Cluster Randomized Trials

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Regulatory Design in Cluster Randomized Trials
Clusters

- Medical Practices
- Hospitals
- Communities

- Unit of Randomization vs
- Unit of analysis
COMMIT (Community Intervention Trial for Smoking Cessation) - tests effectiveness of a comprehensive community oriented approach to influence citizens behaviors.

- Communities were randomized
- Interventions included public education and training health care providers in cessation techniques as well as population based surveys
- Article on COMMIT talks about obtaining information from some individuals in some of the cohorts but no discussion of consent.
Professional Cluster

Enhancements to electronic medical records designed to improve tobacco treatment and counseling: smoking status icons, tobacco treatment reminders facilitated ordering of medication and counseling referrals.

- 26 primary care practices randomized to either intervention or control

- Intervention targeted at health professionals-example of a professional cluster trial
- Goal-increase effectiveness of the intervention through peer efforts
- Outcome-proportion of documented smokers who made contact with a smoking cessation counselor
- Waiver granted by the IRB for clinicians and patients
Individual-Cluster

ObaapaVitA trial-double-blind placebo controlled trial to evaluate the effect of weekly, low-dose vitamin A supplementation on pregnancy-related and all-cause female mortality in Ghana.

- Interventions delivered to individual women
- 1086 small clusters – vitamin A to some, placebo to others
- Informed consent was obtained
1. SACHRP Recommendations on Regulatory Issues Arising in Cluster Randomized Studies
   • 27 page document available on the OHRP website
Recommendation 1

Confirmation of OHRP Policy on whether it is Research

*If one arm is research then the whole project is research.*

1. If any arm of a study is considered research that requires IRB review, then all of the arms must be considered research that requires IRB review.
2. If all arms are considered exempt, then the research is exempt.
Recommendation 2: Assessing Whether Individuals in a Cluster are Human Subjects

Even if a CRT is deemed to be subject to IRB review, not all clusters necessarily involve human subjects.

SACHRP recommends that where individuals in one cluster or level of a cluster will be receiving the same services that they would have received regardless of the study-then it is reasonable to consider that the project does not involve human subjects in terms of the individuals in the cluster.
Recommendation 3: Risk Assessment for Waiver or Alteration of Consent

Different Risk Determinations can be made for each Cluster.

SACHRP recommends that, once it is determined that a CRT is research, it is acceptable for IRBs to make independent risk determinations for individual clusters. Thus, one cluster could involve a waiver of consent while another arm might require individual consent and another cluster could be determined not to involve human subjects. (note different for FDA regulated research)
Recommendation 3: Risk Assessment for Waiver or Alteration of Consent (cont).

SACHRP recommends that it is appropriate to consider the risk level of each arm of the study independently; and, that the research as a whole is not required to present minimal risk in order for a waiver or alteration to be granted in one cluster or several clusters of a study.
Recommendation 4: Delayed Consent

- Inability to identify people at the time of randomization should not necessarily mean that consent must be waived entirely.

- Opportunity to obtain consent at time of randomization Vs

- Opportunity to obtain consent at the time the data will be used for research
Recommendation 4: Delayed Consent

SACHRP recommends that IRBs must consider whether or not obtaining consent at the time of randomization exposes the subjects to an unacceptable level of risk or an unacceptable restriction on autonomy.

Potential subjects should be given the opportunity to consent at the first opportunity. Under the HHS regulations, IRBs should consider whether or not obtaining consent at the time of randomization is justified using an alternation of consent under 45 CFR 46.116(d).
Recommendation 5: FDA-Regulated Clinical Investigations

SACHRP recommends that FDA adopt provisions for waiver of consent.

FDA definition of a human subject in research:
“an individual who is or becomes a participant in research, either as a recipient of a test article or as a control. A subject may be either a healthy individual or a patient.”

- Covers controls in Cluster Randomized Trials.
- No waiver of consent.
When Is a CRT Research or a Clinical Investigation?
(d) Research means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.

Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities.
When Is a CRT Research?

1. Not research under 45 CFR Part 46

- Quality Improvement Project
  1. Implementing a practice to improve the quality of patient care, and
  2. Collecting patient or provider data regarding the implementation of the practice for clinical, practice, or administrative purposes
  3. No evaluation of the practice

- Public Health Project
  1. Interventions not intended to produce generalizable knowledge (varying service delivery sites)
Who Is a Human Subject?

Human subject means a living individual about whom an individual (whether professional or student) conducting research obtains:

1) Data through intervention or interaction with the individual
   OR

2) Identifiable private information
Who Is a Human Subject?

- **Intervention** includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.
  - Interaction includes communication or interpersonal contact between investigator and subject.
  - **Private information** includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record).
  
  ◇ Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.
Who Is a Human Subject?

- Data – broader than identifiable private information
- Manipulation of the subjects environment in the definition of an intervention – SACHRP recommends using a “but for” test
Is the Institution Engaged in Research?

- In a cluster randomized trial it may be difficult to determine which institution is engaged in research
- SACHRP recommended making this analysis for each cluster
How to Evaluate Levels of Risk in a CRT

1. Even one if one arm is research, the whole CRT falls under IRB review.

2. Even if the whole CRT falls under research, different arms may be different levels of risk.
When Can Consent Be Waived

Consider some reasons why a CRT is proposed:

1) Administrative convenience
2) To avoid contamination (segregate placebo from study treatment)
3) It is the most efficient way to address an issue (service delivery variations)

Consider: at the time of randomization individuals are not likely identifiable.
When Can Consent Be Waived?

45 CFR Part 46.116(d)

1) The research involves no more than minimal risk to the subjects;

2) The waiver or alteration will not adversely affect the rights and welfare of the subjects;

3) The research could not practicably be carried out without the waiver or alteration; and,

4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.
When Can Consent Be Waived

1. Applying the word “practically”
   a. Study cannot reasonably be conducted in a different manner whereby consent can be obtained
      I. In a CRT assignment to intervention has already been made or the intervention has already happened (e.g., ointment vs soap in ICU)
      II. Delayed consent—even if randomization has occurred, provide consent to individuals at a point when they can refuse to consent to use of their data in research

2. Applying the phrase “minimal risk”
   a. SACHRP recommends an absolute approach: research risks are those that are potentially different risks than the individual might face without enrollment
When Can Documentation of Consent Be Waived?

- The only record linking the subject and the research would be the consent document, the principal risk would be potential harm resulting from a breach of confidentiality, and each subject will be asked whether the subject wants documentation linking the subject with the research and the subject’s wishes will govern

  OR

- The research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.
CRTs or Individually Designed Research

- Encourage public trust in research and the protection of individuals in research
  - No one ever told me
  - I could have been told
  - You used my data without my permission
Questions?

Thank you!