Hannah Daniel (00:06):

Welcome to MedTech Connect, a new digital Health Regulations podcast from Citeline. I'm your host Hannah Daniel, and I'm a US regulatory reporter for MedTech Insight. Every month we'll interview a regulatory expert in the digital health industry who will help us break down policies and guidances coming out of the FDA as well as other hot button issues such as cybersecurity concerns, the rise of AI and ML, or the fight to protect medical data. New episodes published monthly, so be sure to follow Citeline on Spotify, SoundCloud, apple Podcasts, Google Podcasts, and tune in to get notified when new MedTech Connect episodes come out.

In this episode, I speak to three experts at Hogan Lovells about the food and drug administration's recent draft guidance on decentralized clinical trials, which we also refer to as DCTs in this podcast. So the firm works with many companies who run clinical trials and the four of us sat down to discuss the ins and outs of the draft, what pieces of the guidance still might need clarification and how they expect to see the industry change as a whole. Now that DCTs are becoming mainstream, they also provide some helpful advice for companies looking to run DCTs.

Kristin, Blake, and Stephanie, welcome to the podcast. I'm really excited to have you all here today to talk about decentralized clinical trials. But before we start, would you guys please introduce yourselves, talk about who you are and maybe how you got into your position?

Kristin Zelinsky Duggan (01:28):

Sure. I'm Kristin Zelinsky Duggan. I'm a partner in the FDA medical devices practice of Hogan Lovells. I'm based in Washington, DC. I have a background in biology and economics and so I started out in the consulting world working with medical device companies, trying to get through FDA and then moved into being a lawyer and generally work with companies that are making innovative products and trying to help get them on the US market.

Blake Wilson (02:00):

My name is Blake Wilson. I'm a partner in the FDA regulatory group at Hogan Lovells as well. My practice focuses on FDA's pre-market approval process across medical products including medical devices as well as oversight of clinical trials. So a lot of my time is actually spent with sponsors of investigational products with respect to study design considerations and the use of clinical data in FDA-related materials. And prior to becoming attorney, I worked in clinical research at Brown University and I also hold a master's in biostatistics that I use to help navigate sponsors through the FDA regulated clinical trial space.

Stephanie Agu (02:40):

Hi, my name is Stephanie Agu and I am an associate also at Hogan Lovells and I specialize in FDA pharmaceutical and biotechnology development, and within that practice I work on a variety of issues from exclusivity concerns to clinical research, bioethics, drug marketing and advertising. And I entered this practice just because I had always been interested in government approaches to healthcare and society. And, on that note, it's been a fascinating few years in the FDA world certainly, and I'm excited to discuss this topic with you.

Hannah Daniel (03:14):

Yeah, thank you guys for introducing yourselves. Really cool to hear a lot of bio background. I'm also a former, I was going to say retired bio major, but you never really retire out of bio, but it sounds like this guidance is really important to your work and the work that you do with clients. So we're just going to

jump into the meat of it. So first I wanted to ask you all what about the draft was surprising? What was expected? Did you feel like anything was missing from the draft?

Stephanie Agu (03:43):

Sure.

Blake Wilson (03:44):

This is Blake. I'll kick us off here. And I would say when the draft was issued, I actually thought that it was pretty much in line for the most part with how I thought FDA would step into formally putting out guidance in the decentralized clinical trial space, specifically follow the experience under the COVID 19 enforcement discretion policies related to clinical trials. I think FDA had a lot of time to actually consider and weigh its options and how to implement the procedures for decentralized clinical trials. And I think that you see a lot of those tactics utilized in this newest guidance document.

I would say one thing that I was hoping that would be there that wasn't discussed very much in the guidance document was actually around adverse event reporting. When you utilize ADCT format for clinical trials and specifically around more guidance on exactly when you use an HCP to collect adverse events, how that should reporting should be conducted in order to make sure that it's generalizable with the rest of the study data, and that all adverse events are being collected because I think that this is a critical point and could create issues down the line when you actually are putting in the marking application. So I was hoping that FDA would weigh in a little bit more on that, but I didn't see it here in this guidance.

Kristin Zelinsky Duggan (05:12):

Yeah, I think that makes a lot of sense and I agree. I don't know that I was particularly surprised by any of the elements that are outlined in the guidance, but I will just say that my overall impression, and I think we'll probably talk about this a little bit more later, was really sort of how are people going to practically achieve this? It seems like a really sort of a tremendous logistical burden.

And as I was reading through, it was sort of like these are good ideas, but it seems like it would be a lot of work to do a fully decentralized clinical trial. And so it was really, and perhaps putting a lot of the burden on PIs to handle some of those logistics. For example, working with local sites or local healthcare providers. I know that sponsors are very sensitive about putting more burden on PIs than they need to. Obviously doctors are often very busy in their lives and usually sponsors want to take away a lot of that burden. So that was just one thing I noted as I was reading through the guidance.

Hannah Daniel (06:16):

Before we go into some advice for companies, how do you guys expect to see clinical trials change over time now that we have some kind of formal guidance in place?

Kristin Zelinsky Duggan (06:26):

Yeah, this is Kristen again. So I think that there are a number of things that can be implemented and a number of aspects of the guidance that could be implemented. Perhaps I'm more on the skeptical side from having done this for many, many years. I've seen FDA put out a lot of policies that really sound good in concept and then don't necessarily come to fruition. So I think it remains to be seen how sponsors will implement this, whether they will primarily take a hybrid approach and sort of take aspects of decentralized clinical trials, which they're already doing as Blake noted today in the wake of

COVID and remote visits and things like that that have already been happening and use of digital technologies and trials and take sort pieces of it or go to the fully decentralized clinical trial.

So I think that remains to be seen, but some of the benefits that I think they're hoping to achieve that sponsors would hope to achieve too from the guidance are things like greater subject participation, being able to enroll more subjects, more diverse subjects, subjects that might not be closer to major clinical sites and possibly even sort of just retaining subjects better in trials, perhaps coming to a central site at the beginning of the trial, but then being able to visit their local healthcare provider for follow-up visits.

Kristin Zelinsky Duggan (07:44):

So perhaps increasing follow-up in trials. I think also the use of alternative data sources, the digital health technologies, is obviously something that there's other guidances as well about that specifically and use of electronic health records, but really collecting things in a much more modern way than necessarily has been done to date.

Blake Wilson (08:05):

I definitely think there's going to be a lot of challenges here, but I think within my practice and the sponsors I've been advising on this, we hear a lot of excitement about the possibilities of decentralized trials and one of, I think the key aspects is Kirsten was indicating around enrolling the broader populations, but also being able to potentially speed up enrollment basically to pull everyone from a single large center in the surrounding area and really being able to go out into more communities to be able to leverage those different pools of patients that may be available, and that this would actually bring in a broader perspective from the patient population and give you a more robust, hopefully, data output.

So I think companies are really excited about the potential enrollment opportunities. I think that you'll companies trying to use this with respect to, again, not having to have everything focused within a single site, coordinating all the subjects to come back within that location and instead giving more flexibility to patients to participate in clinical trials by allowing them either to have assessments performed at home or to visit a clinical center or an HCP that is within a shorter distance to their home and allow that more facilitative process.

And so I think the hope there is that you may actually just encourage more patients who would not otherwise think of participating in clinical trial to now become involved. So I definitely think that using decentralized clinical trials is going to become a mainstay of how clinical trials are run, but the extent to which is implemented is going to be the question mark, and we'll just have to see how well sponsors are able to manage it and how well PIs are able to manage this new scope of responsibilities when you have additional participants that are going to be involved in the management of clinical trials and actually providing assessments.

Stephanie Agu (10:04):

I have one thing I wanted to add here as well, and this is Stephanie. To Kristen's point about in the context of diversity and greater diversity, I think something to mention here is that we often think about clinical trial diversity in terms of patients, and I think certainly DCTs do lend themselves to increasing patient diversity, but I think also there's a potential for DCTs to also diversify the trial staff and personnel involved in clinical trials. I think one of the features of DCT is being that those living in geographic areas outside of your typical academic medical center can become more involved in clinical research. The guidance speaks often about the use of local HCPs in clinical trials, and so I think that is a route that can

be used as well for us to see greater diversity in terms of clinical trial staff and other entities involved in clinical research.

Hannah Daniel (10:54):

Yeah, absolutely. We've done a lot of stories over here at Medtech Insight talking about different companies and how they're working to increase diversity in clinical trials a lot of times using hybrid clinical trial models. But yeah, some interesting conversations I've had recently around how do we diversify the staff as well and how do we educate people who are running these clinical trials so that the access is not just given to the patient.

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So a lot of promising things that are coming with decentralized clinical trials being popularized and coming into the mainstream, but let's also talk about some concerns, and something of note is how decentralized clinical trials are going to go through the inspection processes. So what concerns do you have about how these decentralized clinical trials? Will be quality controlled?

Blake Wilson (12:21):

This is Blake, and this is a really great question. I think everyone recognizes, in theory, decentralized clinical trials sound great. The reality is though that the devil's in the details of how it's actually being executed. And so I think you'll see throughout the guidance document that FDA issued, one of their concerns that they raise, and it's a natural aspect of ADCT, is that there's going to be more variability involved because you just have so many more people participating in the trial in terms of who's conducting the assessments, who's reporting the adverse events, and how they conduct each one of those procedures. The benefit of a centralized trial is that you're going back to the same place. Usually a set staff member is conducting those procedures, and so you have a lot of consistency from patient to patient. Once you start to enter into a either hybrid or a fully decentralized clinical trial, all of a sudden you're adding more and more variability into the process.

And so that creates the possibility that people are going to conduct study procedures in slightly different ways that could potentially introduce bias, and this is one aspect of the inspection. It's going to become very important because FDA is going to be looking for those sources of variability that exist and may have skewed study results. And so that is I think, one concern from the inspection standpoint.

In addition, simply the ability to monitor decentralized clinical trials can be very challenging within a centralized aspect. You have a limited number of sites. You can set up monitoring visits on regular schedules. You check to make sure informed consents are being conducted correctly, spot check through the data, and it's a well-established procedure for how you do that. When you start to move into decentralized clinical trials, though, the ones to actually manage and monitor all these different participants who are helping to conduct your clinical trials becomes much more challenging from a logistical perspective.

I think FDA tries to be very clear that the onerous is both on the sponsor to be monitoring the clinical trial at the high level, but on the PI level, they're also going to be in charge of managing anyone that they're delegating responsibility to. And so essentially, whenever you're creating the opportunity for more people to be involved, again, you have this opportunity for more variability to be introduced or for people to not perform the study correctly. And so monitoring is going to have to be a key aspect of how

this is being performed and making sure there is significant coordination between these different groups in order to make sure that the study is being run in a scientifically valid manner. So again, you're going to have to make sure that you have ample training upfront. All these aspects I think are going to become very important.

Kristin Zelinsky Duggan (15:13):

Yeah, no, I think you really covered it, Blake, and I would just add that in addition to all the different players involved and all the different entities involved, devices involved as well, the various monitoring devices, the ways that the data is collected and how it flows, how both for the sponsor when they're monitoring the study, but then also for inspectors, how they're verifying that all the data that may be coming from a wider range of sources really is valid and appropriate and that there's sort of a chain of custody of that information. And I know that's also covered in a different guidance, but the DCT guidance that came out covers that as well. Another source of variability, I think in the trial that you were talking about.

Stephanie Agu (15:58):

Well, I think one thing to mention, which the idea of where inspections can take place, and so there is a component in the guidance that mentions that FDA will inspect the central location and the central locations where all of the trial related records are kept and stored. But it's important to remember that FDA has expanded inspectional authority to really inspect any sites, facilities, and persons involved in or who have engaged with the sponsor in terms of data collection and data analysis for the trial. So even though there is a central location where all of the records will be stored, and that's definitely up for inspection, it's important for sponsors to keep in mind that there's really wide variety of different entities involved in a trial that can be inspected as well.

Hannah Daniel (16:45)

It seems like there are some concerns and there's a lot of variables, and maybe those will be addressed in a final guidance. Maybe those will be addressed in the field, but for companies who are starting to dip their toes into DCTs, who are already full steam ahead on them, for people who are unsure, what advice would you all have for companies who are interested in running a decentralized clinical trial?

Kristin Zelinsky Duggan (17:08):

This is Kristen again. I think one of the things is to really plan for all the logistical challenges that we just talked about. There's a number of considerations in the guidance, figuring out the roles and responsibilities of the sponsor and the investigator who's doing what, who's responsible for supervising whom, making sure you have plans for monitoring plans for ensuring the integrity of the data. I think there's probably going to be a lot of having to develop procedures and SOPs that maybe would be outside of the standard ones that companies would already have for clinical trials. I think another thing is talking to FDA as they put in the guidance and as we sort of always recommend talking to FDA when you're planning your trial and certainly getting their buy-in and their thoughts on the trial design and how you're planning on conducting it could be helpful. And then this is sort of basic, but whether or not the format really lends itself to your trial, I mean for many kinds of medical devices, implants and other things like that, it may just not be all that practical to do. For example, a fully decentralized clinical trial. Obviously you couldn't really do that, but which aspects from this guidance might make sense in the trial and for what kinds of devices it may be appropriate for versus not.

Blake Wilson (18:25):

And I would advise sponsors to be very careful about the assumptions that they're billing into their clinical trial design when they're trying to incorporate a decentralized format. And a lot of that comes down to really thinking about how transitioning from a traditional centralized trial to a decentralized trial could have an impact. And this includes on things like sample size calculation and effect size. If you're using data that is from a centralized clinical trial, in order to establish what you believe a likely effect size for your product is going to be, you need to take into consideration that decentralized trials naturally have more variability and that this will impact what your sample size calculation would be.

In addition, we were referencing digital technologies for remote monitoring and assumptions that may be built in about what validation was necessary to establish the validity of that product for use in a clinical trial, and making sure that you reach out to the FDA before you start to run the clinical trial. These issues are extremely hard to address after the fact and may become a huge hurdle in order to get past a marketing submission.

Stephanie Agu (19:36):

Then on that note, the comment period for the draft guidance is still open. It'll be open until August 1st, so we expect to see many members of the industry submit comments and see if FDA will incorporate them in the next final guidance.

Hannah Daniel (19:50):

Well, that was a perfect way to wrap up, so I wanted to thank you all for being on this episode of Medtech Connect and sharing your thoughts about the decentralized clinical trials guidance.

Blake Wilson (19:59):

Thank you.

Hannah Daniel (20:00):

Thank you so much for your time.

Kristin Zelinsky Duggan (20:02):

Thank you.

Hannah Daniel (20:07):

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