Designing Interventional Studies for Evaluation of ARO Control Strategies

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Randomization

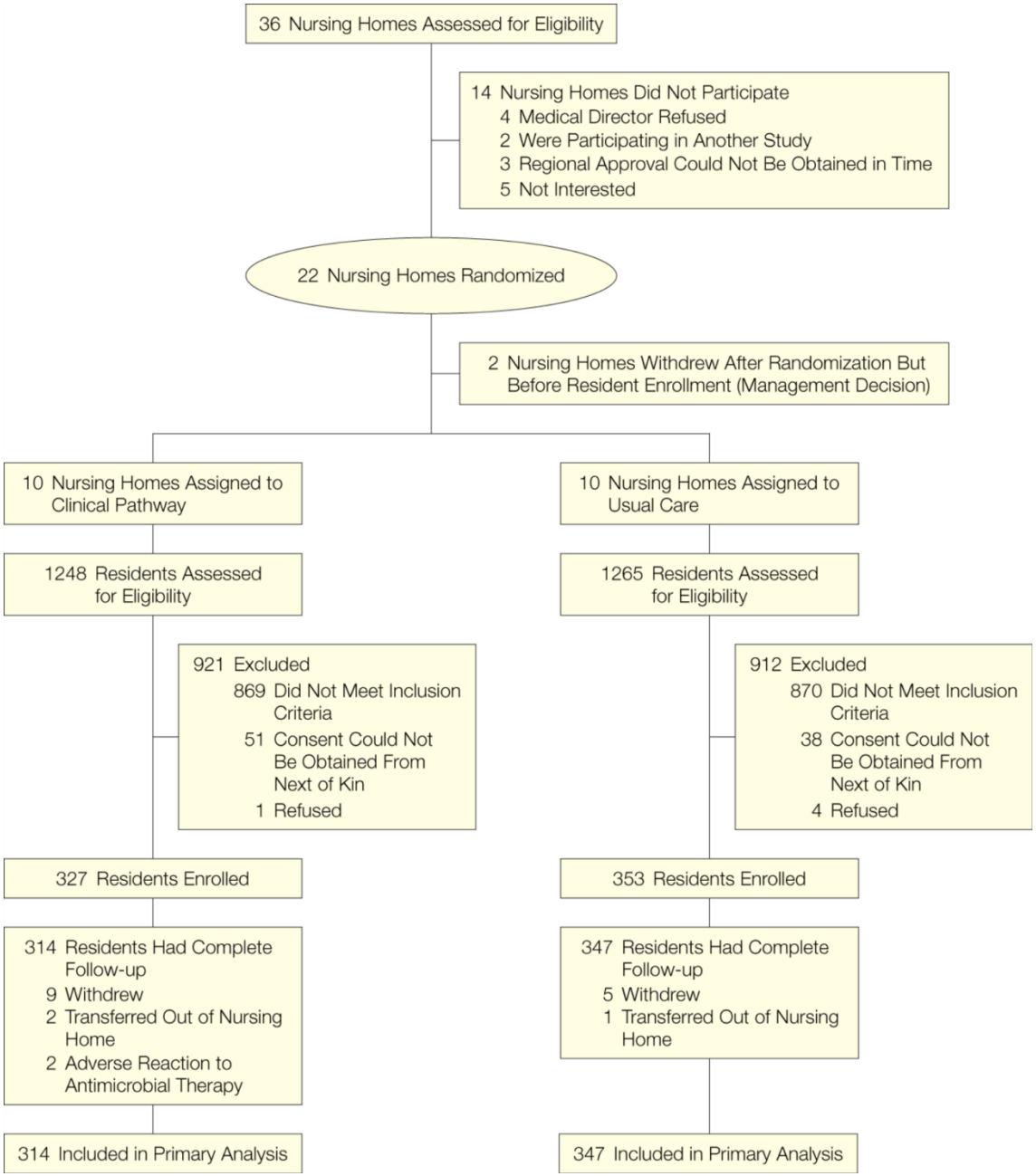
- Assigned treatment will be statistically independent of any covariate at baseline in the population
- The distribution of any measured or unmeasured covariate will be, on average, balanced at baseline
- Builds a strong foundation for causal inference

Campbell and Stanley 1963

	Sources of Invalidity												
	Internal								External				
	History	Maturation	Testing	Instrumentation	Regression	Selection	Mortality	Interaction of Selection and Maturation, etc.	Interaction of Testing and *X*	Interaction of Selection and *X*	Reactive Arrangements	Multiple-*X* Interference
Pre-Experimental Designs:												
1. One-Shot Case Study *X* *O*	−	−				−	−			−		
2. One-Group Pretest-Posttest Design *O* *X* *O*	−	−	−	−	?	+	+	−		−	−	?	
3. Static-Group Comparison *X* *O* --- *O*	+	?	+	+	+	−	−	−			−		
True Experimental Designs:													
4. Pretest-Posttest Control Group Design *R* *O* *X* *O* *R* *O* *O*	+	+	+	+	+	+	+	+		−	?	?	

What is a Cluster RCT?

- A randomized controlled trial where the units being randomized are not individuals but they are clusters
- Based on premise selection bias played no role in assignment of interventions
- Balancing of baseline characteristics between groups


36 Nursing Homes Assessed for Eligibility
14 Nursing Homes Did Not Participate
4 Medical Director Refused
2 Were Participating in Another Study
3 Regional Approval Could Not Be Obtained in Time
5 Not Interested
22 Nursing Homes Randomized
2 Nursing Homes Withdrew After Randomization But Before Resident Enrollment (Management Decision)
10 Nursing Homes Assigned to Clinical Pathway
10 Nursing Homes Assigned to Usual Care
1248 Residents Assessed for Eligibility
1265 Residents Assessed for Eligibility
921 Excluded
869 Did Not Meet Inclusion Criteria
51 Consent Could Not Be Obtained From Next of Kin
1 Refused
912 Excluded
870 Did Not Meet Inclusion Criteria
38 Consent Could Not Be Obtained From Next of Kin
4 Refused
327 Residents Enrolled
353 Residents Enrolled
314 Residents Had Complete Follow-up
9 Withdrew
2 Transferred Out of Nursing Home
2 Adverse Reaction to Antimicrobial Therapy
347 Residents Had Complete Follow-up
5 Withdrew
1 Transferred Out of Nursing Home
314 Included in Primary Analysis
347 Included in Primary Analysis

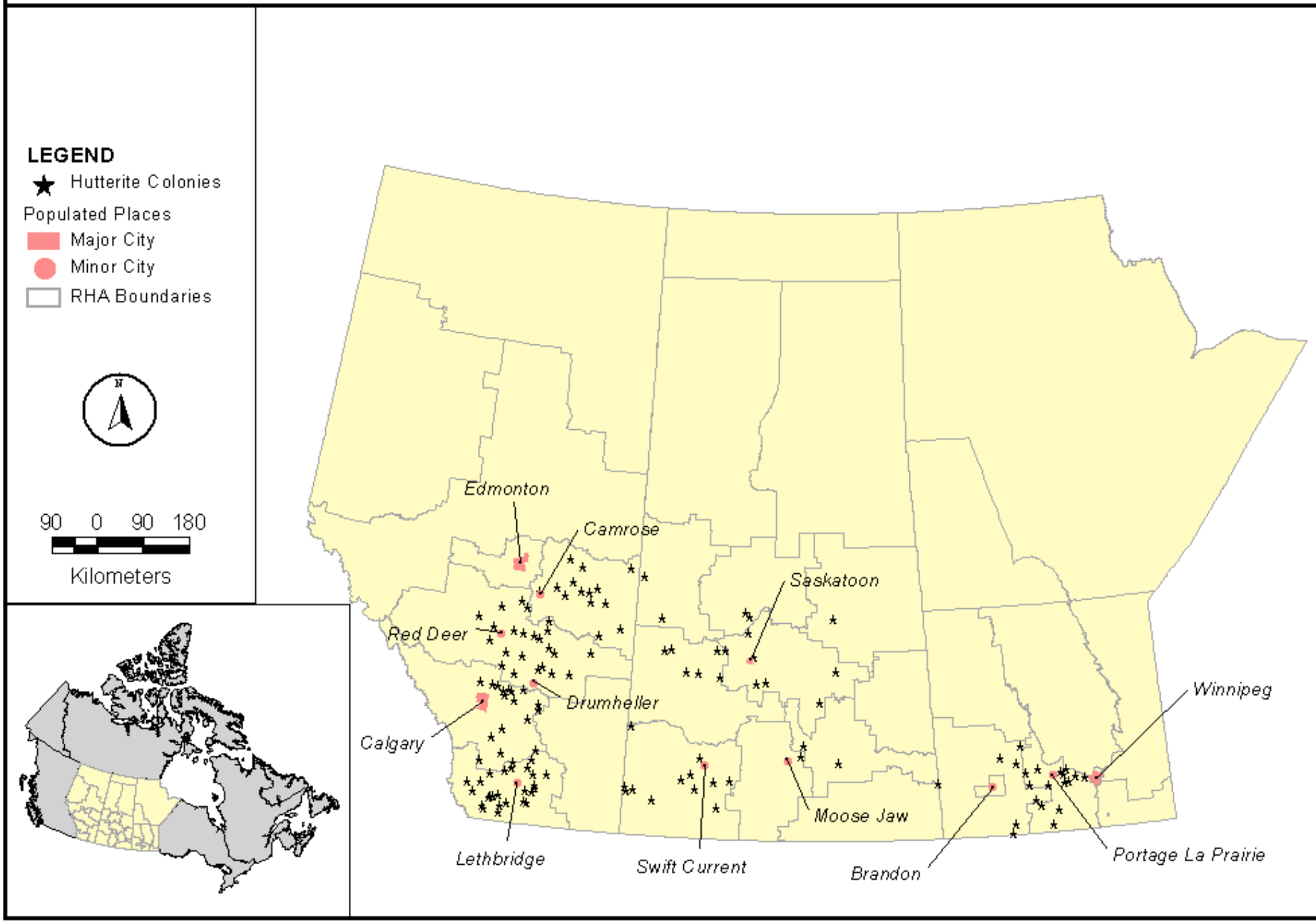
Why do a Cluster RCT?

- Intervention must be directed at a unit > larger than individual e.g. hospital or unit on the hospital

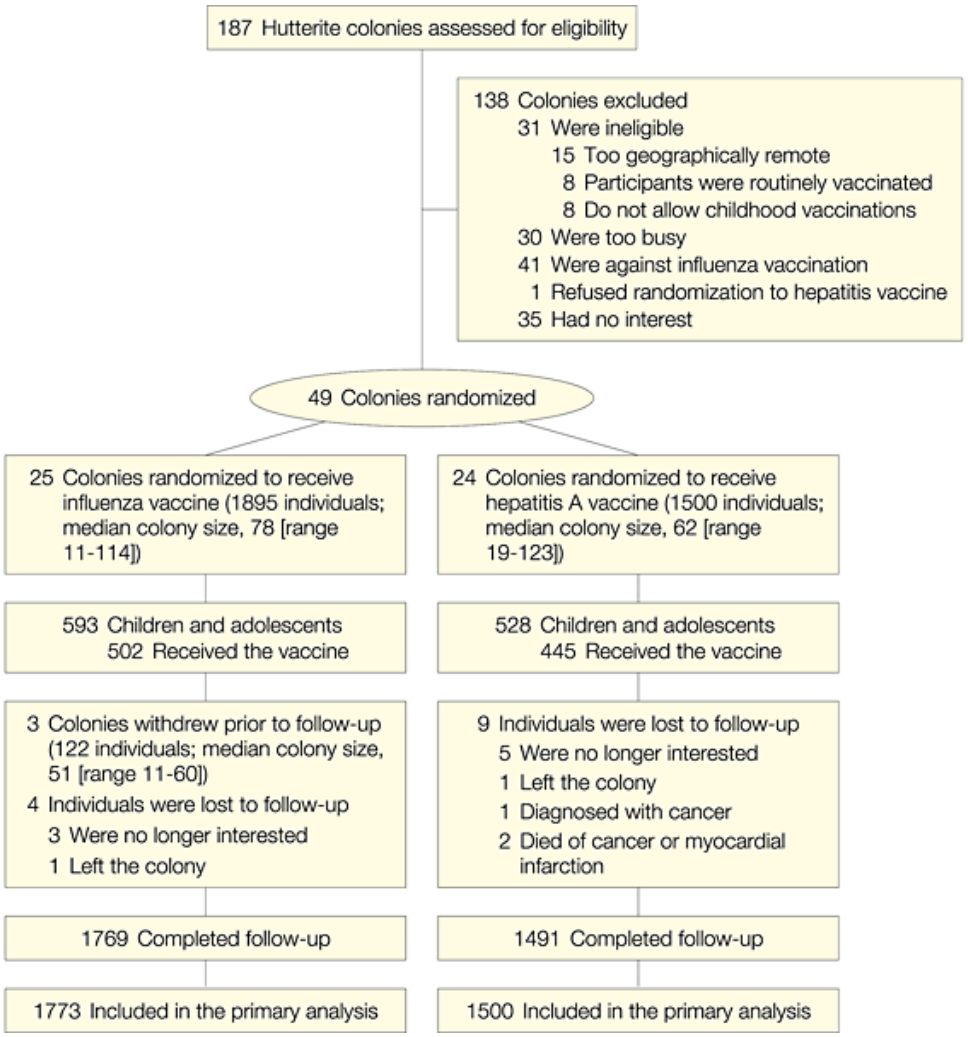
  - contamination likely i.e. need to keep groups separate
  - "ecologic" type of question e.g. antibiotic use
  - health services question (policy)
  - feasibility

- Intervention at the level of cluster is part of the hypothesis e.g. herd immunity

Distribution of Hutterite Colonies Alberta, Saskatchewan & Manitoba



Flow Diagram of Trial



Loeb, M. et al. JAMA 2010;303:943-950.

Inference

- There are two levels of inference in a cluster RCT

  - cluster level and the individual level
- It is key to indicate explicitly the level at which the interventions were targeted, hypothesis generated, outcomes measured, randomization done

What is the impact of Cluster Randomization on design and analysis?

- Challenge is that inferences are often intended to apply at the individual level while randomization is at the level of the cluster
- Lack of statistical independence between individuals invalidates standard approaches to sample size and analysis

  - underpowered studies and spurious claims of association

Sample size

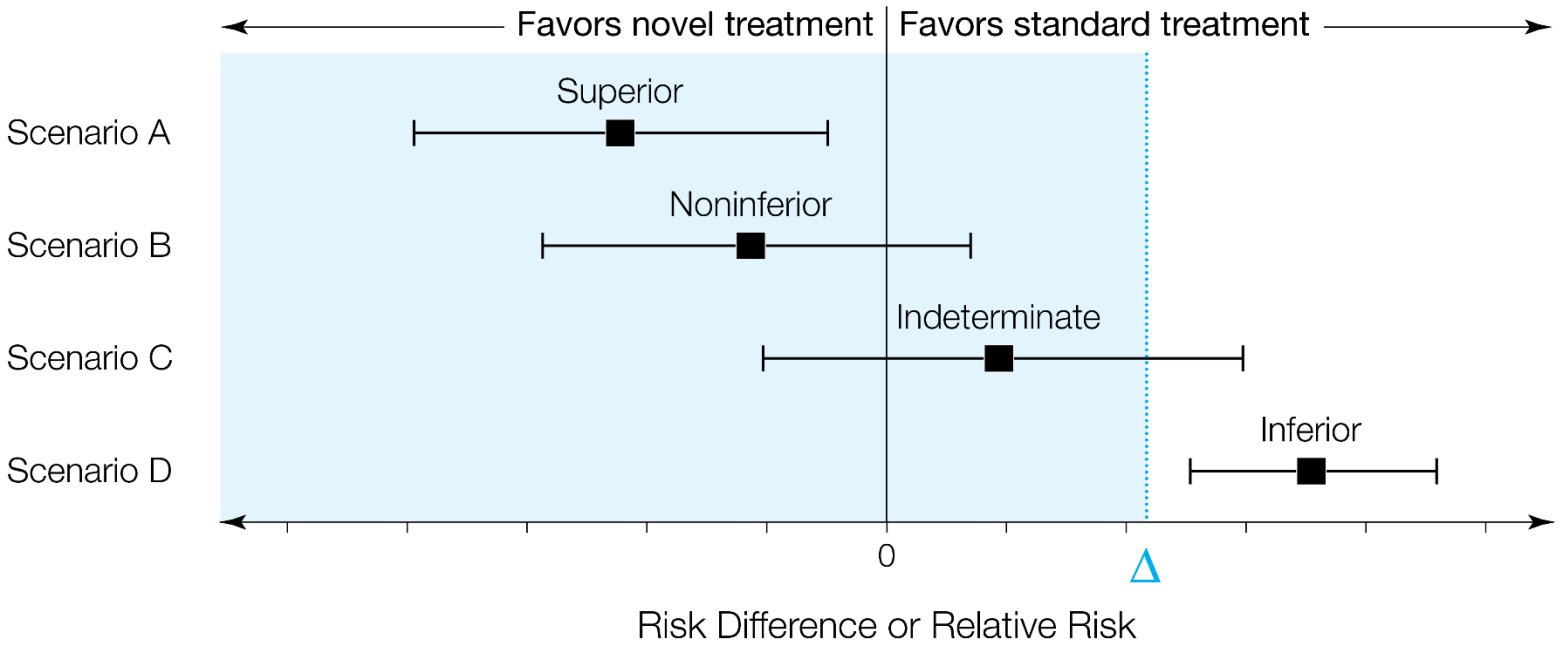
- Calculate sample size needed for individual trial

- Variance inflation factor is given by the formula: $1 + (m - 1)\text{ICC}$

  m= size of cluster

- The ICC refers to $\frac{\text{btw gr variance}}{\text{btw + wth grp variance}}$

What is the Hypothesis?



Eligibility Criteria

- Must be set at the cluster and the individual levels
- Similar considerations given as per individual level RCTs
    - response to intervention
    - generalizability

Most Commonly Used Designs

- Completely randomized
- Matched-pair
- Stratified

Factors that are the same as other RCTs

- Clearly identify the primary outcome
- Select a responsive intervention
- Select a realistic minimum effect size
- Allocation concealment
- Include as much blinding as possible
- Select rigorous measurements
- Do a pilot study

Common Problems

- Contamination
- Uncertainty in ascertainment
- Over reliance on medical records or administrative databases for outcome assessment
- Selection bias
- Lack of appropriate consent procedures
- Unequal baseline rates
- Clusters that do not wish to be randomized

References

- Donner and Klar. Design and Analysis of Cluster Randomized Trials in Health Research (Wiley).
- Kerry and Bland. Stat Med 2001; 20:377-390.