What’s an Endpoint?

Understand what matters most about clinical trial endpoints for both advocates and researchers.

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The following is an edited transcript from an episode of Px Pulse, a podcast from AVAC: Global Advocacy for HIV Prevention. The conversation includes Jeanne Baron, the host of Px Pulse; Matthew Rose, a director at Global Health Strategies; Dave Glidden, a professor of biostatistics at the University of California at San Francisco; Erica Lessem, a senior strategist for the New York City Department of Health and Mental Hygiene; and Meagan O’Brien, the senior medical director of early clinical development and clinical experimental sciences at Regeneron. —Oriol R. Gutierrez Jr.

Baron: 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?

Rose: But designing a trial can go wrong. The trial can fail to deliver an answer. One key to an answer is by defining the endpoints, the outcomes the trial will compare.

Baron: So what’s an endpoint?

O’Brien: The endpoint is an objective measure, a validated measure, an accepted measure that shows whether or not something works.

Lessem: 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.

Glidden: When we’re comparing across different kinds of drugs or regimens in a study, they’re a way of scoring who the winner is.

Lessem: There can be a lot of different endpoints for how we might try to measure the answer.

O’Brien: So mortality would be the hardest endpoint—or survival, said another way.

Rose: For example, for the first decade of AIDS pandemic trials, we were focused on finding treatment that could keep people alive. So researchers were looking at the number of deaths 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.

Lessem: 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.

Baron: 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 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.

Rose: 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.

Baron: 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.

Baron: 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 make sense.

Lessem: The most unworkable endpoint is one that doesn't reliably correlate with an outcome that we care about.

Glidden: I want to stress that endpoints should be something that are highly relevant to a particular population.

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

Rose: 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.

Baron: Up to now, new infections have been the endpoints for clinical trials.

Rose: 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.

Baron: 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.

Glidden: We've seen this in the last couple of HIV prevention trials that have read out incredibly, strikingly low levels of HIV.

Lessem: 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.

Baron: To solve this, brand-new trial designs are already under consideration, and they're going to be complicated.

Glidden: 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.

Baron: 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-19 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.

Rose: 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.

Baron: 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.

Rose: Which is why it's so important that these endpoints make sense. And to take a broader view, think about the research to come in COVID-19, TB [tuberculosis], cancer, malaria and 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.

Glidden: Yes, advocates represent an opportunity for partnership that's critical for the success of research.

O'Brien: 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.

Glidden: Researchers need engaged advocacy. It is incredibly important for good science. I believe that advocacy and researchers make better science together.

Baron: 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.

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