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 them 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 at rethinkingclinicaltrials.org. Thanks for joining.

Stephanie Morain:

Hello, I'm Stephanie Morain, and I'm the co-chair of the Ethics Series for the NIH Collaboratory Grand Rounds. And today, we're here with Emily Largent of the University of Pennsylvania, who will be reflecting on the topic of her recent Grand Rounds "Ethical Considerations When Vulnerable Populations are Subjects in Pragmatic Trials". Emily, thanks so much for joining us.

Emily Largent:

Thanks for having me.

Stephanie Morain:

So, I know we had a very vibrant discussion for your Grand Rounds session, but there are a couple pieces I'm so glad we have the chance to pick up on today. So in your Grand Rounds, you noted that the guidelines and regulations governing research with human subjects often focus on groups as being vulnerable, for example, the federal regulations known as the 'Common Rule' has special provisions for pregnant persons, for children, for prisoners. But you said that this categorical group-based approach risks both under and overprotecting individuals. And I'd love if you could tell us a bit more about what you mean by that. How can something both under and overprotect?

Emily Largent:

Sure. So when we think about a group of people who might be vulnerable, so we can take pregnant persons as a good example, I think it's quite illustrative, we have to realize that there's heterogeneity within that group, right? Not all pregnant persons are going to be equally vulnerable. And that might be because they have, say, intersecting sources of vulnerability. So we might imagine, for example, that we are worried about pregnant people who are also trans, or pregnant people who are low income, or pregnant people who are Black. And we know that Black women, for example, have much higher maternal mortality rates.

And so, there can be structural reasons or other reasons why we think that some pregnant persons are much more vulnerable than other ones. If we are just thinking about, say, the average pregnant person and offer protections to them, I think we might worry that there are some groups where you've just underprotected them. There might be more things that we should be paying attention to or protections we're offering them. The flip side of this is that if we look at certain groups and we just automatically assume like, "Oh, you're pregnant, you're vulnerable," then there could be ways in which we are overprotecting.

In some cases, I think, you serve on an IRB, I'm sure you've seen studies come through where the investigators say, "No, we're going to have pregnancy as an exclusion criterion." That reflects, I think, concerns or a skittishness around the vulnerability of those individuals. And yet at the same time, once we systematically exclude people like that, overprotecting them, we aren't getting important evidence that we might need to figure out how to guide the care of pregnant persons. Or maybe the pregnancy's

not even relevant to the research and so they're losing out on an opportunity to participate in research, to contribute to social value, and maybe even get some direct medical benefit.

Stephanie Morain:

Certainly glad you brought up that issue, and I can see the corollary to the pregnancy case. I mean, I think then that's interesting because we know in the context of pregnancy, this knee jerk reaction to potentially default to excluding pregnant women means we don't have the evidence base we need when individuals are pregnant and need clinical treatment, we then don't have the evidence to guide that decision-making. Have you seen a similar pattern in Alzheimer's or are we getting ahead of this trend and we've actually learned something from pregnancy?

Emily Largent:

Well, so I think one of the interesting things about Alzheimer's disease research, where I spend a lot of my time, is that persons with cognitive impairment are not listed as one of those vulnerable populations in the federal regulations. And we recognize, I think, due to a variety of factors that people who have a diagnosis of Alzheimer's disease, and particularly a diagnosis of dementia caused by Alzheimer's disease are vulnerable, right? They can have impairments in cognition that affect their decision-making capacity, they're highly dependent, sometimes, on others to perform even basic activities of daily living, so you need a care partner to help you with feeding, bathing, dressing, toileting.

And many, though far from all, individuals who have a diagnosis of dementia can be in a long-term care facility, right? And this fact of institutionalization can really exacerbate vulnerability. And so, while those folks are clearly vulnerable, they don't have the regulatory protections that the groups you mentioned at the outset do. So this is, I think, highlights again this idea of under protection. So it's not always clear where people need to go to provide adequate protections to them so people can kind of figure it out as they move along.

But there has really been a recognition that there needs to be research because this is a tremendously pressing public health problem, right? Six million older adults have dementia right now, millions more people are caregivers. We don't have a great evidence base to offer them interventions to help improve their quality of life and care. And so, I've been delighted that the NIA has really recognized the need for this research and funded the IMPACT Collaboratory, for example. So, we keep trying to push forward and figure out how we can include this vulnerable population in research.

Stephanie Morain:

Interesting, as you mentioned, I sit on an IRB and recognize Alzheimer's disease or related dementias isn't one of these categories for which we automatically have a process to ensure that there are additional protections in place. And I wonder then if that actually might relate to one of the other themes that you mentioned in your talk was the importance, potential value of consultation and study design. Would love to hear you reflect more. How is it that consultation can support the ethical conduct of pragmatic clinical trials, particularly when there might be a vulnerable population for whom we need to think about additional protections?

Emily Largent:

One of the phrases that comes out of the disability rights community is, "Nothing about us without us," and there's a sense in which you really need to have voices at the table from the community that you're interested in engaging and working with. It would be overly paternalistic to assume that we could, say,

as somebody who doesn't have dementia, figure out what protections people need. So, talking to people who are affected with the condition of interest, maybe who are living in the setting where you're planning on conducting the study, so people who are in long-term care facilities or their care partners, who even in a facility, family caregivers play a hugely important role meeting basic needs that people have. You know, they play important roles in feeding still, dressing, doing laundry, taking care of tasks.

So talking with them about how the study might affect their daily lives can go a long way to revealing vulnerabilities or considerations that the investigatory team might not have come to on their own. So as an example of this, I'm part of the NIA IMPACT Collaboratory, which is focused on pragmatic clinical trials for people with dementia, and part of the Collaboratory is that we have lived experience panel. So we have a variety of individuals who either have a diagnosis of mild cognitive impairment or dementia, we have caregivers for people, and then we also have some individuals who are really trying to embody the position of a loved one who had dementia and passed away. So they're trying to think about what values that person would have expressed.

And I've had the chance in my role as being co-lead of the ethics and regulation core to talk with this lived experience panel about how they think about study design, and particularly, say, waivers of consent. So as part of my discussions with them, we presented a hypothetical trial where a nursing home was interested in figuring out if there were better health outcomes for residents if the nursing assistants had eight-hour shifts or 12-hour shifts. And we described that we would have this study and we really approached it from the standpoint that from an ethics perspective, this was the kind of study that likely could be done with a waiver of consent but there might be some disagreement on how it would go down.

I`t was quite interesting to me how quickly the family caregivers and the persons who had really been or were residing in a long-term care facility pointed out how critical the relationships are between the nursing assistants and the residents. And that for some people with dementia who maybe become anxious or agitated depending on who's providing care, that there might only be one or two nursing assistants that they prefer to, say, have a bath time or who can really work with them to get them dressed. And they felt that changing up that structure could have a much bigger negative impact on the well-being of residents than we had thought about when we were talking about this as a hypothetical study.

Another thing that they pointed to when they talked about all of this is that because they have been in long-term care facilities and talked with the staff members and the nursing assistants, they pointed out that oftentimes, these are often low-wage jobs, often minoritized communities, high rates of immigrants and females. And they pointed out the way these individuals often work multiple jobs to try to take care of their families. And they became incredibly concerned that by changing the staffing structure we would actually be undermining the ability of these women to earn money that they needed to care for their families.

And so, those were just examples, I think, that nicely highlight the ways in which people who have that lived experience can come and really tell you what's happening on the ground and give you insights that might make you design your study differently or approach it, think about engaging different stakeholders. Our lived experience panel also had great insights about how they wanted dementia-friendly disclosure to go. So if there was a waiver and you went ahead and notified people about that, what they thought it needed to look like. Obviously, consultation can serve many roles, but I think one of them is just having the expertise of people who have lived this and seen it up close.

Stephanie Morain:

We've certainly seen this movement towards greater engagement of patients' families as stakeholders in research, but it does strike me, I mean, you've identified several ways in which consultation can support the ethical conduct of research, particularly in the design. Are there some study types or study populations for whom, or about which, consultation would be especially important? Because I recognize that consultation isn't something that we do in all trials, particularly not in all pragmatic trials.

Emily Largent:

There's a sense in which we think about this and I think sometimes, we're inclined to say, "Well, everybody's a patient," right? And it's true, I seek medical care, you seek medical care, we're all a patient. But when we start to think about patients who have, say, a well-defined illness experience or a very particular diagnosis. In the case of Alzheimer's disease, it's one that's highly stigmatized, it's one that has very particular effects on an individual's ability to self determine and act autonomously. The more specific we are able to define our study population, the more I think it benefits to go and have those individuals at the table to consult with them about what a study might look like. It's not just a diagnosis, it might also be the setting. So if you know that you're doing it in a particular community or a particular study site, that can also be grounds for consultation. Did you have other populations in mind?

Stephanie Morain:

No. I mean, in some sense it's that forced recognition of, "Oh, this isn't something that I've necessarily been recommending that all trials do." And I mean, your thoughts make me think that, okay, maybe we can be more comfortable if we're talking about a study of blood pressure medication, that might be something that's so widely relevant for so many individuals. We don't think it is being a particular population that's discreet and certainly not a stigmatized condition, but then might make us think differently about when it might be appropriate for other types of studies in a way that I haven't reflected on previously.

Pivoting a little bit, you've mentioned several times the role of study partners and caregivers, traditionally in human subjects research, when we're thinking about research ethics, we're usually focusing on the ethical considerations for the patients or the individuals that have the disease that we're studying. What relevant ethical considerations are there when we're thinking about involving people who aren't patients with the disease, in the case of Alzheimer's, you know, caregivers or the study partners that are often required for participation?

Emily Largent:

I think the fact that we often are talking about dyads when we're talking about dementia, it's the patient and their care partner, can raise a lot of considerations. And they look different at different phases of research. So we might think, for example, that this becomes a challenge just at the point of trying to identify potential research participants. It turns out that medical records are terrible at giving us information about who somebody's care partner is. So, if you're looking to have an intervention where you contact the care partner or where you are actually providing the intervention to the care partner, a medical record can be a very difficult place to figure out who those people are.

Of course too once you're talking about somebody with dementia, although you might be much more likely to find that person lacks decision-making capacity, it's not necessarily the case that they do. And even people with severe dementia can express values and preferences around research participation. So sometimes when you think about consent, you have to figure out, does the individual have consent? And if they don't, who's the legally authorized representative or surrogate decision maker? So you're bringing that person back in that direction thinking about consent. Sometimes if you're collecting data

from the care partner, you also need to get their consent, so it's the case that you might have multiple people that you're getting consent from.

Certainly, if you think about pragmatic trials, if you're trying to be very pragmatic and get outcomes from, say the medical record or from billing documents, there often won't be any trace of the caregiver and how your intervention has affected their well-being. So, data collection can become less pragmatic as that process goes on. And then, there can always be the concern that when you have somebody who's highly vulnerable, the person with dementia and their care partner, that you need to be mindful of the relationship dynamics there and think about when you are intervening, does the care partner always have that individual's best interest at heart, or how is the relationship happening between the two of them?

For example, I was part of a consult recently, and elder abuse is a huge challenge. And so, how do you develop better mechanisms for screening for elder abuse when it's oftentimes the care partner who might be a perpetrator, and also the person who brings them into the emergency room? And so, there are so many relational dynamics that you really do have to think about when you start designing studies for these very dyadic settings.

Stephanie Morain:

Important considerations. It seems like some of them we would see parallels to maybe the dyad we're more familiar with thinking about, the parent child dyad. Oth`ers seem distinct and I don't know if you had any reflections about the ways in which you think, particularly for pragmatic trials, the lessons we've learned for thinking about this dyad might also apply in other contexts like the pediatric context.

Emily Largent:

Yeah, I actually think there are many useful parallels. I think that in some ways, the world of older adult research and dementia research has a lot to learn from pediatrics. I think that pediatric medical records oftentimes are actually already better. They anticipate that there's a parent or a guardian involved, there's more record keeping there. They've figured out a little bit more about who gets to give consent because it's clear cut that until a child reaches the age of majority, generally speaking, they cannot give consent for research participation on their own. There are analogies, dis-analogies, and certainly opportunities for bidirectional learning.

Stephanie Morain:

Thank you, Emily. Well, I want to be sensitive to your time. I'm so glad we had the opportunity to get a chance to pick up on several of these themes that we had during the Grand Rounds, but get a chance for a deeper dive. I want to thank you for taking the time, and welcome everyone else to please join us for our next podcast as we continue to highlight fascinating and informative changes in the research world.

Adrian Hernandez:

Thanks for joining today's 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.