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| Jill Harrison: | 00:02 | Hi, this is Jill Harrison, Executive Director of the National Institute on Aging Impact Collaboratory at Brown University. Welcome to the Impact Collaboratory Grand Rounds podcast. We're here to give you some extra time with our speakers and ask them the interesting questions that 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 the companion Grand Rounds content can be found at impactcollaboratory.org. Thanks for joining. |
| Speaker 2: | 00:30 | Hello everyone. Welcome to our podcast from the Impact Collaboratory. Today we'll be introducing Jason Karlawish, in ethics, and a physician, a geriatrician, who just gave a wonderful Grand Rounds on the ethics of doing pragmatic trials in the populations of people living with dementia. And Jason, do you want to try to summarize briefly the content and I have a couple of questions from willing and interested participants. |
| Jason Karlawish: | 01:05 | Yeah, so I spoke about the criteria that allow an investigator to put together a human subjects protection plan that waives, or otherwise modifies, the routine human subjects protection of written informed consent from the subject of the research. And I think the overall theme of my talk was to note how intimately interdigitated are the aspects of what makes a embedded pragmatic clinical trial and an EPCT, and how that interdigitates needs to be thought about as one looks through the five requirements that allow an investigator to waive written informed consent. |
| Jason Karlawish: | 01:47 | And so the message was early in the course of designing one's study to be thinking of that human subjects protection and whether it's going to be necessary or not as one's making design decisions around eligibility, recruitment, delivery of the intervention, et cetera. |
| Speaker 2: | 02:06 | Great. So as I recall, there were some really wonderful examples that you use because those are examples from the group of people who were making applications to get pilot projects from our Impact Collaboratory. And one raised a number of questions that were related to the use of a tuneable lighting fixtures in a nursing home, or other institutional care settings, either in the individual residents living with dementia, their individual home, their room, or in the common areas and the hallway. |
| Speaker 2: | 02:50 | And you made an interesting distinction between under what circumstances things could be pragmatic and practical between |

those two settings with regard to this issue of waiver of consent. You want to comment on that?

Jason Karlawish: 03:03 Sure. Yeah, no, in general of course there's nothing, no case, no ethics as an expression, namely, it's all very well to talk about things in conceptual ways and certainly that's one exercise that's very important in philosophy, but once one gets into the matter of ethics you really need a story, a case, because that's what ethics is about. And so we were really pleased as the core to early on in the pilot process, engage with a couple of pilot applicants who had questions about human subjects protections.

Jason Karlawish: 03:37 And you're right, there were two pilots that emerged as presenting very interesting topics. And one of them in particular was this study that proposed to test a method of manipulating the light in a nursing home setting in an effort to see if it would have an effect upon patient's mood and behavior, resident's mood and behavior.

Jason Karlawish: 04:01 And you're right, it became a very interesting study and a number of questions, case study, first of which was who are the human subjects, and we did agree certainly the residents of the nursing home are subjects of this research because identifiable information will be gathered from them, which is, of course, the definition of the human subject. And then we perceived that they're actually two different kinds of subjects. Namely, there were residents who were going to be in common areas getting exposed to light, but also some residents we're going to have light manipulations performed in their rooms as well. And we reasoned that really those who had both light in the common area and light in their rooms manipulated we're facing a different set of research procedures and risks and benefits than those who were only getting light manipulated in their common area. And so we had to walk through the assessment of waivers and modifications of written informed consent separately for each of those subject groups.

Speaker 2: 05:01 What decisions or what advice would you give the investigator with respect to those two conditions?

Jason Karlawish: 05:08 Yeah, well if we focus on the subjects that are having light manipulated in just the common area, we began to reflect that a common area is just that, it's a space that the polis controls, the city, if you will, the city state. In this case, in the nursing home, it's the owners, the directors of the nursing home. And certainly things could be done in that space by those owners

that the residents should have a say in. Arguably in the governance of the nursing home you want to think about how if you're making changes to the facility in that space you would engage the residents and their families and other representatives talk about what you were doing.

Jason Karlawish: 06:00 But we couldn't see that one should have veto power over what happens in that space. That it's a public space and so what goes on in that space is something that just informed consent wouldn't be relevant. And so we felt that just it wasn't a question of whether it could be practicably obtained. It was a question that it just doesn't need to be obtained if the manipulation is only in the public space.

Jason Karlawish: 06:35 And again, I [inaudible 00:06:36] that. You could imagine manipulations done in the public space where, boy, you really ought to have to ask the residents if this was okay. But in principle, the starting position is renovations to the public space are the charge of those who are in charge of taking care of the public space. Whether that's for research purposes or not.

Jason Karlawish: 06:54 But when you start thinking about the residents who have their rooms manipulated, it's a very different space. Yes, a nursing home, people come in and out of your room all the time. You wish they would knock at least and say hi, introduce themselves, and ask permission. And yet it is a room. It is where someone is living, symbolized by things like they have items from their prior residence oftentimes, their furniture and other decorative items. And we felt it was very important from a rights and welfare perspective, which is one of the five criteria that any modification informed consent shouldn't affect rights and welfare. We felt that from a rights and welfare perspective the default ought to be that if I'm going to do things to your room for research purposes, I ought to get your permission first, or at least let you know what's happening.

Jason Karlawish: 07:45 And secondly we couldn't see an argument from a practicality standpoint that it was impractical to get consent from residents in their rooms. You just walk in the room and ask them at the same time you're going to put the bulb in or whatever is the intervention.

Jason Karlawish: 07:58 So it struck us that that one protocol had two very different human subjects protections depending on whether you were a resident in the common area only exposed to the intervention or you were resident in a room and also in a common area.

Speaker 2: 08:11 So that's great. So just to complicate it a little bit further. What if it's a double room as opposed to a single room, or something like that? You just ask both people and if they disagree [crosstalk 00:08:22].

Jason Karlawish: 08:20 Well, if they disagree, you've got a problem. Welcome to the world of the ironically named semi-private room. But yeah, I would think that you would want to ask both, because they're both going to be subject to the intervention.

Speaker 2: 08:41 Okay. So we have one more, is how do you think about the trade offs between the practicality of obtaining consent in a nursing home population that has advanced dementia and equity. Because there are sometimes disparities into who's willing to say yes and also in terms of their racial and ethnic background and their cultural background, and also the likelihood that those individuals might have a legally authorized representative. How do you deal with that? Because otherwise a consent requirement might end up with a bias in who's represented in the studies and we want to make sure we have other people's perspective as well.

Jason Karlawish: 09:28 Yeah, there's a couple of ways to enter into the conversation about this topic and I'll start with one that really impressed me, which was the idea that there are residents in nursing homes for whom there is no one to serve in the role of a representative or advocate for that person. That struck me as notable. Meaning nevermind research decisions. Well then how are clinical decisions made for that individual? And there's one dictum of research ethics, which is clinical care before research. And this almost struck me as I reflected upon it as an example of how in the course of clinical research, particularly a pragmatic trial where you're really trying to noodle into and otherwise deliver clinical care. What you do when you discover, and I'll use a strong word here, bad clinical care, or suboptimal clinical care, or problematic clinical care.

Jason Karlawish: 10:26 And I'm not saying that residents of long term care facilities who don't have any legally authorized representative are receiving bad care. But I am saying that from the perspective of caring for an individual with cognitive impairment, the inability to have anyone who can speak for them or advocate for them ought to be viewed as someone who is at risk. Because who's going to advocate for them?

Jason Karlawish: 10:49 And so I'm not directly addressing your question because what I'm saying is, is that the absence of a legal or authorized

representative ought to raise concerns that have nothing to do with the ability to do research. But how would you deliver care? Now having made that observation, which isn't very helpful for the researcher, what about in the conduct of research.

Jason Karlawish: 11:12 So let's assume the intervention's no more than minimal risk. I think we come up with some interesting points, which is the inability to get informed consent from people because they can't give consent and they lack a legally authorized representative, the practicality problem is not on the basis of the impracticality of getting informed consent. It's based on that the requirement for informed consent would make the research impractical, not informed consent impractical.

Jason Karlawish: 11:39 So then what you're left with is, well in what way would not getting consent from people who lack LARs make the research impractical. And you say, well, the folks without LARS are going to be a particular kind of subject population that are going to differ from the overall subject population in ways that would lead to a biased or otherwise non-generalizable sample. And so you begin to enter into a conclusion that maybe informed consent would be impracticable, and yet if you then look at the rights and welfare criteria, what you're basically saying is, I'm not going to get informed consent from people who don't have anyone else defend or help them. You could argue that that might run up against the idea that your waiver and modification shouldn't offend or otherwise disrupt the rights and welfare of the individual.

Jason Karlawish: 12:27 That's where I might have a real problem, where how much the practicality standard. I'm trying to balance it against the rights and welfare, but I'd want people to help me understand how that doesn't violate their rights and welfare. That's the one that I think I get stuck on on that one.

Speaker 2: 12:42 That's actually a really good point. That's a great point. And with respect to pragmatic trials, this is the last question because it's a direct derivative of this, if the efficacy studies, the phase three studies, clearly show that the intervention actually works when a researcher does it, and so the real question in the pragmatic trial is absolutely only a matter of can it be generalized and sustained when the healthcare system staff do it, does that alter one's priors regarding the ethics or the implied good that would be provided as a function of the intervention? Because it's no longer thought to be risky at all. In fact, by not doing it, you might be depriving somebody.

Jason Karlawish: 13:36 Well, it's not a research risk I think is the important issue. Remember all the rules around human subjects protection apply to the risks of research procedures. So for example, suppose as a matter of clinical care, I'm getting genetically engineered T-cells to hoover up a tumor and you want to study the effect of that on my cytokines or something. Well, the risks of genetically engineered T-cells are risky, than they are. Those are not research risks and they're not part of the research informed consent. What's part of the research informed consent are the extra tubes of blood you're going to draw to look at my cytokines.

Jason Karlawish: 14:13 And so back to, that was a bad example, it's totally biomedical, but it was a vivid example, which is if you're delivering a clinical intervention that's proven to work and you're delivering it, like the way the clinician delivers it, I would say I don't see the research there on that particular procedure. So whatever its risks and benefits are, they may need clinical informed consent, maybe even written, because it's a whatever, but that's not part of the minimal risk calculation. Because minimal risk applies to research procedures.

Jason Karlawish: 14:44 Let's say you were throwing in a bunch of extra assessments, or you were going to have an RA spend 30 minutes debriefing the person, well then that's a research procedure. And what are the risks of an RA spending 30 minutes talking to me about how I felt after I got whatever the intervention was? The consent would need to be around that issue.

Speaker 2: 15:02 So would you agree with the statement that the more pragmatic the trial and the more evidence based its rationale, the not just the greater the waiver, the greater the minimal risk is and the greater the waiver of consent is merited, because all you're doing is actually gathering data from existing sources and then compiling that at the end? So you do use identifiable data, but you're not collecting any additional data.

Jason Karlawish: 15:34 Yeah, the more what you're doing is exactly like or resembles usual clinical care, the more you're likely to find that when you run through the five criteria for waivers and modifications of informed consent that you're probably going to fulfill them. But I will stand firm on the point, just because you call a study pragmatic clinical trial doesn't mean you can waive informed consent. You still have to look at the five criteria and walk through them. You're more likely to get past them if you're a five on all the [pressie wheel 00:16:07] criteria. In other words,

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| | | extremely pragmatic, but that doesn't guarantee you're going to get a waiver. |
| Speaker 2: | 16:13 | All right, great. Thank you so very much. This was very helpful and I'm looking forward to seeing it up on the podcast. |
| Jill Harrison: | 16:21 | Thank you for listening to today's Impact Collaboratory Grand Rounds podcast. Please be on the lookout for our next Grand Rounds and podcasts next month. |