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What's New in GCP? OHRP Determines Written Consent Waiver Allowed for Pregnant Women

OHRP Works with Large Cluster Randomized Trials on Regulatory Issues

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HHS regulations allow for the waiver of written informed consent for pregnant women, the Office for Human Research Protections (OHRP) has concluded.

The issue arose in a large National Institutes of Health cluster randomized trial in Africa, in which healthcare workers went door-to-door in 21 communities offering HIV prevention interventions. "The household interventions are based on the idea that the individuals are giving consent verbally, and they are being offered a flyer and verbal information [about the experimental program] but they are not signing a full written informed consent. There is an alteration of the informed consent process and really a waiver of the written informed consent process," said Mark Barnes, who is the ethics officer for the trial.

The problem was that the healthcare workers would encounter pregnant women, and the federal regulations specifically dealing with pregnant women (45 C.F.R. Subpart B) "do not have an explicit waiver of written informed consent in it," Barnes said. "We had extensive conversations with the OHRP staff, which was very helpful, and OHRP has taken the interpretation that the possibility of waiver is implied in Subpart B, even though it is not explicit in Subpart B and, based on that, we are able to include the pregnant women in the intervention."

"We do understand Subpart B to allow the applicability of consent and the waiver of consent provisions for pregnant women, but it is not something that we actually offered guidance on. But we are confident that that is the way that the regulations should be interpreted," Ivor Pritchard, OHRP's acting director, told the Secretary's Advisory Committee on Human Research Protections March 12.

OHRP Works with NIH Collaboratory

The NIH Collaboratory also is working with OHRP on regulatory issues that emerge from large, complex trials. "It is unusual when you are designing a trial to have a phone call with OHRP in the middle of it," said Rob Califf, co-chair of the Collaboratory's regulatory and ethics working group. "Some people were afraid of that, as you might imagine, but these phone calls were very productive and useful."

Califf said the deliberations on a number of issues are available on the Collaboratory's website. "We have put the thought processes that led to our approaches on a public website," he said. "We appreciate the time that it took from OHRP to get it done."

"One of the purposes for making these discussion minutes publicly available is to inform institutional review boards, institutions and investigators of how the human subject protection regulations might apply to studies similar to those being conducted," the website introduction said. "OHRP notes that determining how the human subject protection regulations apply must take into consideration study-specific information."

The Collaboratory also has a "living textbook" on pragmatic clinical trials that is being built. The textbook now has sections on informed consent and conflicts of interest.

"We have been participating in discussions about various collaboratory trials and the ethical and regulatory issues that they raise," Pritchard said.

"The research collaboratory is a rather elaborate apparatus that appears to be designed to keep forcing us to pay attention to the kinds of issues that are raised by large-scale trials involving large numbers of institutions and large numbers of subjects in what some people would like to characterize as learning healthcare systems, in which people are carrying out research studies that are more or less integrated into the regular delivery of clinical care and trying to figure out how to manage [those studies] in an efficient way and how to provide appropriate protections for research subjects," Pritchard said.

Collaboratory Issues Detailed

"There has been a great deal of discussion of risk assessment, particularly in the context of informed consent, where you have to find that the study is minimal risk," Pritchard said. He added the discussions generally "seem to suggest that these studies are very low risk" and are altering usual care only slightly. The researchers "believe that there is a reasonable chance that the intervention will lead to positive effects [without] any potential for a downside. They seem to believe that either it is usual standard of care, so there is no added risk because they are just doing what they would have done anyway, or there's the potential for benefit [and very little] potential downside," he said.

Pritchard noted, however, the research community is "reminded on a regular basis that sometimes studies don't turn out the way we expected them to turn out and presumably the reasons for doing these studies in the first place is that we don't have solid gold-standard clinical trial evidence."

Because researchers consider the interventions to be "usual care," there is much discussion about the need for informed consent. In some cases, such as examining antibacterial techniques, it is not "the kind of intervention that hospital staff or physicians normally talk to patients about or offer choices in the course of providing routine care.

So it does really make sense to suddenly be doing this with something that ordinarily wouldn't be the subject of any discussion," Pritchard said.

Another discussion point is control group status. The argument is "they are research subjects, in so far as there is information being collected about them but the risks of the standard of care they receive in the usual care arm should not be considered part of the research study because those are risks they would have run anyway as a function of the therapy that they were going to get, so they should not count toward any risk assessment at all," Pritchard said.

In addition, there have been questions about what information should be given to the control group. The intervention group receives what they normally would receive in an informed consent process with a robust discussion of the interventions they might receive. The question is whether subjects in the control arm should be informed of what the intervention group is receiving so that they can consider whether they want to either opt out of the study or receive the other intervention.

Pritchard noted that one of the "reservations about getting informed consent is that…some people may decline, and if they decline, you have a more limited population to generalize to and you still don't know how well the intervention would have worked with people who decline." Other researchers question whether the informed consent process itself could bias the clinical care outcome. Are individuals who know they are in a study more diligent about following medical directions?

African Trial Confronts Regulatory Issues

Barnes said one of the first ethical/regulatory questions that came up in the African study was whether the control arm of the study was ethical. "What should a control group receive," he asked, if the other two arms of the study were receiving more intense public health interventions.

The decision was that the control group would receive "everything that it got before the study was conceived [and] a little more," Barnes said. "The national health authorities and the research ethics committees thought that a moderate increase in benefit by better funding of basic standard HIV prevention and interventions in the control communities was sufficient to meet the ethical standard for benefit to a community in regard to research, even though we knew that the house-to-house testing offered in [the other arms of the study] are really better and probably have better outcomes," he said.

Although about 1.2 million people live in the 21 communities, data will be collected on only about 55,000, and the decision was made that only those 55,000 subjects would have a written consent process. However, South African research regulations require written consent from all subjects in all studies.

"The South African authorities and research ethics committee decided that all three interventions were arguably a public health standard of care, and therefore they would only require written consent" from those subjects from whom data are collected. They also decided that individuals in the control arm were "not even research subjects" because they were receiving "standard of care just stepped up with better funding," Barnes said.

And although individuals in the intervention arms of the study were "receiving interventions that they didn't expect and without the study they wouldn't have received," the authorities allowed oral consent. The health care workers gave each household written flyers explaining the community-wide study. They also offered each household the ability to opt out of the study. "If the household opts out, they leave and they won't come back as part of the study," Barnes said. "The experience to date has been that almost nobody opts out."

He noted written consent must be given for the HIV testing that is done in the households, but the consent "is because it is the standard of care for health care rather than the standard of care for research."

Another ethical concern was that the study is for three years and, under one of the intervention arms, individuals were referred for treatment even though they were not eligible for treatment under national guidelines. "When the study ends, will the national authorities continue to treat people who are not otherwise qualified to receive the treatment," Barnes asked? The national ministry of health and the local health systems agreed to retain those people in treatment once the study was completed, even if the treatment exceeded the standard of care, if the individuals wanted to receive it.

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