

June 7, 2012.

OHRP webinar when the regs come a'knockin', nuts and bolts of 45 CFR part 46.

The webinar will begin shortly, please remain on the line. The broadcast is now starting, all attendees are in listen only mode.

Greetings, this is Elyse Summers and I'm the Director of the Division of Education and Development at the Office for Human Research Protections. Welcome to our second educational webinar,

When the Regs Come A'knockin' Nuts and Bolts of 45 C.P.R. part 46.” As many of you know, in February we launched our webinar series with “When the Feds Come A'knockin',” featuring Dr. Kristina Borrer, Director of OHRP’s Division of Compliance Oversight. This maiden voyage was a huge success with over a thousand listeners on board.

Buoyed by our success the first go round, we are back for more. Today I will be discussing the history and requirements of the U.S. Department of Health and Human Services regulations for the protection of human research subjects. This webinar is a basic offering, well suited to those of you who are new to the field of human subjects’ protection and those of you who are not-so-new but wish to refresh and reinforce your understanding of the HHS regulatory requirements.

At this point, I would like to take a few moments to cover some of the logistical aspects of our program. First things first. I'm going to launch a poll asking whether or not you can hear me. So here goes. Okey dokey. So there it is. Can you hear me?

And the numbers are rolling in. And it looks great. Over 97% of you can hear me, so I'm going to close the poll. And I will share the results. I closed the poll and I think I shared the results. Now I've hidden the results. Okay. Most of you can, which is the most important thing. If you happen to have difficulty hearing the presentation, you may want to switch your audio selection from telephone to voice over internet provider or VOIP, or vice versa.

Also, during the webinar, your control panel will read "Speaking Samantha Smith." This is just an unavoidable idiosyncrasy of the software. Samantha is one of our fine DED colleagues. I guarantee that in the not too distant future when you see the words speaking, “Samantha Smith speaking,” it really will be Samantha speaking. For now, I would like to take this opportunity to thank Samantha and Lanette Meyers, who are our wizards behind the curtain today.

Next I want to mention that insofar as there may be a thousand or more of you out there in Cyberland listening to my presentation, it will not be possible to take questions at any point during this session. Some of you notice that your reminder e mail contained a request for questions. We did receive questions in advance and I will make every effort, time permitting, to

respond to those within or after my presentation. As always, you may of course send along any questions you have related to this presentation to the general OHRP e mail box, OHRP@hhs.gov. We will answer them promptly in our normal course of activities. Also, if you would like to review this webinar, and/or share it with colleagues, the recorded presentation will be posted to OHRP's YouTube channel within the next several weeks. You will find the link on the OHRP website at that time. Many of you undoubtedly know that our first webinar on compliance activities is already available on YouTube. Now, before I get started in earnest, I would like to get a sense of who is with us today, and I'm quoting liberally from Jimi Hendrix here, "are you experienced?," and so I'm going to launch another poll to see what we have out there. So in terms of your experience in human subjects protections, you are: "brand spankin' new (less than one year experience)." "Getting there, but still a lot to learn, (one to five years)." "Looking to reinforce my understanding, (five to ten years,)" or "By golly, I could teach this webinar, (ten or more years in this field)." And we see the results rolling in. And you all are a very helpful and compliant group because I see that 90% of you have voted, so I'm going to close this off now and this gives me a good sense of who you are with us here today. I'm going to close the poll, and share the results with you so that you can see that, as I say, that shows you're kind of all over the place which is good. Those of you who are very experienced in this field, and you find this repetitive, I will not be at all offended if you play some solitaire or take care of some other important work while we're going through this, and now I will turn to the nuts and bolts of what we're here to do today. I will hide this poll, and return you to the presentation.

What I'm going to cover today includes some of the important historical precedents and ethical principles that got us to where we are today in terms of human subjects research. I'm also going to talk about some of the overarching areas of regulated human subjects research and protections, the application of the HHS regulations, which of course are the regulations that OHRP enforces, and then I'm going to spend the bulk of my time talking about the actual substance of the regulatory protections for research subjects within the regulations.

I'd like to spend a few minutes talking about some important historic precedents in the development of human subjects protections, as you can see on the slide, the three that bear the most relevance to the regulations that we work with every day are the Nuremberg Code, the Declaration of Helsinki and the Belmont Report, and I will spend a little bit of time with each of these in turn. During World War II, as you may know Nazi doctors and others experimented upon concentration inmates. This came to light at the conclusion of the war and the Nuremberg war crimes trials were held. And the doctors were charged with performing medical experimentation upon concentration camp inmates and other living human beings without any permission, any informed consent, and notably there was of course no opportunity for individuals to withdraw if they wanted to. So as part of the verdict from those trials, we got the Nuremberg Code, and the court in its verdict enumerated some rules for permissible medical experiments now known, as I said, as the Nuremberg Code, and these rules include the notion that the voluntary consent of subjects is absolutely essential for the ethical conduct of research;

that benefits must always outweigh risks; and that subjects should be given the opportunity to terminate their participation or withdraw from research at any time and for any reason. And the Nuremberg Code, as I mentioned, came out in 1947. Moving more toward the modern times and further along into the 20th century, in 1964 the World Medical Association gave us the Declaration of Helsinki, and one of the notions within the Declaration of Helsinki which was really a refinement of some of the ideas in the Nuremberg Code. The Declaration included the idea that concern for the interests of subject must always prevail over the interests of science and society. And there are several examples of the notion of the Declaration of Helsinki at work in today's research context, and in the interest of time, I will give you just one. In 1993, researchers were looking at the use of AZT, which at the time was the only known treatment for HIV status, and AZT was being looked at by researchers to prevent vertical transmission from an HIV positive pregnant woman to her fetus and later baby. And in the context of that study, when the results came rolling in, and data came rolling in, the use of the AZT was viewed as quite effective and it really did help prevent vertical transmission. And so the trial was stopped so that every individual woman was given the opportunity to speak with her provider and determine what the right course of events for her was even though if the trial had continued, surely more scientific data and information would have rolled in. So again, the interest of every individual subject must always prevail, even over the interest of science. Now, moving along even further, in 1947, we had the Nuremberg Code. Nineteen sixty four was the Declaration of Helsinki, yet in 1966 Henry Beecher published an article in the New England Journal of Medicine where he documented 22 published studies that presented risks to subjects and that were taking place without their knowledge or approval, and these studies were published in prestigious journals at very well known, highly regarded institutions across the country, and some of these studies you may be familiar with. They involved mentally disabled children, deliberately infected with the hepatitis virus; that was the so called willow brook study of the 1950s. Live cancer cells were injected into 22 senior adults with dementia, and many more examples like that exist. Well, when that article came to light, the U.S. Public Health Service finally took some action regarding that, and the Director of NIH and the Surgeon General requested that the National Advisory Health Council review human subject protections and the Council recommended prior institutional review for PHS-supported research, to protect the rights and welfare of subjects and to assure appropriate methods of informed consent, and to determine the acceptable balance of risks and benefits for subjects. And this policy was adopted by the Public Health Service in 1966. And this was the beginning of the IRB system as we know it today. The beginning of the IRB system.

So in 1966, the Public Health Service policy gave us all of those things on this slide; however, at the very same time, as if in a parallel universe the horrific Tuskegee syphilis study was ongoing in this country. It was a highly unethical American medical research project conducted by the very same U.S. Public Health Service for almost 40 years, and in that study, researchers were looking at the so called natural, natural being that the syphilis was allowed to continue unabated, looking at the so called natural course of untreated syphilis in African American men and the

subjects were all impoverished share croppers from Macon County, Alabama, many of them, most of them were unknowing participants in any kind of study. They were never told that they had syphilis, nor were they offered effective treatment even when the advent and recognition of penicillin as a widely available and accepted cure for syphilis was available in the general community. So that was going on for 40 years in this country. And when that came to light, the government finally took the steps, the Federal Government finally took the steps that brought us to the regulatory framework that we have today. You'll note on this slide there's a picture of President Clinton and Vice President Al Gore. It was not until 25 years later that through the President of the United States the government formally apologized to the Tuskegee survivors and their families, and he acknowledged the profound wrong that was done during the course of that study. In the intervening years, between 1972, when the conclusion of this study occurred and it the fact that it had taken place for all of those years came to light in the press. In 1973 Senator Edward Kennedy called hearings on the quality of health care and human experimentation, and out of that we got the National Research Act, which established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, and for the first time IRBs were required at institutions receiving support from our predecessor agency, which was the Department of Health, Education and Welfare, and that institutions would need to have IRBs reviewing research at those at HEW supported institutions. And the commission gave us what we know today as the Belmont Report, and unlike many government documents, which probably are sitting on your shelf collecting dust, the Belmont Report is very much a dynamic and still living document, and it informs everything we do in this area every single day; and we at OHRP are fond of saying that it should be required reading for anybody involved in research involving human subjects.

It gave us three basic essential ethical principles. The first is respect for persons, whereby we recognize individual autonomy and at the same time balance that with protection of individuals who may have reduced autonomy. The second is the notion of beneficence by which we try to maximize benefits wherever possible and minimize harms and also captured by the notion that physicians have of doing no harm. The third is the notion of justice and that is captured with the idea that we always try to have an equitable distribution of research costs and benefits; and I would just like to note that to give an example of the dynamism of the Belmont Report, when it was written, we were of course just coming out of the horrors revealed with Tuskegee, and the notion was that individuals needed to be protected from research. A lot of pharmaceutical research was being conducted in prisons where the populations were literally captive audiences for the research, and so again the notion of justice was protection from the costs of research. However, again, in the mid '80s, with the advent and recognition of HIV and AIDS, research advocacy groups began to grow and viewed research participation as possible access to new and promising therapies and treatments, and so the goal with justice is to provide sufficient protections from costs of research, but at the same time access to possible benefits of research.

Now, at this time, I'm going to launch another poll about the developments in human subjects protections, just to see if you guys are here, and paying attention. So here we go. Which of the following documents played a role in the development of the current regulations for the protection of human subjects?

And here I would ask you to just pick one. Just pick one, and I don't know how it works, if you can change if you choose one, then you can change later. But there are about half of you who have voted. We'll give you another few seconds, because we have a lot of material to cover here today. Let's see what we have here. And I think I think you're seeing what I am seeing. Yes, you are seeing poll in progress, so that's good. All right. We have this sort of magic okay, that's great. 87% of you voted. That's good enough for me. If 87% of the American electorate voted, then that would be that would be participation we would all be proud of. Okay, we're going to close this. All right. We're just about at 90. We're going to close these polls, and as I suspected, we're going to share the results here, you all are a very, very attentive and bright group. 75% of you chose all of the above, and that is correct. I know I spent a long time talking about the Belmont Report, and in many ways the Belmont Report really was, as I said, the philosophical parent of our regulations, but at the same time, those other documents also played important roles and informed where we are today. So thank you for participating in that poll, and now I'm going to move along with the content of the presentation. So with those historical precedents in mind, I'm now going to talk about the overarching oversight of human subjects' research, and just give you a flavor of who's involved and our piece of the pie.

So there are many federal departments and agencies. Seventeen that are signatories to what we call the Common Rule, and I'll talk about that in just a few moments. FDA also of course has a significant role in the protection of human subjects in research, in industry sponsored research. Some of your states and localities may have further regulations or guidelines in place. I know just by way of example that the State of California has its own statutory framework in place in this area. And then last but certainly not least, each of your institutions plays a very important role in the protection of human subjects, and indeed, the regulations that our office enforces delegate a lot to the institutions and make it your institutions' responsibility as an important role player in the protection. Really where the rubber meets the road. So as I alluded to, the Office for Human Research Protections, we implement and enforce the HHS regulations at 45 CFR part 46. We, OHRP, are the artists formerly known as the Office for Protection from Research Risks. We used to play this role within the National Institutes of Health, and around the turn of the century, this century, this most recent century, we were elevated from within the National Institutes of Health to the Office of the Secretary to give an elevated view toward the production of human subjects, and also because our purview extends beyond just the National Institutes of Health to all of the agencies within HHS, it was felt that the appropriate place for our office was within the Office of the Secretary. As I alluded to, the main bulk of the regulations, subpart A, has come to be known as the Common Rule, and you'll see on this slide the many other federal departments and agencies that have adopted it, and the Common Rule is the rule that goes to the

federal funding and support of research, so for example, if you're conducting research on pesticides involving people that's funded by the Environmental Protection Agency, they have adopted the Common Rule. They would implement it for that research. Now, the HHS regulations, as you hopefully are aware, have additional protections, in subpart B for pregnant women, C for prisoners, and D for children, and one of our fine colleagues who put these slides together found this great picture which we believe is a teen age pregnant woman who appears to be incarcerated, so there you go, and if you happen to have somebody in your research study who is that person, you would have to follow all of those additional protections because they are additive. I just want to make a note, you see on the slide also listed subpart E. That is really an administrative regulation that goes to the formalities of IRB registration. It is required now for IRBs reviewing HHS and federally and HHS and now also FDA regulated research. And again, if you have a federal wide assurance on file with us, you also have a relationship with a registered IRB.

As I alluded to, or as you may have noticed, the Food and Drug Administration was not listed on that slide with the signatories to the Common Rule. That is because they operate from a different statutory and regulatory framework. The good news is that the requirements for IRB in terms of the membership and review of the IRB, those requirements, as well as the requirements for informed consent, are largely congruent between the HHS, which are the OHRP requirements, and the FDA regulations, and again as I believe I've alluded to somewhat, the differences stem from application. The HHS regulations are based on HHS funding or support of research, and the FDA regulations kick in when there is a use of an FDA test article. So if the study involves drugs, devices, or biologics, that's where the FDA regulations would come into play, our regulations come into play where the funding or support is there.

Which is a good segue to exactly how our regulations do come into play. Now, there are several prerequisites to determining whether or not you actually have to follow the regulations in 45 CFR part 46. These are some threshold determinations that you need to make to figure out how and in what way the activities that you're conducting may or may not be covered by the regulations. The first is research involving human subjects conducted or supported by HHS that is not otherwise exempt. Or nonexempt human subjects research that is covered by an assurance of compliance, and I'll take each one of those and spend a little time with each of those.

With respect to the conduct or support by HHS, you will notice that there's sort of a cute little cartoon of money. I want to note that support encompasses more than just money. So for example, if there's a study for which NIH has supplied in kind support such as computers or microscopes or lab equipment, that support would also be considered HHS support. So I just wanted to note that. With respect to applicability derived from your assurance of compliance, as you know, and I'll talk about this a little bit more later, all of you, I'm guessing, if you've signed up for this, but perhaps not, have or are thinking about getting a federal wide assurance of compliance. Within that federalwide assurance of compliance, your institutional official has had to make an election as to which research you want your assurance to apply. So it can either

apply to all of your HHS or federally sponsored research, because that is a requirement under the assurance, or you could have you can elect to have the assurance apply to your entire portfolio of human subjects' research regardless of source of support, and I'll get into that a little bit more later. Now, continuing into determining applicability, there are four questions that we need to ask, and it helps to ask them in this order: The first, does the activity involve research?

Does it involve human subjects?

Is the human subjects' research exempt?

So you do have research, you do have people involved, but is it possible that it's exempt?

And last but not least, is your institution engaged?

So again, you might have research, you might have people involved, it may not be exempt, but there may be an overarching activity being conducted which is nonexempt human research, but your institution's particular little piece of it may not constitute engagement.

And we have a human subjects decisions chart available on our website that I would like you to take a look at, that helps you walk through those determinations and I will somewhat quickly in the interest of time move through each of these. Research is defined in the regulations as a systematic investigation designed to develop or contribute to generalizable knowledge, and it's important to get underneath those words and underneath the labels that we might have attached to a certain activity such as program evaluation or quality assurance. It's important to go beneath the labels and figure out exactly what activity is being conducted. Now, happily, on our website, I would like to point out that we have some frequently asked questions pertaining to quality assurance activities, and what what constitutes quality assurance activities that may be research and what may not be research, and I would recommend to you that you take a look at those, because again, even though those are in the context of QA activities, some of the information really transcends those activities and can be applied to other things that you may be doing at your institution.

The next important definition, threshold definition is does the research involve a human subject? Under the American regulations, a subject has to be a living individual about whom an investigator conducting research obtains data through intervention or interaction with the individual, or identifiable private information. Now, the good news is with respect to data through intervention or interaction, hopefully we all know when we're poking or prodding a person or speaking with them, or giving them medicine, or hooking up an IV, so that one hopefully is fairly straightforward. The more tricky one is the question of whether or not we are using identifiable private information, and I would here, too, recommend that you take a look at guidance we have available on our website that relates to the use of data and tissue, and in that guidance there are examples and frameworks that describe situations where what you're doing, if

proper safeguards are in place, what you're doing may not actually constitute human subjects' research. Maybe research, but you may not be involving a human subject.

Now, next, okay, you have a you have research, you want research, you want it to gain some generalizable knowledge for the world and you're involving living people, the next question is, well, is it possible that what I'm doing is exempt?

And time does not allow us to discuss these categories in any kind of detail so I'll just make a few quick observations about these exemption categories and how they relate to the subparts with the added protections. Good news is, if you're conducting research with pregnant women under subpart B, research with pregnant women can avail itself of these categories of exempt research. The exemptions do not apply to research involving prisoners under subpart C, so if you're conducting research involving prisoners under subpart C, that would have to go before an IRB, and follow all of the additional protections in subpart C. In the area of research involving children, under subpart D, most of these exemptions do apply except the second category, educational tests and so forth is circumscribed when it comes to children. Children can be involved in research involving educational tests under category two, and that can be considered exempt. Research involving children and surveys and interviews is not exempt. And the third prong is limited. So when you're involving children in research, involving observation of public behavior, that's okay, but only okay with children when the investigator does not participate in the activities being observed. So that's the exemptions.

Now, the last question that you ask is "is your institution engaged?" So again, the overarching activity may be human subjects research which is not exempt, but then the question is "is your institution engaged?" And institutions are generally considered to be engaged when their employees or agents obtain for research purposes data about the subjects, or identifiable private information, or -- this is also important for engagement -- if your institution is obtaining informed consent and involved in an informed consent interaction with subjects, then you and your institution are considered to be engaged. Again, here we have some excellent guidance available on our website that details examples of when engagement exists and when an institution is not engaged and I invite you to take a look at that as well.

Now, finally, if you have human subjects research that is not exempt, and in which you are engaged, then the full panoply of regulatory protections for research subjects comes to bear. And the regulations are basically in three sections: The first deals with institutional assurances. The second, IRB membership and review. And the third, informed consent. And I will move through each one of those in fairly hopefully efficient and short order. An institutional assurance is required when your institution is engaged in nonexempt human subjects' research. It's really documentation of your institution's commitment to uphold the human subject's protections regulations, and it is one method of compliance oversight. It's how we establish our relationship with you. And at the present time, the federalwide assurance or FWA is the only assurance option. For those of us who have been around this business for a long time, you may recall the



multiple project assurance, single project assurance, different alphabet super mélange of assurances, now there is only one kind. And it is within the four corners of the FWA that you have to designate a registered IRB as being responsible for the review of your research portfolio. I want to note it's in the first section of regulations, pertaining to institutional assurances, this section of regulations also describes the general overarching obligations of the institution, FWA holding institution in terms of human subjects protections. So if you haven't taken a close look at the regulations here, you might like to.

The next major portion of the regulations talks about IRB membership and IRB review. The membership requirements are fairly straightforward. You have to have at least five members, the regulations talk in terms of you having appropriate experience and expertise represented on your IRB to review the research that will be coming before it. The regulations talk in terms of diversity of members, in terms of gender, and ethnic background. And the regulations explicitly state different categories of membership that must be on your IRB. So you must have at least one scientist, one nonscientist, and one nonaffiliated member. And I'll talk about each one of those in turn for a few moments. In a few moments. I also would like to note that if you are conducting research involving prisoners, you need to have a prisoner representative on the IRB as a member, and we make no distinction between voting members, nonvoting members, the regulations talk about members, and that's what we mean is a member with all the full rights of being a member. And that person must represent the interest of prisoners. So former prisoners, perhaps a prison chaplain. Someone who would view the research from the perspective of a prisoner. Now, turning back to the traditional categories of membership, you need minimum one scientist, one nonscientist. Interestingly, although quite reasonably when you think of the history of the regulations, the regulations require that in order to meet quorum, the nonscientist must be present. So no convened IRB meeting can take place in the absence of the nonscientist. And in determining who fits what role, you want to look at the training, background and occupation of these individuals. And I would note that the regulatory language related to this talks about the primary concerns of the person, so the primary concerns of the person are in scientific or nonscientific areas.

So a registered nurse, by and large we would consider that person to be a scientist. A middle school English teacher. If a middle school English teacher's primary concerns were as a middle school English teacher, we would say that this person is probably a nonscientist. A member of the clergy, also a nonscientist. The biggest thing is that institutions make reasonable and rational decisions in this regard, and I would note also that it is perfectly acceptable from OHRP's perspective for institutions to take a two fer, so for example, it's perfectly possible that your nonscientist and your nonaffiliated could be the same human being. So a middle school English teacher who has no other affiliation with the institution, a member of your community who is a clergy member, could conceivably be your nonscientist and your nonaffiliated. One can certainly maintain their nonaffiliated membership even with certain associations with the institution. So for example, a patient, a subject, a former subject, or needless to say, their service

on the IRB, if that's the only association with the institution, they can still be considered nonaffiliated.

One of the things we like to stress from OHRP, and we think it's important, and useful for people to hear it from us, is that we encourage the use of the flexibility and efficiency inherent within the regulations, that's why we have the lady doing the yoga and the new fangled light bulb. So the regulations themselves talk about the use of expert consultants as part of the IRB review process, so the use of an expert consultant is perfectly appropriate. He or she cannot is not a member of the IRB and does not vote, but again, just by way of example, if an institution has never done research involving children before, and a really interesting project comes along, the institution can have a pediatrician help review the materials and provide their viewpoint on whether or not it's appropriate for children. Now, similarly, but distinctly, OHRP and our predecessor, OPRR, have long recognized the use of alternate IRB members. So in the first example, the expert consultant helps the IRB, not a member, is in the regulations; alternate members, not in the regulations, but, yes, we consider these people, these people are indeed in fact members. Alternate members can be listed on your IRB roster as people with appropriate expertise who can substitute for any other member of the IRB for whom it makes sense and would be appropriate in terms of background and expertise, as it says here they can substitute for an entire meeting or any portion of the meeting. So if you have an alternate sitting on the back bench and the primary member for whom they substitute has to leave for ten minutes or the rest of the meeting the alternate can step in for as much or as little as necessary as long as that alternate is appropriate, and I would also add that it's perfectly permissible for an alternate to be considered an alternate for one or more permanent primary members of the IRB.

Moving along now in terms of IRB membership, I just want to note that interestingly perhaps for some of you, the only place in our regulations where conflict of interest is mentioned is in terms of IRB member conflict, and the regulations state that any IRB member who is conflicted may provide information requested by the IRB but must be recused from the review and the vote, and importantly, conflicted members do not contribute to the quorum. So just as in the situation where an IRB may invite any investigator with a proposal to come before the IRB and answer questions about the proposal and then leave for the deliberations and the vote, so too can an IRB member who has a proposal before the IRB stay to answer questions about his or her proposal. However, when it gets to the part of the deliberations, they should leave, and they may not be part of the vote. And again, it's important to note that conflicted members do not contribute to the quorum so it's important for you to make sure that you will have the appropriate numbers in the room that day to maintain quorum even if the conflicted member leaves.

The next portion of the regulations talks about IRB review, and in terms of the types of IRB review, the substance and the process of review, and this goes to the process of review. The regulations pretty much default to convened meetings where the quorum requirements are met; however, the regulations also describe situations where expedited review is perfectly appropriate and OHRP encourages institutions to use expedited review in the appropriate circumstances.

This is a situation that if we were actually in a room and I was seeing you face to face, I would ask you to show me your hands to see how many of you in your institution do expedited review, and I would expect and hope that it would be a lot of you, for expedited review, as I'm sure you may know, it's allowed when there are minor changes to approved research, whether or not that original review was expedited or convened and also where there is research that is no greater than minimal risk and it's on the list, the quote unquote list that we have available that's in the federal register and that is on our website that lists types of research for which expedited review is permissible. And again, if you're not familiar with what's on that list, I would invite you to take a look at that.

IRB review is described in the regulations, again in terms of the content and process. It is required prior to initiating human subjects' research, again, nonexempt human subjects' research. It is required in the context of continuing review, and the regulations speak about continuing review and that in determining the frequency of continuing review, it must be appropriate to the degree of risk, but not less than once per year. Many institutions default to an annual review, which in many circumstances is appropriate, but there may be situations where an IRB would like to see research come back before it in less than 365 days. IRB review is also required prior to initiating any changes to approved research. That is to be distinguished from the situation where change needs to be made immediately to prevent an immediate hazard to subjects, but if there's going to be any type of ongoing change to approved research, it needs to come before the IRB, and of course the IRB needs to make what we call the 111 findings and it must have in front of it the sufficient information to make those findings, the 111 findings that I'm going to turn to in a moment, as well as the findings required under any of the relevant sub parts. So very quickly here, the findings under 111, and I say quickly only because we've discussed these in other contexts already. The 111 findings very much hearken to the Nuremberg Code, the Declaration of Helsinki and the Belmont Report. The IRBs have to find that the risks are minimized. That the risk benefit ratio is reasonable, that subject selection is equitable, these all ring of Belmont and Nuremberg and of course that informed consent is obtained, and documented appropriately, unless it's waived. Other findings that the IRB has to make is that, where appropriate, data is monitored this would come up in the clinical trial context, the privacy and confidentiality, what provisions are made for it, how will thing be protected as well as safeguards for vulnerable subjects if there may be situations where there are vulnerable subjects who are not those described in the subparts, but maybe economically disadvantaged or have other status situations which would render them vulnerable. It's important to note that in the context of research involving pregnant women, prisoners or children, there are additional findings that need to be made. Unlike research outside of the subparts, research within the subparts, there are categories of permissible research, and the IRB has to affirmatively find that the research being proposed fits into one of those categories. Similarly, where research involves children, informed consent is not the notion at work so much as assent of children and permission of their parents. Substantively, I'll get to this in a moment, the substance goes back to informed consent. There are other considerations in the subparts that go to the composition of

the IRB, secretarial panel process for research that is not otherwise approvable by the IRB, use of expert consultants and so forth, and I know I'm running up a little bit against time here, so I will keep this moving, we have a poll, and I think we'll do the poll, but I'm going to do it real quick. I'll see which see who is still paying attention, and this is actually a little bit of a trick question and we'll do it fast: Which of the following must be considered in determining the frequency of IRB review?

And I see that you guys are doing very well on this also. You can see the poll in progress. And you're sort of moving along here. Let's see what we've got here. All right. There's lots of you still participating and that's good. 72%. I think if we hit close this baby out at 75%. Okay. This looks pretty consistent here. You said 72% of you said that it is which of the following must be considered in determining the frequency of IRB review, and three quarters of you got the correct answer, which is the degree of risk to the subjects. That is the regulatory requirement in terms of determining continuing review. Having said that, 26% of you, more than a quarter of you said all of the above, and I would say that while that is not exactly the regulatory language, it's certainly not inappropriate for an IRB to want to take a look at all these different things that are involved in a study to determine when and how the IRB wants to take a look at it, so I'm going to hide this one now, and keep moving along here. Let me make sure what you're getting is what I want you to get. Okay. Okay.

So now, last but certainly not least, is informed consent. Informed consent really is the first among equals in this whole in this whole business of human subjects research and protections, and the key principles of the informed consent process, really the atmospherics of informed consent involve full disclosure of the nature of the research and the participation, adequate comprehension on the parts of subjects or their legally authorized representatives and -- here again we see Nuremberg loud and clear -- the subject's voluntary choice to participate, and this slide shows the basic elements of informed consent, that informed consent has to say that what we're doing here is research, or an experiment, or a study. You would be surprised that we still see informed consent documents that just launch into what's going to happen without actually telling the person, informing them that they're being asked to participate in research; risks and benefits should be described as closely as possible to ordinary, normal events that might occur in a person's life so that they can understand it in that context. Alternatives where they exist. Confidentiality. How it will be upheld, and instances where it may be breached in the sense that they would understand it. So, for example, if information would be released to a governmental agency, that should be stated in the informed consent. Compensation for injury, if it exists or if it doesn't exist. Whom to contact in three different situations. One, with questions about the research, if a person believes that he or she has been injured in the context of research or if a person has questions about their rights and welfare as a research subject. Here we would suggest that these people be different people so that for example, if the person has questions about their rights and welfare as a subject, perhaps the IRB. Or an institutional ombudsperson, somebody who is not closely tied to the research project itself. The IRB can insist on additional elements

when appropriate. I skipped over that last one, shame on me for doing that, because the last one is really Nuremberg loud and clear, the right to refuse or withdraw, and/or withdraw from research at any time without any penalty or loss of benefits. It has to be made crystal clear to subjects that their participation is voluntary and that they have an option to decline any procedure or withdraw whenever appropriate, whenever they wish to.

Again, the IRB can insist upon additional elements when appropriate such as the consequences of withdrawal, so note, a person can leave whenever they want, but if a person, let's say, is in a study of an IRB, of a high blood pressure medication, it's perfectly appropriate to put in that informed consent, you have high blood pressure, if you withdraw from this study and stop taking high blood pressure medication that could be dangerous for you. So, there are additional elements listed in the regulations that the IRB can insist upon.

The regulations also provide for a waiver or alteration of informed consent under certain circumstances, 116 (c), we rarely see, it has to do with public benefit programs. One sixteen (d) is really the classic waiver or alteration which I'll get to in a moment. Four-oh-eight describes waiver or alteration of assent/permission in children's research and 101 (i) is informed consent in a situation where the research study itself contemplates research in an emergency setting where it would not be possible for somebody to give consent. The the slides are a little behind here. That's interesting, but I hope you're getting them, whoops.

Informed consent, the IRB must find and document, so this has to be documented somewhere that the research itself poses no greater than minimal risk, that the waiver will not adversely affect the rights and welfare of the subjects, that the research could not practicably be carried out with the waiver, and when appropriate subjects will be debriefed following participation. It's this third prong I want to focus on a little bit to say that OHRP has always taken the position that mere inconvenience in terms of getting informed consent typically will not cut it. It really without the waiver the research project itself would be very difficult to begin or carry out. I just want to make a quick note because I see that I'm running out of time here, that the regulations that we enforce include separate requirements for documentation of informed consent, so it's important to note that the substantive requirements for informed consent live at 116. But that the requirements for how that informed consent has to be documented live at 117. And the regulations talk about the long form document, which is the one with which I'm sure most of us are familiar, which would embody all of the elements that the IRB would insist upon. The short form includes an oral presentation using a summary that the IRB has approved. The short form also involves the use of a witness, and it, again, the use of the short form is perfectly acceptable and encouraged by OHRP. We recognize that use of the short form sometimes involves a little more up front work, and work in terms of the informed consent interactions and so sometimes institutions are a little reluctant to use that short form, but there's no regulatory prohibition from using the short form and in fact, again, I would like to stress that we encourage its use where appropriate. Written documentation can also be waived, and I see that I'm going over here just a little bit. I hope you're still with me. And I apologize for going over, but I just have a few more

slides. The written documentation again it's a separate regulatory section, and it's important for you to note that there may be instances where the IRB may still insist upon informed consent, but can perfectly reasonably and acceptably waive the documentation requirement, and it can be waived where the consent form is the only record linking the subject to the research, and that the principal risk of the research is from the breach of confidentiality. So just something for you to consider. Also, documentation can be waived where it's minimal risk research, and the research procedures themselves do not include anything like informed consent if done outside the research context. So again, by way of example, if the research procedure itself is talking to somebody, then that typically does not involve written informed consent in the outside world. So just to sort of close out this notion of informed consent, both the document and the substantive informed consent, it is not to be viewed as a single event or just a form to be signed, rather it should be viewed as an ongoing process that takes place between a researcher and the prospective subject. And it's a good idea for your institution to have policies and procedures in place that really go to how the IRB expects this to be fulfilled. Now I'm going to take my last poll, and I'll see if you guys are still hanging on here. Where is my where are my polls?

Here they are. Just went away. Poll closed. New poll. Are you still with me?

I hope you are. Okay. Going to launch this last baby here. Okay. The Department of Health and Human Services regulations at 45 CFR part 46 include requirements regarding institutional assurances and institutional responsibilities. Institutional review board member and review. Informed consent. Or, all of the above. Let's see how you're doing here. And this is great. I appreciate your continued attention, especially since I do recognize that I'm going over a little bit here. Okay. I'm going to close this out. 80% of you have voted and 96% of you have said all of the above, and those of you who said all of the above oh, I have to share it. That's why I have my wizards here behind the camera. It's not a camera. Behind the speaker. Okay. What are you seeing now?

Let me see, audience view. Okay. So you can see that the vast, vast, vast majority said all of the above, and you are correct. So I'm going to get rid of this poll here, move along to my final slide, the key points. I hope you've gotten them. Belmont Report. Read it. Love it. Who regulates human subjects research?

Well, we of course at OHRP do, but there are lots of different players and you play a very large role in it. How and when do the HHS regulations apply, and the basic protections afforded by the HHS regulations. I hope you've gotten a sense of that today. I want to give one final slide here with contact information. These are ways to reach us. I want to ask your indulgence with regard to our website. It is not the easiest website in the world to navigate, but if you indulge the website and give it four or five or even six more clicks than you think you should have to do, you will probably find lots of great information. If in the words of Bono, you still haven't found what you're looking for, please avail yourself of these other ways to contact us. We are happy and proud to say that we still have a live human being answering our phone and trying to help you or

get you to another live human being who can answer your question. Finally, finally, finally, and I know many of you probably have to go, I want to give a quick shout out for other events we have coming up. On June 22nd we are cosponsoring with the University of Pittsburgh, one of our Research Community Forums, on international research, called “Building Bridges: Research Around the World,” we’re going to have a focus, as I say, on international research. Also, we will be holding one of our quality assessment workshops on July 17th in Seattle, Washington, and that course is a very basic course for those who have to implement the human subjects protections and work as IRB professionals every single day, if you would like information about those conferences, please contact me or any of these contacts on this slide here, and again thank you, thank you very much for your attendance, and we look forward to hearing from you soon. Thank you. Goodbye.