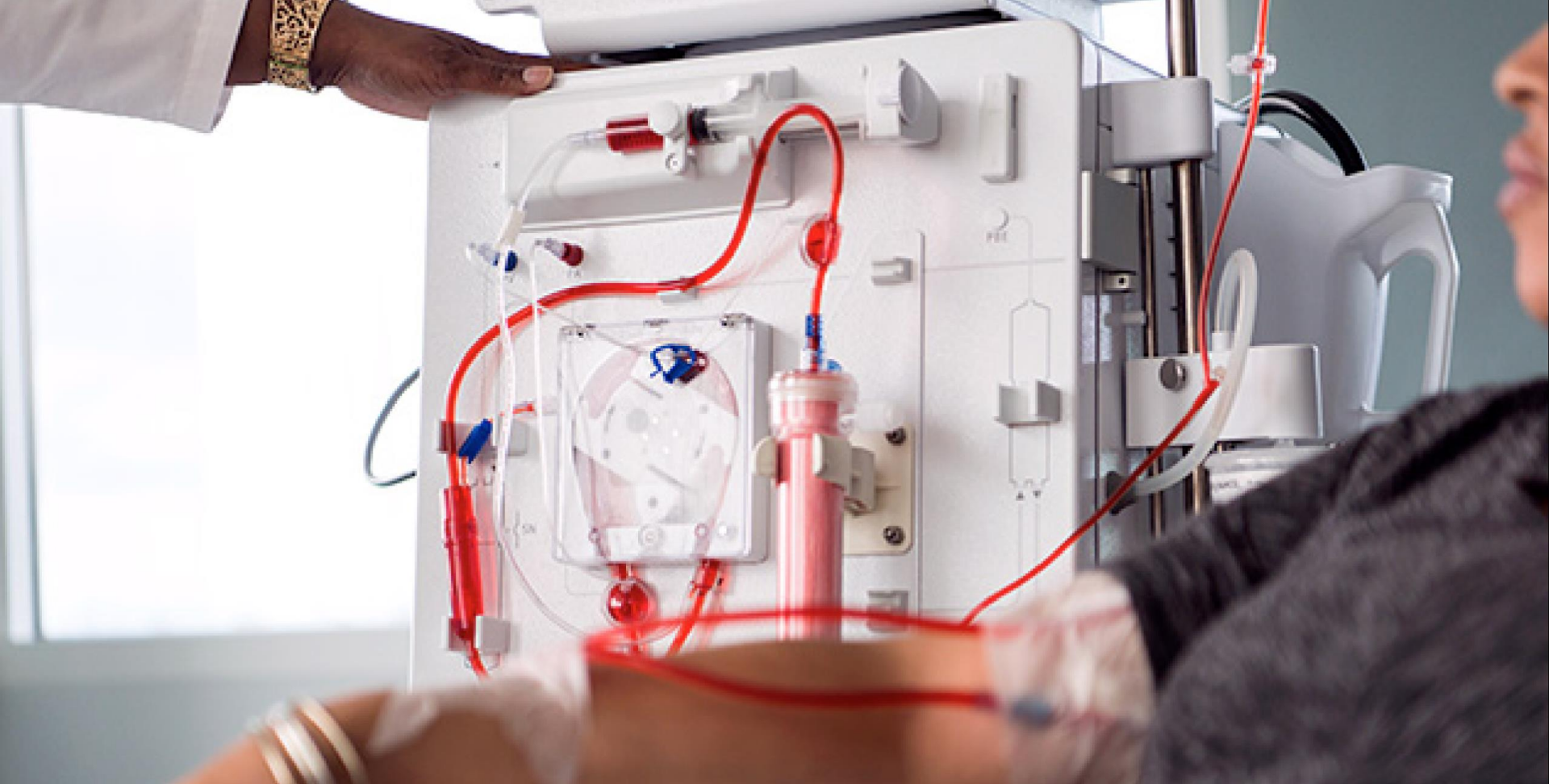


Ethical issues in pragmatic trials in hemodialysis units in Ontario

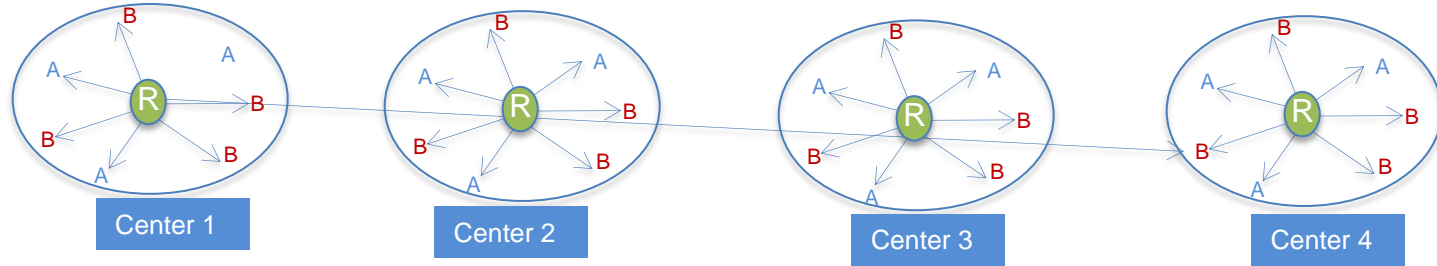
Charles Weijer

@charlesweijer 

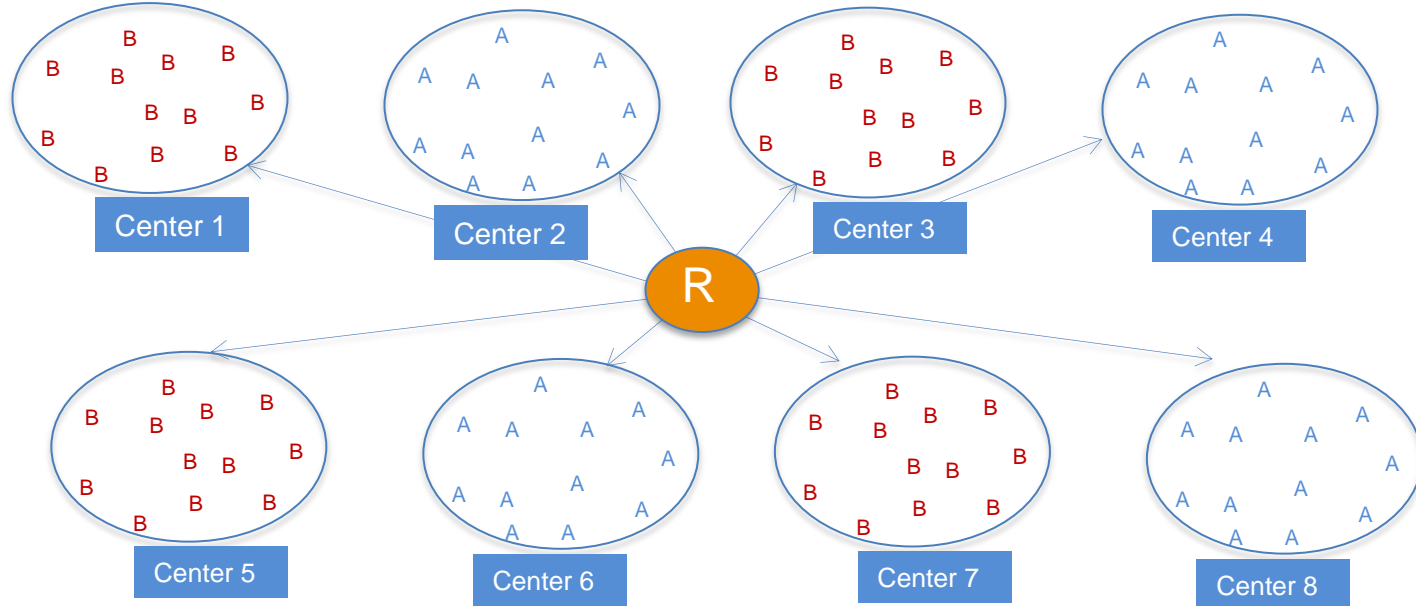




Patient randomized trials



Cluster randomized trials



Cluster randomized trials

- Units of **randomization** are “clusters” or groups (rather than individuals)
- **Intervention(s)** may be delivered to:
 - Cluster as a unit (“cluster-cluster trial”)
 - Professionals (“professional-cluster trial”)
 - Cluster members (“individual-cluster trial”)
- **Outcomes** measured on individuals
- **Cluster randomized trials raise challenging ethical issues.**



Ethical issues

1. How should we protect vulnerable participants?
2. Are usual care interventions research or practice?
3. From whom, how and when is informed consent required?
4. What are the goals of notification and how are they best achieved?
5. What research ethics oversight is required?

Guidelines and Guidance

The Ottawa Statement on the Ethical Design and Conduct of Cluster Randomized Trials

Charles Weijer^{1,2,3*}, Jeremy M. Grimshaw^{1,4,5}, Martin P. Eccles⁶, Andrew D. McRae^{1,3,7}, Angela White¹, Jamie C. Brehaut^{4,8}, Monica Taljaard^{1,4,8}, the Ottawa Ethics of Cluster Randomized Trials Consensus Group[¶]

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Introduction

Cluster randomized trials (CRTs), also known as group randomized, place-based, or community intervention trials, are

systematically explored. As a result, researchers and research ethics committees (RECs) currently lack specific guidelines to help them design, conduct, and review CRTs according to internationally accepted ethical standards. Predictably, the lack of

Developing ethics guidance

- CIHR SPOR Innovative Trials Grant
- **Objective 4:** Work with ethicists, patients, and other stakeholders to develop a responsible ethical framework to guide the conduct of pragmatic trials that are integrated into routine hemodialysis care.
 - Empirical studies (interviews; systematic review; etc.)
 - Ethical analyses (identifying questions and potential answers)
 - Consensus guidelines process.

1. How should we protect vulnerable participants?

- Vulnerability: “an identifiably increased likelihood of incurring additional or greater **wrong**” (Hurst, 2008)
 - Autonomy wrongs
 - Beneficence/ welfare wrongs
 - Justice wrongs
- Pragmatic trials in HD units have few eligibility criteria and simplified recruitment. Vulnerable patients may be “hidden”.

1. How should we protect vulnerable participants?

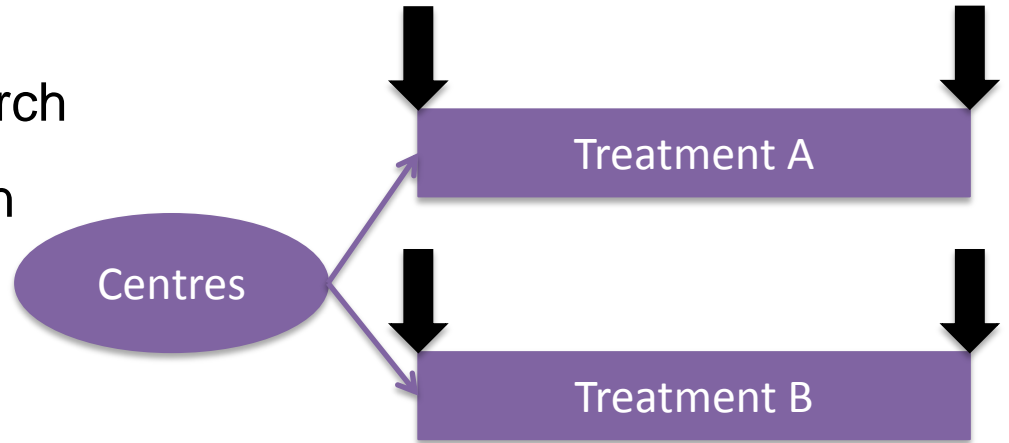
- **Autonomy wrongs:** Patients who lack decision making capacity
- **Beneficence/ welfare wrongs:** Patients with co-morbidities
- **Justice wrongs:** Socially marginalized patients
- **Not a reason to exclude from participation** as patients may be denied access to benefits of research.
- What additional protections should be in place to protect the vulnerable?

2. Are usual care interventions research or practice?

- Pragmatic trials may
 - Compare treatments used routinely in medical care, OR
 - Assigned treatment may be adopted by cluster as local “standard of care”
- Studies as a whole are research, of course
- Should usual care **interventions** be considered part of clinical practice or research?

Are usual care interventions practice?

- First step in REC review: separate practice from research
- Treatments A and B fall within usual care and are practice
- As they are not research interventions, they do not fall within the purview of the REC.

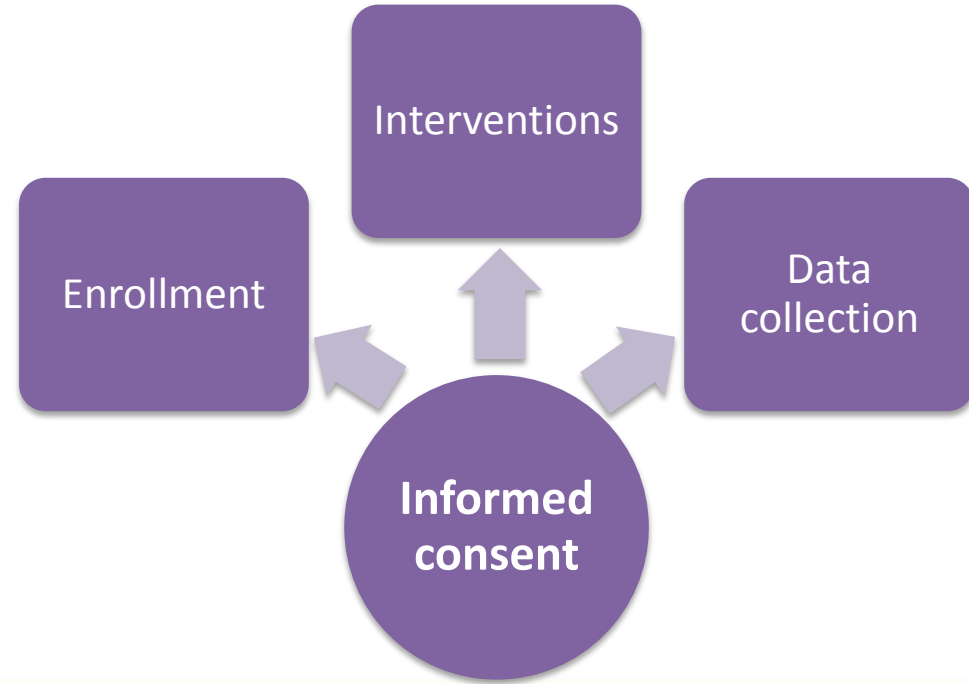


Are usual care interventions research?

- Usual care treatments A and B ought to be considered research
 - They are assigned randomly
 - Not the result of the physician's individualized judgment on behalf of the patient
 - Not the product of joint deliberation and agreement between physician and patient.

3. From whom, how and when is consent required?

- “Researchers must obtain informed consent from human research participants in a CRT, unless a waiver of consent is granted by a REC under specific circumstances” (Ottawa Statement, 2012)
- Heuristic: “Get consent where you can”



3. From whom, how and when is consent required?

- Waiver of consent
 1. Research is socially important
 2. Participation poses only **minimal risk**
 3. Requiring consent would make the study **impracticable**
- Can a study with mortality as an outcome be ‘minimal risk’?
- What is an adequate justification for ‘impracticability’?
 - Generalizability? Bias? Cost? Failure to recruit?
 - What if intervention is not disclosed in clinical practice?

Informed Consent for Pragmatic Trials — The Integrated Consent Model

Scott Y.H. Kim, M.D., Ph.D., and Franklin G. Miller, Ph.D.

Integrated consent

- Pragmatic trials are carried out in real-world settings
- Shift to a more clinical-style of consent for research
- Fulfills ethical requirements of consent in the context in which pragmatic trials are conducted (Kim and Miller 2014).

Learning health care systems hold great promise for improving medical care by systematically integrating the delivery of medical services with clinical research. In such systems, the generation of knowledge would be “embedded into the core of the practice of medicine,” leading to “continual improvement in care.”¹ But is the goal of systematically integrating knowledge generation with health care delivery compatible with current research-oversight procedures²⁻⁴ — for example, when a comparative-effectiveness study compares two standard-of-care interventions⁵⁻⁶ In some pragmatic, randomized clinical trials comparing two commonly prescribed medications for an outpatient condition such as hypertension, the only material departure from clinical practice may be replacing the physician selection of treatment with a randomized selection.^{4,7} It seems unlikely that such a study can be seamlessly “embedded” in routine clinical care delivery if the traditional informed-consent process for research participation (with the usual complex, lengthy document) is required. But what are the alternatives?

A recent Department of Health and Human Services invitation for public comment specifically asked, “Should an IRB [institutional review board] be allowed to waive informed consent for research involving randomization of subjects to one or more standard of care interventions?”⁸ One group has developed a sophisticated moral framework for evaluating the ethics of learning health care activities⁸ and argues, following others,⁹ that these principles yield a surprising result: in some pragmatic comparative-effectiveness trials, the fact of randomization need not be disclosed to patients, and thus no express informed consent for research participation is ethically necessary.¹⁰

We share the goals of the learning health care movement¹ and are deeply concerned about unnecessary regulatory obstacles to important research¹¹; however, we find the proposal to not disclose to patients the fact of randomization even in low-risk outpatient pragmatic trials (hereafter called the no-consent model) problem-

atic for both ethical and practical reasons. We propose instead that the consent process itself should reflect the ideal of learning health care of integrating medical care and clinical research, and we propose an integrated consent model for some types of pragmatic, randomized clinical trials. Notably, such a model can reasonably be seen as compatible with existing regulations.

THE NO-CONSENT PROPOSAL

In the no-consent model, patients would be unaware of the fact that they are in a randomized clinical trial.¹⁰ This cannot be accomplished without the physician actively concealing the patient’s inclusion in the study, much in the way that clinicians sometimes prescribe placebo treatments without patients’ knowledge.¹² Imagine a patient asking why a particular treatment is chosen. Although in a narrow sense a physician can “accurately” say to the patient who is randomly assigned to a particular drug that “this drug is an effective drug that I commonly prescribe to treat high blood pressure,” an ordinary patient will not appreciate the artful choice of words. This lack of transparency would be intended. However, transparency is presumed in communications between physician and patient and between researcher and study participant. Are there sufficient reasons to override this presumption? We doubt this, for both ethical and practical reasons.

From an ethical perspective, the reasons in support of the no-consent model seem insufficient to overturn the presumption against concealment. First, the no-consent model incorrectly presumes that as long as welfare interests of patients are addressed, so are their autonomy interests: “Because the [pragmatic, randomized clinical trial] will have no adverse impact on patients’ clinical outcomes or experience, and imposes no nonclinical burdens and no more than minimal nonclinical risks, the study is presumptively respectful of patients’ rights and dignity.”¹⁰ This seems incorrect. We ordinarily judge that bypassing a person’s agency — unless the per-

4. What are the goals of notification and how are they best achieved?

- Notification is commonly used in conjunction with a waiver of consent
 1. **Respect for autonomy**
 - Informational brochures
 - Information plus option to opt out of study or data collection
 2. **Preservation of trust**
 - Posters in HD units
 - Public messaging
 - Community consultation.

5. What research ethics oversight is required?

- Proportionate review
- Pragmatic trials in HD units commonly involve usual care interventions or minor modifications thereof, and use routinely collected health data
- What level of review is appropriate?
- Does it just depend on risk or others factors as well?



Thank you!



Panelist

Role Perspective

Manish Sood

Nephrologist

Charles Cook

Patient

Betty Hogeterp

Nurse Practitioner

Sanjay Pandeya

Nephrologist

Erika Basile

Director, Office of Human
Ethics