included:
- 1) **wide acceptance of both** proposed management strategies (universal vs selective intubation) as standards of care;
- 2) MSAF is frequently not noted until moments before delivery, obviating the ability to counsel parents; and
- 3) inherent difficulties in obtaining valid informed consent from a mother undergoing the pain of labor.
- We estimated that if we were to attempt to obtain informed consent, even during **prenatal visits**, at most we would **only be able to enroll 70% of eligible infants**.
- Moreover, the population of enrolled neonates would not be representative of the entire population of infants born through MSAF.”

# Issues to consider in ethical evaluation of PCTs

# 1. Does the PCT have clinical equipoise?

- Should the claim of “standard practice” and “widely used” be verified by surveys or studies? Can we just take trialists impressions and opinions as valid?
- Especially important for non-regulated interventions (i.e., not drugs or devices but things like ICU protocols).
- See: Macklin R, Natanson C. Misrepresenting "Usual Care" in Research: An Ethical and Scientific Error. *Am J Bioeth.* 2020;20(1):31-39.

## 2. What is the research risk in the proposed PCT? i.e., does ‘randomization confer no additional risk’?

- SOC PCTs are special (and different from RCTs of novel interventions), as by definition we can assume two things:
  - That there is clinical equipoise.
  - That the interventions are not too risky to use in RCT
- But these special features do not tell us what the research risks are.
- Research risk = incremental risk incurred by subject by being in the study vs not being in it.

## 2. PCT research risk, 2

- There must be a real prospect that  $A > B$  (or  $B > A$ , depending on ex ante evidence). Otherwise, no need to do the study.
- This prospect translates into the prospect that someone receiving B in ordinary care could face a DIFFERENT welfare outcome by entering the PCT (since she could receive A instead).
- Since every PCT will have such a prospect, every PCT has some risk of different welfare outcome (better or worse) for an individual.
- Given this, I suggest we generally use nature of main outcomes as basis for whether or not the PCT is low risk. (Recall our examples)

### 3. Is a waiver or modification of consent permissible? (45CFR46.116d)

- The regulatory requirements include:
- The study would have to be deemed minimal risk.
- Plus it would need to meet other criteria:
  - Research impracticable without waiver/alteration.
  - Not adversely affect rights and welfare of participants.
  - Debriefing after the fact.



**Some suggestions (that do not conform to current regulations) and food for thought...**



# Suggestion 1

1. In general, no *individual* intervention PCT should receive a *complete* waiver of consent. (e.g., well justified cluster-cluster PCT might be exceptions)

If we are trying to conduct PCTs that closely mimic clinical practice, it makes no sense to hide how we chose between the interventions A and B.

# Suggestion 2

2. For SOC PCTs, the informed consent process should **mimic CLINICAL consent** practices as much as possible.

--the truly important elements are:

--**discussion of two alternative treatments**, at the level of detail that would occur in clinical practice when patients are told there are two options [would do this clinically anyway]

--**randomization** as selection method

--the other required elements should be disclosed included very briefly (or even dropped altogether for some)

- Should take only a little more time than regular clinical consent.

# Suggestion 3

3. Criteria for a complete waiver vs an alteration of informed consent should be different.

Also, alteration of informed consent should be allowed for SOC PCTs even if it is greater than minimal risk: transparent, streamlined, and consistent with clinical consent.

--OF COURSE, this would require a regulatory change!

# Summary

- The fact that a PCT is comparing two 'standard of care' interventions does not by itself create a special ethical category of 'low risk research' that may be done without consent.
- Instead, careful case by case analysis is required because PCT design raises complicated issues for risk assessment.
- Some SOC PCTs may indeed be minimal risk; many will not be.
- We do need to recognize the uniqueness of PCTs, with flexible consent procedures that integrate clinical and research ethics.

