Adrian Hernandez:

Hey, this is Adrian Hernandez and welcome to the NIH Collaboratory Grand Rounds podcast. We're here to give you some extra time with our speaker and ask some of the tough and interesting questions you want to hear most. If you haven't already, we hope you'll watch the full Grand Rounds webinar recording to learn more. All of our grand rounds content can be found @rethinkingclinicaltrials.org. Thanks for joining.

Hi, I'm Adrian Hernandez, one of the moderators for Collaboratory Grand Rounds, and today we're here with Stephanie Moran and Pearl O'Rourke who will be continuing the discussion that we had recently in Grand Rounds on an important topic for all of us in clinical research. And that is around waiver or alteration of informed consent for minimal risk clinical investigations, discussing what has been going on with FDA regulation development and the research landscape. So Stephanie and Pearl, really thank you for sharing your insights and experience here.

Stephanie Moran:

Yeah, really glad to be here, Adrian. Thanks.

Pearl O'Rourke:

Thank you, Adrian.

Adrian Hernandez:

How did we get to now? There's a long history here. I don't need the day by day, but just briefly, how do we get to now and why are we talking about waivers and alterations of consent? I thought consent was just consent.

Stephanie Moran:

I can start us out and Pearl can correct me wherever I go awry. One of the exciting things for now is that the FDA just released a final rule about permitting waivers or alterations under certain conditions. And this is something that we've had a long history with under the common rule, but prior to 2016, the FDA actually didn't permit waivers or alterations of consent except for a very narrow class of research studies related to emergency research. So this is an important step forward to expand the potential range of studies that might be able to be conducted.

Pearl O'Rourke:

Correct, and I think to emphasize one of the points that Stephanie made is that a waiver of informed consent has been allowed under the common rule. So in non-FDA regulated research, a waiver of consent, or an alteration of consent, was always a possibility, again, if the research met specific criteria.

Stephanie Moran:

What changed in 2016 is the 21st Century Cures Act. One of the provisions in there required the FDA to move forward with making this additional expansion to permit waivers or alterations of consent for FDA-regulated research and, to the extent possible, to harmonize with common rule. So since then, the FDA has essentially exercised its discretion to say they're not going to object to institutions permitting a waiver or alteration of informed consent, but we now finally have the final rule that sets out the criteria by which studies can permissively be conducted with waiver or alteration.

Adrian Hernandez:

Now, one thing you both brought up here is that this is from the FDA, and there's certainly other parties in the federal government that oversee this space. Can you talk a little bit about that and how this intersects there?

Pearl O'Rourke:

OHRP works under the common rule, which has numerous other federal agencies, and with the common rule, the options are full informed consent and the common rule lists the mandated criteria that must be included and then also some other elements to be considered. It also allows for an alteration or a waiver of consent. And the requirements for both of these are identical, and it must be no more than minimal risk research. Again, there are other criteria, but I would like to point out that an alteration of informed consent just means that one or more of the required elements are not in the consent itself. So in an alteration, there still is consent, but it just isn't the full consent. Whereas with a waiver, there is no consent. Now with alterations, that's usually been used for deception research and I don't think it's really been used broadly for other types of research.

So, under those regulations, really waiver is the way that usually people try to go. And I think as Stephanie also pointed out, the common rule also does have the emergency research possibility, EFIC, which is also a very, has to be a life-threatening situation. There are no other alternatives for the therapy, and it's a really very tiny piece of the pie. So if you think about it, it's full consent, possibly an alteration of consent, which would be, again, consent but with some of the criteria not fulfilled there, or a waiver of consent. And it's really almost an on off switch of whether consent or not consent.

Adrian Hernandez:

Wow, okay. Not necessarily a continuous spectrum here. It's, as you noted, on and off, or a couple of categories. So it does seem like this is a really important step for the FDA and maybe Stephanie, can you just describe a little more about the situations or rationale for this? I'm sure there are ethical considerations here and there's balances around that. So Stephanie, maybe you can help us understand that.

Stephanie Moran:

Well, I think one rationale is going to be one that sounds bureaucratic, but I think it's really important ethically, is this move towards harmonization. So prior to this new rule, you had institutions and investigators having to look at two different sets of rules, two different sets of guidances. One which was operating from the common rule and one which was operating through the FDA. The effort to harmonize means that there's one standard set of rules and one guidance by which everyone can have the same criteria. And that does help to streamline, and streamline in an important way. It helps IRBs to be focusing on the types of things we really care about and spending less time box checking or paying attention to the rules. We want people to be focused where the attention is most appropriate. As far as the broader ethical considerations for waivers and alterations of consent, there are criteria by which to assess the appropriateness, and part of what we are trying to do is balance the ability to conduct socially valuable research.

So, a lot of the motivation for the Collaboratory is we know that there are many questions that are important to everyday clinical practice, but for which we don't have clear guidance about evidence. And for some of these types of studies, it would be impractical to be able to get consent from every individual participating. So one of the classic examples would be a cluster randomized trial of two different strategies for infection prevention. It would be really hard to go up and ask every individual

patient who might be coming through a hospital, "Is it okay if we randomize you between this infection prevention mechanism or this one?" Patients don't generally have a choice about those things anyway. So what we're trying to do is be able to conduct the socially valuable research that matters, but in a way that also protects the rights and welfare of individuals and finding the circumstances in which we are not unduly intruding upon valued rights. So we're not entering upon the circumstances in which that patient choice is meaningful, while also being able to conduct research that's important to improve from the conduct of future clinical practice moving forward.

Adrian Hernandez:

Okay, good. So it sounds like there's been a lot of work here that underpins this. Tell us about what's the next steps here from the FDA, where do things go? So it's a draft guidance, but what's next?

Stephanie Moran:

So we actually have the final rule that's been released saying that waivers or alterations of consent will be permitted and the next step is going to be to develop guidance. And so FDA guidance is kind of, investigators should do it, but it's not a must. It's not a regulatory requirement, but it's really going to be putting forward the FDA's thinking about, they're saying that waivers or alterations would be permitted, but then starting to get more granular about for what types of trials, for what types of investigations. So the next step is going to be work from the FDA and potentially also harmonized along with OHRP to try to give investigators and IRBs some more help with the types of examples or the types of considerations for the studies for which using a waiver or alteration would be appropriate to really help us strike that balance of being able to promote socially valuable research that can advance important knowledge, but also continues to appropriately protect the individuals who are included in that research.

Pearl O'Rourke:

The focus right now is on trying to define minimal risk. Waivers are only allowed on no more than minimal risk research, and there's a paucity of guidance, shall we say, on how to classify what is minimal risk research. There are some people who think only observational research is minimal risk and that any intervention at all should be put up to more than minimal risk. That is not universally accepted. So I think what the FDA is trying to do, which would be incredibly helpful I think to investigators and to IRBs, is to really come out with some concrete examples of how to go through the framework of identifying what is no more than minimal risk and what is more than minimal risk.

Stephanie Moran:

And if I can build off that, I think that piece is really important. And another piece that would be a great opportunity for this guidance is to really move beyond viewing consent as an on-off switch. As Pearl identified previously, historically people have tended to think it's a waiver so we don't ask people permission, we tell them nothing, or we do the full lengthy informed consent process. And the regulations under the common rule, it's a waiver or alteration. There's a lot of actual flexibility in how we design consent, and part of the opportunity for this guidance, hopefully, would be to help do what could be considered rightsizing consent really to the circumstances. So hopefully also providing some guidance about if you're going to waiver or alter consent, the circumstances under which an alteration might be more appropriate. So maybe you don't have to go through the 27-page informed consent document and meet all of the elements of informed consent, but still could look for opportunities, for example, to notify people that the research is underway and potentially to offer them an opportunity orally to decline.

Adrian Hernandez:

I love the explanation you all have given in terms of making sure to emphasize that this is an opportunity to really address the alteration of consent or fit-for-purpose consent. There are often scenarios we talk about where we literally can offer a heart transplant to a patient that is one page front and back that includes a risk of death, stroke, and infections, and all sorts of other things that are unknown. Yet, like, the same person may be offered a research study that would entail something even over the counter, like a vitamin, and that may be 20 pages.

Stephanie Moran:

Three pages of which you're talking about confidentiality. Yeah.

Adrian Hernandez:

That's right. So I guess I want to hear, Pearl, from your perspective, you have a long history overseeing these efforts within institutions. Does this help the IRBs around the nation? Will this help the research community that is responsible on the front lines for protecting participants?

Pearl O'Rourke:

I would say yes. IRBs have had a long history of considering non-FDA regulated research and seeing whether or not a waiver of consent is appropriate. I do not have data to support this, but my impression from informal discussions with a number of IRB chairs is that alterations have really not been used other than for deception research. The other uses are few and far between. So I am hopeful, as Stephanie pointed out, that this whole discussion of the FDA now coming into the waiver fold could really energize a discussion about alterations. I do think there could be a lot of flexibility in there and really getting to the direction of the rightsizing consent. I think that this will be a very helpful thing for IRBs. The other issue is the fact that IRBs have always had to deal with both FDA regulations as well as the common rule. Now, most of the regulations are virtually identical, but the waiver issue really is one of the more impressive disharmonies up to this point. So I think getting all of that under one roof would be fabulous.

Adrian Hernandez:

What's next? How can the Collaboratory community and others support this effort?

Stephanie Moran:

I have one request and hope for this community is once the draft guidance comes out from the FDA, typically public comments are invited and public comments are really important to help shape up what those final guidance documents look like. We certainly saw for the development of the final rule, the FDA has a really lengthy discussion about the ways in which it considered the comments that were offered to the public and adjusted its rule in relation to those comments. And similarly, given, particularly, this question about what types of randomized trials would be acceptable, when is it appropriate to consider a randomized trial minimal risk, as Pearl identified that's an area of continued controversy. Having the concrete examples from the Collaboratory community to really help ground that discussion about the types of research that are not considered appropriate for waiving or altering informed consent would be hugely helpful to make sure that the guidance is really grounded in real life and is responsive to the real world needs of the clinical community.

Pearl O'Rourke:

I think Stephanie is brilliant and has said it fabulously, but I would just add that you cannot overestimate the importance of public comments. And so I truly think if this issue is important to you, and it should be a thing for anyone doing pragmatic trials, this is something you need to keep on your radar screen, and be it a group comment or individual comments. But I do think once the guidance does come out for comment, it's really in everyone's best interest to submit something. Even if you think it's perfect, say that.

Adrian Hernandez:

Well, I'm sure there are many out there who can help shape this guidance because it really does have importance and it has importance and impact for years to come. So Pearl, one of the things that people often wrestle with is that these discussions often are around the theoretical, but there actually has to be some examples of the applied, and it seems like the Vanderbilt Group has done some great work in terms of applications. Can you talk a little more about that and what they've done there to show this can be real?

Pearl O'Rourke:

Oh, absolutely. I think the Vanderbilt Group has done a fabulous job and I encourage everyone to listen to the whole grand rounds. I think a study that they put together over a very fast period of time, actually, in order to present it at the grand rounds, they looked over one year period at research that met the NIH definition of clinical trial, and they looked at JAMA and the New England Journal of Medicine and they looked at about 250 studies that met those criteria. And of those, 217 did get informed consent. 33 or 13% were done without informed consent.

So say, okay, so only 13%. Well it was 13% of 250, which these are number. But I think another thing that was very impressive is they looked at the number of participants in these studies. And if you looked at those for which informed consent was obtained, there were 390,000 participants. For those where there was no informed consent there were 3,036,000 participants. So from the trials they looked at, and again, it was only from two journals that the not getting consent prior to the research was more common in trials that had more than 20,000 participants, which again, for pragmatic trials, that is often the case. Also, the issue is very time sensitive, think about COVID situations, and where the drugs or the intervention being looked at has already had approval at some level. But I do think having just those numbers in front of you does help to, I think, frame the discussion in real world.

Adrian Hernandez:

Hopefully we can see more going forward. Thanks everyone for joining this podcast, and please join our next podcast as we continue to highlight important changes in the research world. Special thanks to Stephanie and Pearl for doing this with us. Thanks for joining today's in NIH Collaboratory Grand Rounds podcast. Let us know what you think by rating this interview on our website, and we hope to see you again on our next Grand Rounds, Fridays at 1:00 PM Eastern Time.