SOH draft recommendation

Regulatory issues in cluster studies

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Definition of a Cluster Randomized Trial

The central defining feature of a Cluster Randomized Trial (CRT) is that randomization occurs on a group level rather than an individual level. In a traditional randomized clinical trial, subjects are randomized sequentially as each subject is identified and then enrolled in a study. In contrast, in a CRT the randomization occurs as a function of being a member of a group. There can be several layers of groupings as well, for instance by school district, school, and class. Another possible model is by health care facility, medical provider, and each medical providers' patients.

Four examples of cluster studies follow. First is study of a diagnostic device intended to measures biomarkers and through the application of an algorithm, provide a patient's 5-year risk of developing type 2 diabetes. The study design is a 6-month duration, with 400-500 patients at 40-50 study sites. The investigators will be randomized to either receive education about the test and use the test in their patients with prediabetes (Active Arm) or not have access to the test (Control Arm). The primary endpoint will be the percent of patients that the investigators send to formal diabetes prevention programs and patient completion rates of these programs. The hypothesis that having access to the test will increase referrals to and adherence with prevention programs.

Second is a study of the effectiveness of after-school sports testing-programs for illegal drug use. School districts are randomized to either having an after-school sports testing program for illegal drugs, or not

having such a program. Students are tested at regular intervals to determine illegal drug use to determine the effectiveness of the program.

Third is a study of study of community-based distribution of misoprostol for prevention of postpartum hemorrhage in rural Indonesia. One hundred villages will be randomized to either have access to misoprostol or not. In the active arm of the study, pregnant women will be asked to consent to participate in the research, and will receive tablets of misoprostol in a small baggy with directions on use presented in pictures. After they have their children, the women in the active arm will be interviewed to see if they had postpartum bleeding and used the misoprostol. In the control arm of the study, pregnant women will be identified by professional surveyors, but there is no intervention in their care and they will not be asked to provide consent. After they have their children, the women's level of postpartum bleeding will be determined by professional surveyors.

Fourth is a community intervention trial for smoking cessation. The goal is to evaluate the effect of a multi-modal, community-level cessation intervention, including bill boards, media, and targeted messages. Twenty two communities are randomized to either having the intervention campaign or not.

Fifth is a study of the best use of sedation in children in a ICU setting. Hospitals are randomized to x v y.

In all of these designs, the randomization of subjects occurs at a group level rather than an individual level.

[Do we need more content for the definition section?]

Scientific validity

Provide description of how these trials can be more or less robust than standard clinical designs.

[need a volunteer with knowledge of study design issues to draft this part]

Are CRTs ever proposed in order to avoid the need to consent subjects?

Overlap with QI projects as defined in OHRP FAQs

Often CRTs will meet the definition of "research" in 45 CFR 46[i], and the various definitions of "clinical investigation" in the FDA regulations 21 CFR Parts 50, 56, 312,and 812[ii]. However, CRTs may also meet the definition of a quality improvement project as defined in the OHRP FAQs on quality improvement projects.[iii] Thus, one of the threshold regulatory issues to consider with a given CRT is whether or not it is research or a clinical investigation under the regulatory definitions. If a CRT does not meet those definitions, then as a regulatory matter the project does not meet the requirements for IRB review and informed consent.

[need more analysis here]

Who is a subject?

An essential issue in the application of the regulations to CRTs is determining which participants meet the definition of a human subject under 45 CFR 46[iv] and the FDA regulations[v]. In the first example listed above, the access to the investigational diagnostic device is randomized by physician practice. The outcome is whether the physicians use the device and then encourage their parents to prevent development of diabetes. Are the physicians subjects under 45 CFR 46? [discussion]. Are the physicians patients subjects under 45 CFR 46 in this proposed study? [discussion]. Are the physicians subjects under FDA regulations? [discussion]. Are the physicians patients subjects under FDA regulations in this proposed study? [discussion].

In the fourth example of a CRT above, communities are randomized to be exposed or not to a smoking cessation campaign. Are the members of the communities all subjects under 45 CFR 46. [discussion].

When is consent necessary for subjects?

Under 45 CFR 46.116(d), consent can be waived if four conditions are met. [discussion using examples above]

Consent after randomization

One issue that arises in CRTs is that often subjects have often already been randomized on a group basis before being approached for consent.

Opportunity to decline participation

Another issue that arises with CRTs is that subjects often may not have an opportunity to decline participation after their group has been randomized. For instance, in example four above, subject located in the communities randomized to either have the smoking cessation campaign or not have no choice as to whether to participate. They will either be exposed to the campaign or not. The same issue holds true in the second example, the randomization of the after school drug testing program.

When can deception be used in a CRT to help blinding?

Forty five CFR 46 also allows for partial waivers of consent, and this approach is commonly used to allow deception in certain types of research in order to strengthen the validity of the research. [discussion]

Identifying the risks and benefits of the research

The criteria for IRB approval[vi] require that IRBs determine that risks are minimized and that the risk/benefit ratio is appropriate. In addition, subjects must be informed of risks and benefits as part of the consent process. There is not uniformity in designating which risks are in fast research risks. The regulations direct that, "in evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research)." This is a clear cut issue when an investigational new product is being tested, but it is not as clear when the research involves a registry, a phase IV study, standard of care arms, and public health interventions. In many RCTs, it is hard to identify the risks of the research, particularly in those arms that involve standard of care interventions.

Which institutions are engaged in research?

When an institution is engaged in research, then the institution is required to oversee the research in compliance with HHS regulations, including issues such as IRB review, informed consent, and registration with OHRP. In cluster randomized trials, it can be difficult to determine which institutions are engaged in research, particularly in studies such as the fourth example involving a community smoking cessation program. An analysis must be performed for each entity involved in the research to determine if they meet the requirements.

Subparts B, C, and D

The application of subparts B, C, and D to CRTs can be difficult, particularly in regard to the extra requirements for risk and benefit findings for the vulnerable populations.

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[i] 45 CFR 46.102(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.

[ii] There are four different definitions of clinical investigation found in 21 CFR 50 and 56, 312, and 812:

21 CFR 50.3(c): Clinical investigation means any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that are subject to the provisions of part 58 of this chapter, regarding nonclinical laboratory studies.

21 CFR 56.102(c): Clinical investigation means any experiment that involves a test article and one or more human subjects and that either must meet the requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or need not meet the requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that are subject to the provisions of part 58 of this chapter, regarding nonclinical laboratory studies. The terms research, clinical research, clinical study, study, and clinical investigation are deemed to be synonymous for purposes of this part.

21 CFR 312.3(b): Clinical investigation means any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects. For the purposes of this part, an experiment is any use of a drug except for the use of a marketed drug in the course of medical practice.

21 CFR 812.3(h): Investigation is a clinical investigation or research involving one or more subjects to determine the safety and/or effectiveness of a device.

[iii] OHRPFAQs on QI, http://answers.hhs.gov/ohrp/categories/1569

[iv] 45 CFR 46.102(f) *Human subject* means a living individual about whom an investigator (whether professional or student) conducting research obtains

[v] There are three different definitions of human subject found in 21 CFR 50 and 56, 312, and 812.

21 CFR 50.3(g) and 56.102(e): Human subject means an individual who is or becomes a participant in research, either as a recipient of the test articles or as a control. A subject may be either a healthy human or a patient.

21 CFR 312.3(b): Human subject means a human who participates in an investigation, either as a recipient of the investigational new drug or as a control. A subject may be a healthy human or a patient with a disease.

21 CFR 812.3(p): Subject means a human who participates in an investigation, either as an individual on whom or on whose specimen an investigational device is used or as a control. A subject may be in normal health or may have a medical condition or disease.

[vi] 45 CFR 46.111; 21 CFR 56.111.