Podcast 42: FDA Draft Guidance on Real-World Evidence

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 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.

Richard Platt: Hello, everyone. This is Richard Platt representing the NIH Collaboratory Coordinating Center. We're here today with John Concato of the FDA, who's going to talk with us about a deeper dive on the topics that he covered during the June 24th Collaboratory Grand Rounds that were focused on the FDA's draft guidance on real-world evidence. Before we dive in, John, it would be great to have you introduce yourself and explain to our audience what your title and role is at the FDA, particularly with regard to this real-world evidence initiative.

John Concato: Thanks very much. I'm pleased to be here. And I'm in the center for drug evaluation and research in the Office of Medical Policy. And what me and my team do is coordinate activities related to real-world data and real-world evidence, but certainly, with the collaboration and support of other offices, and for that matter, other centers at FDA, we try to work hard, even though there are different applications of real-world data, real-world evidence to have a unified approach, to the extent that makes sense from a capital P policy perspective.

Richard Platt: So you explained to us, I think, that this initiative really follows a mandate from the US Congress as part of the 21st Century Cures Act. If that's correct, could you tell us how the FDA respond to a congressional act that instructs it to do something?

John Concato: Well, I'll limit my answer to how the FDA reacted to this congressional mandate, given that I've been at the FDA for four years, which is not as long as would be necessary to provide a broader perspective. But I think I'll start with highlighting the fact that within two years of the 21st Century Cures Act being passed, which was late 2016 as we know, I would say that the publication of the framework for FDA's real-world evidence program, and secondly, the formation of the Real-World Evidence subcommittee, both in 2018. And I could talk as much or as little as we want to about these two. These are foundational responses because the framework outlines the structure and focus of the Real-World Evidence program that I described on the 24th of last month. And the Real-World Evidence subcommittee oversees the implementation of that program. Again, they're not solely responsible, but they're the center of gravity. And I would say that, beyond that center of gravity, there are multiple offices and centers. The subcommittee includes senior leadership representation on the subcommittee to make sure, again, that we have effective communication.

One of the challenges was to determine what's in and what's out, what's in scope. I would just point out that the definitions of real-world data and real-world evidence in our 2018 framework dictate what's in scope, but I'll also fast forward to say that, ultimately, it's the review divisions that decide on approval of submissions as they do with other sources of data and study design, such as traditional randomized trials.

And then one other thought, Rich, from another perspective, one could say that drug outcome associations exist if we had a way to identify capital T truth. So our job at FDA is to evaluate submissions of such associations regardless of the data and design approach taken by sponsors if that helps you.

Richard Platt: Well, it does. One thing that interested me enormously, I mean, I've been paying some attention to this topic for a while. And the term real-world evidence was top of mind for a lot of people before the 21st Century Cures Act came along, as has been the case other times, FDA really gives body and substance and definition to a concept that can mean a lot of different things to a lot of different people. And I hear you that this committee and this document are foundational. How does FDA take a congressional mandate and turn it into that foundational activity? Is there a way that the FDA processes that instruction?

John Concato: Well, I think it's a case-by-case approach with a lot of similarities across different topics, but that would be a discussion unto itself. I think, again, I wasn't around for all of this, but my sense, since I have joined, is that given that underlying sources of data and types of study design, while they're evolving, and we could talk more about what I had in these slides regarding big data and when the terms real-world data, real-world evidence started to really catch on, despite the fact that they've been around for decades, I think, again, underlying fact, is that data sources and designs haven't radically changed. So basically, yes, it's been true that, for decades, FDA has seen mainly "traditional" randomized controlled trials, and now we're broadening that scope to say when and how can other data sources and study designs meet our standards for drug approval. That is standards of substantial evidence of effectiveness.

And by the way, we've been using what we now call real-world data, real-world evidence for safety associations to look at safety for decades and just didn't call it real-world data, real-world evidence until now. So I think really we have to keep things in perspective. And here, I'm not saying it was easy. It took a lot of work in a lot of people, but we looked at the mandate, and we responded, and we were able to, for example, in a very concrete way, thanks to Congress for the cures act, and for the support, and for the clarity that they provided, but the work products correspond to the mandates, including the guidance documents within five years of passage, which we honored by publishing the four guidance documents that I mentioned by the end of 2021.

Richard Platt: Right. So you've touched on a pretty important topic. Help us out. Were those guidance documents just topics described in the act or did the agency need to partition the larger topic that way?

John Concato: Yeah. I certainly looked at the act, and I would have to go back to be sure, but my recollection is they were not identified per se in the act. Rather, I do know that the 2018 framework mentions guidance topics from, I would call it, a general or conceptional viewpoint. The titles weren't there, or even pseudo tentative titles. I would say that the high level decision might be characterized informally as do we lump or do we split. Lump would be a single uber guidance that tries to cover it all. Split would be what we ended up doing, if that's not obvious. We had two guidances on specific types of real-world data.

It's actually three types, but EHR and medical claims were lump together in one guidance. Registry data as a second guidance or type of data, if I'm being clear. And then the third guidance of four is on data standards more, I don't want to say administrative, but more practical in terms of getting the data into FDA since, again, for decades, the norm had been trial data. And then the fourth on regulatory considerations because our investigational new drug applications, IND regulations, under, sorry, 21 CFR part 312 pertained to trials were drafted with trials in mind. So we wanted to give sponsors another stakeholders and idea of what to do when B12 "doesn't apply."

Actually, one other common, Rich, before I lose the thought. You pointed it out, and I had it in my slides at RWD, RWE appeared in the medical literature actually probably premed line, but certainly, in the '60s, and more so in the '70s, but a trickle compared to what it is now. And it was really in various contexts, just meaning, in a very general sense, real-world, not the way we have it now. So I think the FDA isn't solely responsible, but the regulatory aspect and the drug development focus, I think, changed a lot. Didn't change everything, but made a difference in terms of how we're talking about real-world data and real-world evidence at this time if that makes sense.

Richard Platt: It makes plenty of sense. I think I said it earlier in this conversation, but to be perfectly explicit, this is an example of FDA leadership really providing definition that extends, I think, well beyond the FDA's own regulatory interest, and I think will provide a template for uses throughout our society.

John Concato: We hope it could be helpful. I mean, we don't have blinders on. We recognize our authorities and where they end, but we certainly want to reach out, and engage, and try to be helpful in that regard, recognizing that we're just one agency in one part of the challenge. I'm not a historian, sociologist, anthropologist, or whatever combination thereof would apply here, but I do think, to get back to your original question, was changed is mainly big data, which probably needs a definition. We talked about that in the presentation, but it's really the availability of more data. Yes, evolution of methods. But I'll give a nod to my former mentor, Alvan Feinstein, who published a book in 1985 called *Clinical Epidemiology*, talking about non-trial methods. And I'm not saying

such designs were dismissed, but clearly, for a long time, "observational research had a second class citizenship status."

And I'm not saying that was not totally surprising or necessarily unwarranted. There are more ways for observational studies to get the wrong answer. But I think it's a fascinating of, just to use a single term, historical perspective of how things are changing. And it's crystal ball gazing to try to determine what will happen going forward, but our view, and certainly, my personal view is strong science, rigorous methodology, and looking down a road a bit, but one step at a time, try to do things fundamentally right is probably the best step forward. And we'll know in 2020 hindsight, over time, what works and it doesn't work, and we'll build on success.

Richard Platt: So that's all true. And you're being gratifyingly modest. I'm going to stick with my view that when we use our 2020 hindsight, we'll say that this set of guidances that FDA is developing really proved to be a turning point for our making appropriate use of this avalanche of data that is accruing in our society.

John Concato: Well, thanks. Can I make two quick points?

Richard Platt: Sure.

John Concato: Just that popped into mind. One is that I'll give a nod to the Center for Devices and Radiological Health that, in 2017, so a year prior to the 2018 framework, they published a guidance. So two things, one is I should have mentioned already, the 2018 framework is CDER and CBER, Center for Drugs and Biologics, obviously. And by extension, the Oncology Center of Excellence. Whereas, the device center, devices have their own regulations. So it's not a good or bad or one is right and one is wrong. Rather, this is speculation on my part. But given that it was a bit earlier in the era, a single guidance was more manageable.

We decided to go this split route, and this is hindsight, but it was the right decision. It's more of what might be called a modular approach. Yes, you have to read all of them to get the full picture, but if we tried to put all of this into one guidance, I think it would've been less useful to stakeholders. So maybe, over time, we could revisit that, but I'm talking years not months. And certainly, our first order of business is to convert draft guidance to final guidance, as you know, in an 18 month timeframe. And we have comments in the docket to work with from stakeholders, which we appreciate. So that's further description of the process inside the FDA operations.

Richard Platt: Terrific. Thanks. In addition to you and your colleagues being thoughtful, the FDA and your office in particular have sponsored some primary research. And you describe that nicely in your presentation. Could you talk about how the results of that research has influenced the actual guidances that you've created?

John Concato: Thanks for the question. And actually, coming from academia, 25 plus year career prior to joining FDA, this is, I guess, near and dear to my heart, as can be said. But I would offer that I think our Real-world Evidence demonstration projects are a very important component of the CDER, CBER program that I just described. As you alluded to, the Office of Medical Policy coordinates over 20, and some of these have been completed, but our portfolio, cumulatively, is up to 20 plus, I'll call them, core projects, but they don't represent all such projects at FDA, nor even all projects related to Drugs and Biologics. For example, other offices in CDER and CBER, as well as the Oncology Center of Excellence, also support RWE-related research. It's just too numerous to mention, but we have several different funding mechanisms, including health and human services, U01 awards that four out of 31 applications. I think I had a slide on that are very prominent, but the others are equally important.

I invoke the phrase, seeding the field intentionally, again, with the best science. This is not just putting money here and there. Rather, it's a competitive environment. But in the three categories that I alluded to of improving the quality and use of real-world data, exploring methods to generate real-world evidence, that's where study design might be in parentheses if I were jotting this down, and developing tools to move the field forward. They're not really mutually exclusive. They're more informal categories, but I will say the results that we have, a summer interim, some are final summer are pending, but they've informed our draft guidance. And also, they've informed the field. I think they will continue to be impactful going forward.

I really hope that the return on investment from these projects... Actually, more than hope. I'm cautiously optimistic or bordering on confident that the return on investment from these projects can and, hopefully, will be, if not huge, large, both intangible, and even if they're intangible ways, just to basically invoke the phrase. And if I use this in the presentation, I feel an urge to apologize for using it twice, but a rising tide lifts all boats. We really need to just roll up our sleeves and do work in this area. And even if some of the projects... They're not all high risk, but if some of the high risk projects fail, in the name of good science, I think we have to go there. If everything we do is so safe, we're probably selling ourselves short in terms of making progress.

Richard Platt: Okay. So I'm hearing you say that, to some extent, these projects will inform the final guidance, and, to some extent, they will contribute to better capabilities after the guidances are finalized. Is that a fair?

John Concato: Yes. Yes. I mean, again, I'm not averse to talking about projects in detail, but in the interest of time, I don't want to suggest that naming one means that the others aren't equally worthy. A couple come to mind. One source at UCSF is trying to improve the quality of real-world data. I think I had a slide on this, where why wouldn't clinicians want so-called research grade data, but if we can improve the quality in the second bucket of design, the RCT-Duplicate project with an award to Brigham And Women's Hospital, that's where trial emulations, which is a topic unto itself. Again, we think of it as a new topic. It goes back to...

Pick a decade. I could give you authors, '60s, '70s, '80s, '90s, but now it has more meaning. Now that we have big data, we could take observational analyses of, say, claims data and see if we can replicate clinical trials.

And it's not as if we're citing these projects necessarily superscript references, Rich, in the guidances. Rather, they provide a more rigorous context for our thinking about the guidances, but mainly, the guidances provide stakeholders with the path forward. As the blurb says in the introduction of each guidance, FDA's current thinking, FDA's recommendations, they don't have the force of law regulation, but they help communication between FDA, and sponsors, and other stakeholders.

Richard Platt: That's a great intro to one of the things I was hoping we could talk about. That is, if an organization would like to use RWE to support a request to FDA, how can it find out whether the FDA is likely to accept what it has in mind since the guidances will leave us with a framework, but won't be a checklist that will automatically let somebody know whether they're on solid ground?

John Concato: Right. Checklists and good science, it's not that simple as a checklist in any case. I will say there's a lot to unpack with your question. A great question. So I'm trying to think of how best to be concise here. Well, first, whether before or after the guidance are finalized, I think it's always true that early engagement with FDA is important and sometimes underappreciated. And by that, I could offer the example of, we sometimes get submissions from sponsors who've done extensive work on an idea that just doesn't hold promise from our perspective. So even like a pre IND meeting, as early as that, for example, can be held to as discussed ideas.

A second issue, and this came up in the presentation was the need for pre-specification and transparency to oversimplify, unlike clinical trials, where data are collected once according to a research protocol. We know real-world data sources, first, there are many to choose from. They could be more easily manipulated. And non-interventional study designs, they present a situation where multiple analyses can be done, providing an opportunity to pick the winner, say, regarding significant findings if a sponsor doesn't follow best practices. So we are working to address these issues, but I will, again, for those listening, offer that stakeholders can work together to make progress in this area. Again, in the name of rigorous science, that gives us the confidence to reward research that is rigorous.

But to get to the core of your question, if I understood it is, this was definitely one of the slides. I don't remember the number. It's very high level. It's not so much a reviewer systems for my clinical training. It's more of how we frame the history of present illness, but sorry, I digress. But the three consideration categories are, first, whether the data are fit for use, second, whether the study design is adequate to address the research question, and third, whether the study conduct adhered to FDA regulations. They're all important, but what we see probably most often is whether the data are fit for use, criterion not being

met, that sponsors might do the best they can with the data, but the data just weren't up to the level of reliability and relevance needed to address the question of interest, scientific regulatory question. So it's important to remember that FDA has and will retain one evidentiary threshold regardless of the data source or the study design.

And actually, I've thinking of one other thing that I hadn't mentioned in the rounds, which is we have a guidance. It's not that we're not happy to talk about it, but it seems very administrative. It's called submitting documents using real-world data and real-world evidence to FDA for drugs and biologics. It's actually about to be published as a final guidance.

I want to emphasize that, here and now, because it's basically a way to flag real-world evidence being submitted to CDER and CBER, so in that sense, we're asking sponsors to help us to help themselves by having this become a little bit more standardized because there are examples of false positive and false negative real-world data, real-world evidence. We might not have time to get into that, but I'll just give two quick examples.

A false positive would be, we use real-world data to finalize our eligibility criteria or to select trial sites. Well, with all due respect, trials, since streptomycin in the 1940s, needed to find patients somewhere. So that's not real-world data directly pertaining to the drug-outcome association, it's preparatory to the study. And I would say the false negatives are, we get submissions, like with external control arms, that have real-world data. And they just describe the study as an external control trial, which it is. And that's fine. That occurred before 21st Century Cures.

So, it's not so much that the review process would be affected, but in terms of a new congressional mandate, when PDUFA VII is reauthorized by Congress, we will have a new mandate to track real-world data, real-world evidence. So we want to be precise with our terminology, which is another hallmark of good science.

Richard Platt: Great. You've hit on a couple of things that I think is really important for us to make clear. One is, when you say we make a decision, that's the reviewing divisions that are ultimately charged with making those decisions? Is that correct?

John Concato: Yes. The authority for approving drugs, and in fact, in biologics, etc, is not different for real-world data, real-world evidence. There's no two-track approach. But as is true for that matter with traditional trials, the strength of FDA is in the quality of its staff. And I'm new enough to be able to say this without, hopefully, it sounding too whatever. But the point is that the real-world evidence subcommittee, the Office of Surveillance and Epidemiology, the Office of Medical Policy Real-world Evidence Analytics, there are many different offices that can be brought to bear across the spectrum of different mechanisms to make sure that the details or even the nuances of the real-world data, real-

world evidence are part of the process in the review. Again, we talked about Prograf Tacrolimus in the laboratory Grand Rounds, as an example. Again, we could only scratch the surface of the process involved, but I would offer it was a wonderful experience, a very satisfying, professional experience of everyone involved at the FDA. So many people, and countless person hours, but to get this right.

And if I didn't mention it in the talk, I think I did, the review for Prograf, the most recent approval for lung transplantation is available. We had that publicly released in advance of anyone requesting it, just to show that we want to be transparent with our processes. Now, it's an N of 1. One has to be careful not to assuming that you could copy paste or transplant, sorry, no pun intended to a different clinical area, but it does show that we maintained or evidentiary threshold for adequate and well-controlled studies. And just found that that particular case, the data, and the design, and the conduct of the study met our criteria, if that makes sense.

Richard Platt: Yeah. Terrific. And the other thing that you touched on is agency accountability for using RWE. You mentioned you expect the commitment in PDUFA VII. And PDUFA is the Prescription Drug User Fee Act, right?

John Concato: I'm sorry. Yeah. I had that spelled out on a slide, but I'm chuckling because whether, at the VA, or FDA, or other federal agencies acronym's right. But the Prescription Drug User Fee Act, yes. Time probably is too short to go into a lot of detail, but among various commitments, there's an advancing real-world evidence program that has several parts. But if I could summarize, one that I did not include in the slides, and I don't want to go into detail now. Nothing to hide, but the letter is published. One could Google it and read it. Basically, we want to have a formal process with the early engagement that I was describing and endorsing earlier, where we will accept a set number of very brief submissions, but we want, basically, the secret sauce, so to speak, here is to get sponsors to come in before they write hundreds, sometimes it could be over a thousand pages of a submission. And they do all this work only to find that FDA didn't see the same way at an early upstream point about, say, the data source of the design. So that's part of it.

But part of it as well is to have an ability to, or not an ability, a responsibility to track or classify a report on real-world data rule evidence. And that's where, again, we want to get this right. Some of the reports to be blunt, some of the publications now that are quantifying real-world data, real-world evidence. It's not that they're incorrect, strictly speaking, but they make dozens of decisions about what is or what isn't real-world data, real-world evidence. In fact, one, not that we predicted this, but I think we're on record. I'm on record early on, the year or two ago, was saying if one defines real-world data permissively enough, then 100% of studies are real-world evidence. And low and behold, a publication came out and said, I don't remember whether it was EMA or whose regulatory submissions they were looking at, but they found 100% of studies involved real-world data.

Now, maybe that's accurate, but I would say, what value added information does it provide if we get to that point? It just means that, if we think about it, again, it's a confluence of a scientific methodologic approach to data and design with a regulatory overlay of 21st Century Cures.

And we said in a recent new England Journal of Medicine article... And I'm not a trialist. I come from the observational world. We published in 2000 about observational results compared to trial results. But let me be clear. Trial patients exist in the real world. It's more of a continuum, not in either or, and trials sometimes lack generalizability, but again, it's not a binary space. It's not that they're totally non-generalizable. Some are less or more generalizable than others, and real-world data tends to be more generalizable, but you can also run into issues with a certain real-world data set, say, that's only available if the healthcare is only available for those who have higher socioeconomic status. So it's more of a continuum than in either or, and that was one of the misconceptions in our new England Journal piece, that it's not randomized trials versus observational studies. But again, we could talk about this for much longer than the podcast.

Richard Platt: Right. My take on what you've been describing for the past few minutes is, to me, a very admirable description of the agency being clear about not simply dancing with words to meet a congressional objective, but to really roll up its sleeves and put meaning and value to the instruction. Personally, I think that's really extraordinary. It's just what we taxpayers hope for, and you're delivering it.

John Concato: Well, thank you. And I'll put in a shameless plug for the federal government and being a good steward of taxpayer funds. The tech problems approval, Prograf, that I mentioned that I may or may not have mentioned this, but the data came from the Scientific Registry of Transplant Recipients, which is also a HHS-supported activity. So again, it's not intangible, but it would've been an intangible return in investment for those designing the registry back in the '80s when it launched. So in any case, we try to take advantage of what's available. And it's not as if it should be the federal government's responsibility alone, but I would say that we are most open to having our efforts be discussed, described, and criticize. In terms of a constructive criticism, we're always trying to do better. So thank you.

Richard Platt: Okay. Well, terrific. So John, thanks very much for spending this time with us. It's been really illuminating. Any parting thoughts you have that we should get on the record?

John Concato: Well, we've covered a lot of ground. I'm sure there's topics we missed, but I just want to emphasize that attention to fundamentals is key. I think we did talk about using precise terminology, selecting appropriate data sources and study designs, and conducting those studies and analyzing results rigorously. I do want to mention the slide, I don't remember the number, but that described representative problems when using real-world evidence should not be

underappreciated. There are so many ways it can go wrong. Sometimes I get feedback. Well, if there's a Gartner hype cycle, we don't want inflated expectations. We want the plateau of productivity. But I would just close by saying that big data has fundamentally changed the research landscape for drug development. And it's also true that research methods are continually evolving, but existing principles of epidemiology and clinical research apply to real-world evidence. So shortcuts can represent an ill-chosen route if one isn't careful. And I'll end on that cautionary note. Thanks.

Richard Platt: Okay. Terrific. Well, thanks very much. So I'll end the podcast by inviting our audience to join us in the next podcast as we continue to highlight the fascinating, informative changes in the research world.

Adrian Hernandez: 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 PM Eastern Time.