# Ethical Issues in Pragmatic RCTs

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# Disclaimers and Disclosures

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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 tension 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)

  - Potential for **'blurring' of research and usual care**→ethical **implications?** (Kass et al, *HCR* 2013)

# PCTs can have various RCT designs

- Traditional
  - Individual randomized
  - Pre-randomization consent, if consent required
- Cluster randomized
  - Individual cluster—individual intervention, but grouped into clusters
  - Professional cluster—e.g., randomize work hours of MDs, unit coverage, use of suture techniques
  - Cluster cluster
- Post-randomization consent variations
  - Zelen—recall lecture by Robert Truog in this course
  - Trials within Cohorts—Relton et al
  - "Just in Time" Consent—Vickers et al

# 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?

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- 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?

# Two views about the problem

- PCTs are *ethically special*. They are not really different from usual clinical practice→therefore we need to relax the usual ethical oversight rules.(Kass et al, HCR 2013)

  - PCTs do have *special features* but they only make it difficult to identify the 'research' elements. (Kim&Miller, JAMA 2015)
    – In fact, significant potential for missing important ethical issues is a real danger.
    – Careful case by case scrutiny still essential.  Mere fact that a study is a PCT could be misleading…

# 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

- "…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 and Caplan 2013)

- "institutional review board (IRB) needs to determine whether equipoise exists between the options under study… Implicit in the IRB's determination is the assurance that the net risks and benefits of the diagnostics or treatments being compared are not thought to be materially different."(Editors, NEJM 2014)

- (See also Lantos et al 2015 in Clinical Trials)

OK, enough of theory and 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
  - Usual coverage

- Primary outcome: composite of readmit/revascularization

- **What was the study's 'research risk'?**

- **Is informed consent needed?**

- 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

- Research risk of harm seems remote; research 'risk' of benefit seems possible → 'no or minimal research risks'

- Could the study as designed be conducted with individual informed consent?  Seems unlikely.

# Waiver of consent rationale given in the paper
## (Choudhry et al, NEJM 2011)

- "Because all patients, at a minimum, received their usual level of prescription-drug coverage, no specific patient-level written informed consent was sought. This study was approved by the institutional review board at Brigham and Women's Hospital."

- My view: agree with conclusion, but the reasoning is flawed.

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# 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 50th 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?**

# MINT trial (NCT02981407)

- Does liberal RBC transfusion strategy reduce negative outcomes in MI patients who have low RBC, compared with restrictive RBC transfusion strategy?

- Hospitalized MI patients with low RBC (Hgb<10)
  - **Will** transfuse to keep at 10 g/dL vs
  - **Permitted** to transfuse if 8 or below; **strongly rec** if 7 or below

- Primary outcome: composite mort/morb x 30 days.

- **What is the 'research risk' of this trial for a participant?**

- **Is informed consent needed?**

# Risks section of MINT consent form

- "Some blood transfusions cause problems. [Long description of side effects and risks of blood transfusions in general follows:] These bad effects of blood do not happen often and most of the time get better with treatment. The most common of these rare side effects is high temperature, chills, and allergic reactions. More rarely blood can transmit viral infections such as hepatitis (liver infection) or lead to extra fluid in the lungs. The important risks of blood transfusion are also described in the consent form that the hospital will have you sign before receiving a transfusion.

- There may be risks and discomforts resulting from having blood transfusions or from having transfusion delayed <u>that are not yet known</u>." [underline added]

- Is this a sufficient description of the risks of entering the study?

# HeadPoST study (Anderson et al, NEJM 2017)

- Does lying flat after acute stroke improve outcomes?

- Cluster randomized by hospital, but individual intervention
  - Supine   vs. Sit up 30 degrees
  - 24 hours, even for eating/drinking/toileting

- Primary outcome: 90 day disability

- **What is the risk level of this study?**

- **Is informed consent required?**

# 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

- "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—<u>heparin or bivalirudin (new, $$$)</u> 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."

# 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
  - 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 (my opinion!)

# 1. Does the PCT have clinical equipoise?

- Clinical equipoise: insufficient evidence to support a practice favoring A or B above the other→no participant is knowingly disadvantaged

  – How should the claim of equipoise be substantiated?

  – Should the claim of "standard practice" be verified by surveys or studies?

  – **Especially important for non-regulated interventions (i.e., not drugs or devices).**

# 2. What is the research risk in the proposed PCT?

- Note that clinical equipoise may justify a study but it does not directly provide a sense of what is at stake for the participants.

- Every PCT must meet two conditions:

    – It is uncertain that A>B or B>A: the basis for equipoise.

    – It is uncertain that A=B: if this were not true, then no need to do the PCT.

# 2. PCT research risk, 2

- If it is uncertain that A=B, then there is a real prospect that A>B (or B>A, depending on ex ante evidence).

- 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 <u>some</u> risk of different welfare outcome (better or worse).

- Given this, we can use nature of main outcomes as basis for whether or not the PCT is low risk.

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

- 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.

# Note on 'impracticability' of research

- What kind of considerations are relevant?
  - If it makes the study too expensive to conduct?
  - Cluster design is necessary to science?
  - Impingement on the pragmatic nature of study—i.e., if it makes the study more explanatory than pragmatic?
  - Is it a matter of degree?

# Would forgoing or modifying informed consent violate rights and welfare of subjects?

- Difficult to interpret
  - Rights could refer to other existing laws or regulations
  - Odd mention of 'welfare' given the minimal risk condition

- Interpret as: *otherwise entitled or expected rights or benefits* are not compromised.

- Thus, subjects' **reasonable expectations** are key.

# SOC RCTs often involve preference sensitive decisions

- A and B may seem to have similar R/B ratio in some quantitative sense (e.g., expected QALYs)

- But the burdens might be very different in kind

- Or there is a tradeoff in efficacy and burdens/risks.

- But these are the very situations that require shared decision-making.

# Other reasonable expectations

- Clear majorities of public expect transparency regarding RCT in clinical setting, even if risk is minimal (Nayak et al 2015)

- Current default?: Lack of transparency about RCT (even very low risk SOC RCT) would be seen as violating a reasonable expectation.

# Summary Points

- PCTs have special features that make identification of ethical issues challenging. They still require the usual case by case scrutiny.

- Whether the PCT is consistent with equipoise still needs to be asked
  - Especially for non-regulated interventions

- Clinical equipoise answers whether it is permissible to enroll; does not directly identify RCT research risks beyond that, i.e.,
  - What are the risks that need to be communicated?
  - Is the RCT minimal risk?
  - Is a waiver of consent permissible?