Dr. 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 some of 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.

Dr. Adrian Hernandez:

Hi, I'm Adrian Hernandez, one of the moderators for Collaboratory Grand Rounds, and today we're here with Chris Lindsell, who will be reflecting on Searching for a Unicorn: Understanding Stakeholder Perspectives when Selecting Outcomes for Outpatient Trials. So, Chris, thanks for joining us on this podcast.

Dr. Christopher Lindsell:

I'm delighted to be here. Thank you for inviting me, Adrian.

Dr. Adrian Hernandez:

Well, Chris, this is such an interesting topic and title, I have to say. What's the unicorn that you're aiming to help address?

Dr. Christopher Lindsell:

It's a good question. I titled the talk Searching for a Unicorn because of the challenge that is faced by investigators every day. What we're trying to do is we're trying to extract as much information as we can out of a study, but at the same time we're trying to extract information and present it in a way that physicians, patients, regulators, and other stakeholders can understand. Trying to find measurements that contain good information, that are easily understood is a very difficult task. In particular, it's very difficult to do it during a pandemic when people have many preconceptions about what matters. Here, really the conversation was around how do you define a unicorn? How do you define something that is really singular and that is going to mean something important to everyone?

Dr. Adrian Hernandez:

That's fascinating. So you just named off five, essentially, stakeholders that may have different views in terms of types of endpoints or timing of when to have data. So is it possible to actually get those views to converge into the so-called unicorn?

Dr. Christopher Lindsell:

I wish there was an easy answer to your question. I believe it's possible, but it's only possible if we listen to each other and we understand the question we're trying to ask and the veracity with which we're trying to answer it.

Dr. Christopher Lindsell:

So if I put that a little bit differently, I do think it's possible to find a unicorn if we listen to all of the many people who have a stake in the answer to the question, and we understand from them how they're going to use the information that we provide. If we do that correctly, then we should be able to provide something that is meaningful to everybody and that they are able to act on as it impacts their life.

Whether it's a participant who is taking a medication to impact their life. Whether it is a provider who is ordering a medication, or a researcher who's studying it, or whether it's a regulator who's making decisions on whether or not a medication should be used in general medical care, all of those decisions require an information input. The key, the unicorn key, is the piece of information that everybody can understand together and therefore understand the answer to the question of does the medicine or does the intervention work.

Dr. Adrian Hernandez:

Interesting. Chris, as you think about things, it sounds like you don't necessarily approach these questions as answering the question with a singular endpoint, but considering the totality of data or information that we can learn. Is that correct, or am I misunderstanding?

Dr. Christopher Lindsell:

No, I think you're right, Adrian. I think when we focus on a single piece of information ... So maybe if we focus on something like mortality. Mortality is a really meaningful outcome, but for many trials, particularly in the outpatient setting, mortality is exceedingly rare. If we pin all of our hopes on mortality, then ultimately we may actually be helping to save lives in the long term, but we will never generate enough information because we don't see enough events happening. We have to see events happening to be able to learn about what causes them. If they don't happen very often, it's not a good outcome in a clinical trial. The proposal and the way to navigate it is to say death is important, absolutely. If you think of it on its own, it becomes less important. It's the same as saying symptoms are really important, but if you think of them absent the idea of mortality, they become a little bit less important. So we have to pull them both together and say the symptoms matter if you are alive.

Dr. Adrian Hernandez:

This presentation was stimulated by research that you're leading. Perhaps give some background to that and how that stimulated the topic and discussion.

Dr. Christopher Lindsell:

Absolutely. So several years ago now, it seems as though it was just yesterday when the pandemic started, but several years ago we were asked to try and find a unicorn so we spent a lot of time trying to do so. What we realized is that the statistical methods that are currently available to people doing clinical research are really not sufficient to take into account the full information that is available in a clinical trial.

Dr. Christopher Lindsell:

So the statistical methods that we prefer are fairly simple, and they allow us to answer questions about whether the medicine works, but usually only on a single measurement and usually only at a single point in time. What we've been doing is a body of research that says, how do we get better than that? How can we use information on multiple measurements made at multiple points in time? We've been doing a fair amount of methodologic research to show if we're able to make measurements regularly and we're able to make more than one kind of measurement, then we should be able to draw conclusions about the medicine working faster than we would otherwise. More information in gives us a quicker answer.

Dr. Adrian Hernandez:

That's interesting. So how do you protect against the two common issues that we face? One is overstating a potential effect, when there could be, let's say, harm, or missing an effect because of, I'll just say the totality of data that's being collected, but that effect could be meaningful.

Dr. Christopher Lindsell:

It's a very, very good question. In my talk, I referred to this as a trial having a sensitive goal or a specific goal. A sensitive trial is one that is designed to find small signals, but the risk is that you actually have a study say the drug works when it doesn't really work very well. So that's a risk in a sensitive study.

Dr. Christopher Lindsell:

On the flip side, the risk of not doing a sensitive study is that you never actually find the signal that leads to benefit. Now, how do you balance sensitive with specific? Specific is really making sure that the drug really does work for the indication that is recommended and that the evidence is sufficient to say the benefit does outweigh the risk. So in the specific study, there are some downsides if we design a specific study. We may miss the signal.

Dr. Christopher Lindsell:

How do you balance it? How protect against it? The answer is really to make sure that in your design, you understand the operating characteristics, what the magnitude of those errors might be, and that you position the design so that each of the different stakeholders that we earlier mentioned: patients, providers, researchers, and others, if each of these people have some say on the balance between sensitivity and specificity, then we can help to produce information that should guide that decision.

Dr. Adrian Hernandez:

You and I have been working on ACTIV-6 where you're employing a lot of these approaches, perhaps share what the issues were and how you aim to solve them with our unicorn.

Dr. Christopher Lindsell:

ACTIV-6 is a fascinating study. If anybody is unfamiliar with ACTIV-6, it's a platform trial, and we're looking at repurposed medicines in the outpatient setting for COVID-19. The work that we've done here has been really interesting. Very early, the goal was to find a sensitive signal. As we started to move forward with the study, the surrounding context, the other trials that were evaluating similar agents, data coming from other countries, and input coming from different groups suggested that maybe the most sensitive endpoint that you can come up with may not be the right thing for the trial overall because we also need to make sure at the very end, the answer was correct. So what we've done is we've woven a sensitive component and a specific component together.

Dr. Christopher Lindsell:

Early in the trial, we're using a very sensitive screening approach. Later in the trial, we're using a very specific approach using a very hard endpoint. Now, there's a real advantage to this. It's very much like we see in medicine or we see in drug development or we see elsewhere. Early in the evolution of something, we're looking for any signal. As we get closer to that something being real and we get closer to that something moving into public use, the risks get much higher. As we go from screening early in the trial and we're looking for any signal, moving to a specific endpoint that de-risks the outcome is actually, I think, quite a sensible approach.

Dr. Adrian Hernandez:

Very good. I think we've certainly seen a lot of interest from all stakeholders in this approach and type of endpoint. Hopefully we'll be able to really leverage that for, as you said, understanding different issues about drugs in a sensitive and specific way.

Dr. Adrian Hernandez:

So last question. A lot of attention has been how to do this in the setting of COVID-19 and the pandemic where people want answers yesterday. How does this apply for non-COVID outpatient studies? Is it relevant? Should we be considering this for other studies as we go forward?

Dr. Christopher Lindsell:

Adrian, I am so glad that you asked me this question. COVID has been devastating, but it has also opened up some opportunities. Here COVID pointed at a problem that we as an experimental world or as a clinical research world have landed in, and that problem is that we really haven't understood the pathway from sensitive to specific. We really haven't accommodated that in our day-to-day worlds. I would argue that the approach we're taking, which is to screen and to screen efficiently, and when you find something, move into a specific area, it's really no different than the normal drug development pathway, but we've put it onto a much shorter timeline.

Dr. Christopher Lindsell:

In addition, the thinking that we have had about the importance of outcomes, what matters to patients, what matters to clinicians and what matters to stakeholders, that is the same regardless of whether it is COVID or not. I might even argue and say the time pressures of COVID, if we applied those in other areas, we may see a similar kind of disruption as we've seen in our conversations around endpoints and actually improve the trial process outside of COVID-19. That was the long answer.

Dr. Christopher Lindsell:

The short answer is these methods absolutely apply outside of COVID-19. I really think that it is important for us as a clinical research community to think more deeply about how we pick the outcomes and how we pick outcomes that match with a statistical design to create the most efficient research. The most information from the smallest number of people to get the fastest answer.

Dr. Adrian Hernandez:

Well, Chris, I certainly agree with all that. As the COVID cloud clears a bit, we still have a lot of other public health problems to address, and so the approach here certainly is important and can be impactful here as we go forward.

Dr. Adrian Hernandez:

So, Chris, thanks for spending time with us. It's been a great conversation. I encourage everyone to take a closer look at what Chris shared regarding how to search for a unicorn in selecting outcomes for outpatient trials.

Dr. Christopher Lindsell:

Thank you, Adrian. It was a pleasure.

Dr. Adrian Hernandez:

Thanks everyone for joining us. Please join us for our next podcast as we continue to highlight interesting changes in the research world. Thanks for joining today's NIH Collaboratory Grand Rounds Podcast. Let us know what you think by rating this interview on our website. We hope to see you again on our next Grand Rounds, Fridays at 1:00 PM Eastern Time.