Ethical Issues in Pragmatic RCTs

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Outline

- **What are pragmatic trials?**
- **Why kinds of ethical questions** do pragmatic RCTs raise? Two examples of RCT design.
  - Standard of care RCTs (SOC RCT)
  - Trials within Cohorts (TwiCs)
- Conclude with brief **systems level** ethical questions

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)

Pragmatic ideal: two example types of RCTs

- Comparison of two 'standard of care' interventions: SOC RCT

- Comparison of a new intervention (or new way of using an intervention) and treatment as usual: I will discuss "Trials within Cohorts" (TwiCs) design.

'Standard of care' RCTs address a common situation

- Treatments (e.g., drugs or procedures) A and B are both commonly used. (Can be more than two, of course).

- Both are considered 'within the current standard of care'
  - not known which is actually better (benefits and harms)
  - reflected in variations in practice and
  - lack of consensus in the field.

A vs B RCT are valuable for various reasons….

- B is new & it is 100x **more expensive**.
- B is **more burdensome** to use, but there is some observational data that suggests it ***might*** **also be more effective**.
- B has all the **rigorous comparative data**; **yet A** is a very similar drug and the manufacturer has been good at **dominating the market**.
- A and B are commonly used **procedures**, but not regulated and unknown which is better.
- B has been adopted as the **standard based on one old study, or on theoretical grounds**, but never been tested against prior alternative A.

So what's the problem?

- The vision of a "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?

Maybe SOC RCTs are special by virtue of comparing two SOC interventions?

- The interventions are 'accepted' ('standard of care') medical practice.
- ***Everyone*** **will receive SOC treatments or interventions—whether inside or outside the RCT.**
- **No special research measures**; EHR used.
- Therefore, there is a strong intuition that the ethics of such studies must somehow be different than usual.(Platt et al 2014)

(Nearly) exhaustive list of options: determining whether, in a proposed study, it is…

- **Ethically acceptable** to forgo or modify traditional IC by using variations such as:
  - Shortened form
  - Simplified opt out (e.g., European Directive for some cluster trials)
  - Verbal consent (mimic oral consent; document in EMR)
  - General notification and broad consent
  - No consent or notification
- **Ethically NOT acceptable** to forgo traditional IC:
  - Modify RCT, conduct with IC—less pragmatic RCT but 'pragmatic enough'?
  - Not conduct *some* pragmatic RCTs since modification to accommodate IC will make the study not worth doing

But how to decide?

- Requires analysis of 'waiver and alteration' criteria of the regulations (45CFR46.116)
- These regulations capture, at a general level, the ethical issues well.
- Research must be:
  - Impracticable unless IC waived or altered
  - **No more than minimal risk**
  - **Waiver or alteration does not violate rights and welfare**
  - [Debrief for some types of research]

Is the SOC RCT minimal risk?

- If two SOCs are being compared, does that by itself imply minimal risk?
- No. Cannot answer without further details about the RCT.
- $\Delta W=[W_A - W_B] \cdot [P(A_i) - P(A_o)]$ (Chen & Kim, *Clinical Trials* 2016)
- But intuitively…

Example Study Type	Clinical Context
1	Comparative evaluation of 2 Food and Drug Administration (FDA)-approved drugs for hypertension. Limited data suggest that drug A might be better, but drug B is much more widely used.[3] They have a similar mechanism of action; in clinical practice instructions to patients are identical. The primary outcome is blood pressure readings for 1 year. Cardiovascular events are monitored but are not the focus. The only research element of this pragmatic trial is randomization.
2	Comparative evaluation of 2 FDA-approved anticoagulants in emergency treatment of ST-segment-elevation myocardial infarction. Drug A is more expensive than an old drug B but theoretically better. Limited time and the clinical state of patients are obstacles to obtaining traditional informed consent. The primary outcome is a composite of serious clinical outcomes (including death) and a safety outcome of bleeding incidence, powered based on data.[4]
3	Comparison of 2 surgical procedures for cancer. One procedure is much more invasive and disfiguring, with greater potential adverse effects but thought by many surgeons to be more effective. The primary outcome is cancer-free survival and overall survival, powered based on existing evidence.[5]
4	Comparison of angioplasty and stenting plus medical management vs medical management alone for intracranial artery stenosis. The burdens and adverse effects are different for surgery and medical management. Primary outcome is clinical (stroke, death) powered using existing data.[6]
5	Comparison of an FDA-approved agent for macular degeneration with a biologically similar agent approved for cancer. Both are used by ophthalmologists, but drug A is much more expensive than drug B. Primary outcomes are improvement in visual acuity and safety.[7]
6	Comparison of a standard-of-care treatment (widely used but without proven efficacy) with supportive treatment only. Endotracheal suctioning prior to resuscitation of nonvigorous neonates with meconium-stained amniotic fluid is currently recommended, but there are concerns about its efficacy and its burdens (delayed resuscitation, complications of suctioning). Primary outcome includes need for oxygen and ventilatory support.[8]
7	Comparison of morning vs evening dosing of FDA-approved antihypertensive drugs. Most people take their medications in the morning. A recent randomized clinical trial (n = 2156) showed robust effect of reducing major cardiovascular events and the American Diabetes Association recommends taking at least 1 blood pressure medication at night, although some might suggest that a definitive US study is necessary. More than 5000 participants will be randomized, and primary outcome will be major cardiovascular events, including death.[9]

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.

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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.

A note on impracticability

- Problem: research would be impracticable without the waiver or alteration.
- Solution?
  - Alter informed consent process
  - Alter the design of RCT to make it compatible
  - Or both
- Requires case by case analysis

Another RCT design example

- Build and conduct a cohort study based on a condition/disease
  - Informed consent
    - Broad consent for use of EHR data
    - ± periodic questionnaires
- Select subgroup within cohort using eligibility criteria for RCT→ trial within cohort or **TwiC**
  - Randomize
  - **Active arm with post-randomization informed consent**
  - **Control arm**
    - Treatment as usual—absolutely no difference in experience
    - **EHR data used, based on initial broad consent**

Some advantages of TwiCs

- 100% recruitment and retention of control arm.
- Refusals and dropouts in active arm, while diminishing power, provide rich data for estimating uptake in real world use.
- Control arm: save resources, time, effort and patient burden by dispensing with traditional consent.
- **But is it ethical?**

Ethical issues in TwiCs

- Active arm:
  - Is post-randomization informed consent ethical?
- Control arm:
  - Is randomization without consent ethical?
  - Is the initial broad consent for EHR use sufficient?
- Thoughts?

Active arm post-R consent ok?

- Perhaps there is incentive for portraying (by investigators) and perceiving (by subjects) intervention (too) positively?
  - An old concern about Zelen designs;
  - Need not be a deliberate mis-portrayal
  - i.e., a usual element in equipoise assessment and portrayal absent?

- Still, prior to initiation of intervention, receives **all** of the 'usual' IC information.
  - Only difference is that it is after randomization

Is randomization without prior consent unethical?

- Imagine a biobank based experiment
  - Assume biobank is disease specific
  - Donors give broad consent for use of tissues and cells; frozen for later use; then…
  - Researcher randomizes subgroup, then conducts experiment on that disease using one half as control
  - It seems there is no need for disclosure and consent for randomization here, is there?
- If so, then why isn't it acceptable in TwiCs?

Is the initial broad consent sufficient for use of control group EHR?

- Broad consent seems to have a reasonable scope
  - Disease specific
  - EHR specifically mentioned
  - No other interaction or intervention with subject
  - No real concern about non-welfare interests

But suppose that some people in the control group feel that..

- Although not harmed or burdened and
- Although they gave broad consent for EHR use,
- They have been **'used'** inappropriately
- **Perhaps even misled** in some way.
- Is this a justified/reasonable reaction? Discussion.

Perhaps the biobank analogy is wrong?

- Problem: the TwiCs investigators know and intend to conduct TwiCs at the time of enrolling you into cohorts.
- Since in obtaining consent for cohort study, **they could easily have obtained consent for:**
  - Random selection in future for TwiCs
  - More specific permission for use of data for TwiCs…
- There is an intentional lack of transparency. What is its ethical significance?

A common theme?

- In pragmatic RCTs,
  - the *experience* of subjects is similar inside and outside RCT, i.e., all receive SOC—SOC RCT
  - there are identifiable groups whose clinical experience is not affected at all—TwiCs control arm

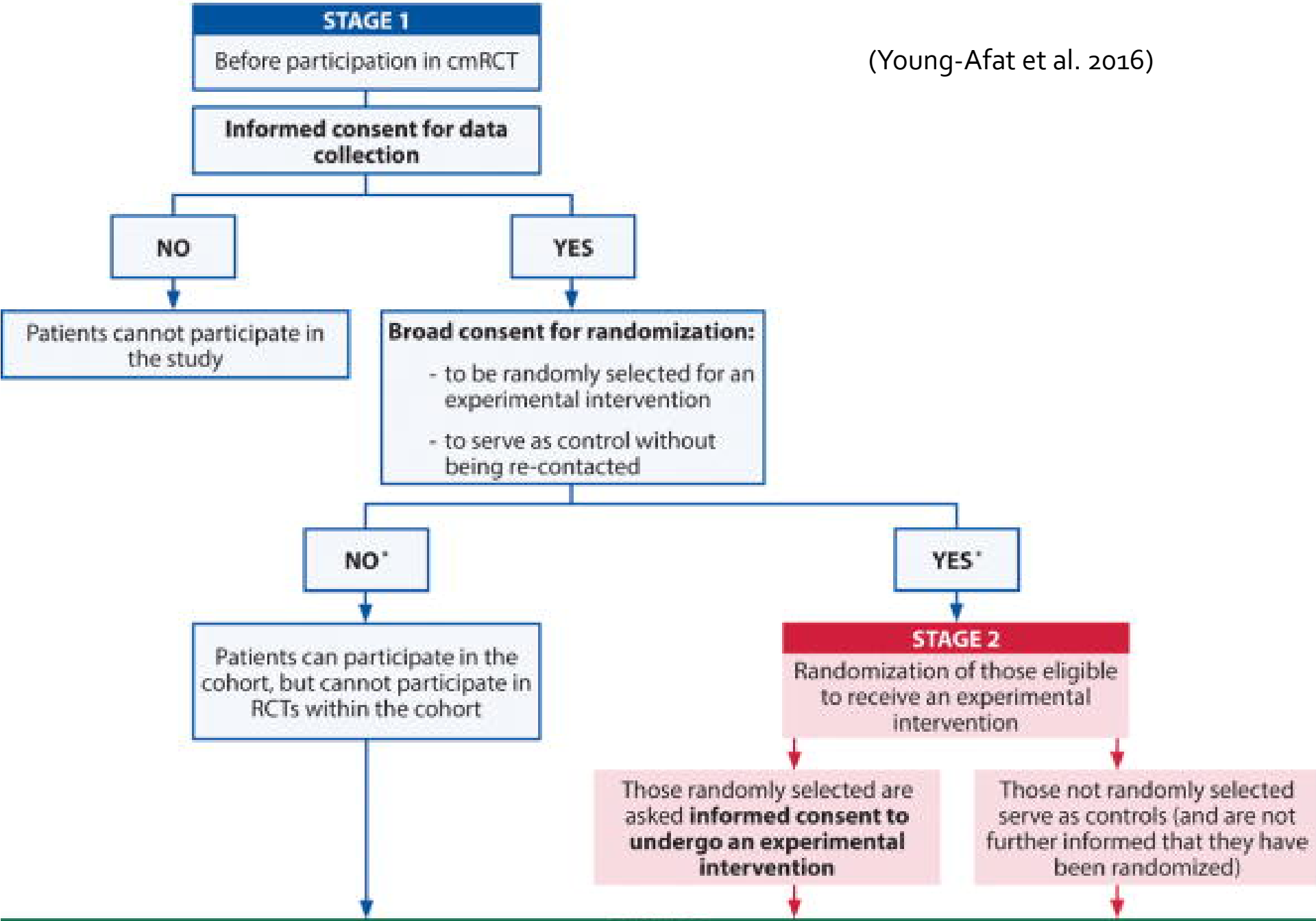
- Therefore, the usual rules about disclosure and consent could be altered for all (SOC RCT) or some (TwiCs) who participate in such studies.

But there is another common theme in these debates (Kim & Miller, *NEJM* 2014; Nayak et al, *Annals Int Med*, 2015)

- Informed consent may have other functions (even when research risks/burdens are low):
  - Transparency expectations—and conditions for trust
  - Control—including who decides what is 'relevant' to disclose
  - Congruence of subject values and choices
  - Subjective interpretations of welfare (e.g., in preference sensitive choices)

- Especially for clinical research in a treatment setting where the <u>expectations are fairly strongly in favor of disclosure and consent</u> (Nayak et al, *Annals Int Med*, 2015)

Staged-informed consent model for cmRCT



(Young-Afat et al. 2016)

Final Point: System level ethical issues in LHS

- In LHS:
  - Entire health system as one large 'research' cohort
  - Clinical policy/practice decisions (e.g., formulary decisions) and research decisions are not so separate given the goal of seamless integration of the two spheres

Some ethical implications…

- If TwiCs used in LHS, then even pre-randomization broad consent may not be enough (since patients will develop new diseases and conditions they had not anticipated on entering the LHS).
- To the extent that **research and treatment have distinct purposes**, any attempt to integrate them need to address potential conflict of roles
  - In LHS, this will be at the highest level of decision-making.
  - In general, incentive for the LHS will be in the direction of collective benefits over individual preferences.
- Despite these caveats, the *benefits* of LHS may outweigh the potential risks, but these issues need to be addressed adequately.

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