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Real-World Data and the Quality of Evidence in Reversing Anticoagulation: I'm Not a Skeptic… Just a Purist of Clinical Trials!

Announcer:
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Dr. Crowther:
Again, just to highlight some of the differences and the approach that you need to have when you're interpreting clinical trials data that is rigorously done, randomized, or not necessarily randomized, but at least prospective and defined and enrolled data with real-world data, you have to understand the positives and negatives of the two of them.

So the first and most important thing is that clinical trials data, it must pre - come before real-world data to demonstrate that the intervention actually works, because you can show essentially anything you want from a dataset about whether a product actually works when you're dealing with frequency - outcome frequencies that aren't hugely different, as Paul identified. Hemostasis efficacy is going to be very similar. And the problem then is that in real-world data, you can make lots of different stuff look real. And that's what I call the fake news of real-world data. Rumor and innuendos inform its effectiveness rather than facts. So you want to have definitive evidence that the intervention actually works.

And you want that definitive evidence, particularly when interventions have small incremental benefits or when the outcomes are uncommon. Because perceptions of efficacy in that setting will outweigh the realities of what the data suggests. And this happens all the time in medicine. I can cite many examples. One of them, you know, for example, how many people in this room take a vitamin every day? Yeah, so people are putting their hands up, like there's no evidence that vitamins do anything, right? You just basically - it's more efficient to take the vitamin tablet and drop it directly in the toilet. Because that's essentially what you're doing if you eat a reasonable North American diet. And yet, there's a widespread idea that they do something, and, oh my god, antioxidants reduce cancer. Actually, the big studies that have been done suggest it increases cancer. So you know, there's - the perception of real-world efficacy can outweigh the evidence. The evidence is that if you eat a reasonably normal North American diet, you don't need to use vitamins.

So we continue the theme, the real downside of clinical trial data, as I mentioned earlier, is the expert center effects. It ignores issues such as cost because the drug is provided for free; access, because if the study is open, you have access to the drug, and you can provide it; training of staff, because all of the staff are experts, they're trained in how to provide the intervention. And as a result of that, you can make the assumption very reasonably that any center participating in a clinical trial meets the minimum standard required to be able to deliver that. Whereas in real-world data, you can't assume that. If you're in a randomized control trial, and you're enrolling 10 patients a month, you're going to develop an expertise. And then if you're in a small clinical center, and you're going to use that intervention three times in a year, you're just not going to have that expertise. And so you need to build that into your planning about how you're going to use it.

Another thing, the issue of covariates. So if the intervention is really expensive, then people with great insurance are more likely to get the intervention. But those people with great insurance are more likely to get all interventions and to get better quality rehab, and to actually have better follow-up. And so you know, how much of the real-world result that you're seeing is because of the fact that patients were selected based upon their socioeconomic circumstances.

And another area is you might consider using real-world data in areas where there's limited data. But where there's no really scientific data yet. And so for example, it's very likely that in the real world, andexanet alfa is going to be used in the perioperative setting. In fact, there's papers published suggesting that. And of course, there's no prospect of data to support the efficacy of that intervention. It makes

sense. You know, I think if I was on rivaroxaban, and I had a big triple A that burst, and I had taken my dose 2 hours ago, and I was going to go have an open triple A for some reason - repair, I'd probably want some andexanet alfa.

I think that would actually be quite reasonable. But there's no prospective data to support that. So there, we do have to rely on real-world data, in order to be able to justify that use until the clinical trial comes along. And again, as I mentioned in my talk yesterday, if you heard it, that study is actually starting up, which is what we need in order to get the approval, which will then allow us to use it, not off label.

And the outcomes, as you've heard repetitively during the course of this anticoagulation forum, you know, 10 years ago, bridging was all the rage, and yet, bridging kills people. It increases the risk of major surgical complications in some settings by tenfold, and bridging is hardly ever used anymore. But if you - if you'd ask people in this audience 10 years ago, do you bridge people? Almost everybody had bridging almost everybody. We used to bridge almost everybody. And that was because there was a perception based on real-world data, that bridging was a highly effective intervention.

Just remember that when you're talking about real-world data in the setting of anticoagulation reversal, that the outcomes that you're talking about are extraordinarily soft. So Paul highlighted some of these, time to effective hemostasis and normalization of bleeding.

Real-world data applies to a population, not to an individual. So because we understand the individuals enrolled in randomized controlled trials, if the person sitting in front of you would have been eligible for that study, which is a big if, you can say with some confidence that the results of that study can be directly extrapolated to them. Whereas, you can't do that with real-world data, because the average patient is kind of got big confidence intervals around them. So it's hard to say to an individual patient that this intervention is going to work with this frequency.

Whereas real-world data, it's great for applying to a population. So if you have really good real-world data, like Paul presented on andexanet alfa, you can say with confidence, that if you implement it in your site, you're going to achieve some of those same benefits. But it's hard to translate that to the individual patient, because you can't distill that data down to the same kind of knife-like edge that you get in clinical trial data.

And so to meet the needs of full disclosure and informed consent of patients, you really do need clinical trials data, so you can tell people about what actually happened in the studies. But when you're talking to the patient in a general sense about the benefits to them of receiving this therapy, you really need real-world data, as well as the clinical trials experience, so that the patient can really understand what may happen to them, particularly with respect to rare outcomes.

So in summary, although real-world data is useful in informing treatment, clinical trials data is a necessary prerequisite to inform factual decision-making, and to avoid the influence of what I call fake news. And remember, the vitamin thing, that vitamins are fake news, as is beta-2 glycoprotein 1, who heard my talk yesterday, and David's going to highlight tomorrow. But real-world data, it's incredibly valuable. And it's something that we really need to have, because it provides very useful information in the many clinical areas and specific subgroups, where we just will never have clinical trials data. And that's going to be the large majority of the clinical circumstances.

Announcer:
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