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Intro: [00:00:01] 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 rethinkingclincaltrials.org. Thanks for joining.

Adrain Hernandez: [00:00:24] This is Adrian Hernandez. I want to welcome you to today's Collaboratory Podcast and I'm here with Gred Simon and Susan Ellenberg who are going to reflect and discuss a recent Collaboratory Grand Rounds on data and safety monitoring and pragmatic clinical trials. Really a terrific session where they really discuss when DSMBs should be put together for pragmatic trials, how it should be done and what are the difficult issues and this type of setting. So let me start with you Greg, you've been really dealing with this in a very impressive trial trying to understand suicide prevention. And from your perspective what are the special issues concerning a DSMB for a pragmatic trauma, especially a trial that's embedded within the health system.

Greg Simon: [00:01:12] Well I think it's important to start by saying that in any clinical trial but especially a clinical trial that deals with people at risk, for instance people at risk for suicide attempt, it's important to have a data safety monitoring plan and in some cases maybe a data safety monitoring board, and we can talk about the distinctions between those two things. But when you're doing a pragmatic trial you may sometimes be looking at somewhat different questions regarding safety monitoring than you would in a more traditional clinical trial. And sometimes you may be trying to answer the same questions but you might have different data so you might have to go about it a different way. To me one of the big differences is that in traditional clinical trials we're often studying new treatments. So we may have questions about some unexpected risk of a new treatment. In pragmatic trials we're more often studying treatments that are well-established and have been used for years. So that possibility of discovering a new risk may fade in the background while some other questions may come more into the foreground.

Adrain Hernandez: [00:02:13] Now, Susan, if you start thinking about pragmatic trials that are truly embedded in the health care delivery system where we're actually supposedly monitoring the safety of patients coming through there, do you even need a DSMB?

Susan Ellenberg: [00:02:29] Well I think you need a DSMB, or a DMC Data Monitoring Committee as they're also often called, any time there is a need to keep watch at the interim comparisons to see whether either one treatment is so much better than the other that you might want to just call a halt to the trial and report the results or whether there's some emerging harm that may not have been anticipated. And I would say that even when one is looking at treatments that have been widely used, if you're comparing one treatment approach to another you might find that something that you didn't expect that there is actually more more events of concern on one arm than the other. We have found over the years problems with drugs that have been on the market for some time, when they've been compared to other treatments in a larger trial, we see that there are actually some adverse events. So when there's, when there's a need to keep track of the interim comparisons you need an independent group looking at that because if the investigators themselves were looking at it they might not be fully objective about whether any kind of action should be taken.

Adrain Hernandez: [00:03:39] You mentioned an action could be taken. You think that because these studies that we're talking about are actually randomized trials as opposed to just observational studies where it's a clear ability to see if there is a difference in outcomes. Is that why that would be important here for a DSMB? It's actually you could have clear data that there's either a benefit or

harm?

Susan Ellenberg: [00:04:02] Yes, that would play into it. Certainly when there's a lot at stake in a clinical trial and the end results are expected to inform clinical practice, especially if it's going to be going on for some time you have a longer term endpoint. It might be valuable to have an independent group be watching over the data. And I would say that even when you know people are not necessarily so concerned about safety outcomes there's a basis for having a group you know kind of looking over the shoulder and making sure that the trial is being conducted properly.

Adrain Hernandez: [00:04:39] Often we think about DSMBs as really evaluating the endpoint in terms of safety or early efficacy being demonstrated but there are probably different components of these types of trials where the DSMB would be pretty helpful here. So Greg, as someone who's really been running these types of trials for a while, could a DSMB help someone out in areas such as the fidelity of the intervention?

Greg Simon: [00:05:05] Yeah, I think I would agree there are times when an independent judgment is important. You know there data that may develop over the course of a trial for instance even regarding recruitment to say is this trial recruiting participants at an adequate rate that we'll be able to get a valid answer to the question. Or in terms of the delivery of an intervention. There may be cases where we'd say that the uptake or adherence to or the quality or fidelity of an intervention is low enough that we don't think we're really going to answer a question about how this intervention would perform in the real world. In those cases the information is not private. The investigators are well aware of it. But an independent judgment by outside experts who know the area is sometimes necessary because an investigator may want to persevere in a trial longer than is a good idea or may underestimate the importance of one of those problems. The other area I think where an independent DSMB or board or committee is important is when some analyses need to be confidential. So especially if we would be analyzing the primary outcomes for evidence that a new intervention might be harmful or a new intervention might actually increase risk. Those analyses usually should be confidential from most of the study team. And there you clearly need an independent board.

Adrain Hernandez: [00:06:23] Now let me ask some just practical things. So some of these trials, they may have an intervention and the outcome data may not be collected until a lot later. Is that an issue for these types of studies and how do you address them?

Greg Simon: [00:06:40] Well that exact issue comes up in our trial of suicide attempt prevention because the intervention itself lasts up to a year and for most people at least several months, and we're interested in looking at the outcome of suicide attempt or suicide deaths over up to a year for each participant. Suicide attempts may be known to the study database immediately, but if people make a suicide attempt and are seen at an outside hospital, the healthcare system might not be aware of that for months. Suicide deaths sometimes are delayed by months or even more than a year if we rely on state mortality data to ascertain those. So we will do interim analyses using the best data we have available at any point but our statistician and the members of our DSMB are very much aware of what data are available and what are not. So there may be some judgment involved in making a decision if they ever had to make a decision about the outcomes, knowing that they're making that decision based on not complete information.

Susan Ellenberg: [00:07:40] That's right. They're always short term outcomes that are of interest even if their primary's outcome is longer term. And as Greg mentioned if it becomes clear early on that the sites are not implementing the interventions to be compared in a way that's in the long run going to lead to anything reliable in terms of comparing the effects, you know that's important and somebody needs to be looking at that.

Adrain Hernandez: [00:08:08] Another practical question is that in a vision for learning health system nationally is that these types of studies, these pragmatic trials would be done fairly routinely. And in other parts of the world such as Google and Facebook they're doing AB testing all the time in a randomized fashion. If we're to fulfill the vision of learning health system where they're embedded trials being done within health systems every day with AB testing, is that becoming a big issue for DSMBs, or the thought of having a DSMB? How would you address it?

Greg Simon: [00:08:45] Well I think that the old fashioned way of doing safety monitoring which say would be you know human beings reviewing narratives about individual events obviously cannot scale. But I don't think we're talking about using that old method in pragmatic trials. In pragmatic trials, I hope, you know we would be thinking of using the data that are automatically generated in the healthcare setting about what treatments were delivered and using the data that are generated about the outcomes, and developing processes so that we would be able to extract those data and organize those data relatively efficiently on an ongoing basis. So that's a model that can scale. The old fashion model really can't scale at all.

Susan Ellenberg: [00:09:29] I think this is a challenge that we need to be dealing with right now because you know hopefully that is where we're going to be, that we're going to be doing more and more trials you know widely spread out using systems that are different from what we're used to in traditional trials. And we need to be thinking about how we're going to do accurate and reliable monitoring of those trials.

Adrain Hernandez: [00:09:53] Greg and Susan, thanks for spending time with us discussing these important issues around pragmatic trials and addressing what the needs are, evaluating safety and the roles of DSMBs. So as a reminder we will have another podcast coming up and we'll hear from Rich Platt and Chris Granger on IMPACT-AFib, an 80,000 person randomized trial using Sentinel Platform.

Closing: [00:10:21] 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 p.m. Eastern Time.