



PODCAST TRANSCRIPT

Research Fundamentals: What is an Endpoint?

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Jeanne Baron [00:00:01] Designing a clinical trial is serious business. If it's done correctly, researchers are going to be able to answer the central question: Are we studying something that makes a difference? Does this drug or this vaccine—is it helpful?

Matthew Rose [00:00:19] But designing a trial can go wrong. The trial can fail to deliver an answer. One key to getting an answer is by defining the endpoints, the outcome the trial will compare.

Jeanne Baron [00:00:32] Right, an outcome between two groups, one group that got something new and one group that didn't.

Matthew Rose [00:00:37] And in this episode of the Px Pulse series, Research Fundamentals, we're going to be talking about endpoints and why they matter with three experts:

Meagan O'Brien [00:00:47] My name is Meagan O'Brien, and my title is Senior Medical Director of Early Clinical Development and Clinical Experimental Sciences at Regeneron.

Erica Lessem [00:00:58] My name is Erica Lessem. I'm the Deputy Executive Director at Treatment Action Group and we are a science and community-based activist organization.



David Glidden [00:01:07] My name is Dave Glidden and I'm a professor of bio-statistics at UC San Francisco.

Jeanne Baron [00:01:18] So first, what's an endpoint?

Meagan O'Brien [00:01:21] Yeah, the endpoint is an objective measure, a validated measure, an accepted measure that sees whether or not something works.

Erica Lessem [00:01:30] What research is really trying to do is ask a question and get that answered. And so I think of the endpoint as the measure of that answer.

David Glidden [00:01:40] When we're comparing across different kinds of drugs or regimens in a study, they're a way of scoring who the winner is.

Erica Lessem [00:01:52] There can be a lot of different endpoints for how we might try to measure the answer.

Meagan O'Brien [00:01:56] So mortality would be the hardest endpoint, or survival said another way.

Matthew Rose [00:02:02] For example, for the first decade of the AIDS pandemic trials, we were focused on finding treatment that could keep people alive. So researchers were looking at the number of mortalities as an endpoint. For prevention, up until now, the endpoint has been the number of infections. As researchers learn more about a disease, the endpoints change. Take the tale of HIV treatment:

Erica Lessem [00:02:28] When we didn't have a good way to measure the HIV virus itself or even the immune response to the virus, one of the only ways that we had to

measure whether drugs were doing something was to look at how sick someone is getting, or whether they die.

Jeanne Baron [00:02:41] It's not like that anymore. Scientists now know how to measure HIV in the body and suppress it. A trial can test new treatments and use a person's so-called viral load as the endpoint. That means nowadays trials are not tracking if they're keeping people alive with a new treatment. They track the viral load long before anyone is even sick. But when it comes to prevention, researchers have yet to find something to look for in the body as a sign that a prevention drug is working.

Matthew Rose [00:03:11] Because when it comes to prevention, we're not entirely sure what the body needs to do to protect itself. That holy grail of HIV prevention research is called the "correlate of protection".

Jeanne Baron [00:03:20] Once found, prevention studies will track that correlate of protection. That will be the new endpoint, enabling researchers to know something works before anyone's even exposed to HIV.

Jeanne Baron [00:03:34] But the thing to remember is the endpoint should tell you what the intervention is good for: cure, prevention, milder symptoms, a quicker recovery? And that endpoint better makes sense.

Erica Lessem [00:03:47] The most unworkable endpoint is one that doesn't reliably correlate with an outcome that we care about.

David Glidden [00:03:53] I think I really want to stress that endpoints should be something that are highly relevant to a particular population.

Jeanne Baron [00:04:04] So endpoints need to be relevant, explainable and achievable. One great example are the studies the tested oral PrEP. They used new infections as an endpoint and ultimately showed that oral PrEP did in fact protect against HIV.

Matthew Rose [00:04:21] I love a good nerd moment, but why is it so important to know about this stuff right now? Why do we care about endpoints so much right now? So in HIV prevention, the field is really sweating over endpoints. Two big facts bedevil trial design today. The number of new HIV cases has been really high for decades.

Jeanne Baron [00:04:41] And up to now, new infections have been the endpoints for clinical trials.

Matthew Rose [00:04:46] But oral PrEP works really well if you take it. And trials provide PrEP to their participants to stay negative. Together, this all means that the world needs more trials to test new options. But reaching the endpoints will be a challenge.

Jeanne Baron [00:05:01] So just to reiterate, in the real world, something like 1.5 million people are getting HIV every year, which means today's HIV prevention tools are not reaching them or fitting into their lives. But in trials, the number of people who will get HIV might be very tiny because the trials do a good job of supporting people to use existing prevention tools.

David Glidden [00:05:25] We've seen in the last couple of HIV prevention trials that have read out incredibly, strikingly, low levels of HIV.

Erica Lessem [00:05:40] It makes the trial a lot harder to conduct because you have to enroll a lot more people to get the potential number of endpoints to be able to see a difference in the arms of the study.

Jeanne Baron [00:05:51] To solve this, brand new trial designs are already under consideration, and they're going to be complicated.

David Glidden [00:05:59] A big part of my life these days is assessing ways that we might credibly estimate how many people in a study might have become HIV positive had they not received a prep agent.

Jeanne Baron [00:06:17] So endpoints are a big deal in HIV prevention right now, because the field is struggling to find an endpoint other than new infections. COVID research also shows why understanding endpoints is so important. When trials for a COVID vaccine began, the endpoints were tracking if the vaccine candidate prevented severe disease or death, but the endpoints did not track if the candidates prevented infection.

Matthew Rose [00:06:44] The [trials] were actually designed to test if the vaccines reduced severe disease and reduced death. Those were the endpoints the trials were looking at.

Jeanne Baron [00:06:51] But not everyone understood that. There's been a lot of confusion about breakthrough infections. But with millions now vaccinated, the results are in. COVID vaccines do not stop all infections. They do protect people from dying, and they lower the risk of severe disease. Those are the endpoints the trials were tracking all along. In other words, COVID vaccines are fulfilling the promise seen from the trials. But you have to understand the endpoints to see that,

Matthew Rose [00:07:19] Which is why it's so important that these endpoints make sense. And to take a broader view, thinking about the research to come in COVID-19, TB, cancer, malaria, HIV—scientists, advocates and community members, all stakeholders need to be looking at trials and checking the endpoints. It's like kicking the

tires on a car, you know, make sure that these things are relevant, are achievable and matter to your community.

David Glidden [00:07:46] Yes, advocates represent an opportunity for partnership that's critical for the success of research.

Meagan O'Brien [00:07:56] More and more, it's highly recommended that even in the design of studies, we should be involving advocates and patients that suffer from the disease. Even in the very first stages of the idea.

David Glidden [00:08:13] Researchers need engaged advocacy. It is incredibly important for good science. I believe that advocacy and researchers make better science together.

Jeanne Baron [00:08:32] In HIV prevention research, better science may involve endpoints based on estimating how many people in a trial might have become infected if they hadn't received Prep. And those endpoints will continue to evolve. Taking all these next steps must include a partnership between researchers and advocates, because if the endpoints don't reflect a research question that's relevant to people, you'll end up with a product nobody uses. Thanks for listening to PX Pulse.