McMaster University

Pragmatic cluster-randomized trials in anesthesia: opportunities for MPOG

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PACT | Canadian Perioperative Anesthesia Clinical Trials

Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

Disclosures

1. I have received career and training support from CIHR and the Michael G DeGroote Foundation.

2. I hold active research funding from the McMaster Surgical Association (MSA), Physicians' Services Incorporated (PSI) and CIHR.

Objectives

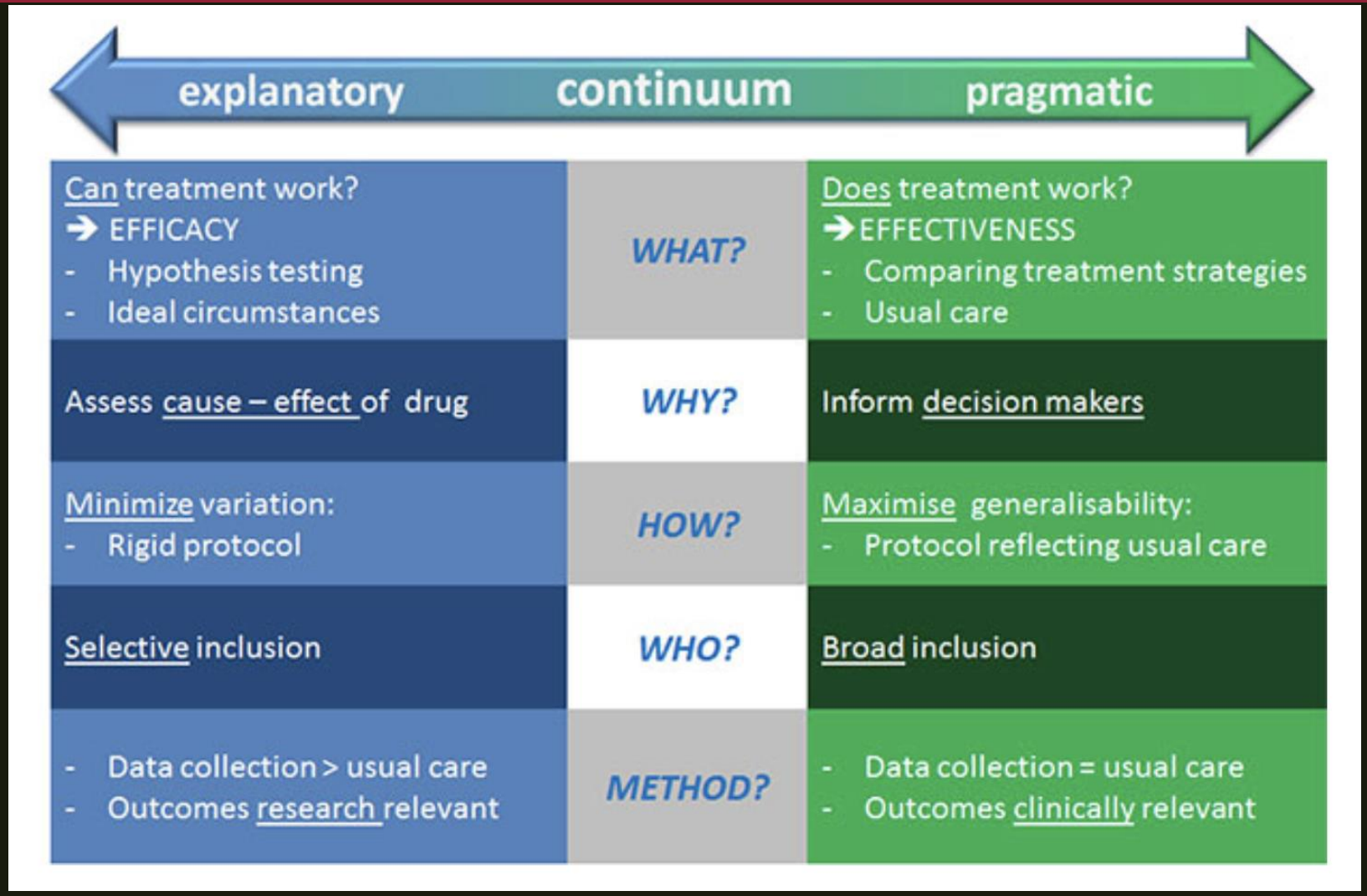
1. To define pragmatic cluster-randomized trials and discuss when this design is appropriate to answer clinical questions in anesthesiology.

2. To discuss the steps involved in designing and conducting a pragmatic cluster-randomized trial in anesthesiology, using examples from the Benzodiazepine-free cardiac anesthesia for the reduction of postoperative delirium (B-Free) trial.

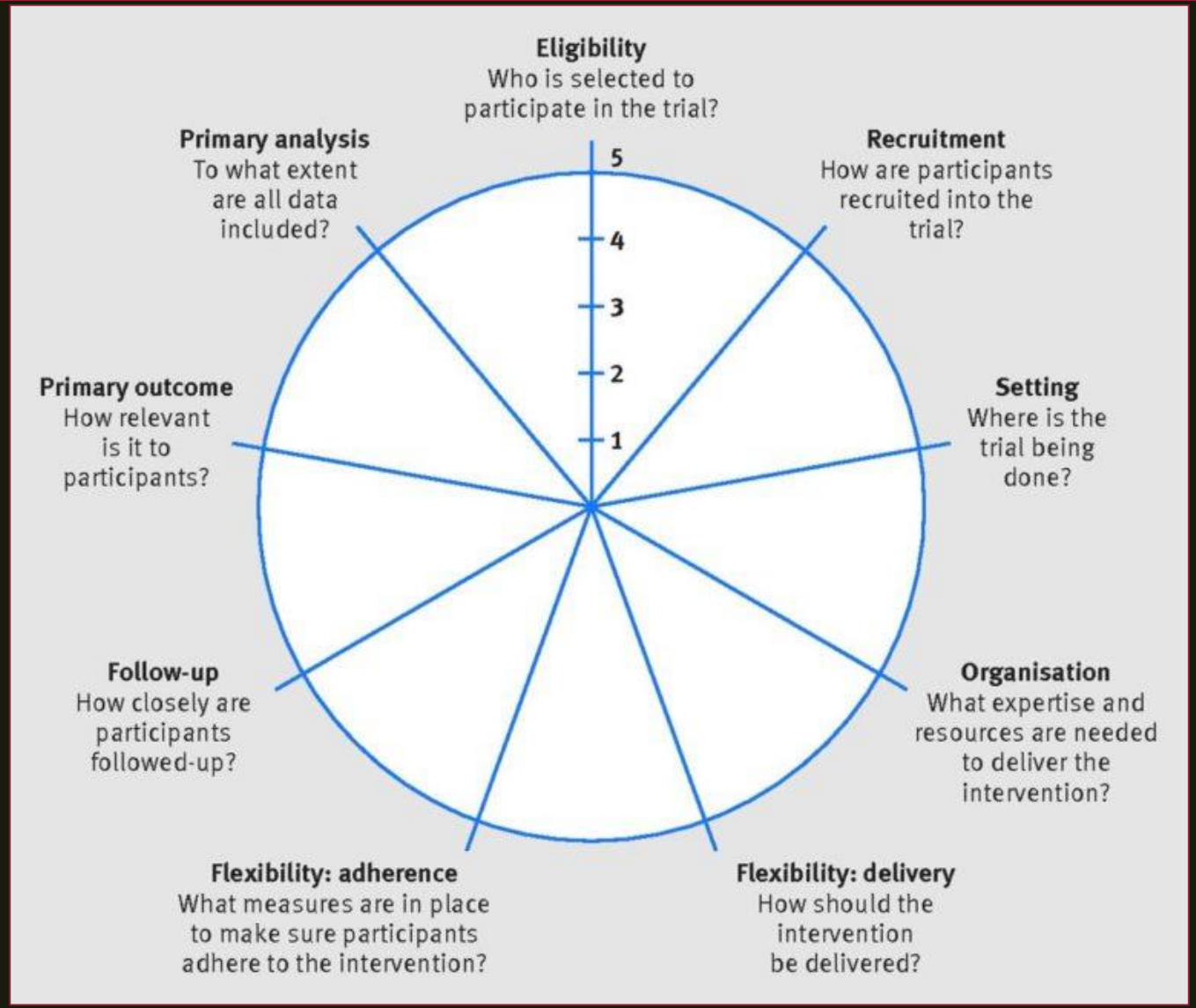
Pragmatic vs Explanatory Trials

- Pragmatic = Effectiveness
- Explanatory = Efficacy
- Efficacy trials determine impact of an intervention in selected populations under optimal conditions.
- Effectiveness trials determine impact of an intervention in every day clinical practice.
- Wide variability in routine practice in anesthesiology, e.g. withholding/giving home medications, FiO2, fluid administration, etc.
- Pragmatic trials are required to answer these questions

Pragmatic vs Explanatory Continuum



PRECIS-2 wheel



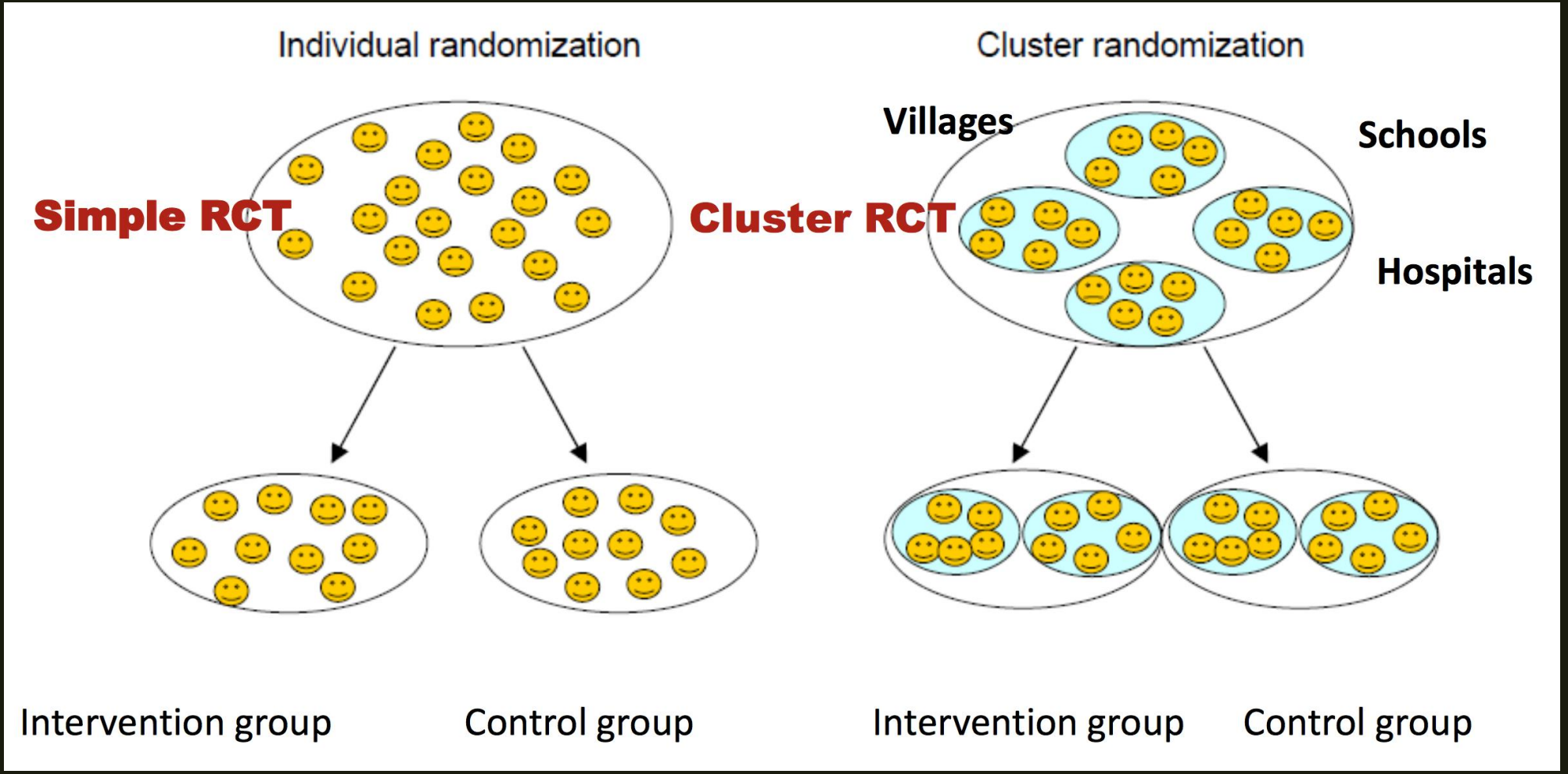
Cluster-randomized trials

- Used to evaluate broad-based approaches applied at the level of a system
- Traditional RCTs randomize individual patients
- In cluster RCTs, the unit of randomization is a group of patients
  - Examples of clusters: hospitals, clinics, ICUs, schools
  - Examples of interventions: crystalloid used, policy-based care, small tubes for blood testing, educational approach

Why use cluster-randomization?

- Intervention is applied at the level of the cluster
- The research question seeks to determine the impact of the intervention at the level of the cluster
  - Takes into account knowledge translation, patient selection

Cluster randomized



Randomized cluster crossover

Site 1	Control	Intervention	Control	Intervention	Control	Intervention	Control
Site 2	Intervention	Control	Intervention	Control	Intervention	Control	Intervention
Site 3	Control	Intervention	Control	Intervention	Control	Intervention	Control
Site 4	Intervention	Control	Intervention	Control	Intervention	Control	Intervention
Site 5	Control	Intervention	Control	Intervention	Control	Intervention	Control
Site 6	Intervention	Control	Intervention	Control	Intervention	Control	Intervention
Site 7	Control	Intervention	Control	Intervention	Control	Intervention	Control
Site 8	Intervention	Control	Intervention	Control	Intervention	Control	Intervention
Site 9	Control	Intervention	Control	Intervention	Control	Intervention	Control
Site 10	Intervention	Control	Intervention	Control	Intervention	Control	Intervention
Site 11	Control	Intervention	Control	Intervention	Control	Intervention	Control
Site 12	Intervention	Control	Intervention	Control	Intervention	Control	Intervention
Site 13	Control	Intervention	Control	Intervention	Control	Intervention	Control
Site 14	Intervention	Control	Intervention	Control	Intervention	Control	Intervention
Site 15	Control	Intervention	Control	Intervention	Control	Intervention	Control
Site 16	Intervention	Control	Intervention	Control	Intervention	Control	Intervention
	Period 1	Period 2	Period 3	Period 4	Period 5	Period 6	Period 7

Stepped wedge design

	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12
Site 1	C	I	I	I	I	I	I	I	I	I	I	I
Site 2	C	C	I	I	I	I	I	I	I	I	I	I
Site 3	C	C	C	I	I	I	I	I	I	I	I	I
Site 4	C	C	C	C	I	I	I	I	I	I	I	I
Site 5	C	C	C	C	C	I	I	I	I	I	I	I
Site 6	C	C	C	C	C	C	I	I	I	I	I	I
Site 7	C	C	C	C	C	C	C	I	I	I	I	I
Site 8	C	C	C	C	C	C	C	C	I	I	I	I
Site 9	C	C	C	C	C	C	C	C	C	I	I	I
Site 10	C	C	C	C	C	C	C	C	C	C	I	I
Site 11	C	C	C	C	C	C	C	C	C	C	C	I

Ethics of cluster-randomized trials

- Often not possible for a patient to choose to avoid or consent to an intervention being applied at the level of the health system
- As a result, cluster randomized trials present unique challenges to researchers and ethics boards
- Modifications to traditional consent processes may be required
- Emerging area; important to have bioethicist involved in trial development

Ethics of cluster-randomized trials

- For waiver of individual patient consent FDA/TCPS2 requires:
  - Altered consent required to answer question
  - Research involves minimal risk
  - Lack of *a priori* consent will not adversely affect participant welfare
  - Information provided to participants when possible
  - Benefits outweigh risks of not obtaining *a priori* consent

Statistical Considerations for Cluster Trials

- Intracluster correlation (ICC) = measure of variation of outcomes between centres
- High ICC = need a larger number of clusters
- In general, number of clusters more important than number of patients
- In cluster crossover and stepped wedge trials, also need to take into account the interperiod correlation (IPC)
  - Statistical representation of period effects
- Complex; key to have a biostatistician on your team

So… you want to design a cluster-randomized trial…

Step 1: Review the literature

Delirium in the CVICU

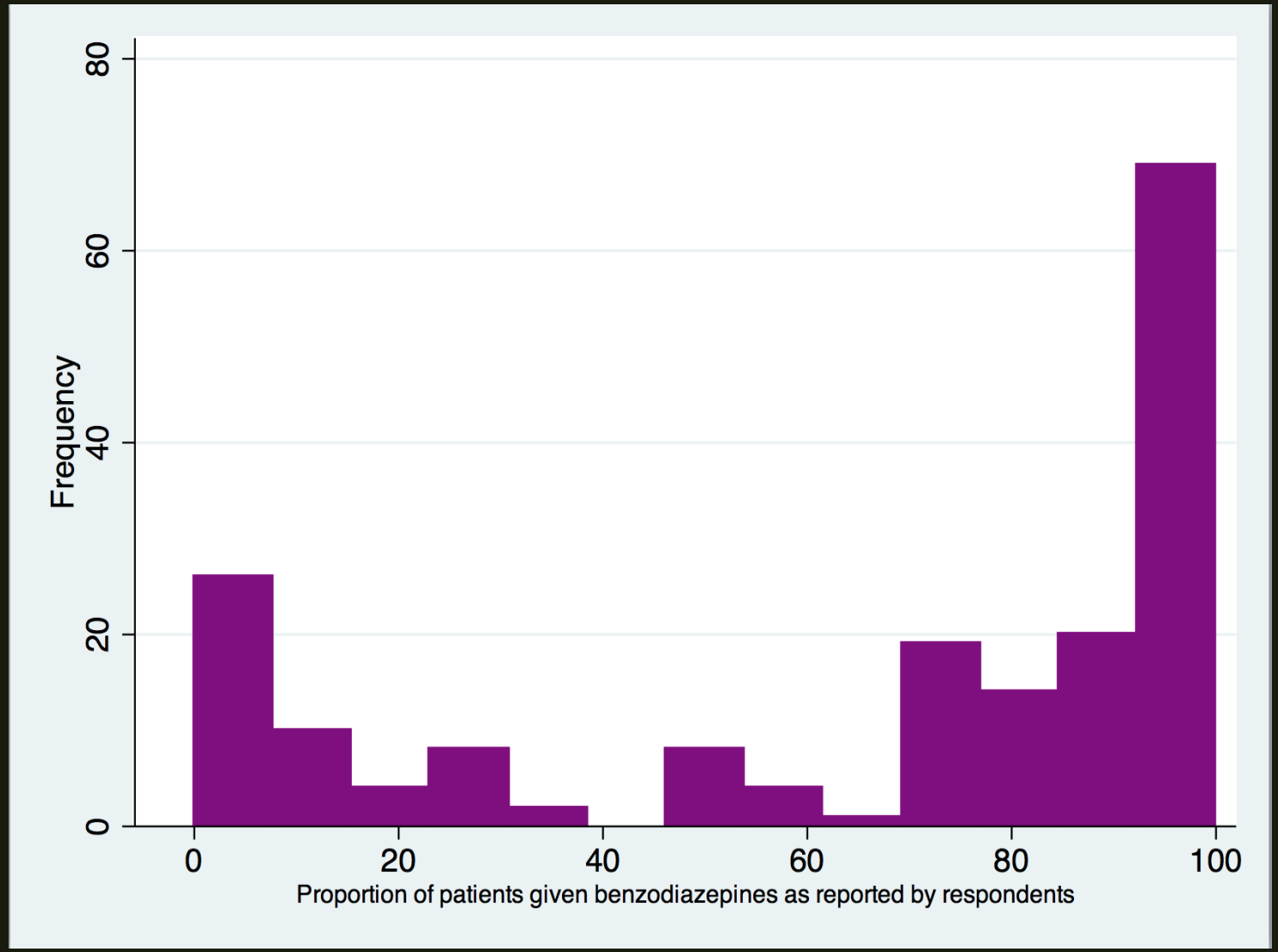
- **Delirium is a serious problem for patients!**
  - Incidence **15-30%** after cardiac surgery
    - Relative risk 8.3 compared to noncardiac surgery
  - Associated with increased cognitive decline, functional decline, institutional discharge, and death
  - Modifiable risks: polypharmacy, psychoactive medications, physical restraints
    - Benzodiazepines recurring theme

Arguments *For* and *Against* Benzodiazepines

- PRO: minimal effect on hemodynamics, anxiolytic, possible protection against intraoperative awareness
  - Level of evidence: Very low quality; 291 patients
- CON: delirium, cognitive decline
  - Level of evidence: Low quality; 1007 patients

Step 2: Establish equipoise

Equipoise in benzodiazepine practice



Step 3: Develop your question

What kind of trial?

- Cardiac surgery provided in specialized institutions using standardized policies to optimize outcomes.
- In the majority of cases, anesthesiologists choose whether or not benzodiazepines based on personal preference, rather than because of patient considerations
- The most logical way to test impact of limited approach to benzodiazepine use during cardiac surgery is to standardize care at the level of an institution.
- This can be done by assessing change in institutional policy as it may occur in every day clinical practice.

Study question

Does an institutional policy of limited intraoperative benzodiazepine use reduce incidence of delirium after cardiac surgery?

Study Interventions

Limited Benzodiazepine Policy

- No routine administration of any benzodiazepines
- Accepted administration of benzodiazepines according to anesthesiologist discretion
- (Expected administration of benzodiazepines to 10% of patients)

Liberal Benzodiazepine Policy

- Administration of 0.03 mg/kg Midazolam equivalent
- Accepted avoidance of benzodiazepine administration according to anesthesiologist discretion
- (Expected avoidance of benzodiazepines to 10% of patients)

Site Considerations

- Hospitals randomized to a policy for 4 weeks, then crossover
- Require cardiac anesthesia group to agree to policy implementation
- All other activities are per standard of care

Study Outcomes

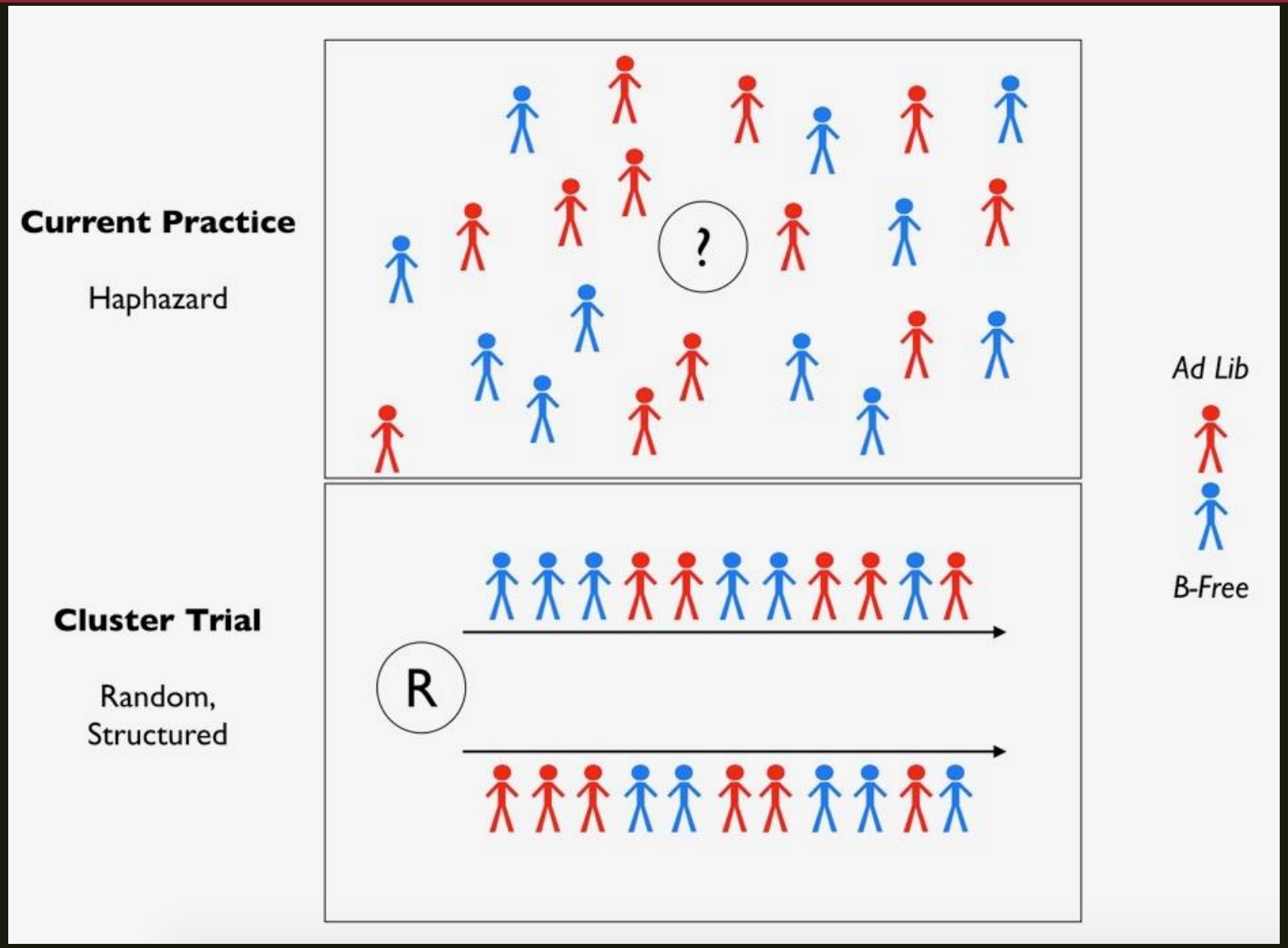
Primary Outcome

Incidence of in-hospital delirium

Secondary Outcomes

- ICU LOS
- Hospital LOS
- In-hospital mortality

Study question



Step 4: Consider ethical issues

ETHICAL ISSUES

- The intervention being studied within B-Free is being applied at the level of the hospital.
  - Clinicians determine whether or not it filters down to individual patients
- Opted to use a waived consent model
- Engaged a clinical bioethicist and intensivist to be a member of our steering committee

ETHICAL ISSUES

- **For waiver of individual patient consent FDA/TCPS2 requires:**
  - **Altered consent required to answer question**
    - Can't understand impact of broad-based policy change without it
  - **Research involves minimal risk**
    - Clinical equipoise; both approaches used
  - **Lack of *a priori* consent will not adversely affect participant welfare**
  - **Information provided to participants when possible**
    - Letter of information provided; participants may withdraw data
  - **Benefits outweigh risks of not obtaining *a priori* consent**

ETHICAL ISSUES

- Central ethics approval obtained in Ontario, BC, Alberta, Québec
- Site level approval obtained in Winnipeg, Halifax
- Site level provisional approval obtained in Saskatchewan

= Ethics approval at 19/20 sites

Step 5: Calculate your sample size

B-Free Sample Size

- Population: All cardiac surgery patients
- Treatment effect: 15% relative risk reduction
- Sample Size
  - 16 sites with average case volume 1,000 patients/year
  - ~ 16,000 patients
- Study Duration: 12 x 4 week crossover periods = ~ 1year

80% power to detect 15% relative risk reduction

ICC = 0.02 and IPC = 0.5*ICC

Step 6: Decide how you will collect data

Data Collection

- As much as possible through hospital administrative electronic records
  - Cumulative data transfers every 2 months
  - No data manipulation required
- Minimal data entry (may vary by site)
  - Delirium scales
  - Perioperative medications

Step 7: Establish feasibility. Conduct a pilot study!

Pilot Trial Objectives

Evaluate Feasibility

1. **≥ 80% adherence to each treatment policy**
2. **Complete outcomes collection using nurse-administered delirium scales**

   1 delirium scale in 95% of patients

   1 delirium scale per ICU day in 90% of patients

3. **Awareness screening in 1 site**

   Incidence not greater than upper 95% CI (i.e. 2%) during limited benzodiazepine period

Pilot Trial Methods

- 2 centres (Hamilton and Winnipeg)
- 4 x 4 week crossover periods
  - Randomized to first period then alternate

Feasibility Outcomes

1. 88.6% adherence to limited benzo policy; 92.3% adherence to liberal benzo policy

2. 96% with one delirium scale; 92% with one delirium scale per ICU day

3. 1/521 (0.2%) cases of awareness
   -managed during limited policy but received benzodiazepine

Other Outcomes

- Both REBs approved alterations to individual consent

- Enrolled 800 patients over 8 periods

Conclusions

Full trial is feasible

- ✓Can engage cardiac anesthesia providers
- ✓Acceptable outcomes collection using nurse-administered CAMs
- ✓No increased risk of intraoperative awareness

Step 8: Collaborate!

Anesthesia research in Canada

PACT | Canadian Perioperative Anesthesia Clinical Trials

Step 9: Get funded!

Funding Plan

- CIHR funded; Ranked 1st out of 43 applications
  - Entire trial to cost $469,000

Step 10: Get it done!

Questions?

Proposed Study Timeline