Real-World Evidence Webinar Series: Integrating Randomized Controlled Trials for Drug and Biological Products into Clinical Practice November 22, 2024 | 1-1:45pm *(eastern)*

Transcript

Welcome

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

Susan Winckler (00:33):

Hello and welcome. Thank you so much for joining us today. I am Susan Winkler 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 The Foundation is pleased to host this important discussion about recent draft guidance from FDA on the topic of integrating clinical trials into routine clinical practice. So let's take a look at our agenda for the next 40 minutes or so. In just a moment, I'm going to turn the video control and the stage over to Dr. John Concato, who will provide some opening remarks. Then we will hear from Dr. Leonard Sacks and policy analyst Heather Stone with some details about the guidance. And then as noted, we will be moving to a question and answer session. We will walk through some of the really helpful questions that you submitted as part of the registration process.

(01:32):

Now, for those who have been joining us regularly, you may have kept track that we have completed six webinars on each of six guidance documents that have been released by the FDA. And today we are learning about the seventh guidance document. If you are interested in viewing the recordings of the prior webinars, those can be found at the Foundation website at reaganudall.org. So now a reminder of why we are here today. As noted, FDA recently released draft guidance on the topic of integrating randomized controlled trials [RTCs] for drug and biological products into routine clinical practice. A link to the guidance document will be in the Zoom chat now and is on our website with other event materials. As I've suggested in the other webinars, it's really helpful to have a copy of the guidance document with you. I have mine with my highlights and I'll be making notes as we hear from Dr. Sacks and from Heather. It's with pleasure that I introduce our first speaker, Dr. John Concato, who serves as the associate director for real-world evidence analytics in the office of medical policy in FDA's center for drug evaluation and research. Dr. Concato, I'm going to turn the stage over to you.

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 Administration

Dr. John Concato (03:00):

Thank you very much Susan and thank you all for joining this webinar on integrating RCTs for drugs and biological products into routine clinical practice. First, as a reminder, and this slide indeed has been

shown for each of the webinars that Susan mentioned, we're representing the Center for Drug and Evaluation and Research as well as the Center for Biologics and the Oncology Center of Excellence. We coordinate with our Center for Devices and Radiologic Health colleagues, but they do have separate regulations for devices and their own real-world evidence program. Back to drugs and biologics. We're not here to talk about the entire landscape of activities, but please be aware that we are busy with internal agency processes including consults, external engagements, including listening sessions or today's webinar for that matter, demonstration projects. The R in CBER [Center for Biologics Evaluation and Research] and CEDAR [Center for Drug Evaluation and Research] stands for research and we don't have as big a budget as other agencies and entities, but we do help to improve the knowledge of real-world data methodologic approaches and specific tools as we call them but that's a discussion for another day.

(04:05):

What we are here today to talk about of course is guidance development. So, from the 2018 framework that it should have mentioned specifically that was shown on the prior slide. Just as a reminder, the regulatory definition of real-world data (RWD) are data relating to patient health status or the delivery of healthcare routinely collected from a variety of sources. So, an obviously very simple definition, which is operationally used to include electronic health records, medical claims, product and disease registries and other sources as shown on the slide on the left. Real-world evidence is defined as the clinical evidence regarding the benefits and risk of a medical product derived from the analysis of real-world data. So again, linked to real-world data, but very simple in terms of the evidence that's generated.

(04:52):

What's often underappreciated or sometimes misunderstood is in the yellow highlight. Real-world evidence (RWE) can be generated using various study designs including but not limited to randomized trials. I'll pause for emphasis. Externally controlled trials and observational studies. It's a false dichotomy to say real-world evidence versus randomized trials for reasons that should become clear in the next minute or so. This slide is back to our guidance development over the past several years, as Susan mentioned, and as the webinars have documented. But this tabular view shows it organized by the middle column of category. We have our first row EHR claims and second registry data. Those are data sources, data considerations, and both of those have been finalized. We appreciate that the regulations for submitting data to FDA were developed during the clinical trial era before real-world evidence. So, the data submissions or data standards guidance tells you all how to submit data when they weren't collected according to a trial protocol. In the middle of this table, regulatory considerations and submitting RWE, they're grouped. One of them has to do with the fact that our I&D regulations, investigational new drug regulations, didn't anticipate the submission of real-world data, real-world evidence, but we found them very flexible in terms of being able to do so currently.

(06:11):

Actually, Susan, you mentioned paying close attention. There were seven rows on your slide. There are eight here because submitting real-world evidence is a procedural guidance. We chose not to do a webinar for that guidance. It basically tells sponsors how to flag that they're using real-world data, real-world evidence so we could track it better. But the last three rows are the most pertinent to today's discussion. Externally controlled trials, Non-interventional studies, and RCTs in clinical practice settings listed in vertical order of their publication. But basically it's the design portion of the landscape, which should be self-evident. And the arrow indicates that we're here to talk about randomized trials in clinical practice settings when they incorporate meaningful real-world data and generate real-world evidence.

(06:53):

This slide as a figure shows the same information as on the prior slide as a table, but hopefully it emphasizes the logic involved. We divided the landscape into data considerations, regulatory considerations and design. In the middle, the regulatory considerations guidance was sufficient on its own. On the left, we have the EHR claims registries and data standards as shown. On the right bottom portion of the slide, we see randomized trials in practice settings, externally controlled trials and non-interventional studies with the red arrow indicating what Leonard and Heather are about to tell us more about. This is one last chance to clarify misunderstanding and misconceptions about real-world data, real-world evidence. The top row is randomized interventional studies, non-randomized and still interventional, non-randomized and non-interventional. A little bit clunky, but very accurate in terms of describing the architecture of study design. The main take-home point is reflected by the bracket at the bottom.

(07:51):

The generation of real-world evidence starts not with traditional randomized trials on the left, which of course use what we now call real-world data to assess enrollment criteria and trial feasibility or to select sites. But if you have say a point-of-care trial as we'll hear about where the outcome is collected via the EHR, that's real-world evidence and certainly externally controlled trials and observational studies are real-world evidence. We see that the three guidances logically cover the portion of the landscape that generate real-world evidence. Leonard and Heather could be here wearing their clinical trial hats, and I'm pleased to say that they're here today to serve the purpose of illuminating more regarding real-world evidence as generated by clinical trials. And with that, I will pass the baton to Leonard and Heather. Thank you very much.

Susan Winckler (08:38):

Perfect. Thanks so much, John. And, I will pick up, just so we can give everyone the titles for Dr. Sacks and Heather Stone as they are ready to pick up the microphone and review the guidance. I also have to say I personally appreciate the visual representation to help us understand how all of these documents fit together. So now to get into the specifics of the document, I am pleased to introduce Dr. Leonard Sacks, who serves as associate director of clinical methodologies group in the office of medical policy in CDER and Heather Stone, who is the health science policy analyst in the clinical methodologies group within the office of medical policy in CDER. So, Dr. Sacks, if you are ready, we are ready to listen to what you have to share.

Overview of Draft Guidance

- **Leonard Sacks, MBBCh, Associate Director, Clinical Methodologies, Office of Medical Policy, Center for Drug Evaluation and Research, U.S. Food and Drug Administration**
- **Heather Stone, MPH, Health Science Policy Analyst, Clinical Methodologies, Office of Medical Policy, Center for Drug Evaluation and Research, U.S. Food and Drug Administration**

Dr. Leonard Sacks (09:27):

Well, thank you very much, Susan. My job is to give you a little bit of background to the guidance, and then I'll hand it over to my colleague Heather, who will take you through some of the content. I think everyone knows that the medical literature includes many examples of point-of-care trials or trials with pragmatic elements and large simple trials. And what all these trials have in common are these designs rely on the integration of clinical research with clinical care. Now, these approaches have not been significantly adopted by drug developers for their clinical programs. And the draft guidance that we'll be

discussing today is really aimed at supporting such integrated clinical trials. A little bit of context for the guidance. Clinical care and clinical trials are not usually integrated. They often involve different locations and they often involve different personnel. Now, in the modern world of technological advances, there are many new opportunities for integrating trials with routine practice. These technologies include interactive communication technologies, allowing video communications, telephone communications, chat, and so on. And they also facilitate a lot of sharing of information. Maybe sharing of data, sharing of images, sharing of documents. So, this certainly facilitates the integration of care and research.

(10:55):

Now, unlike trials with decentralized elements, which is something that we published guidance on previously, where the goal is to shift trial-related activities to patients' homes or to other convenient locations, these integrated trials take place at locations where patients go for their care. It may involve hospitals, clinics, and other care networks, and it may include the participation of patients or their local healthcare providers. And integrated trials are appealing as they may allow rapid recruitment and convenience for patients and so on.

(11:32):

A couple of the opportunities that we are looking at. First of all, there is a wealth of clinical experience in the clinical care environment that may be applied to clinical research, but this is largely untapped and we feel that this is an opportunity for expanding our research capacities. The next thing is that clinical care environments, including healthcare institutions, treatment networks, and healthcare systems are a resource on their own for clinical research. They provide infrastructure, they provide locations, they provide access to patients. I think an important point to remember when thinking about these integrated trials is that it's necessary to simplify them as appropriate. That's an important strategy to improve efficiency while maintaining data quality. Then other advantage is that you can rely on existing data, which reduces the burden on sites and participants, and that may allow the development of trials that are rapidly responsive to evolving needs. And we'll give some examples later on.

(12:40):

And finally, these trials, these integrated trials allow for patients who live far from trial sites, including those, for example, with rare diseases to access research opportunities and to participate. FDA has supported trial modernization, and I just wanted to emphasize that integrated trials take advantage of first of all, the widespread use of technology, which now interoperative with many systems and allows us to get into databases that are used in healthcare systems. Interoperative EHRs. And finally, another important modernization feature is engagement with the clinical practice environment. So at this point, I'm going to turn over to Heather Stone, my colleague who will present some of the contents of the guidance, and then we'll move on to the questions and answers. Heather.

Heather Stone (13:31):

Thank you, Leonard. So to begin, I'll talk to you about the goal of integrating randomized controlled trials into clinical practice. To conduct clinical trials where participants get their routine care. Trial design and activities are streamlined to align with clinical practice. Real world data from healthcare records may be used, trial related activities may be conducted as part of routine practice with participation of local healthcare providers, and dedicated trial staff may participate to perform research specific activities if and when needed. Healthcare institutions play an important role in this trial design. Sponsors may engage healthcare institutions such as health maintenance organizations, hospitals, or clinical networks. This may in turn facilitate the rapid enrollment of large numbers of patients by improving accessibility and convenience to participants. Agreements should document responsibilities of

healthcare institutions, their employees, and the tasks that they will perform as well as the responsibilities of the sponsor.

(14:36):

Sponsors should ensure that institutions and local healthcare providers are suitably credentialed. Clinical investigators require oversight. Clinical investigators are responsible for ensuring that a trial is conducted according to the signed statement and the investigational plan. And for protecting the rights, safety, and welfare of participants in the trial. Clinical investigators must also review pertinent trial-related records provided by local healthcare providers and must ensure the accuracy and completeness of the data. One of the big questions is about the role that local healthcare providers may play in this trial design. According to the draft guidance, local healthcare providers working as part of healthcare institutions or an individual practices may be engaged to perform trial-related tasks. And we'll go into some of the details on the next slide. It's important to note however, that these activities should not require trial-specific knowledge, trial-specific training, or research expertise. And local healthcare providers may however need limited instructions to ensure that these activities are performed as required.

(15:48):

Examples of activities that may be performed by local healthcare providers include performing routine medical procedures such as blood draws, radiographs, vital signs and clinical examinations as specified in the protocol, collecting routine clinical data for the trial using a template, or following prompts in the electronic health record to document specified clinical events such as death, myocardial infarction, stroke, or seizure. There are, however, activities that must instead be performed by trial staff. These are procedures or processes that contribute directly and significantly to trial data and require study-specific training or detailed knowledge of the protocol. Examples of such activities that must be performed by trial staff include determining whether a candidate satisfies the trial's enrollment criteria, conducting specialized assessments required by the protocol that require trial-specific training and expertise, such as evaluating tumor responses using resist criteria, assessing whether a trial-related adverse event is attributable to the investigational product, applying protocol-specified criteria for dose modification or discontinuation of investigational products, and confirming that a trial participant has reached a trial endpoint.

(17:08):

Trials that are potentially suitable to be integrated into routine clinical practice. First and foremost, are trials of FDA-approved drugs such as those for new indications, new populations, new routes of administration or doses. It may in some instances be possible to study unapproved drugs with well-understood safety profiles in clinical practice environments such as when members of an existing class are studied, or those where the safety is already well-characterized from prior trials. There are some Quality-by-Design considerations that should be considered. These focus on factors that are critical to quality, including appropriate flexibility and trial protocols to align with clinical practice. For example, the timing of trial visits. Eligibility criteria should be minimal and straightforward. Informed consent documents may be embedded in electronic health records. Randomization and blinding are still recommended whenever possible. Flags in electronic health records may alert local healthcare providers to comorbidities or concomitant medications that are not allowed. And real-time monitoring of electronic health records and or calls to participants can be included to capture adverse events.

(18:22):

So, what is novel in this guidance? The guidance addresses trial settings that are convenient for participants and may support rapid recruitment of broad populations. It focuses on efficiencies using

existing healthcare institutions and staff, real-world data and streamlined trial designs. And it supports the engagement of large healthcare institutions, healthcare networks, as well as community healthcare facilities that have historically been less involved in FDA-regulated clinical trials. In addition, it describes roles that local healthcare providers can play in conducting trial-related activities, supports the use of data collected during routine clinical practice in order to avoid duplication of data entry and reduce the need for dedicated trial sites, and supports a spectrum of trials ranging from those that rely completely on data generated during routine clinical practice to those that require supplemental activities by dedicated trial staff.

(19:20):

There are, however, still regulatory requirements that must be satisfied, as in any trial. These include that clinical investigators are responsible for ensuring the trial is conducted according to the signed investigator statement, investigational plan, applicable regulations, and for protecting the rights, safety, and welfare of participants. Activities that contribute directly in significantly to trial data and require study-specific training or detailed knowledge of the protocol must be performed by trial staff such as obtaining informed consent. Sponsors remain responsible for ensuring that the institutions and individual local healthcare providers they engage are suitably credentialed and qualified to participate in the research. Sponsors must ensure that source records or certified copies of source records to support clinical trial data submitted to FDA are available for review by FDA upon request. An integration of randomized controlled trials into clinical practice should not interfere with the appropriate delivery of patient care. Many acknowledgments thank you to all the offices in FDA's Center for Drug Evaluation as well as those in the center for Biologics and Oncology that participated in the drafting of this guidance.

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 Administration**
- **Leonard Sacks, MBBCh, Associate Director, Clinical Methodologies, Office of Medical Policy, Center for Drug Evaluation and Research, U.S. Food and Drug Administration**
  Heather Stone, MPH, Health Science Policy Analyst, Clinical Methodologies, Office of Medical Policy, Center for Drug Evaluation and Research, U.S. Food and Drug Administration

Susan Winckler (20:38):

Great. Thank you so much Heather and Dr. Sacks for walking us through and helping us distinguish not in the randomized controlled trial versus real-world evidence, but and how this guidance document would help sponsors and others pursue this. I'll say there's been some activity in the Zoom Q&A, which I appreciate. We've moved all those questions into my queue so we can consider them. So, let's bring back the people who can answer them. Dr. Concato, Dr. Sacks, and Policy Analyst Stone, I hope you're ready because I've got a rapid-fire list of questions to ask you. So, for the first one, I want to turn to a question that might help turn the concepts we've been talking about into reality. Could you share some examples of RCTs which have been integrated into routine clinical practice? Well, Dr. Sacks, I saw you on mute. Would you pick that one up?

Dr. Leonard Sacks (21:39):

Sure, Susan. I'm happy too. I think the poster child for this kind of trial was the recovery trial, which was done in the UK at basically healthcare centers throughout the UK for COVID-19. And that was a good

example of a trial which actually supported regulatory approval of Tocilizumab for the treatment of hospitalized patients with COVID. But these sorts of trials are not really new. Many on the call may be familiar with the GISSI trial, which was done in the 1980s. This was a trial that was done through cardiology treatment centers throughout Italy and resulted in the recognition that Streptokinase was a very important adjunct to treatment of patients with myocardial infarction. There's another genre of trials which are often conducted in this environment that safety outcomes studies.

(22:36):

We've seen a lot of these done for new diabetic agents to look at the cardiac complications, and these certainly are amenable to being done in the healthcare environment. They rely on endpoints like myocardial infarction, stroke and so on. So these are captured in the healthcare environment. And then I guess as I mentioned earlier, the literature has many examples of point of care trials and pragmatic trials as they're sometimes known. And many of these focus on comparative effectiveness on comparing the effectiveness of known approved medical products. In fact, there's one good example, which is the VA Diuretic Comparison trial, which was a trial which involved 13,000 participants in the VA network and looked at a comparison of Chlorthalidone and Hydrochlorothiazide for hypertension. Basically showed equivalent safety profiles. So I think many different examples of these both in the literature and elsewhere.

Susan Winckler (23:41):

That's great. I was thinking we'd have one and there's many, which is great and helpful to ground folks in thinking through. You mentioned the recovery trial. Can you tell us more about its use to support regulatory decision-making? And Heather, would you pick that one up?

Heather Stone (24:02):

Sure. I'd love to. Thanks, Susan. So yes, the recovery trial is a good example. Unfortunately, there haven't been many examples of point-of-care trials that have been used to support regulatory decision-making at FDA, at least not in terms of efficacy. As Leonard mentioned, sometimes where safety outcomes they're more frequently used. However, recovery is really the prime example of a trial that was used. So, the recovery trial, as Leonard mentioned, supported the use of Tocilizumab for hospitalized patients with COVID-19 requiring oxygen support or mechanical ventilation. The recovery trial was a randomized controlled open-label platform trial that was integrated into the national health system in the UK. National Health Service. Excuse me. And evaluated the efficacy and safety of potential treatments in hospitalized adult patients with severe COVID-19 pneumonia. Patients were randomized to standard of care or standard of care plus Tocilizumab. In this case, 35% of patients who received the standard of care arm unfortunately did not survive in comparison to 29% who received standard of care plus Tocilizumab. So, there was a significant mortality benefit. This evidence was in turn used along with several other randomized controlled trials to support the addition of an indication for severe COVID-19 pneumonia to the FDA labeling in hospitalized patients for Actemra or Tocilizumab for the FDA label.

Susan Winckler (25:35):

Okay. Very helpful. So applied there in what you mentioned, a not-yet-usual case, but clearly showing that it can be used in efficacy regulatory decision-making. Great. So, I'm going to choose one. This question is somewhat related but takes us in a slightly different direction. Are there approved drugs that use evidence generated by study designs other than randomized trials? I'm feeling John like that might take us into your territory.

Dr. John Concato (26:11):

Thanks, Susan. And I feel a little guilty about talking about other than randomized trials in today's webinar, but I'm happy to answer that question. And some in the audience might be aware but I think it's worth mentioning a landmark approval based on non-trial generated real-world evidence by CDER. It was in 2021 July, as I recall. Again, we're not endorsing any drugs we mentioned, but the drug trade name is Prograf, otherwise Tacrolimus. It had been approved for prophylaxis of organ rejection in patients who receiving liver and then later kidney and heart transplants based on traditional randomized trial evidence. Importantly, the drug was used in clinical care. So real-world data were available including for lung transplants, but for various reasons what might be called lung trials had never been submitted to FDA. So, to move the story along in brief, a sponsor submitted a supplemental new drug application entirely using real-world evidence for lung transplants.

(27:10):

Importantly, the data came from the Scientific Registry of Transplant Recipients. Well, I am praising that registry. I'm not selling it. But basically, the generalizability is unquestioned. It's all US lung transplants or transplants that are part of the registry. And here's the important take-home point. The reliability and relevance of the data were equal to what a clinical trial would have collected. So, the study design was an observational treatment arm compared to historical controls. No trials were involved. Just stating the facts. Not a clinical trial. Yet a review by FDA determined the study to be adequate and well-controlled to generate substantial evidence of effectiveness. I'll add, however, this is a rare situation, but it is was in approval. And what helped was the outcomes of organ rejection and death are virtually certain to occur without therapy. So that dramatic effective treatment helps to preclude bias as an explanation of results. But again, if there's one take-home message is it's the evidentiary standard is the same, but when there's real-world data involved, the processes are different. And we have our real-world evidence program to help including this guidance to help give sponsors and other interested parties a sense of our current thinking and our recommendations. Does that help Susan?

Susan Winckler (28:28):

It does. And I can see weaving together the path that can be used by sponsors when it's appropriate. And then obviously there's the assessment by the agency of the standards being met. So I've got a question about data quality and then some of those standards being met. How would you describe the minimum expectations for data quality in point-of-care trials? Heather, I saw you nod, therefore you get the call to answer that question.

Heather Stone (29:01):

Sure. I can take that one as well, Susan. So at its most simple, the expectations for data quality are the same for point-of-care trials as they would be for any other trial. A consideration for conducting these trials though is that they really need to be for suitable conditions. There are some conditions that are much more readily suitable to integration and routine practice than others. So, one has to be judicious about what can be studied in these settings as well as what can be done by local healthcare providers. In many cases, designs that integrate some amount of oversight by clinical investigators or either remotely or in person may be the best option, so that when data quality issues arise, they're able to provide remote or in-person supervision and participation by study staff. In addition, follow-up calls to patients can sometimes be helpful in these situations to enhance data quality.

(30:04):

So, I think when designing a trial, you really need to make sure that you're doing the right trial and that it's appropriate for integration into clinical practice and can be easily and reliably streamlined into

routine care. One other consideration when it comes to data quality is that the parameters that you're looking at in the trial should ideally be objective. So for example, the diagnostic criteria should be very clear, something like a blood culture or an outcome of in-hospital mortality and having criteria that are straightforward and well accepted can help to reduce variation and improve the quality of the data that you're collecting.

Susan Winckler (30:44):

Heather, that's really illustrative in particular. I'm actually glad you emphasized the judicious part because it seems like essential to this is thinking about what it is that you're studying and that intersection in connection with routine clinical care. So maybe let's dig a little more into that. What are some features that make it easier to have that integration of research into clinical practice? Dr. Sacks, I see you unmuted again. So this one, it's coming to you unless you deflect it.

Dr. Leonard Sacks (31:24):

Sure. I'm happy to take it, Susan. So, I think the crux of successful integration of trials into clinical practice is really that they're aligned with clinical practice activities and procedures. I think it's important to have streamlined trial designs as Heather was talking about. And when I talk about streamlined trials, I think the idea there is that they have simple inclusion criteria that are readily captured in clinical practice, that they involve procedures that are part of clinical practice and involve endpoints that are easily captured in the clinical practice environment.

(32:00):

Generally hard endpoints, things like stroke, hospitalization, myocardial infarction, and death. These are very clear endpoints that are generally pretty reliable in the healthcare environment. I think as far as drugs that are suitable for being investigated in these trials, we generally believe that the drugs that are suitable should be fairly well characterized, fairly well understood in terms of their safety profiles so that trials can rely on targeted safety reporting and don't require very extensive reporting about the safety. So that would be a consideration about the drug. And then if a trial requires very specific assessments, obviously specific types of response scores and so on and so forth, these would be very difficult to integrate in clinical tractors. So I think a lot of the features that make it easy to integrate in clinical tractors, so really overlapped with the features that determine the quality of these trials, which Heather had spoken about earlier.

Susan Winckler (33:14):

Okay. I can see there too, the straightforward and what's consistent with clinical practice. And you mentioned hard endpoints as an important consideration, and I think that's hard as clear, not hard as difficult. Right. So clear endpoints. Which might bring us back to the issue of whether real world data are fit for use. John, can we take that one back to you?

Dr. John Concato (33:50):

Yes. I would say that I think Leonard's comment about our endpoints actually aligns nicely with what our real world data guidance is emphasized. That is the real world data need to be relevant and reliable. Relevant refers to clinical issues such as having the right covariates and having enough patients at the end of the day to work with. And reliability is not synonymous with quality but we've settled on reliability because quality can be defined in so many different ways. But reliability we operationally define as accuracy, completeness, and traceability. And I would say please look at our real world data guidances in that category if anyone wants more information.

(34:29):

But whether a data source is suitable for generating evidence for regulatory decision making, ultimately is a case-by-case definition. So, we don't certify or endorse a data set for all purposes. There might be similarities. So, you don't have to redo a validation, but you can't just assume that it's fit for purpose. And one other thought, since it's on my mind. Our 2018 framework uses fit for use. I might've just utterly ... Fit for purpose. I think it's fair to say in many contexts they're synonymous. If folks want to split hairs and say that they're defined differently, that's fine. But for practical purposes, we're talking about from the FDA real world data, real evidence point of view, relevance and reliability is synonymous with fit for use. Thank you.

Susan Winckler (35:16):

Got it. And so the question of ... Certainly you must show relevance and reliability, and that depends on the question that you're exploring.

Dr. John Concato (35:24):

Right. A covariate might be critical in one drug outcome association evaluation and not just a table one factor in another. That's an example of how the relevance varies. Thank you.

Susan Winckler (35:37):

Excellent. Thank you. Well, this seems a little more obvious, but I think it's important to underscore, what are some of the potential advantages of these types of designs over traditional trials? Oh, Heather moved before the other two of you. So Heather, this one's coming to you.

Heather Stone (35:58):

Thank you. Yes. I have given this a lot of thought. So, I think there are a number of potential advantages to point-of-care trials. However, I do think that it really depends on the scientific question being asked. As we stated before, there are some scenarios in which this design is really appropriate and can be very useful, and there are others where it's not so appropriate. But where it is appropriate, where a trial integrated into clinical practice is appropriate then I think some of the advantages include things like the potential for rapid enrollment with large numbers of patients, which we saw in recovery, access to a larger pool of potential trial participants, infrastructure that's already in place, which could reduce startup time and make that shorter. The trial population may in turn be more representative of the population that will ultimately get the drug, and patients can continue to see their trusted providers and therefore may be more willing to participate in clinical research.

(36:58):

And as Leonard pointed out earlier, the ability to locate rare disease patients within a large healthcare system and incorporate and make the trial accessible to them is another big advantage. I just want to make one related point, which is that the CDER Center for Trial Innovation C3TI recently announced an opportunity for demonstration projects called Streamline Trials Embedded in Clinical Practice or STEP, since everything in government has to have an acronym. The goal is to partner with sponsors planning innovative clinical trials in addressing issues around trial design and conduct. And lessons learned from participating projects will be made available broadly and could be used to inform updates to relevant CDER guidances such as the one we're discussing today. So, for more information about C3TI and STEP, please go to the C3TI website, which I think somebody will enter into the chat. But encourage anyone who might have a demonstration project to consider participating in that.

Susan Winckler (37:59):

Great. Thank you, Heather. I was just looking up C3TI on the website a couple of days ago, and so I'm going to ask the ... I'll ask the team, I'll the foundation team, if you could drop a link to that in the chat. I think it will be helpful to others. I know we're running short on time, but I'd love to ask at least one more question if our speakers are amenable. This has to do with the role that local healthcare providers play in RCTs integrated into routine clinical practice. What role can they play and what level of knowledge of study protocol is required of those individuals? So, what is it that healthcare providers might need to do to step up?

Dr. Leonard Sacks (38:45):

Perhaps I can take that Susan. I think healthcare providers are really a cornerstone of this approach. Healthcare providers are part of a highly regulated healthcare environment, and they're qualified to do a lot of the same tasks that are required of clinical study staff. The only difference, of course, is that healthcare providers are not familiar with the protocol with the investigator's brochure, and they may not know anything about the drug. So in trials integrated into clinical practice, really the idea is to get local healthcare providers to do those things that they normally do in clinical practice and not anything that requires research or study-specific expertise. And these could be things like ordering x-rays, ordering a blood test, doing a routine clinical examination, measuring vital signs and so on.

(39:35):

Of course, if study procedures require any study-specific activities like filling in scores and so on, this would have to be done by dedicated study staff. I think it's important to remember that we would not regard local healthcare providers as part of the study staff. We wouldn't expect them to be listed on the investigator's agreement, which people would recognize as form 1572. And I think that really summarizes our position. So I think the bottom line is the task that local healthcare providers do should not require any specific expertise or training. They're just what they do regularly in clinical practice.

Susan Winckler (40:18):

Fabulous. That seems like a pretty clear delineation. Obviously there'll be some specifics, but that's a construct that has some clarity. I think we're going to take two more questions. So let me pick the ... All right. So this next one is thinking beyond this study design guidance. Are there other planned guidance documents in the works and what's next for the RWE program? I think those bigger questions tend to come back to you Dr. Concato. Would you pick that one?

Dr. John Concato (40:58):

Sure. Looking at the clock, we don't have a lot of time, but I would just try to summarize by saying, please consider what was on the earlier slides as a, so-called first Generation of guidance on real-world data, real-world evidence. It's almost a modular approach of use. What is most relevant to the challenge at hand. But two other thoughts come to mind. One is that early engagement is very often cited in virtually all of these guidance(s). The second--Heather put in the plug, I'll put in the plug. We have a December 12th public workshop hosted by FDA and the Duke-Margolis Institute where we'll be talking about looking forward. But I will say more guidance isn't always necessarily better. We want to look for gaps in knowledge and be judicious. We've met our 21st Century Cures mandate. We've met our PEDUFA commitments. So, we're trying to look for opportunities where some lesser travel paths can be illuminated. But right now, what we are trying to do is finalize the three draft versions of the design guidances that are still out in the public domain.

Susan Winckler (41:57):

Got it. Okay. I think this last one may be quick as well. And so John, I'm just going to stick with you, but you can hand it off if you prefer. So what are some considerations regarding statistical methods for RCTs integrated in clinical practice versus traditional RCTs?

Dr. John Concato (42:15):

We're in penalty time here, but I would say that most of our guidances have a similar phrase. Basically, we do not recommend a particular approach. We're not copying out, rather, we think the right tool for the job varies on a case-by-case basis. So it's about fundamentals of epidemiology, biostatistics, and other scientific disciplines. There will be some commonalities and there's a state of the art, but even that state of the art evolves over time. Propensity score matching has some critics, for example, that's not necessarily relevant to ... It isn't relevant to most randomized trials. But I would say that the tools that work for randomized trials should work here. It's mainly about that point of care outcome. Is it reliable for the stated purpose? But that's a short answer which deserves a longer question. I apologize for the brevity.

Susan Winckler (43:03):

That's all right. It makes it very clear and I think it's a reminder to me that one of the most important things that can happen here is the conversation about potential analyses with the appropriate FDA review division. Okay.

Dr. John Concato (43:17):

Thank you.

Closing Remarks

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

Susan Winckler (43:19):

Excellent. All right. Well, let me then take this to ... I'll close this out. Thank you to Dr. Sacks, Dr. Concato, Policy Analyst Stone. You've helped bring this paper to life, which always just helps us think a little bit more about the words on the page and have a better understanding of what's there. I want to thank everyone for attending and for submitting questions for the speakers. You helped us have a great conversation. I'll remind you to submit your comments and questions about the draft guidance to the docket. Those comments are due December 17th so you still have some time, but welcome you providing your input. With that, thank you so much for joining us today. Take care and have a great rest of your Friday.