Speaker 1: 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.

Susan Mitchell: Well, hi everyone. This is Susan Mitchell, one of the principal investigators of the NIA IMPACT Collaboratory and I'm delighted this afternoon to have Stuart Nicholls, who is a senior clinical associate in the Ottawa Hospital Research Institute. Last week, Stuart was a grateful enough to give us a great Grand Rounds presentation, which was entitled "Ethical Challenges with Pragmatic RCTs." And it was a terrific Grand Rounds which generated a lot of questions.

So Stuart, I'm going to start in on some of those questions, if that's okay with you.

Stuart Nicholls: Sure.

Susan Mitchell: I was sort of fascinated with the results from your literature review, which was a synthesis of dementia, dementia related investigators, self-identified pragmatic studies or trials. And I was sort of fascinated, mostly struck by really the wide variety of study design features. Some of which didn't sound particularly pragmatic if you're looking at the [pressy 00:01:42] to a framework, even understanding that there is this continuum from efficacy to pragmatic trial design. So first I was wondering if you can just remind our listeners some of which may not have attended your Grand Rounds of the key findings of that literature synthesis. And my particular question is if looked at these studies sort of in retrospect, how many would you consider pragmatic trials even with a reasonably liberal definition of that?

Stuart Nicholls: Sure. Yeah, so we conducted some previous work which took a sort of bigger picture of sort of landscape what we call a sort of landscape paper to look, trying to capture a broad range of pragmatic trials. And so that study brought together just over 4,300 trials. And then we, from that, we identified a subset trials that were pertinent to Alzheimer's disease and dementia, and for trials relating in some way, shape or form to persons living with dementia. And from that, we identified this sample of 62 trials, which is the sample I presented the of.

Now, these commonly involved interventions at the system or the professional level, but also individual level intervention. So, sort of multi-level different interventions were commonly seen. And around a third of the trials were individually randomized, but two thirds were obviously cluster randomized, which is a sort of higher than we see in the literature or in other literature reviews. But at the same time, a lot of the data collection was a primary patient

data collection. So whether it was research specific examinations or sort of questionnaires to the patient or their caregiver, and many of the studies involved individual level consent often requiring substitute or proxy decision maker consent as well. So these were all trials identified by our search filter, which was highly specific based on the validation work we'd done to sort of say these are very specific pragmatic trials, and based on that sort of objective texts using the title of the abstract.

So as I mentioned in my talk for the listeners, and if others want to sort of view it later, most trials, as you mentioned, will be sort of more or less pragmatic on different design features. But again, as I talk about in the webinar, there's no consensus around when a trial should no longer necessarily be considered pragmatic or, so you're right. There's features such as that research specific data collection, which might make the trial less pragmatic. But at the same time, I don't think personally necessarily that excludes a trial as a whole, from being pragmatic. We might say it's less pragmatic in that way. So I think it's an important consideration in the context of that finding here is that pragmatic trials are intended to address a question, questions have a utility as they're part of the informative decisions. So, we're trying to inform a practical decisions, which drug should we prefer, for example, and in some ways pragmatic trials might go hand in hand with that patient oriented research.

So, we want questions that need to be addressed, are important to patients. And in order to address those questions, you need to understand what the outcomes are for patients, patient relevant outcomes. So ensuring that our question is best answered, we need to sort of have the data that best addresses that question. And I think sometimes this may necessitate us gathering that data from the patients, if this isn't part of sort of routinely collected data, if the data to best answer that question isn't available in existing repositories or the clinical data, then I think that necessitates getting that extra data. But at the same time, I don't think that the unit of randomization isn't of itself necessarily something that determines if a trial is pragmatic or not. Again, we might have reasons to think that cluster randomized trials would tend to be more pragmatic, but there's probably examples where we might have a cluster trial where we think a lot of it isn't pragmatic, or that we have an individually randomized trial that might score high on a [pressy 00:06:20] two assessment by the investigators on the other domains in that greasy wheel.

So I think, yes, you're right. You're absolutely right. There were probably trials with features we might see as less pragmatic, but I don't know whether those in and of themselves sort of preclude any of those trials from being deemed to be pragmatic on a whole.

Susan Mitchell: Yeah, it is. It's a little bit of a conundrum because the IMPACT Collaboratory was built to help build a national capacity for doing pragmatic trials in patients living with dementia and we've really struggled a lot with the basic question at IMPACT about what is a pragmatic trial, even understanding that there's a

continuum because NIA tends to have other mechanisms to fund trials that are pilot studies that are more upstream and the NIH stage model. We kind of have to stay in our lane. So when we have a pilot program and try to pick among the applications, which ones to fund, we were hoping that we're picking ones that are more along the pragmatic spectrum and so that the next step after the pilot would be a full embedded, pragmatic trial. We've been instructed to stay in our lane. But as you see in your review, the field is young and everyone has a seems to have a varied definition on what is a pragmatic trial. So what advice would you give us?

Stuart Nicholls: Yeah, so you're right. It's a fundamental question. And even if we sort of apply [pricey 00:07:54] two prospectively, I think it's a challenge to say that this trial is pragmatic enough or it's too explanatory. I think in many ways, pragmatic trials are a bit like Sorites paradox, the term's kind of vague and indeterminate. And for example, how we think about that sort of paradox in other contexts, how little hair does a man need to be called bald? What height should a person be before they can be called short or tall? I think there's an inexactness in the language around some of those terms when we're describing measurements, if we think about [pricey 00:08:31] two, if we're describing continuous measurements or distributions or someone, I've spoken with the authors of [pricey 00:08:39] two, they talk about multiaxial continuums. I think sort of trying to sort of figure out where we draw that line. There's this sort of boundary work kind of process going on.

So I almost wonder sometimes whether rather than asking what is a pragmatic trial, it might be simpler or simply be better to ask what sort of trial are we concerned with. So again, I think the Collaboratory's identified some characteristics that it's prioritized. And I think that serves a great purpose, but I don't necessarily think we have to say that pragmatic trials are only trials that have these specific features. So what I personally, again, personally think is important is saying why we feel that these certain features are important. So for example, it might be that trials that emphasize or only used routinely collected data for outcomes, they're prioritized because it's felt these trials can more easily be launched after that sort of pilot study you mentioned. And so they don't necessarily require much additional infrastructure to get off the ground.

And again, that might help with knowledge translation or translation into practice and minimizing that research clinical practice gap. So again, I think that's fine but then one has to then knowledge that the limitations of imposing certain restrictions, if we're going to say within certain designs or what's of interest, and some of those might sort of detract from pragmatism in other aspects or from the trial in different ways.

So again, if the outcome that would be best suited to evaluating an important patient centered question isn't available in routinely collected data, then the trial to answer that question might not be feasible under the restrictions in post. And so the design might limit the conduct of some patient oriented trials.

However, it may mean that those other trials that you identified, as I say, can be completed more quickly and then integrated into care more quickly and you generate major benefits there. So I think to me, the advice I would say is the transparency is the main thing, transparency about what's being done and why, but then also transparency about the limitations that those choices pose. And that's kind of where I think we should be.

Susan Mitchell: I think it's especially pertinent with the outcome ascertainment because yes, it's a lot more pragmatic to get things that are in the EMR or in administrative files, but we're becoming increasingly aware, particularly with dementia and how it impacts patients and their families, that those may not be the most important outcomes to them. And yet, of course, as you mentioned to get at some of those more patient-centered outcomes may require more added on infrastructure that's not part of the usual clinical flow of a healthcare system. So it is a big tension.

So you mentioned health equity in your talk. This is so important because as you know, there's a lot of well-known disparities in dementia care, and we're really trying at IMPACT to integrate issues of health equity into all aspects of the EPC design. So it becomes just a natural, regular consideration sort of embedded in the science of the whole protocol and it's not just an add on report for example, of how many minority patients were recruited. So for example, health equity can be pertinent to the selection of the healthcare system, the equitable implementation of the intervention, or how to identify minorities in a valid manner from secondary data sources. So really very little has been written about the intersection between health equity and the conduct of pragmatic trials. So can you share your thoughts on this area and how we can advance this particular aspect of pragmatic trials?

Stuart Nicholls: Sure. And I absolutely agree that health equity is a major consideration, although I should, I acknowledge I'm not a scholar who is embedded in the equity field. And so my experience expertise comes from my own research from being advised by the people we've interviewed, for example. So I think, first and foremost, pragmatic trials, because of their focus on the the [pracy 00:13:08] domains, one of them is about the eligibility and recruitment of trial participants. I think they have a great opportunity to improve equity and I think having as the health equity team at the Collaboratory has done, they've sort of laid out those [pracy 00:13:22] domains and sort of indicated the areas where equity can be considered within each of those domains. I think that's a great suggestion and a very practical tool that can be used.

And I think there's several challenges and the focus to date has often been on the sort of looking at populations that have been excluded from trials. But I think, and as I mentioned in the webinar, one area of concern, and this was raised predominantly by the patient partners, we interviewed in our interviews was the concern about access to trials and whether or not the systemic or systematic barriers that may potentially exclude people or prevent people from

taking part in trials, even though they were eligible. And I know this isn't necessarily specific to pragmatic trials, but I think it's, again, it's emphasized given that the potential for pragmatic trials to address inequities. And again, if we think about the administrative data, you've already mentioned this, but are there limitations around health administrative data when we think about equity and the ability to analyze inequities potentially from our intervention?

So I think there are ways around that people have used small area estimation where individual level characteristics aren't available with the data. I think using tools like the health equity team table that they produce, but also the progress framework I mentioned, I think working to maybe work with the clinical side of things, to try and integrate some of the information that we would want to use in research. I think that's another avenue. But I think there's also improvements we can make in terms of the reporting. So I know for example, there's a console health equity extension. So again, if we can sort of work from sort of before the study, during the study and after the study, I think all those components will sort of help to come together and sort of improve that awareness maybe around health equity as in the work of the Collaboratory. And I know there are other projects going on in this space that can only be beneficial.

Susan Mitchell: Great. Thank you. Well, I think there's lots of work to be done. We greatly appreciate all you've contributed and I'm sure we'll continue to contribute to the field and appreciate your Grand Rounds. And you're speaking with me today, so thank you Stuart.

Stuart Nicholls: No, thank you.

Speaker 1: Thank you for listening to today's IMPACT Collaboratory Grand Rounds podcast. Please be on the lookout for our next Grand Rounds and podcast next month.