Cluster randomized trials (CRTs):

A type of randomized controlled trial in which groups, or “clusters”, of individuals (rather than the individuals themselves) are randomly allocated to study arms, and outcomes are measured on the individual cluster members.

For instance, we randomize different communities, clinics, or cities to treatment A or B, or to receive or not to receive a particular intervention. The unit of randomization is not the individual.

CRTs have also been termed:

• group randomized trials
• place-based trials
• community intervention trials
Cluster randomized trials (CRTs)

The introduction of CRTs

- Cluster trials originated from educational research.
  - Intact classes or schools were randomised to an intervention or no intervention.
  - Educational researchers have all but abandoned RCTs in favour of qualitative research.
Cluster randomized trials (CRTs)

**CRT Advantages:**

- Ability to study interventions that cannot be directed toward selected individuals
  - Efficacy of different pedagogical technique in educating nurses in anti-smoking techniques
  - Mass media versus individualized advertising or outreach
  - Vitamin supplementation of school breakfasts
  - Decision support tools in electronic medical records

- Ability to control for "contamination" across individuals
  - Vaccine trial in which herd immunity will impact outcome
  - Outcome of change in school lunch program

- To enhance subject compliance
Cluster randomized trials (CRTs)

**CRT Disadvantages:**

- Greater complexity in design and analysis
- Increasing requirement for more participants to obtain the same statistical power.
- Dependence (clustering) of an outcome on the unit of randomization
- Possible selection bias
- Inadequate uptake of intervention by either group reduces study power.
Complexity of CRTs

Interventions intended for one group but measured through another
Education of nurses in anti-smoking; outcome: patient smoking cessation

Additionally, the lack of independence among individuals in the same cluster, i.e. between-cluster variation, creates special methodological challenges in both design and analysis.

Compared to RCTs, CRTs reduce the statistical efficiency for the same number of individuals and require special approaches for calculation of sample size.

And beware: with 10 or so clusters simple randomisation is likely to lead to chance imbalance.

Must also address how many of the target outcome group to sample.
Increase sample size may increase cost.
Complexity of CRTs: Between-cluster variation

• Subjects frequently select the clusters to which they belong
  • Different hospitals may serve very different patient populations

• Covariates at the cluster level affect all individuals within the cluster in the same manner.
  • This may be important for stratification (e.g. use pairing that matches clusters on an important covariate and randomly allocate one member of each pair to the intervention).
  • Surgical infection rates may be related to the operating room techniques or temperature and not to the intended antibiotic intervention

• Individuals within clusters frequently interact and, as a result, may respond similarly
  • Education strategies or therapies provided in a group setting
  • Tendency of certain infectious diseases to spread more rapidly within than among families or communities.
1) How should research subjects be identified?
2) From whom, how and when must informed consent be obtained?
3) Does clinical equipoise apply to CRTs?
4) How does one determine if the benefits outweigh the risks of CRTs?
5) Who are gatekeepers, and what are their responsibilities?
6) How ought vulnerable groups be protected in CRTs?

Weijer et al. Ethical issues posed by cluster randomized trials (CRTs) in health research. *Trials* 2011; 12: 100
Cluster Randomized Trials: Ethics, Regulations, Statistics & Design
Thursday November 3, 2016

1:00 – 1:15  Overview of Cluster Randomized Trials

1:15 – 1:50  Ethical considerations in Cluster Randomized Trial Design
            Holly Fernandez Lynch

1:50 – 2:25  Statistical Issues in the Design of a Cluster Randomized Tuberculosis Prevention Trial
            Michael Hughes

2:25 – 2:40  Break
Cluster Randomized Trials: Ethics, Regulations, Statistics & Design
Thursday November 3, 2016

2:40 – 3:15  *Design of a Community Randomized HIV Prevention Trial in Botswana*
Rui Wang

3:15 – 3:50  *Regulatory Design in Cluster Randomized Trials*
Michele Russell-Einhorn

3:50 – 4:30  *Open Discussion and Wrap up*
All speakers, Barbara Bierer
Questions and Discussion