To examine key design choices in pragmatic randomized controlled trials and their implications for sample size and study feasibility

Using the FLUID trial as a case example

I have no conflicts of interest related to this presentation
Objective: Compare two types of resuscitation fluids commonly used in hospital: Ringer's Lactate vs Normal Saline

Primary outcome: Composite of death or readmission to hospital within 90 days of the index admission

Design: Pragmatic cluster randomized cross-over trial involving 30 hospitals and 300,000 patients across Ontario over two 3-month periods

Data: Solely routinely collected data within ICES

Pilot trial funded by CIHR (July 2015)

CASE STUDY

KEY DESIGN CHOICES

THE FLUID TRIAL

Pragmatic: Determine if an intervention works in real-world conditions, so that results can be directly generalized to everyday practice and support decision-making by patients, providers, and healthcare policymakers.

Explanatory: Determine if and how an intervention works under well-defined and highly controlled conditions

Design implication: May need to reduce effect size to account for pragmatic setting

KEY DECISIONS AT DESIGN STAGE

- Explanatory vs. pragmatic?
- Cluster vs. patient randomization?
- Cluster vs. patient intervention?
- Primary data collection vs. routinely collected data?
- Which consent model is ethically appropriate?

All have profound implications for sample size requirements and/or feasibility
Cluster RCTs naturally tend to be more pragmatic, but have major methodological and ethical implications:

- Substantial increases in total sample size may be required to account for intra-cluster correlation.
- Desired power may simply not be achievable given a restricted number of clusters.
- Very large cluster sizes may make no contributions to power but may have ethical and resource implications.
- Subject to increased risks of bias — avoidable under a waived consent model.

For these reasons, a clear rationale is required for the choice of cluster randomization.

Interventions in cluster RCTs may be implemented at cluster-level or individual-level.

Choice of cluster randomization is obvious in the case of a cluster-level intervention — less obvious for individual level interventions:

- Individual interventions in 17% of 300 CRTs (2000-2008)

Ethical implications of patient therapeutic interventions implemented as “usual care policy” (especially under a waived consent model) need to be explored.

May give rise to a situation where unit of randomization dictates whether or not informed consent is obtained.

Increasing use of routinely collected data (ICES):

- Choice of outcomes limited to routinely collected ones.
- Issues of reliability and validity need to be addressed.

**BUT...**

- Opportunity for inclusion of very large N at very low cost (especially under a waived consent model).
- May allow detection of small effect sizes that are nevertheless important at population-level.
- Opportunity for more reliable sample size calculation (e.g., estimates of prevalence, variance, intra-cluster correlation coefficients).
**Key Design Choices 5**

**Ethically Appropriate Consent Model**

<table>
<thead>
<tr>
<th>Consent Model</th>
<th>Notification</th>
<th>Informed Consent</th>
</tr>
</thead>
<tbody>
<tr>
<td>No consent</td>
<td>Approved by REC</td>
<td>Full written</td>
</tr>
<tr>
<td>Consent</td>
<td>Consent</td>
<td>informed consent</td>
</tr>
<tr>
<td>Not research</td>
<td>Not research</td>
<td>Partial</td>
</tr>
<tr>
<td>(&quot;Quality Improvement&quot;)</td>
<td>Posters, patient</td>
<td>Consent</td>
</tr>
<tr>
<td></td>
<td>letters</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Verbal discussion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>integrated with routine clinical care</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Full written informed consent</td>
<td></td>
</tr>
</tbody>
</table>

**Inclusion Rates**

- 100% inclusion
- ~100% inclusion
- <100% inclusion
- Potentially <<100% inclusion

**Difficulties Encountered by Clinical Researchers**


**Explanatory Setting**

- ES = 3%
  - Normal Saline: $p_1 = 0.18$
  - Ringer’s Lactate: $p_2 = 0.15$

**Pragmatic Setting**

- ES = 2%
  - Normal Saline: $p_1 = 0.17$
  - Ringer’s Lactate: $p_2 = 0.15$

**Routinely Collected Data**

- ES = 1.6%
  - Normal Saline: $p_1 = 0.156$
  - Ringer’s Lactate: $p_2 = 0.14$

**Not Exposed**

- $p_0 = 0.10$

**Prevalence of Exposure**

- $\theta = 0.8$

**Effect Size**

$$ ES = \frac{\theta_1 p_1 (1-\theta_0) p_0}{\theta_0 p_0 (1-\theta_1) p_1} - \frac{\theta_1 p_1 (1-\theta_0) p_0}{\theta_0 p_0 (1-\theta_1) p_1} $$

**Case Study**

- Illustrate implications of alternative design choices on sample size and feasibility in FLUID
ASSUMPTIONS 2: CLUSTER PARAMETERS
- Calculate required number of hospitals (K) given number of admissions per hospital (n)
- Fix duration of accrual at 6 months
- n = 10,000 admissions per hospital per 6 months
- Intra-cluster correlation coefficients:
  - ICC: \( \rho = 0.008 \) (same hospital, same period)
  - IPC: \( \eta = 0.0055 \) (same hospital, different period)
- Calculated in ICES using formulas for binary data in split-cluster designs (Donner et al., 2004)

ASSUMPTIONS 3: ELIGIBILITY AND RECRUITMENT

<table>
<thead>
<tr>
<th>% Eligible</th>
<th>% Included</th>
</tr>
</thead>
<tbody>
<tr>
<td>Explanatory – full informed consent</td>
<td>30%</td>
</tr>
<tr>
<td>Pragmatic – opt out consent</td>
<td>70%</td>
</tr>
<tr>
<td>Routine data – waived consent</td>
<td>100%</td>
</tr>
</tbody>
</table>

Cost per center: \( c = \$10,000 \)
- Cost per subject
  - \( s = \$1,000 \) under full informed consent model
  - \( s = \$0 \) under waived consent model
- Cost function: Total Cost with K clusters of n patients per cluster
  \[ \text{Total Cost} = K(c + s) \]
- Excluding all costs that do not depend on sample size
Three designs: patient RCT, parallel arm cluster RCT, cluster cross-over trial

Use published design effects to calculate $K$ given $n$
- Parallel arm CRT: $1 + (v - 1)\rho$
- Cluster cross-over design: $1 + (v - 1)\rho - \eta q$
- Coefficient of variation of hospital sizes = 40%

CASE STUDY

SAMPLE SIZE CALCULATION

RESULTS

<table>
<thead>
<tr>
<th></th>
<th>Patient RCT</th>
<th>Cluster RCT</th>
<th>Cluster X-over</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aims</td>
<td>Explanatory</td>
<td>Pragmatic</td>
<td>Pragmatic</td>
</tr>
<tr>
<td>Consent</td>
<td>Full informed</td>
<td>Opt out</td>
<td>Waived</td>
</tr>
<tr>
<td>Effect size</td>
<td>3%</td>
<td>2%</td>
<td>1.0%</td>
</tr>
<tr>
<td>#patients</td>
<td>4,799</td>
<td>10,542</td>
<td>554,400</td>
</tr>
<tr>
<td>#clusters</td>
<td>4</td>
<td>2</td>
<td>88</td>
</tr>
<tr>
<td>Total Cost</td>
<td>$4,839,000</td>
<td>$10,562,000</td>
<td>$555,280,000</td>
</tr>
</tbody>
</table>

SUMMARY OF RESULTS: TOTAL COSTS

- Explanatory patient RCT: $140,000,000$
- Pragmatic patient RCT: $220,000$
- Cluster RCT: $100,960,000$
- Cluster cross-over trial: $1,280,000$
- Cluster cross-over waived consent: $220,000$


Cluster RCTs require larger N than patient RCTs
Cluster RCTs can offer substantial cost savings over patient RCTs when waivers are appropriate
“...various forms of cluster randomization offer advantages and may help avoid the need for informed consent.”
Ford & Norrie: “Pragmatic Trials” (NEJM 2016)
“An inappropriate reason to adopt a CRT is the mistaken belief that the need to seek informed consent can be avoided by using cluster randomization.”
Ottawa Statement (recommendation 1)
Ethical issues need to be addressed

CONCLUSIONS

To avoid contamination (patients commonly receive different fluids in different areas of the hospital), hospitals will exclusively stock only one type of fluid
Substantial increases in logistical complexity and costs associated with allocating individual patients within hospitals
Intended inferences pertain at the level of the healthcare system (implications for cost)
Outcome data (but not exposure data) are available from routinely collected data
Fluids are routinely used in nearly all admitted patients

RATIONALE FOR CLUSTERED DESIGN IN FLUID

CASE STUDY