Jill Harrison, PhD:

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.

Hello everyone. I'm Jill Harrison, one of the executive directors at the NIA IMPACT Collaboratory. Welcome to today's podcast. I'm joined today by Dr. James Flory, an endocrinologist and clinical epidemiologist at Memorial Sloan Kettering Cancer Center, specializing in the management of hyperglycemia and diabetes in cancer patients. Dr. Flory's major research focus is now a PCORI funded methods development project, to work on a novel pragmatic trial design called DART: Decision Architecture Randomization Trial. DART is intended to permit extremely efficient, low cost, and safe studies of clinical comparative effectiveness questions that would not be likely to attract the resources needed for a traditional clinical trial. This is the companion podcast that accompanies a presentation you made last week at our monthly Grand Rounds on the topic of DART. Welcome, Dr. Flory.

James Flory, MD, MSCE:

Hi. Thank you for having me.

Jill Harrison, PhD:

Of course. So the purpose of the podcast is to summarize, for listeners, the topic of the Grand Rounds. Please give listeners tuning in today a high level summary of the DART trial and the lessons learned.

James Flory, MD, MSCE:

The DART trial started out as a thought experiment, that's been kicking around for about 10 years under different names. And we're currently in a phase of trying to move it into the real world by carefully studying the ethics and the underlying statistics, and carefully standing up one, or two pilot studies. The idea behind the study is that, instead of doing a traditional randomized trial where you assign people to definitely receive intervention A or intervention B, in a DART trial you just do something that nudges people in one group to be a little more likely to get the intervention. And a good example of how you could do that is by making a certain drug come up first on a dropdown list that people are picking prescriptions from. These kinds of design choices in an electronic interface are often called nudges because they make somebody just a little more likely to choose or receive a certain intervention, but they don't absolutely determine it.

And the property they have that is really nice is if you know what you want, if you have a preference for a certain drug, you're not going to choose another drug just because it was first on the list. You're only going to choose the first item on a list, if you were really in a very balanced state where you didn't have much of a preference. The feature of DART that's a little bit hard to explain in the abstract, but that I think is also really attractive if you're doing clinical research is, these nudges can create a situation where people become more likely to get an intervention that's randomly chosen but only if they really don't have a preference. If they have any preference, that overrides the randomization, and they get the intervention that they would've wanted and benefited most from anyway. And what that combination of features allows us, we hope, to do is run randomized trials that are very, very simple and very, very safe, but still give us high quality evidence about which interventions, for example, which drugs are best for patients.

Jill Harrison, PhD:

Thank you. That is a very clear explanation. And I'm reminded of a situation, to oversimplify, where someone is perusing the grocery store aisles and at eye level are a certain type of potato chip, for example. And making that connection with what you're describing in terms of, if you have no preference, you may just go with what's at eye level. But if you really know what kind of chip you want, you're not going to accept what's there, you may look for it. Is that an oversimplification that makes sense?

James Flory, MD, MSCE:

Yeah. I don't think that's an oversimplification, I think that's just right. This is a concept that's a lot more common in other parts of the economy, other parts of society than healthcare, where often what you have for breakfast that day is going to be determined by something really arbitrary. Like, what happened to have moved to that point of the front of your fridge by then. When things are nearly random like that, it's possible to make them really random without disrupting anything important. That's the idea that we're trying to apply here.

Jill Harrison, PhD:

Wonderful. We had some questions remaining from the Grand Rounds, so listeners of the Grand Rounds were able to pose questions in the chat. And I'd like to get to some that were outstanding, that we simply ran out of time for. And I wanted to start with the ethical questions. So one of the listeners raised the question of, what are the ethical issues here? And how are they different or similar to other randomized controlled trials?

James Flory, MD, MSCE:

From an ethical point of view, I think there are some ways in which this design actually has clear advantages over a traditional randomized trial. And the most important one, is that it preserves patient choice. With a traditional randomized trial, the way it has to work is once somebody enrolls in the trial, they're going to be randomized to, let's say, drug A or drug B. And if they're randomized to that drug, for the trial to work, that's the drug they need to take. Patients always have the right to withdraw. And patients often will, if they really have a strong preference and have the option, will find a way to switch over to the treatment they wanted anyway. But for the trial to work, there really has to be this expectation that's conveyed to everybody that they'll really try to stick with what they were randomly assigned to. And we're able to do randomized trials because, if you're very careful, you can do this in an ethical way. You can make sure patients know exactly what they're involved in.

And you can make sure you're comparing treatments where both choices are very similar to each other, and you expect most people in the trial won't have a very strong preference. But these things don't get rid of the fact that you probably are getting some people in the trial to take a treatment, treatment A, where, if they'd had freedom to do absolutely whatever they wanted, they probably would've opted for treatment B. And that's one of the reasons it's so important to get informed consent for trials, because all of this breaks down if patients aren't very keenly aware that they've been randomized. If they were randomized to A and they don't even know that that happened, that may really deprive them of the opportunity to switch to a treatment B they might've preferred.

DART steps around that because in this design we don't ever tell you what you have to take. We don't even pressure you, or give you any expectation that you ought to take drug A or drug B. All we do is do subtle things, make certain drugs more immediately accessible in an ordering menu, or something like that, to the point where if you really don't care, just really have no preference at all, our little change to

how things are presented may change what you pick. But if you care at all, you're not even going to have to think about it. We're not even going to ask you to give it a second thought. You just go a little bit further down the menu of options, and pick the thing that you wanted in the first place.

So I think that is an ethical advantage to DART. The big question it raises about DART, the first ethical question that comes to mind, at least when researchers talk about this design, is what should happen with informed consent in that case? In a traditional randomized trial, I kind of fall in with the school of thought that you almost always really have a very clear obligation that you must get explicit informed consent from participants. Because of that issue I mentioned earlier where, if people don't have informed consent, they're not actually as empowered as they need to be to withdraw from a trial, or walk away from a trial, if they don't like what they were assigned to.

For a DART, because your freedom to choose was never compromised, it's not as clear that you must have explicit informed consent to protect yourself. And it might actually be the case that getting informed consent is kind of intruding on a patient's care and taking up a patient's time in a way that isn't actually the best thing, ethically. So to give an example of what I mean, one of the DART designs that we think about doing a lot would be a doctor choosing medications for a patient, looking at a number of options, let's say for insulin, where the options are all really, really similar. And either making a personalized choice, based on their conversation with the patient for the insulin that the patient prefers, or if nobody has any preference, they just pick the first insulin on the list. It's not clear to me that engaging a patient in a full conversation about informed consent for a study like that is going to make much sense to the patient, or advance their interests in any way.

So maybe if all that's happening is that a provider is seeing slightly different versions of a list of medications, but still picking the one they think is best for their patient, it's not clear that having an informed consent process every time the provider pulls up the order, and makes that treatment recommendation, it is not clear that that is really even going to make sense to a patient. Because the patient had freedom to choose what they wanted anyway, it's not clear how it's going to leave the patient better off. So maybe DARTs can be run without that kind of explicit consent process. This is clearly not something that I should be making up the answer to. We are talking to a lot of patients in a lot of different settings to walk through the issues with them, and see what patients, and other stakeholders as well, think is the best way to conduct this kind of study.

I think that's the critical ethical question for DART. I don't think the question is whether or not DART is ethical. Because I think for at least some questions, it's arguably more ethical than the kinds of trials we're already doing. But the question is, should the things we do to protect patient's rights and autonomy like informed consent, should they be done at all differently for DART? Because it is inherently somewhat safer than a traditional trial.

Jill Harrison, PhD:

Thank you for that. You took something extremely complex and explained it so clearly. The next question is around how fidelity will be measured in DART.

James Flory, MD, MSCE:

As I recall, this is a question I couldn't answer in real time, because I wasn't sure what fidelity meant in that context. My understanding, having done a little bit of homework, is that the intent of the question was, if we're using DART to study some kind of intervention like a drug, or perhaps a more complex intervention like a specialist, or consulting a specialist team, how do we make sure that that intervention is being applied consistently, and applied in ways that it might be used later on outside of the DART? Probably at least for the earliest wave of DARTs that we pilot, you want to address this question by

choosing a very simple intervention where fidelity is not likely to be difficult to measure or maintain. So I think something like, whether or not you administer a specific drug, for example, whether or not you give a patient long-acting insulin when they're first diagnosed with diabetes in a hospital, is probably the kind of intervention you want to focus on.

I think that more complex interventions where maintaining fidelity is harder, there's no reason DART couldn't be used to study an intervention like that. But you're then layering a complicated study design issue on top of a new design that's already complex. And you might encounter inherent challenges, because DART is supposed to be very unobtrusive, very low touch. You don't want to be disrupting routine practices of care, or requiring members of the clinical care team to take extra steps to document fidelity, or purposes of clinical trial conduct. So that might make it harder to use DART, at least initially, to study really complex interventions where fidelity is a question. To make my answer concise, I think there are a lot of things you could do to maintain fidelity in a DART. Because the design is so new and already involves so many new complexities, I think sticking to very simple, one-step interventions, like administering a standard of care drug, is probably the right initial focus for the design.

Jill Harrison, PhD:

Wonderful. Thank you so much. I do think you captured the spirit and intent with which that question was posed by one of our listeners, so thank you. Let's move on to a question about the design. So have you considered a parallel cluster randomized trial with staggered implementation, rather than a stepped wedge design?

James Flory, MD, MSCE:

We haven't considered that design specifically. I don't think there's any reason that that wouldn't be a good fit for DART. In general, we're finding the design, at least from a implementation point of view, combines well with approaches like cluster randomization, staggered implementation, the sort of simpler version of stepped wedge. And that that is helpful to us right now for very simple technical reasons, which is that, to run a DART you have to do something through the electronic health record to nudge providers and patients towards one choice or another. And that turns out, just practically speaking, is a little easier to implement on certain floors or at certain sites, than it is to do it randomized to the level of a provider or a patient. That's the reason I talked a lot about stepped wedge in my presentation last week, because stepped wedge is kind of well suited to that floor-by-floor, or site-by-site deployment of an intervention.

I will say that a lot of the appeal of those kinds of cluster randomized methods, and the stepped wedge method, has to do with that very practical challenge to implementation, just that, we're still solving technical problems with applying randomized nudges at the level of the individual. I actually think for many questions that the design is at its best if we are randomizing at the individual level, because that offers a lot of methodological advantages, and higher power for a lot of questions, and that's the approach that's most challenging with a traditional randomized trial design where, I think, DART has the most to offer. Although, I think in early stages we're mostly using it for these kind of clustered or stepped wedge designs, I actually don't think that's going to be the long-term future of the method. I think the long-term future of the method is going to be looking more at individual-level randomization.

Jill Harrison, PhD:

Thank you so much. We have one more question that we were unable to get to during Grand Rounds, and you've been speaking to this in some ways. And the question is, if the treatment options are more

than A and B, and the provider patient prefer C or D, how would you handle it from the design and analysis perspectives?

James Flory, MD, MSCE:

So I think there are two ways to interpret that question. One, which is kind of an easy out is, what if there are several treatments that we're all interested in comparing, like A versus B versus C versus D, and we essentially want to do something like a four arm study, randomly nudging people to one of those? That's the easy question for me to answer, because I think that's a pretty straightforward extension of DART. You just set up more arms of the study, and you work with a nudge that can nudge people in each of those different directions, instead of just in two different directions. The other thing this question may be getting at, which I think is a lot more complicated to address is, let's say that I'm using DART to study insulin A versus insulin B. And I've got an order set that really encourages use of one of those two things. But there's a bunch of other insulins, there's C and D and maybe many more, and people are actually quite interested in those, and often will go off in that direction and assign patients to that treatment instead.

That could pose, not an insuperable difficulty, I don't think it's a reason DART can't work, but it could pose a challenge for the method that I'm thinking through right now. You would be in good shape if the nudge meant that if you were in arm A, you were more likely to get A, and your chance of getting B was lower, and your chance of getting C or D was about the same as it would be otherwise. And then in arm B, you'd be in good shape if that was all kind of symmetrical. Like, you're more likely to get B, you're less likely to get A, and your chance of getting C and D doesn't change much. And fortunately you could watch as you were doing the DART to make sure that was what actually happened.

If instead, you got a more complicated pattern, where if you nudge someone toward A, they're more likely to get A, but, for some reason that was hard to anticipate, their probability of getting C also shoots up measurably, and that doesn't happen in arm B, that starts to create problems for the design. If you have something like that, where the nudge is having an unexpected secondary effect you weren't anticipating, like, it doesn't just make people more likely to use A, but it also makes them more or less likely to use C, that violates some of the assumptions that we have about how the nudge works. That's going to pose a problem for interpreting the DART. That kind of statistical subtlety is one of the things our grant is creating space and time to study. We're doing a lot of work in retrospective data looking at when these kinds of nudges have been rolled out in our health system in the past, just for quality improvement to see if nudges are really targeted in the way we need them to be, where they really only affect that A versus B choice, or whether it's really common for nudges to have spillover effects, where they affect lots of other treatment decisions downstream, or that you weren't expecting them to affect.

We're assuming that we can identify nudges that are pretty targeted, that don't tend to do that. If that assumption turns out to be wrong, it's a problem for DART. We'll keep you posted on what we find out.

Jill Harrison, PhD:

Please do. As you know, the IMPACT Collaboratory is focused on improving dementia care through non-drug interventions embedded in healthcare systems. So those embedded pragmatic clinical trials targeting people living with dementia, caregivers, and care partners, and of course healthcare systems. Can you envision, if we could just be aspirational and creative for a moment, can you envision a place for DART within that universe to improve dementia care using non-drug intervention? So perhaps a nudge within an EHR for a non-drug intervention targeting dementia care outcomes. What could that look like in your mind?

James Flory, MD, MSCE:

Let's try to extend DART beyond just the drug model. And, as you heard me say earlier, I like the drug model for these initial phases of developing the method just because it cuts down on some potential complexities. But I'm glad you asked, because the design is definitely not that narrow in application. You should be able to use it for lots of different things. So let's move to something slightly more complicated, but not much, where I think DART could be useful. And that would be referral to, not necessarily a very complicated multidisciplinary intervention, but to involvement of one additional specialist, or one additional type of team. I don't know dementia care well enough to confidently toss off just the right example, but in the area where I do a lot of work, which is kind of the overlap between diabetes and cancer supportive care, nutrition is a good example of an intervention that we don't quite always know what to do with.

I'm confident that there are patients I meet where a nutritionist referral can make a huge difference for them, and I refer them. And I'm confident there are patients I meet who are not going to listen to a nutritionist, have already decided exactly what they're going to eat, and there's no point in making that referral, and we really just need to talk about drugs, and medications, and the other things that I do as someone who mostly prescribes. There's a lot of patients in the middle where I really don't know if, when I'm first seeing them for a metabolic problem, like diabetes or weight loss, if a referral to a nutritionist is a good use of resources or not. And I make that decision nowadays really, really arbitrarily. I think it really depends on what I'm thinking about that day, how many other things we had to talk about in the visit, how long it's been since I sent someone to our nutritionist, because I know they get busy. And I would really like a clearer answer to whether or not that specific type of referral is beneficial to those patients.

It might be really helpful, it might not. We just don't know. So that's a reasonable application for a DART. If you did something to my practice environment, where you made it a little easier at certain times or in certain practice locations to order a nutrition referral, that could provide the seed for a really interesting DART. So say that, some of our providers have an interface when they're seeing visits where if they click one button, it appropriately places an order for nutrition. And other providers don't have that button in place. The providers who can order a nutrition consult with a single click, are likely to do so more often. And so we'll create a situation where, in one part of the practice people are being referred to nutrition only at the usual rate, and in the other part of the practice they're being referred 10%, 20%, 30% more often.

We could collect those data, look back after a certain period of time. And figure out if those patients on the margin who got a nutrition referral because of the nudge who wouldn't have gotten one otherwise, if they do better in terms of weight loss, in terms of how many diabetes drugs they need, in terms of other outcomes. So I think that's a good example of applying the DART methodology to something that's not a drug. And I would imagine that there are similar questions about referral to specific services in the care of people living with dementia, that it would be amenable to the same design.

Jill Harrison, PhD:

Thank you for that. Another big piece of our mission is to train junior and early investigators that are interested in these pragmatic clinical trials to improve dementia care. And so I'm wondering, for listeners who are really interested in DART, who are really interested in nudge trials for dementia, really want to dig deeper into this, where should they start? What are the training resources, readings, grand rounds, webinars, resources that you would direct them to?

James Flory, MD, MSCE:

So in terms of systematic training resources and webinars, I don't think there's a lot out there yet. I think this is probably one of the first. Certainly not the very first resources that's out there to study concepts like nudges, or the role of nudges in quality improvement. But if you're interested specifically in using nudges for comparative effectiveness research, a la the DART design, I think the best place to refer people right now is to kind of their traditional peer-reviewed literature to start reading. And hopefully over the next few years we'll have things that are a lot more user-friendly, and help speed dissemination a lot more.

So I'm going to recommend three readings. The first is a little bit self-promoting, but is also the most targeted to the topic of DART, and that's a paper our group published recently. It's in the journal "BMJ Evidence-Based Medicine" and it's called "Decision Architecture Randomization: Extremely Efficient Clinical Trials that Preserve Clinician and Patient Choice?" And that is exactly what we spoke about today, but in paper form. I think it would also be interesting to look, for readers, or people who are interested, to look at a paper that was published, that describes a design that's really similar to DART.

It is not quite the same thing. It differs in important ways, but it's very well-articulated and I think you can learn a lot by looking at it. And this trial also came out in one of the BMJ outlets. It came out in "BMJ Open." It's called "Embedded point of care randomization for evaluating comparative effectiveness questions: the PROSPECTOR-critical care feasibility study protocol." And it's written by Matthew G. Wilson and colleagues. And what it describes, is actually a little further along than our project. It looks and sounds a lot like a DART. The big interesting difference is it's extremely explicit, whereas DART tends to run in the background and the people involved tend not to be constantly aware of it, this study works through an explicit pop-up box that says, "Hi, we're trying to nudge you to prescribe a different drug here." Very interesting kind of contrast and complement I think to the idea we've been talking about. And moving even a little bit further away from DART but still conveying a lot of useful information, is a paper in the New England Journal of Medicine that came out in 2019.

It's called "Creating a Learning Health System through Rapid-Cycle, Randomized Testing," written by Leora Horwitz and colleagues. And it also describes something that looks and sounds a lot like DART, but the critical difference is that they are deploying randomized nudges for quality improvement purposes. What they're doing is not really clinical research, per se. DART takes very similar concepts and infrastructure but applies it to do comparative effectiveness for two interventions where we don't know which is which. But reading this paper certainly taught me, and I think could teach anybody, a lot about the practical aspects of implementing this kind of idea. And then it's also very interesting to think about how this use of randomized nudges in quality improvement differs from the use of randomized nudges if what you're trying to do is really true clinical research.

Jill Harrison, PhD:

What fantastic resources. Thank you so much for taking the time to share these resources and your work with us. Dr. James Flory, our listeners thank you. Thank you so much for what you do for patients every day and thank you so much for your time.

James Flory, MD, MSCE:

Thank you very much.

Jill Harrison, PhD:

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.