SOH draft recommendation

Regulatory issues in cluster studies

Outline:

Definition of a Cluster Randomized Trial

Scientific validity

Overlap with QI projects as defined in OHRP FAQs

Which institutions are engaged in research?

Can CRTs meet the definition of exempt research under 45 CFR 46.101(b)(1) through (b)(6)?

Who is a subject?

Identifying the risks and benefits of the research

When is consent necessary for subjects?

- Waiver of consent
- Consent cannot be obtained until after randomization
- Voluntary participation
- Refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
- When can deception be used to help blinding?
- The role of gatekeepers.

Subparts B, C, and D

Introduction

Cluster randomized trial (CRT) designs are frequently used in human subjects research. These trials bring up unique issues of regulatory application. The purpose of this recommendation is to address the application of US HHS and FDA regulations to cluster randomized trials.

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 the study. In contrast, in a CRT the

randomization occurs as a function of being a member of a group. In addition, there can be several layers of groupings as well, for instance by school district, school, and class, or by health care facility, medical provider, and each medical providers' patients.

Examples of Cluster Randomized Trials

It is useful to distinguish between different kinds of CRTs based on the level at which the intervention is delivered. In a *cluster-cluster* trial, the intervention is delivered at the cluster-level. Usually, the intervention is "not divisible at the individual level" and is therefore necessarily delivered on a cluster-wide basis. In a *professional-cluster* trial, the intervention is delivered to health or other professionals working within clusters (providers, teachers, employers), while outcomes are then collected on the individual cluster members (patients, students, workers). An *individual-cluster* trial most closely resembles a standard randomized controlled trial in that the intervention is delivered directly to the individuals themselves. Usually, in an individual-cluster trial it would be possible to randomize by individual rather than cluster, but the cluster method is used for a methodological reason such as the prevention of exposure to trial aims among subjects. Another factor of the individual cluster design is that subjects have the ability to decline participation. Three examples follow to provide illustration.

Cluster-cluster

The COMMIT study (Community Intervention Trial for Smoking Cessation) was designed to test the effectiveness of a comprehensive, community-oriented approach to influence citizens' smoking behaviors.iii As the intervention is delivered at the community-level, this is an example of a cluster-cluster trial. Twenty-two communities with populations between 50,000 and 250,000 in the USA and Canada were randomly assigned to intervention or control. The intervention included activities focused on public education using mass media and organized community events, training of health care providers in cessation techniques, promotion of smoke-free policies in health care facilities and worksites, promotion of policies to restrict the sale of tobacco to youth, and development of smoking cessation resources and activities in each community. Population-based surveys, using random digit telephone dialing, were used to measure outcomes. Before randomization and at the end of the study, cross-sectional samples of approximately 2500 households per community were surveyed about their smoking behaviors. In addition, cohorts of approximately 550 heavy and 550 light-to-moderate smokers, willing to be contacted annually about their smoking status, were identified in each community. Main outcome measures were cross-sectional changes in the prevalence of smoking from pre- to post-intervention, and quit rates in the cohorts of smokers. Although the intervention significantly improved quit rates among light-to-moderate smokers, there was no significant effect on quit rates among heavy smokers or on the community prevalence of smoking.

Professional Cluster

Linder et al.iii used a cluster randomized trial to test a set of novel enhancements to electronic health records, designed to improve tobacco treatment and counseling in primary care. The enhancements included smoking status icons, tobacco treatment reminders, and facilitated ordering of medication and counseling referrals. Twenty-six primary care practices (521 clinicians) using electronic health records in

Massachusetts were randomized to intervention or control. The enhancements were introduced to intervention practices with an introductory e-mail to clinicians, a practice visit by an investigator, and periodic e-mails to encourage use of the enhancements. Clinicians in control practices received no intervention. Because the intervention was targeted at health professionals, this is an example of a professional-cluster trial. Practices instead of physicians were randomized to facilitate the introduction of the intervention, reduce contamination, and potentially increase the effectiveness of the intervention through peer effects. The primary outcome was the proportion of documented smokers who made contact with a smoking cessation counselor. Secondary outcomes included documentation of smoking status in the electronic records and prescription of cessation medications. Over a 9 month period, data on 315,962 visits by 132,630 patients in the control and intervention practices were collected from the practice electronic records. The institutional review board granted a waiver of informed consent for participating clinicians and patients. The intervention significantly increased contact with a cessation counselor as well as documentation of smoking status, but no difference was found in prescription of smoking cessation medications.

Individual-cluster

The ObaapaVitA trial was a 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.iv As interventions were delivered to individual women, this is an example of an individual-cluster trial. A total of 1086 small clusters of compounds were randomized to either vitamin A or placebo capsules. Fieldworkers visited all compounds over a 1-2 month period to recruit women for the trial. All women of reproductive age who provided informed consent were enrolled in the trial (104,484 women in the treatment arm and 103,297 in placebo). Capsules were distributed during home visits undertaken every 4 weeks. Fieldworkers gathered data on pregnancies, births, and deaths. The study found no significant effect of Vitamin A supplementation on pregnancy-related or all-cause maternal mortality. Although individual randomization could in theory have been used, the use of cluster randomization considerably simplified the trial organization and fieldwork. The trial area was divided into small geographical clusters of compounds, designed to contain a maximum of 120 women each. Each fieldworker was responsible for an area of four contiguous clusters and expected to visit women in one cluster per week over a 4-week cycle. Randomization of clusters also minimized the possibility of women receiving the wrong capsules as fieldworkers only had one type of capsule in their possession during any week. Furthermore, cluster randomization allowed implementation of an extensive information, education, and communication campaign to promote adherence through radio messages, loudspeaker vans and drum beaters, messages delivered through churches and mosques, posters, and health workers.

Scientific rationale for use of CRT designs

Generally, the reasons for adopting a CRT almost always rest on practical (e.g., cluster-level intervention), logistical, or other considerationsvvivii (see below). The CRT offers few scientific advantages over an individually randomized trial. The advantages that do exist need to be weighed against several disadvantages and limitations.

Advantages/Reasons for Use

The appropriate use of the CRT is driven by the nature of the intervention, the logistics of implementing the intervention, and the particular scientific question of interest.**Error! Bookmark not defined.**

When the trial is evaluating a cluster-level intervention (cluster-cluster trial), a CRT is the only design option. For example, a large-scale community health trial for the prevention of cardiovascular disease involving television, radio and billboards, cannot possibly be evaluated using individual randomization. Other examples of cluster level interventions requiring a CRT include interventions that involve changing the environment, such as fluoridation of community water supplies, and innovative changes in health service delivery or administration, such as the provision of improved HIV testing services at designated centers.

Another common reason for choosing a CRT is to avoid contamination. This is a common justification in both professional-cluster and individual-cluster trials. Contamination occurs when individuals in the control arm are partially exposed to the intervention through interaction with individuals receiving the study intervention, thus biasing the results towards smaller effect sizes. Contamination may arise at both the health professional and individual levels. For example, in a trial of an educational intervention administered by a health provider, it would be difficult for a health provider to educate some patients and not others; further, at the individual level, patients attending the same clinic may discuss the educational intervention in the waiting room. The only way to avoid these risks is to randomize health providers, rather than patients. The risk of contamination is particularly great in the case of unblinded or behavioral interventions.**Error! Bookmark not defined.** For example, in a CRT for prevention of coronary heart disease, worksites may be randomized to minimize the likelihood of workers in different intervention groups sharing information about the trial. Increasing the sample size of an individually randomized trial to allow for contamination may sometimes be preferable to adopting cluster randomization, given the methodological challenges presented by this design.viii

Another reasons for choosing a CRT occurs when indirect effects of a study intervention are of interest. For instance, in vaccine studies the overall effectiveness of a vaccine is a combination of individual immunity conferred by the vaccine and the reduced chance of encountering an infectious person (so-called "herd immunity"; see below).

Other common reasons for adopting the design in individual-cluster trials relate to logistical or administrative convenience. Cluster randomization may considerably simplify fieldwork (see example 3 above). CRTs may offer cost savings in some circumstances. For example, a trial that requires the use of expensive equipment or personnel (e.g., nurse specialists) would be less costly when implemented as a CRT, because the equipment or personnel need be provided to only half the centers as opposed to all centers if individuals within centers were randomized. In some trials, the outcome measure may be a rate defined at the level of the cluster with the data easily obtainable from routine administrative databases available for each cluster; individual randomization would require data directly from individuals with accompanying increases in cost and administrative requirements.**Error! Bookmark not defined.** Cluster randomization may help ensure that the intervention is fully or properly implemented.

For example, in example 3 above, cluster randomization may have helped to prevent sharing or swapping of medications among community members (in the hope of getting some benefit should they be randomised to placebo). Cluster randomization may enhance compliance, promote publicity at the cluster level, or reinforce the effective use of a new technology within a cluster.**Error! Bookmark not defined.** Cluster randomization may be required for political reasons.**Error! Bookmark not defined.** For example, a design whereby only half of the members in a community receive an intervention may not be acceptable to decision makers or village elders, and may cause resentment among those being denied the intervention. Similar reasons may apply in professional-cluster trials: for example, it may not be acceptable to physicians to have only some of their patients offered a screening intervention. In these trials, the only feasible way to secure cooperation and successfully recruit participants is to use cluster randomization.

Whereas individually randomized trials provide information only about the direct effect of an intervention on the people who receive it, CRTs allow one to also study whether people benefit from an intervention provided to other members of the community (i.e., indirect effects of an intervention).**Error! Bookmark not defined.** Indirect effects are particularly important in studies of infectious diseases. For example, the effects of vaccines that are designed to block the transmission of a parasite that spreads malaria cannot be evaluated in an individually randomized trial. To examine the effect of such a vaccine on infection rates in the community, a CRT is required. Similar considerations apply in studies of HIV transmission where an intervention may be designed to reduce the "infectiousness" of HIV-infected individuals to their sexual partners. Such an effect could not be measured in an individually randomized trial.

Disadvantages

The CRT design is statistically less efficient than an individually randomized design.ixx For the same total number of subjects, CRTs with positive intracluster correlation always have less power than an individually randomized trial; the sample size calculation must take the intracluster correlation into account to ensure an adequately powered trial.**Error! Bookmark not defined.**,**Error! Bookmark not defined.** This means that a larger sample size is required to yield the same power as an individually randomized trial. The loss of efficiency is a direct result of positive correlation among responses from individuals in the same cluster. CRTs require special methods to be used in sample size calculation as well as in statistical analysis as standard methods are usually invalid.xixii CRTs are therefore more complex to design and analyze. Results from CRTs may also be more difficult to interpret.xiiixivxv First, selection biases are a more serious concern in CRTs than in individually randomized trials, particularly when randomization of clusters is necessary prior to participant recruitment and allocation concealment is not possible. Second, imbalances between study arms are more likely in CRTs because the number of clusters randomized is often quite small. Given these methodological challenges associated with cluster randomization, individual randomization is always the method of choice, unless there are cogent reasons for adopting a CRT design.

Overlap with Quality Improvement (QI) projects as defined in OHRP FAQs

Often CRTs will meet the definition of "research" in 45 CFR 46[xvi], and the various definitions of "clinical investigation" in the FDA regulations 21 CFR Parts 50, 56, 312,and 812[xvii]. However, CRTs may also meet the definition of a quality improvement project as defined in the OHRP FAQs on quality improvement projects.[xviii] 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.

The OHRP FAQs provide two examples of QI activities that do not meet the definition of research. First, the HHS regulations for the protection of human subjects in research (45 CFR part 46) do not apply to quality improvement activities conducted by one or more institutions whose purposes are limited to: "(a) implementing a practice to improve the quality of patient care, and (b) collecting patient or provider data regarding the implementation of the practice for clinical, practical, or administrative purposes.**"**

This type of QI activity could be conducted using a cluster randomized design. For instance, two hospitals could be randomized, with one hospital implementing a practice to improve the quality of patient care, while the other hospital does not implement the practice. Examples could include having nursing staff wash their hands once an hour, or having two additional nursing staff working on each shift. The fact that this was done using a cluster randomized design would not in and of itself cause this activity to be research under 45 CFR 46.

Similarly, this type of cluster randomized QI activity involving FDA regulated products may not meet the definition of a clinical investigation. For example, a hospital could use one type of approved air mattress for burn victims in one wing of a burn unit, and a different approved air mattress in the other wing, and then collect provider impressions of the preferable mattress. Alternatively, the purpose of such a trial could be to provide data on cost effectiveness rather than to establish the safety or effectiveness of the mattresses. In both cases, this trial would not meet the FDA definition of clinical investigation of a device.

The OHRP FAQs also provide second example of QI activities that do not meet the definition of research. **T**he HHS regulations for the protection of human subjects in research (45 CFR part 46) do not apply to quality improvement activities if their purposes are limited to: "(a) delivering healthcare, and (b) measuring and reporting provider performance data for clinical, practical, or administrative uses.**"** A cluster randomized design could be used to deliver different healthcare methods on two floors of a hospital. For examples using one brand of catheter on one floor and a different brand on the other floor for the purpose of addressing the observation that medical providers are reluctant to make use of a newer less expensive model at the hospital. As long as the data collected is used for clinical, practical, or administrative uses, the project would not qualify either as research under 45 CFR 46. As long as the purpose is not to collect safety or efficacy data, it also is not a clinical investigation under 21 CFR 56 or 812.

Public health projects

Public health authorities often will try various methods of public health interventions, varied across neighborhoods or other jurisdictional units, in an effort to determine the most effective or efficient interventions. For example, within one city jurisdiction, a health department that provides school nursing services may determine to vary vaccination delivery practices among schools or school districts, providing required vaccinations directly and on-site in one set of schools, but in other schools, requiring parents to seek vaccinations from public health clinics or private physicians. The public health authority then can compare vaccination rates among the sets of schools, all in order to understand whether on-site vaccination services are effective and efficient in achieving acceptable vaccination rates among school children. Similarly, delivery of STD and HIV screening services, and community promotion of those services, can be varied by clinic and neighborhood, in order to determine the most effective and efficient use of limited screening resources.

In these cases and others, the purpose of varying the intervention among service delivery sites and neighborhoods is not to derive generalizable knowledge of any sort, even though aggregated experiences, if accompanied by adequate data gathering, might give rise to publishable findings that tend toward generalizable knowledge. Instead, the purpose of these interventions –which typically are discretionary public benefit interventions, not interventions dictated by patient "rights" to care and services – is to promote the most optimal allocation of limited public health resources. Randomization is done at a level far beyond the individual patient because (1) such a design is massively more efficient than individual randomization and moreover (2) the public health authority's own success and failure is measured on an aggregate, not individual patient, level. Such public health activities are most often regarded not as "research," but as the delivery of an acceptable range of public health interventions, grouped and then measured by service delivery site or neighborhood. Recipients of public health services are not thought to be required to undergo a consent process regarding the variant of service that they are receiving.

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 example involving a community smoking cessation program. An analysis must be performed for each institution involved in a CRT to determine if it meets the criteria of being engaged in research.

Can CRTs meet the definition of exempt research under 45 CFR 46.101(b)(1) through (b)(6)?

Yes, CRTs can be exempt research under all of the exemption categories if they meet the exemption criteria. The CRT design does not determine that the criteria are met or not.

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[xix] and the FDA regulations[xx]. Often, each of the levels

of individuals (such as medical providers and patients) will be research subjects. A difficult issue is determining whether individuals whose care or exposure to a health measure is affected by the cluster randomization of medical providers are subjects.

Under 45 CFR 46, the definition of a human subject is:

> (f) *Human subject* means a living individual about whom an investigator (whether professional or student) conducting research obtains
>
> (1) Data through intervention or interaction with the individual, or
> (2) Identifiable private information.
>
> ***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.

It is important to note that the definition includes a disjunctive "or" between the two subclauses, such that an individual becomes a subject if the obtains data through intervention or interaction or identifiable private information. Obtaining either suffices to make the individual a subject, both conditions do not have to be satisfied.

To illustrate the issue of whether providers are research subjects, consider a CRT in which outpatient surgical centers are randomized to have different types of training on approved laparoscopic surgical techniques. Some centers are randomized to have the surgeons receive in-person training on laparoscopic techniques with an experienced mentor. Other centers are randomized to have the training provided through an automated computer program. The purpose of the trial is to determine the relative efficacy of the two types of training. The goal of the CRT is to determine which training on surgical technique results in better patient outcomes, which will be stratified by surgeon as well as center. As part of that stratification, the outcomes of the individual patients will be identifiable. In addition, the surgeons will be asked to provide their opinions on the effectiveness of the training programs through surveys and interviews.

Are the surgeons subjects under 45 CFR 46? Yes. The surgeons will receive differential training for research purposes, will participate in interviews and questionnaires, and private identifiable information will be collected about them. Thus, under 45 CFR 46, the surgeons are subjects in this research.

Are the surgeons' patients subjects under 45 CFR 46 in this proposed study? Yes, the physicians' patients are subjects under 45 CFR 46. The research involves interaction with the subjects because the surgeons performing surgery on them have received different types of training on laparoscopic surgery. Thus, the patients' care is directly affected by the existence of the research. Under the definition of a human subject at 45 CFR 46, an individual becomes a subject when an investigator obtains "Data through intervention or interaction with the individual, or identifiable private information." An intervention

includes “manipulations of the subject or the subject’s environment that are performed for research purposes.” Thus, these patients could be subjects solely on the basis of being subjected to an intervention, because their environment is manipulated by the different training techniques that were implemented for research purposes. Separately from that, the status of subjects could also be established by the collection of private identifiable information, regardless of whether there was an interaction or intervention. Thus either part of the definition of a human subject could lead to the patients being subjects under 45 CFR 46 in this case, and obtaining only de-identified data about the patients’ outcomes would not be sufficient to cause them not to be subjects.

Thus, in a professional cluster trial, the patients of the professional can be subjects on two bases. First, they can be subjects because the researchers (not the professionals) interact or intervene with the patients, and that intervention can include “manipulations of the subject or the subject's environment that are performed for research purposes.” Alternatively, the patients of the professionals can become subjects because the researchers obtain private, identifiable information about those. Clearly, the most difficult conceptual issue is deciding when the research interaction with the professional creates “a manipulation of the subject or the subject's environment.” That analysis must be made on a case by case basis.

It is worth noting in the example above that if the separate training programs had been adopted by the different surgical centers for non-research purposes, and then a researcher had decided to study the difference through the collection of data that did not include private identifiable information about the professionals’ patients, then the patients would not be research subjects.

Are the surgeons subjects under FDA regulations? No, the surgeons are not subjects under the FDA regulations because they are neither the recipients of a test article nor used as a control. They are randomized to either in person or computer based training on laparoscopic surgery, but this alone does not cause them to become subjects as defined by FDA. Also, they do not become subjects due to their participation in interviews and questionnaires or the collection of data about their performance.

Are the surgeons’ patients subjects under FDA regulations in this proposed study? No, the surgeons’ patients are not subjects in this research. They are neither the recipients of a regulated test article nor used as a control. The results of the study will provide information on the safety and efficacy of the training, but not on the safety and efficacy of the laparoscopic surgery devices.

To further illustrate this issue, consider a CRT in which ICUs are randomized to the use of either antibiotic ointment or antibacterial soap on the patients to prevent the spread of staph infection.

Are the ICU patients subjects under 45 CFR 46 in this proposed study? Yes, the ICU patients are subjects under 45 CFR 46. The research involves interaction with the subjects because they are exposed to different products used in the ICU to prevent the spread of staph infection.

Are the ICU patients subjects under FDA regulations? Yes, the ICU patients are subjects under the FDA regulations because the safety and efficacy of medical products are being tested in the research, and it qualifies as a clinical investigation that requires IRB review. It is likely it would not need an IND, because

if fits under the IND exception at 21 CFR 312.2.. However, that does not alleviate the need for IRB review and oversight.

[Note, Sara Goldkind is following up at FDA on the question of whether comparison effectiveness studies are clinical investigations. –Similar question arises with observational registries where the choice of drug is not directed by the study.]

[Another question that arose during discussion is whether changing from an individual randomization design to a cluster randomization design can change the status from being a clinical investigation to not being one. Our general consensus was that it did not change the status, but it is worth one more round of discussion.]

In the smoking cessation 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? Yes, they are subjects under 45 CFR 46, because they are exposed to an intervention in their environment. However, as discussed below, this research will qualify for a waiver of consent because the manipulation involves minimal risk.

Each proposed CRT research project requires a careful analysis as to whether the various levels and clusters of participants are research subjects. Even if certain clusters of individuals are found not to meet the definition of research subjects, the IRB or institution may wish to consider whether there are issues of unacceptable risks, lack of informed consent, or other issues affecting that cluster population.

Identifying the risks and benefits of the research

The criteria for IRB approval[xxi] 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. The risks and benefits to the subjects in each level and cluster must be considered (e.g., randomized medical providers and their patients).

One issue that arises is that there is not uniformity in the regulated community in designating which risks are in fact 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, arms in which standard of care is provided, or public health interventions. In many RCTs, there is not uniformity as to identify the risks of the research, particularly in those arms that involve standard of care interventions. Some IRBs will consider the risks of a standard of care arm to involve the risks of the clinical interventions as the risks of the research, and also consider the benefits of that arm as research benefits. Other IRBs will consider the risks of a standard of care arm as not being research risks, and the benefits as not being benefits of research.

In the example involving the randomization of ICU units to antibiotic ointment or antibacterial soap, the use of both approved products fall within standard of care. The risks include the fact that one product may cause more adverse events, such as skin irritation to the soap or allergic reaction to the antibiotic,

or that one product may not be as effective in preventing the spread of staph infection and subjects may develop treatment-resistant staph infection.

For another example of the risks involved in CRTs, consider a study of study of community-based study to address the recognized problem of post-partum hemorrhage in rural Indonesia. One hundred villages will be randomized to either have access to misoprostol, a inexpensive drug to treat post-partum hemorrhage, or have no access. 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. In the active arm, the women face the risks of misoprostol, particularly if they take it while still pregnant prior to the birth of the infant. In the control arm, the women face the risks of untreated postpartum bleeding. This illustrates that there can be above minimal risk in CRTs.

Informed consent in CRTs

The HHS and FDA regulations require that research subjects consent to their participation in research unless a waiver of consent is acceptable. The standards for waiver of consent under the two sets of regulations differ. Under HHS regulations, there are certain waivers of consent possible.[xxii] Under the FDA regulations, there are separate waivers of consent possible.[xxiii] The most common of these waivers is 45 CFR 46.116(d), whereby consent can be waived if four conditions are met:

(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.

However, FDA has not adopted these regulatory criteria for waiver of consent. Therefore, to determine if consent can be waived, there first must be an analysis of which regulations apply, and then for each cohort of subjects, this analysis must be applied in order to determine if consent may be waived.

The CRT is a design that requires careful justification. There are usually cogent reasons to adopt a CRT: in the case of cluster-cluster and professional-cluster trials, the reasons are usually obvious; in the case of individual-cluster trials, individual randomization is possible — at least in principle — but contamination, efficiency, or political factors argue for the use of a CRT. The use of a CRT does not change the general presumption that individual informed consent is required, unless conditions to justify a waiver of consent obtain. According to the Ottawa Statement, "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".xxivxxv

Is it acceptable to obtain consent after randomization?

One issue that arises in CRTs is that clusters of potential subjects will be randomized on a group basis before being approached for consent. In these cases, when consent is required, the investigators must obtain consent at the earliest possible opportunity. At that point, subjects may exercise their right not to participate in the research or allow the use of data collected. This issue does not automatically cause the research to be unacceptable from a regulatory perspective. The IRB must consider whether the delay in obtaining the consent exposes to the subjects to an unacceptable level of risk or restriction on autonomy. From a regulatory perspective, IRBs can consider whether the delay in obtaining consent must be justified as an alteration of consent under 45 CFR 46.116(d). In the examples involving surgical training or staph infection prevention, potential subjects would have been given the opportunity to consent at the first opportunity and thus consent has not been delayed. [add better example of delay in obtaining consent]

Voluntary Participation; Opportunity to decline participation

Another issue that arises with CRTs is that when the intervention is administered at the level of the cluster, such as the community or the institution, the subjects often may not have an opportunity to decline participation after their group has been randomized because the entire cluster is affected. For instance, in the smoking cessation example above, subjects 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.

Refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled

Another regulatory issue that can arise is that subjects must be informed that their refusal to participate in the research will not lead to any penalty or loss of benefits to which they are otherwise entitled, and that the same applies if they discontinue participation. In the SATURN study, school districts were randomized to having or not having after drug testing programs for after-school sports. One potential subject complained that if she did not participate in the research then she could not participate in after-school sports.[xxvi]

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

45 CFR 46 also allows for alterations 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. This same technique could be used in a CRT if the criteria at 45 CFR 46.116(d) for an alteration of consent were met.

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. For example, in a CRT involving children the IRB must determine the category of child research. This requires an assessment of the risks and benefits of the research for the children, as well as a determination of whether or not assent is necessary and how it will be documented.

The Role of Gatekeepers

As with any research project, researchers performing CRTs must obtain the agreement of gatekeepers such as nursing home directors, school principals, and other officials to conduct research at a given organization. However, as a regulatory matter, that permission cannot substitute for the informed consent of the subjects in a CRT.

Conclusion

We offer these recommendations to help the Secretary provide advice on the application of US regulations to cluster randomized trials.

---

1. [i] The COMMIT Group: Community intervention trial for smoking cessation (COMMIT): II. Changes in adult cigarette smoking prevalence. Am J Public Health 1995, 85(2):193-200.

2. [ii] The COMMIT Group: Community intervention trial for smoking cessation (COMMIT): I. Cohort results from a four-year community intervention. Am J Public Health 1995, 85(2):183-92.

3. [iii] Linder JA, Rigotti NA, Schneider LI, Kelley JHK, Brawarsky P, Haas JS. An Electronic Health Record–Based Intervention to Improve Tobacco Treatment in Primary Care. Arch Intern Med. 2009;169(8):781-787.

[iv] Kirkwood BR, Hurt L, Amenga-Etego S, Tawiah C, Zandoh C, Danso S, Hurt C, Edmond K, Hill Z, Ten Asbroek G, Fenty J, Owusu-Agyei S, Campbell O, Arthur P; ObaapaVitA Trial Team. Effect of vitamin A supplementation in women of reproductive age on maternal survival in Ghana (ObaapaVitA): a cluster-randomised, placebo-controlled trial. Lancet. 2010 May 8;375(9726):1640-9.

[v] Donner A, Klar N: Design and Analysis of Cluster Randomization Trials in Health Research. London: Arnold, 2000.

[vi] Hayes RJ, Moulton LH. Cluster randomised trials. Chapman and Hall/CRC, 2009.

[vii] Eldridge S, Kerry S. A practical guide to cluster randomised trials in health services research. Chichester, Wiley, 2012.

[viii] Torgerson DJ: Contamination in trials: is cluster randomisation the answer? *BMJ* 2001, 322:355–7.

[ix] Hayes RJ, Bennett S: Simple sample size calculation for cluster-randomized trials. *Int J Epidemiol* 1999, 28(2):319–26.

[x] Donner A, Klar N: Statistical considerations in the design and analysis of community intervention trials. *J Clin Epidemiol* 1996, 49(4):435–9.

[xi] Donner A, Klar N: Methods for comparing event rates in intervention studies when the unit of allocation is a cluster. *Am J Epidemiol* 1994, 140(3):279–89.

[xii] Campbell MK, Mollison J, Steen N, Grimshaw JM and Eccles M: Analysis of cluster randomized trials in primary care: a practical approach. *Family Practice* 2000, 17**:**192–6.

[xiii] Puffer S, Torgerson D, Watson J: Evidence for risk of bias in cluster randomised trials: review of recent trials published in three general medical journals. *BMJ* 2003, 327(7418):785–9.

[xiv] Hahn S, Puffer S, Torgerson DJ, Watson J: Methodological bias in cluster randomised trials. *BMC Medical Research Methodology* 2005, 5:10.

[xv] Eldridge S, Ashby D, Bennett C, Wakelin M, Feder G. Internal and external validity of cluster randomised trials: systematic review of recent trials. *BMJ 2008;336:876*

[xvi] 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.

[xvii] 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.

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

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

[xx] 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.

[xxi] 45 CFR 46.111; 21 CFR 56.111.

xxii 45 CFR 46.116(c);45 CFR 46.116(d), and OHRP 1996 guidance "Informed Consent Requirements in Emergency Research."

xxiii 21 CFR50.23(a) through (c); 21 CFR50.23(d); 21 CFR50.23(e); 21 CFR 50.24; FDA Guidance "Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable."

[xxiv] Weijer C, Grimshaw JM, Eccles MP, McRae AD, White A, Brehaut JC, et al. The Ottawa Statement on the ethical design and conduct of cluster randomized trials. *PloS Med* 2012;9:e1001346.

[xxv] Taljaard M, Weijer C, Grimshaw JM, Eccles MP, the Ottawa Ethics of Cluster Randomised Trials Consensus Group. The Ottawa Statement on the Ethical Design and Conduct of Cluster Randomised Trials: A précis for researchers and research ethics committees. *BMJ* 2013;346:f2838.

[xxvi] Cite to SATURN study. OHRP letter?