Real-World Evidence Webinar Series: Considerations Regarding Non-Interventional Studies for Drug and Biological Products
May 30, 2024 | 2-2:45pm *(eastern)*

Transcript

Welcome
Susan C. Winckler, RPh, Esq., CEO, Reagan-Udall Foundation for the FDA

Susan Winckler (00:01):

Hello everyone, and welcome. Thank you for joining us. I am Susan Winckler and I have the privilege of serving as the Chief Executive Officer of the Reagan-Udall Foundation for the FDA. The foundation is pleased to host this important discussion about recent draft guidance from FDA on considerations regarding non-interventional studies for drug and biological products. I have a few light housekeeping that we need to cover. I will note we have over 3,000 people registered for today's workshop and we are so pleased that you all could join us. For those who submitted questions as part of the registration process, we have those, and I'll be raising as many of those as we can in the question and answer session of this webinar. You may also throughout the webinar, submit questions or comments using the zoom Q&A function. As many of you know, but it's important to remind you, speakers will not be discussing any specific regulatory actions nor decisions in today's discussion.

(01:01):

The recording from today's meeting and the slides will be posted on the Foundation's website after the meeting. We also encourage you to submit your comments and questions about the draft guidance to the federal register. Now before we dive in, let me give you a brief overview of the agenda. In just a moment, Dr. John Concato will provide some opening remarks. Then Dr. Tala Fakhouri and Senior Counsel Stefanie Kraus will present an overview of the draft guidance and then we will turn to a time for questions and answers with our team from FDA. For those of you who've been joining us regularly, we have completed five webinars on each of five guidance documents that have been released by the FDA. Today we are exploring the sixth guidance document. If you're interested in viewing the recordings of the prior webinars, please visit the Foundation's website at reaganudall.org.

(01:55):

So a reminder of why we are here today. FDA recently released draft guidance on the topic of considerations regarding non-interventional studies for drug and biological products. A link to the guidance could be found in the Zoom chat now or on our website with the other event materials. I'll note that I have my copy at the ready as we prepare to hear from our speakers. I'll note again that FDA is very interested in comments and questions from the public about the guidance document, so please submit those to the docket, or if you have questions you would like considered to be addressed today, submit through the Zoom Q&A box.

(02:35):

With that, I am going to step out of the way and introduce our first speaker, Dr. John Concato. He serves as the associate director for Real-World Evidence Analytics in the Office of Medical Policy in the Center for Drug Evaluation and Research at FDA. Dr. Concato, I'll step away and you may have the microphone.

Opening Remarks

John Concato, MD, MS, MPH, Associate Director for Real-World Evidence Analytics, Office of Medical Policy, Center for Drug Evaluation and Research, U.S. Food and Drug Administraiton

Dr. John Concato (02:54):

Thank you very much, Susan. Welcome, everyone. Next slide, please. Since Susan mentioned the title of the guidance, I'll say next slide again, please. We can link today's discussion back to FDA's Real-World Evidence Framework for Drugs and Biological products of 2018. As the title implies, it is relevant to the Center for Drug Evaluation and Research, the Center for Biologics Evaluation and Research on the Oncology Center of Excellence. Although we collaborate and communicate frequently and readily with our Center for Devices colleagues, they have separate regulations and their own real-world evidence program back to drugs and biologics. The program has different work streams including internal agency processes such as consults to review divisions, external engagements such as listening sessions for a real-world evidence subcommittee demonstration, aka research projects such as Health and Human Services, UL-1 awards. And last but not least, what we're here to talk about today, guidance development, which happen to address congressional mandates and prescription Drug User Fee Act commitments.

(03:58):

Next slide, please.

(04:01):

So relevant to today's webinar topic, terms for study design in clinical research include interventional studies, aka clinical trials, which are defined in part by participants being assigned to a treatment according to a study protocol. With regard to today's guidance, we are talking obviously about non-interventional or otherwise known as observational studies where patients receive treatment during routine medical care, even if they receive a laboratory imaging procedures per a research protocol. Next slide, please. But this slide we step back to take a look at the broad landscape of real-world data and real-world evidence. Focusing on the center of the slide, we have three categories of randomized interventional studies, non-randomized, but still interventional studies, and finally, non-randomized and non-interventional studies. A little bit of jargon, but the next row down is more familiar to those of us who work in this space. Traditional randomized trials can use real-world data in planning such as to assess enrollment criteria or trial feasibility, or to support the selection of trial sites, but FDA does not consider that use of real-world data to be generating real-world evidence on a drug outcome association.

(05:15):

The three boxes to the right however do so, i.e. Generate real-world evidence. So trials in practice settings are one example where say a point-of-care trial collects outcomes using electronic health record data or the next box over externally controlled trials for a single-arm trial as an external control group that is derived from a real-world data source. And then of course, what we're here to talk about today, again, happens to be on the right-hand side of this slide, observational studies, whether they be cohorts, case controls or other types of observational studies. Next slide, please.

(05:51):

In terms of the figure just shown, this slide shows that FDA guidance over the past couple of years is covering the entire real-world evidence landscape. Starting at the top, we have a procedural guidance on submitting real-world evidence to the FDA. The next two rows down, EHR claims data as well as registry data are real-world data sources.

(06:10):

So the data considerations guidances, we appreciate that our data standard regulations did not anticipate the era of real-world data world evidence, so we have a guidance to talk about the submission of real-world data to what was otherwise clinical trial-based data sources. Next, we have regulatory considerations that covers the entire waterfront in terms of where regulations do and do not apply. And then the last three rows you see are design considerations. The prior webinar was on externally controlled trials. This webinar is on non-interventional studies, and we have a randomized trials and clinical practice setting guidance, which is under development. Next slide, please.

(06:51):

So with this introduction providing hopefully helpful background and context, we can now dive into the guidance document itself. Thank you.

Overview of Draft Guidance

Stefanie Kraus, JD, MPH, Senior Regulatory Counsel, Office of Regulatory Policy, Center for Drug Evaluation and Research, U.S. Food and Drug Administration
Tala Fakhouri, PhD, MPH, Associate Director for Policy Analysis, Office of Medical Policy Initiatives, Office of Medical Policy, Center for Drug Evaluation and Research, U.S. Food and Drug Administration

Susan Winckler (07:03):

Excellent. Thank you so much, Dr. Concato. Now I am pleased to introduce our next set of speakers who provide an overview of the draft guidance. Tala Fakhouri is the associate director for policy analysis in the Office of Medical Policy Initiatives in the Office of Medical Policy at CDER. And Stefanie Kraus is senior regulatory counsel within the Office of regulatory policy within CDER and FDA. So Stefanie, I'm going to turn to you first and we're looking forward to your comments.

Stefanie Kraus (07:33):

Great, thank you so much, Susan. We can go ahead to the next slide. Great. As John noted, we have a suite of complementary real-world evidence guidance documents and Tala Fakhouri and I will now walk you through our non-interventional studies guidance. Generally, this guidance focuses on non-interventional studies that are used to provide substantial evidence of effectiveness or safety of a drug. It provides considerations regarding the design and conduct of non-interventional studies that sponsors should consider when using these studies for regulatory purposes. Next slide, please.

(08:09):

We begin by defining certain terms used throughout the guidance. FDA has harmonized the definitions of real-world data and real-world evidence across the agency. Real-world data are data relating to patient health status and/or the delivery of healthcare routinely collected from a variety of sources. Real-world evidence is clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of real-world data.

(08:37):

We also define a non-interventional, otherwise known as observational study as a type of study in which patients receive the marketed drug of interest during routine medical practice and are not assigned to

an intervention according to a protocol. Next slide, please. The guidance is grouped into three sections, an overview, a background for the guidance and considerations for conducting non-interventional studies. Next slide, please.

(09:05):

Let's start with the introduction section. This section provides the definition of a non-interventional study that I just talked about, gives examples of these types of studies and explains how this guidance relates to other guidances in our suite of real-world evidence guidance documents. Next slide, please.

(09:22):

In the background section we talk about the impact the confounding and other sources of bias can have on inferences that can be drawn from non-interventional studies and stress the importance of identifying and addressing confounding and other forms of bias so we can distinguish a true treatment effect from other influences.

(09:40):

Next slide, please. Moving on to the consideration section. This section is designed to assist sponsors in identifying and addressing commonly encountered challenges when using a non-interventional study for regulatory decision-making. Next slide, please.

(09:56):

Let's start with the overview. Next slide, please.

(10:00):

The overview summarizes a key take-home message from the guidance, which is that sponsors should engage with the FDA in the early stages of designing a non-interventional study. We understand that detailed information may not be available or feasible to include at the time of early engagement with the FDA, but that shouldn't prevent early engagement. Successful proposals for non-interventional study design should ultimately address each of the elements that we describe in section three of the guidance. Now, I'll turn this over to Tala to discuss those elements and the remainder of the guidance.

Dr. Tala Fakhouri (10:35):

Thank you Stefanie, and thank you everyone for joining us today. If we could move to the next slide.

(10:41):

So what I'll do now is I'll walk you through the remainder of this guidance starting with the summary of the proposed approach. Next slide, please.

(10:48):

In this guidance, we note that sponsors should finalize the study protocol, including the research question of interest and the rationale for the study design before initiating study conduct. We also note that sponsors should describe briefly the approaches and candidate data sources they considered before deciding on the proposed approach and discuss why alternative approaches such as randomized trials or single-arm trials were not feasible in answering the specific study question. Then we also note that the discussion should reflect really an in-depth understanding of the use of the drug or the drugs of interest, the outcome or the outcomes of interest, as well as the capture of exposure outcomes and relevant covariates in the proposed study population. Next slide, please.

(11:49):

Now to enable FDA to evaluate proposals for non-interventional studies, sponsors should provide information on a list of attributes that we provide and the guidance and are listed here on this slide.

Specifically, we ask for information on the research question or the study objective and hypothesis, the rationale for using the proposed non-interventional study design, the choice of the study design, whether it's a cohort study, a case control study or self-controlled. And then finally, proposed selection of data sources to address these study objectives and hypotheses as well as any alternative data sources that may have been considered. Next slide, please.

(12:31):

Additionally, and also to enable the FDA to evaluate these proposals for non-interventional studies, we note that sponsors should provide information on study attributes that are listed here and in the guidance, specifically provide information on the results of any preliminary or feasibility studies conducted to assess which data source is fit for use to address the research question that is being posed and to estimate, of course, the statistical precision of a potential study without evaluating the outcomes for treatment arms. We also would like information on the proposed approach to support causal inference, whether you're using a target trial emulation or another conceptual approach in order to address confounding and other types of bias. And then we also ask for information or description on how ethical considerations such as issues related to human subject protection were addressed. Next slide, please.

(13:32):

After the summary of the proposed approach, we go into the study design and that's section 3(C). Next slide, based on the pre-specified research question that's identified, we also ask the sponsor to provide information and critical elements that are included here on this slide and in the next few slides, but also included in the guidance specifically, we ask for a description of the schema that describes the overall study design as well as the causal diagram to specify the theorized causal relationship. We also ask for information on the source population, and this is the population from which the study population will be drawn. And then for eligibility criteria information and the study population. And the study population is basically the population from which analyses will be conducted. And we ask for conceptual and operational definitions for key variables of interest and the status of any validation efforts that's been conducted to that point for these operational definitions as relevant.

(14:42):

Next slide, please. Also, in the study design, we ask for information on any relevant covariates and corresponding strategies to address potential bias. Importantly, we would like to have information on the index time, also known as time zero for all study arms and the approach to assigning that index date, including strategies to address potential bias that may be introduced by issues related to immortal time. We also ask for a description of the start and end of follow-up adverse periods, the planned approach to censoring and anticipated losses to follow-up, including the depletion of susceptible patients. Next slide, please.

(15:31):

After this study design, we list important attributes that we'd like information on as it relates to data sources. Next slide. Okay, so for data sources, sponsors should demonstrate the appropriateness of the proposed data source or data sources to address the specific hypotheses and research questions. Given that as many of you may know that the data sources used in non-interventional studies are often generated for purposes other than research, it is important that sponsors understand the potential limitations of such data sources and determine whether those limitations can be addressed, or if another data source should be pursued. Next slide.

(16:20):

Now for the data sources section, we also list a list of attributes that we'd like information on that includes the description of the proposed data source or data sources, how that data was originally collected, the rationale for choosing the data source or data sources, the relevance of the data to the drug outcome association of interest, and that is being studied, the appropriateness of the information on relevant confounding factors, and then of course, available information on data reliability including the method of accrual from the source data. Next slide.

(16:59):

The data sources section continues with additional lists of important attributes, and that includes a description of common data models that may have been used to provide a standard structure for sharing data from the various sources and the rationale behind the choice of this specific common data model. Available information on the timing of assessments for key data elements and the completeness of these key data elements is also important. And then the explanation of how the proposed coding is appropriate based on operational definitions of key variables. And finally, the appropriateness of the data relevant to the target patient population. Next slide.

(17:48):

That data sources section actually ends with three additional attributes, and that includes the quality assurance activities that will be performed on the extracted original source data, existing or potential links to other data sources. So you can think about merging data from an EHR or an electronic health record to claims databases, or linking a real-world data source to a mortality database to confirm outcomes, and then of course, plans for any additional data collections as applicable. Next slide. We end the guidance with section 3(E), which is on analytic approaches. And as you can see, a lot of these sections are really interrelated, so you might see some information that may be connected or repetitive with some of the other points. Next slide, please.

(18:44):

For the analytic approach, we note that the pre-specified statistical analysis plan should address the specific study objectives and detail the primary analyses and any secondary analyses. The plan should include information on various attributes that are listed here and in the guidance, and this includes the assessment of feasibility including sample size calculation and anticipated operating characteristics such as statistical power. Also, the statistical approach or method used to evaluate the treatment effect, including specification of the estimate end. We provide examples such as handling of intercurrent events and rules for censoring. We also ask for information on this specific approach to account for potential confounding factors including assessment of unmeasured confounding. Next slide.

(19:45):

The pre-specified SAP or statistical analysis plan should also include information on the evaluation of potential over-adjustment for intermediate variables that may be on the pathway between the drug outcome relationship. Then the approach and rationale for subgroup analyses if these analyses were done and as applicable, and then the approach to address the potential for unequal detection of outcomes across compared groups. This is really addressing that issue of differential surveillance or differential misclassification. And then the approach to evaluate the potential for early manifestation of the outcome prompting the exposure, and really this is touching on an important issue in non-interventional studies, and that is reverse causality. Next slide.

(20:36):

The pre-specified statistical analysis plan should also include information on the approach to handling missing or misclassified data. Another issue with the use of some of these data sources and the approach to handling multiplicity. We also asked for a description of planned sensitivity analyses,

including details on which factors are proposed to be changed and the rationale for such changes. Next slide, please.

(21:09):

So we are really looking forward to all of your feedback on this guidance, and as noted earlier, the comment period is open until June 18th. We welcome your feedback either via an electronic submission or as a written submission. The FRN notice includes this information listed on this slide, but we also have access to it now in case you need direction on how to submit your comments. Next slide.

(21:40):

I would like to acknowledge all of our colleagues within the CDER, the Center for Drug Evaluation and Research, who were really instrumental in writing this guidance. Specifically colleagues, other colleagues from the Office of Medical Policy, office of New Drugs Regulatory Policy, the Office of Strategic Programs, Surveillance and Epidemiology, and of course the Office of Translational Science. We also collaborated on this guidance with colleagues from other offices and centers, including our colleagues in the Center for Biologics Evaluation and Research or CBER, the FDA Oncology Center of Excellence, and then our devices, colleagues in the Center for Devices and Radiological Health. Thank you very much. And I think now we move on to the closing remarks and questions.

Question and Answer

Moderator: Susan C. Winckler, RPh, Esq., CEO, Reagan-Udall Foundation for the FDA
John Concato, MD, MS, MPH, Associate Director for Real-World Evidence Analytics, Office of Medical Policy, Center for Drug Evaluation and Research, U.S. Food and Drug Administraiton
Stefanie Kraus, JD, MPH, Senior Regulatory Counsel, Office of Regulatory Policy, Center for Drug Evaluation and Research, U.S. Food and Drug Administration
Tala Fakhouri, PhD, MPH, Associate Director for Policy Analysis, Office of Medical Policy Initiatives, Office of Medical Policy, Center for Drug Evaluation and Research, U.S. Food and Drug Administration

Susan Winckler (22:29):

Exactly. Thank you so much, Dr. Fakhouri And Counselor Kraus, that was really helpful to walk us through the content of the document, and I can say from the questions that we got before this event, as well as the questions that are coming in through the Zoom Q&A chat that we have quite a few to sift through. So let me first remind our attendees that we will be posting the slides that you just reviewed on the Foundation's website after today's event that is reaganudall.org and under events. And so now let's turn to discussion. I don't think we are going to get through all of the questions that have been submitted, but we will get through as many as we can. So to get into the discussion, I welcome our speakers, Dr. Concato, Dr. Fakhouri, and Senior Counsel Kraus to come back on screen and let's dig in. I'm going to start with one that... Well, it digs into the word interventional. So here's the question.

(23:34):

Would you clarify what you mean by interventional studies and then how are interventions defined in a non-interventional study? Do you want to take the first shot at that one?

Dr. Tala Fakhouri (23:48):

Sure. I'm happy to take that one. And this is the essence of this guidance. Non-interventional studies. So this is described in the guidance. We've also touched on that elsewhere, and John just presented on this, but a non-interventional study is a type of study in which patients receive the drug of interest during routine medical practice, rather than receiving that drug according to a protocol. In contrast to a non-

interventional study, interventional studies, which sometimes we refer to as a clinical trial, are a type of study in which participants either healthy volunteers or volunteers with certain specific conditions or diseases being studied, they are assigned to one or more intervention with a drug according to a study protocol to evaluate the effects of those interventions on subsequent health-related biomedical or behavioral outcomes. Importantly, and we provide examples. John provided that example.

(24:52):

Examples of non-interventional study designs for evaluating the effectiveness or safety of a drug include things but not limited to just these examples, observational cohort studies in which patients are identified as belonging to a study group according to the drug or drugs received or not received during routine medical practice and subsequent biomedical or health outcomes are identified.

(25:20):

There are other categories including case control studies in which patients are first identified as belonging to a study group based on having the outcome, the health-related biomedical or behavioral outcome. So outcome first, not drug first. And antecedent treatments that are received are then identified. Then there's a third category, and we include that as an example in the guidance, and John mentioned that too, this includes self-controlled studies such as case crossover, or self-controlled case series types of studies where the person serves as their own control. So these are some examples of non-interventional studies, and I hope this draws this contrast between interventions and non-interventions.

Susan Winckler (26:11):

That was great, and I think what was most helpful is we avoided using intervention and non-intervention in the same... We helped explain it without saying intervention any more times. So excellent. Because of our time, I'd like to move to another question unless John or Stefanie, you want to add anything to that one? Okay, let's move to a second one. Oh, this one is a bit about timing. So this question asks, does the agency require that non-interventional protocols be submitted prior to study initiation? Stefanie, does that fit in your bailiwick?

Stefanie Kraus (26:53):

Yep. Happy to answer that one. It's generally in a sponsor's best interest to talk to FDA early in the design of an non-interventional study, and especially before finalizing the protocol and initiating the study. We actually discussed this topic at length in our guidance on regulatory considerations when using real-world data and real-world evidence to support regulatory decision-making for drugs and biological products. And so what we state in that guidance is that early engagement will actually help identify challenges with the proposed non-interventional study design or selected data sources in answering the questions of interest and how those challenges can potentially be addressed. So definitely please come talk to us early.

Susan Winckler (27:34):

I was going to say in moderating these webinars, I underline that as a key component of most of these, and it came up in a discussion about rare diseases and natural history studies. So it's a similar, I think structure come in early and have the conversation. Thank you. Okay, so here's one. This might be best for you, John, but I'll let you determine that. Can real-world evidence generated from non-interventional study designs be used to support labeling claims such as to add a new indication?

Dr. John Concato (28:14):

Well, thanks, Susan. I'm happy to take this question. The short answer is yes, potentially. A long answer is that the evidentiary standard to support a labeling claim for effectiveness is the same. You cannot emphasize that enough regardless of the data source involved or the study design used. So to support a new indication, sponsors must provide and many of the substantial evidence of effectiveness from at least one and often two adequate and well-controlled investigations. These adequate and well-controlled investigations are described in FDA regulations. None of us memorize this. We just know it's 314.126 if you're curious to look it up or Google it. But regardless, FDA uses those criteria independent of whether a sponsor submits an interventional or a non-interventional study as the three of us have described in this webinar. Does that help, Susan?

Susan Winckler (29:07):

It does. And so I appreciate it and internalize the yes, potentially.

Dr. John Concato (29:16):

Well, and by that I mean FDA is open-minded, we are willing to consider, but the truth is that there are more challenges to conduct non-interventional studies in general vis-a-vis interventional studies or clinical trials. So that reality should be recognized.

Susan Winckler (29:31):

And I think that might be helpful. That might be a good transition to talk about the data sets, which is the question I'm going to pick up next. So moving from the evidence generated back to that source material, what are the agency's expectations on fit for use data sets involving sources of real-world data? Dr. Fakhouri, do you want to pick that one up?

Dr. Tala Fakhouri (29:57):

I can take that one. It's also... We talk about data sources, the importance of the data and the guidance. This is also an issue that we address in the other RWD guidances, and it's a very important issue and a very important question. As we note in the non-interventional studies guidance, but also in the other guidances, FDA's focus is on the reliability and the relevance of real-world data. And we describe what we mean by these two concepts. We view reliability as including accuracy, completeness, traceability of the data. We also describe the term relevance, and we say this includes the availability of key study variables including exposures, covariates, and outcomes. And I emphasize that in the presentation just a few minutes ago, as well as having sufficient numbers of representative patients in the final analysis, determining whether an RWD source or sources are reliable and relevant can be difficult. It can be challenging, and it doesn't lend itself to a checklist approach. So instead, this really takes a lot of multidisciplinary approach where you have clinical, statistical and regulatory evaluations to make sure that the data is actually fit for use.

Susan Winckler (31:26):

And within that, I think it's accurate that it also... It's fit for use depending on the question that you're exploring.

Dr. Tala Fakhouri (31:34):

Right. And this is where when we think about relevance, it has to include all of the key variables, all of the key elements to be able to answer the research question.

Dr. John Concato (31:46):

Susan, may I interject?

Dr. Tala Fakhouri (31:46):

Please.

Dr. John Concato (31:48):

I agree with everything that Tala said. I would just also add that sometimes we see sponsors do what might be described as a good job with the data set available in terms of the study design and the analysis. But the data set itself as Tala and Stefanie said in their comments is just not sufficient, not up for the task, not fit for use. So I think sponsors have to be realistic in evaluating whether or not the context is suitable for a non-interventional study. The most elegant design and rigorous analysis doesn't make up for data that are not reliable and relevant as Tala mentioned. Thank you.

Susan Winckler (32:26):

Great. So it's that two-fold part. You have to have an excellent and well-structured plan and approach, but you'd also need to be working from data that is appropriate for the question that you're exploring.

Dr. John Concato (32:39):

And as a clinician, I'll add somewhat tongue-in-cheek, we don't blame the clinicians at the bedside for having collected the data for the purposes of patient care, not knowing that a sponsor or FDA or anyone else as a researcher would come along years later and try to do an analysis. Thank you.

Susan Winckler (32:55):

So that's really helpful in helping us connect how we construct the study and then the components about the data. So I want to pick up another data question, and this relates to data standards. So will the FDA accept data standards other than CDISC for real-world secondary databases? And what has been the agency's feedback on submissions of non-interventional study data that's in the CDISC format? I feel like if I said CDISC format that that needs to come to you, Counselor Kraus, does that sound right?

Stefanie Kraus (33:33):

That sounds right. I'll take this one. It's a great question. And there actually also was a question about this in the Q&A that relates to SDTM data files, which is part of the CDISC standards. And we appreciate the opportunity to discuss another guidance in our suite of real-world evidence guidances. So we address this issue in length in our guidance on data standards for drug and biological product submissions containing real-world data. In that guidance, we emphasize that our study data standards apply regardless of study design or data sources. We also discuss the challenges, as John mentioned earlier, in applying our current data standards to study data generated from real-world data sources. But we do provide means by which those challenges can be addressed. So if sponsors are going to seek a waiver of any requirement for submitting study data in CDISC format, they would follow the same process regardless of the data source.

Susan Winckler (34:27):

And so that's a good reminder. I think you had it structured this way in the beginning, Dr. Concato, where the guidance documents were together, they really interrelate in our building blocks in thinking through this process.

Dr. John Concato (34:41):

Yes, this issue comes up from time to time. One could theorize that we might've attempted to write a single so-called uber-guidance, but that would've been very long and arguably hard to find what you need. So it's more of a modular approach. We've received positive feedback about that. We hope that most sponsors and other external entities find it helpful.

Susan Winckler (35:05):

Sometimes it's the only way to get through a big topic is to address discrete components of it. Great. Well, so then let me turn to a question about... This is from one of our folks who I guess wants to learn from those who have gone before them and maybe avoid similar mistakes. So here's the question. Based on FDA's experience thus far, what are the biggest mistakes that sponsors make with regard to the design and conduct of a non-interventional study? Dr. Concato, do you want to keep the mic for that one?

Dr. John Concato (35:45):

Sure. Thanks. I think in answering the question, I'll first point out that among the mistakes that can be made in designing and conducting a non-interventional study, it's what I referred to earlier that sponsors don't recognize the inherent limitations of the real-world data source being analyzed. One has to be really honest and realistic about that evaluation. So stated another way, the best design, I think I said this earlier, and the most sophisticated analysis cannot overcome the problem of data that are not reliable and relevant.

(36:17):

But going beyond that, I think other problems that we see would include the expected challenges of sources of bias and confounding, and I think I saw a question in the chat about, well, exactly what type of biases should we worry about? I don't want to cop out by saying "it depends", but it really does depend on the context. So this takes just like there's rigorous rules for conducting clinical trials, there's rigorous rules for conducting observational aka non-interventional studies, which should be followed. So having the right expertise is critically important. Also, on the list, what comes to mind, and this was mentioned as well, is pre-specification.

(36:52):

I think it was in Tala's section of the slide presentation, where clinical trials not only are wonderful randomized clinical trials have randomization to their credit, they also have that prospective infrastructure. There can be fraud and abuse, but there's a set of data that typically are very credible. Here it's not that the data may not be accurate, may not be complete, may not be traceable, but there's also the problem that a sponsor or anyone could do 99 analyses... Sorry, I probably have said this before in another webinar, get a P-value greater than 0.05 each time, do the 100th analysis and get a P-value of 0.049 and say, "I'm going to submit that to the Food and Drug Administration because it's a statistically significant finding, which has a better chance of being accepted among other considerations."

(37:39):

So basically our guidance addresses all of these issues and others as well. But as I think Tala and/or Stefanie said, there isn't a checklist. We do not offer one. We're looking for fundamentally good solid

work, but that's another reason to come to us early to put our heads together. We're trying to help the public improve the public health, and we understand that everyone has a role to play. Thank you.

Susan Winckler (38:01):

Excellent. So that's helpful and is back to the idea of know your data, know your plan, and then have a conversation early on. I recognize the guidance can't say it quite that way, but perhaps I can, as the moderator. Let me ask another. Okay, this one relates to regulatory requirements related to safety. So specifically, do regulatory requirements for safety reporting differ between interventional and non-interventional studies? Who? All right, Dr. Fakhouri, I'll send that one to you.

Dr. Tala Fakhouri (38:43):

I'll take it, because we addressed that in another guidance that Stefanie and I were the co-technical leads on too. So we covered this issue and we lovingly call it the regulatory considerations guidance, which is considerations for the use of real-world data and real-world evidence to support regulatory decision-making. Very briefly, and you could visit that issue and this other guidance when non-interventional studies examine the use of a drug in routine medical practice, the agency requires that applicants comply with post-marketing safety reporting regulations regarding the occurrence of relevant adverse events.

(39:26):

But we also understand that for these types of studies, the sponsors will often use only a subset of the data. Normally this is called an analytic data set, and it's a part of a larger real-world data set to conduct their analyses to support a labeling change. If the sponsor is conducting a study to support a specific labeling change, FDA does not expect the sponsor to search the entire database regarding all uses of the product for adverse events that would meet the reporting requirements under FDA's post-marketing reporting regulations. But if during the course of conducting a non-interventional study, a sponsor identifies adverse events that are subject to these reporting requirements, then such events must be reported in accordance with applicable reporting requirements. I hope that helps.

Susan Winckler (40:24):

I got it. And I know that every one of our participants is smarter and more engaged on this, so I think they have too. I am looking at the clock, and I think we have time for two more questions if we could. So this one, actually, I can tell in looking at this one that I think it's definitely one that should come to the attorney on our panel. So does the acceptance of real-world evidence generated from non-interventional studies dilute the regulatory threshold?

Stefanie Kraus (40:58):

Happy to take that one, because it's a very simple answer. Absolutely not. Our evidentiary standards don't change based on the type of evidence being provided. Real-world evidence is evidence that is derived from real-world data sources while traditional evidence is generated from data collected for the purposes of a study. So either way, our evidentiary standards for approving a marketing application are the same. Yet in some cases it may be more difficult to meet those evidentiary standards when relying on data that were generated for non-research purposes, given the potential limitations of the data that we discuss across our real-world evidence guidance documents.

Susan Winckler (41:36):

And so the same regulatory threshold and the guidance documents help you think through when and how the real-world data might be an appropriate way to approach it to generate real-world evidence.

Counselor Stefanie Kraus (41:49):

Exactly.

Susan Winckler (41:50):

Okay. One last question.

Dr. John Concato (41:54):

Actually, Susan, before we get there-

Susan Winckler (41:56):

Yes, please.

Dr. John Concato (41:57):

... can I just sneak in? FDA has been approving what we now call real-world evidence prior to 21st Century Cures Act, but that's a discussion for another day. But if it helps some in the audience understand what's going on here, I'll offer that comment. Thank you.

Susan Winckler (42:12):

It's very helpful. It reminds us that yes, absolutely can be used, and then here are some ways to think through successful use thereof. Okay. Last question, what are the best ways to engage with FDA on using real-world data studies and what is the earliest time point in the FDA scientific advice process to address real-world evidence? I feel like that comes right back to you for the last word on this.

Dr. John Concato (42:41):

Well, thanks. I guess redundancy in this case is good. Everyone has heard it before. I think Stefanie answered a question earlier, so I'll summarize it with the same wording or the same take-home point that early engagement is key. I can offer perhaps more details by emphasizing that based on efforts over the past few years that the slide that alluded to, CBER and the Oncology Center are very comfortable evaluating real-world database studies that generate real-world evidence as part of our normal day-to-day operations. It's not that we do it in our sleep, as they say, rather, we've put together a strong team consultations where needed to provide the extra expertise. Also, this question gives me a chance if time allows Susan to mention a new PDUFA that is Prescription Drug User Fee Act, PDUFA VII program. It's called the Advancing Real-World Evidence Program. It's a new resource in addition to not in lieu of our normal meeting procedures.

(43:38):

So this initiative invites sponsors to describe importantly before protocol development or study initiation, exactly what regulatory question they seek to address, their proposed study design and the candidate real-world data sources that they might consider using. So this is an early upstream attempt to avoid the sponsor doing a lot of work just to have the FDA say, "What were you thinking? We really don't see it the same way as you do." So the value added is early dedicated meetings focused on designing a study that potentially can answer a regulatory question. Again, that ultimately is a review decision, but the value added to the sponsor is before too much work is done, countless hours of full-

time equivalent effort, and countless pages of documents. So more information can be found on our real-world evidence website. Again, the "advancing real-world evidence program". That's only one of many resources that CDER, CBER, and OCE have to offer in this space.

Closing Remarks

Susan C. Winckler, RPh, Esq., CEO, Reagan-Udall Foundation for the FDA

Susan Winckler (44:35):

Great. So it's another door to come in early and have the conversation. All right, that is truly all of the time that we have today for questions. So I want to thank the three of you for providing such great baseline information and then responding to those questions. And I'll thank all of our folks who submitted questions for us to explore. Let me do one final reminder with the slide to submit your comments and questions about the draft guidance to the docket. There is more information on the event page at the foundation's website. I also want to just thank you to all of our speakers for participating today, and a special thank you to the planning committee members at the agency. Thank everyone in the audience for attending and submitting questions. I learned a lot. I hope each one of you did too. So thank you so much. We'll close out. Take care and have a great rest of your day.