

FDA Webinar: Implementation of Final Rule on Human Subject Protection: Acceptance of Data from Clinical Investigations for Medical Devices

**Moderator: Irene Aihie
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Coordinator: Welcome and thank you for standing by. Today's call is being recorded. If you have any objections, you may disconnect at this time. All participants will be in a listen-only mode for the duration of the call. During the question and answer session if you would like to ask a question please press star one. I would now like to turn the call over to Irene Aihie. You may begin.

Irene Aihie: Hello, and welcome to today's FDA webinar. I am Irene Aihie of CDRH's Office of Communication and Education. February 21st was the effective date of the Final Rule on Human Subject Protection; Acceptance of Data from Clinical Investigations for Medical Devices.

This final rule updates the standards for accepting clinical data from clinical investigations conducted inside and outside the United States to protect human participants and to ensure the quality and integrity of data obtained through such investigations.

Today (John Doucet) and (Jayna Stohlman) from the Clinical Trials Program here in CDRH will discuss the final rule. Following the presentation, we will

open the line for your questions related to the information provided during the presentation.

Additionally, there are other Center subject matter experts to assist with the Q and A portion of today's webinar. Now I give you (John).

(John Doucet): Yes, good afternoon everyone, and welcome to the presentation. My name is (John Doucet) and I'll be presenting with my colleague, (Jayna Stohlman). We're both members of the Clinical Trials Program in the Office of Device Evaluation. Also in the room with us is (Soma Kalb), the Director of the Division of Bioresearch Monitoring.

So today, (Jayna) and I will discuss the requirements outlined in FDA's final rule on the acceptance of data from clinical investigations for medical devices when the data is submitted to support an IDE, or device marketing application or submission. And for your reference, these requirements are codified at 21 CFR 812.28.

So the final rule was issued on February 21, 2018, with an effective date of February 21, 2019. On the same day we issued the final rule, we also published an associated guidance to help sponsors and applicants understand and comply with the requirements.

The purpose of the rule was to update the requirements for FDA acceptance of clinical data from investigations conducted both inside and outside the United States, and when those data are included in an IDE or marketing application or submission.

The rule was intended to help ensure the quality and integrity of clinical data and the protection of human subjects that participate in device clinical

investigations, and it does that by explicitly incorporating Good Clinical Practice, or GCP, requirements in the regulations.

The GCP requirements for device clinical investigations harmonize with those for drug clinical investigations, and by focusing on the conduct of investigations, the rule helps to ensure our regulatory decisions are based on valid, ethically-derived clinical data.

The final rule aligns with CDRH's vision that patients in the United States have access to high-quality, safe, and effective medical devices of public health importance first in the world. We recognize that more multinational investigations are being conducted, and as a result more research and marketing applications rely on foreign clinical data.

By establishing GCP requirements for acceptance of clinical data, we help ensure our decisions are based on valid, ethically-derived data, and at the same time, we provide predictability, consistency, and transparency to sponsors and applicants regarding the requirements for acceptance of the clinical data they submit to the FDA.

The agenda for today's presentation is that I will provide a brief background and then discuss the requirements outlined in the rule. At that point, (Jayna Stohlman) will discuss aspects of our implementation, and some recommendations for complying with the requirements, and then we'll have some time to take your questions.

So here are three things we'd like you to walk away with today. First, we want you to understand the purpose of the rule. Second, to learn the required statements and information that must accompany investigations included in

premarket submissions. And third, to understand where you can find recommendations and resources for complying with the rule.

But before we get started, just a few definitions. When (Jayna) and I use the term "investigation", we mean research involving human subjects to determine the safety or effectiveness of a device. US investigations take place solely inside the United States, OUS investigations solely outside, and we'll use the term "multinational investigation", for those that are conducted at sites both within and outside the United States.

An IDE application is a mechanism to request FDA approval to conduct a significant risk clinical investigation with an unapproved device or unapproved use of a device. And we'll use the term "marketing application or submission" to mean 510(k)s, De Novos, PMAs, PDPs, and HDEs.

So for the next three slides, they'll focus on how we arrived at this point and why the rule was issued. In 1986 -- over 30 years ago -- the FDA issued PMA regulations that indicated we will accept data from an OUS investigation if the data were valid, and the investigation was conducted in conformance with the Declaration of Helsinki, or the laws and regulations of the country where the investigation was conducted, whichever one of those afford a greater protection to the subjects. The standards for protecting human subjects have evolved considerably over the last 30 years, for example, the Declaration of Helsinki has been amended six times since the PMA regulations were first issued.

The evolution of these standards is one reason FDA issued a proposed rule to update the PMA requirements for accepting data from OUS investigations and apply them to IDEs and other kinds of marketing applications and submissions. After revising the rule to address public comments, we issued

the final rule on February 21st of last year and indicated the effective date would be one year after publication.

So here's a summary of the public comments we received in response to the proposed rule. There were concerns about our proposed application of the rule, for example, the required supporting information for OUS investigations was initially proposed to be the same for non-significant risk and significant risk investigations.

The effective date was initially proposed to be six months after issuing the final rule, and many outside stakeholders stated that wasn't enough time to incorporate these new requirements into their plans. There was a concern that FDA was requiring a GCP standard for OUS investigations, even though there wasn't a single international standard for conducting device investigations.

Several comments noted that stricter privacy laws in different countries may present challenges for complying with the requirements. And finally, there were several comments indicating that non-compliant investigations may still provide useful information for regulatory decisions, and therefore FDA should still consider investigations that were not conducted in conformity with GCP.

So in response to these public comments, we made some changes before issuing the final rule, and three examples are displayed here. One change is that we delayed the effective date from six months to one year. We also adjusted the supporting information requirements for OUS investigations so that they vary by study risk. We added additional regulatory flexibility for complying with the GCP requirements, for example, sponsor and applicants submitting data obtained from OUS investigation can request that one or more requirements be waived, if they provide adequate justification to support the waiver request.

We also clarified certain aspects of the rule in the preamble. For example, we clarified the rule does not specify one GCP standard that all investigations must comply with, rather, it provides a definition of GCP that must be met for the standard that is chosen. Another example is there were concerns about complying with the GCP requirements for certain kinds of IVD studies, and so we clarified that FDA's policy regarding informed consent for IVD studies using leftover, de-identified human specimens may be used when submitting data obtained from such studies.

Now I'll describe the scope of the rule and the actual requirements. So I mentioned earlier that the scope includes clinical data submitted in IDEs and all marketing applications and submissions.

It's important to note that the requirements only apply to investigations that begin on or after the effective date of the rule, which is February 21, 2019. And the beginning of an investigation is the day the first subject agrees to participate by signing the informed consent documents.

In response to public comments on the proposed rule, we clarified in the preamble that the scope only includes investigations meant to support an IDE, or device marketing application or submission, and not supplementary clinical data that may be submitted.

For example, investigations within the rule's scope are those submitted in a 510(k) to demonstrate substantial equivalence, or in a PMA to demonstrate a reasonable assurance of safety and effectiveness. When clinical data are submitted as supplementary information and not as support, demonstrating conformity with GCP is not required.

For investigations within the rule's scope and conducted outside the United States, our acceptance of the data for regulatory decision making requires a statement that the investigation was conducted in accordance with Good Clinical Practice.

The regulatory definition of GCP is a standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical investigations in a way that provides assurance that the data and results are credible and accurate and that the rights, safety, and well-being of subjects are protected.

The regulatory definition of GCP also includes obtaining the review and approval by an Independent Ethics Committee. And obtaining and documenting freely-given informed consent of all subjects prior to their participation in the investigation.

Many parts of this GCP definition for OUS investigations, such as monitoring, auditing, and obtaining informed consent, are incorporated in regulations that govern the conduct of investigations conducted inside the United States, including parts 812, 50, and 56. For example, the regulation for Part 50 includes the informed consent requirement for clinical investigations.

The GCP requirements for accepting clinical data from investigations conducted inside and outside the United States address the principle objective of the rule, which is to help ensure our regulatory decisions are based on valid, ethically-derived clinical data, regardless of where those investigations are conducted.

This slide, and the next few, display the GCP requirements for US and OUS investigations. To accept data derived from US investigations for regulatory

decision making, we require a statement that the investigation has complied with 21 CFR Parts 50, 56, and 812. Or, if those investigations were not conducted in compliance with 50, 56, and 812, the sponsor applicant must provide a statement of the reasons for noncompliance with applicable parts of those regulations.

To accept data derived from OUS investigations for regulatory decision making, a statement is required that the investigations were conducted in accordance with GCP as defined in the regulation. Alternatively, if the investigation was not conducted in conformance with GCP, a waiver request is required for one of the requirements, or a brief statement is required of the reason for not conducting the investigation in accordance with GCP, and a description of steps taken to ensure subjects were adequately protected, and to ensure the quality and integrity of the data obtained during the investigation.

The rule also requires the submission of supporting information for certain OUS studies to demonstrate conformance with GCP. And on this slide, and the next one, we'll take a closer look at the supporting information by specifying each of the 11 distinct items that are required to be submitted for an OUS investigation, or for the OUS sites in a multinational investigation.

The supporting information is intended to verify the statement that the OUS work was conducted in accordance with Good Clinical Practice. The list of supporting information includes: a summary of the protocol and study results, a description of the device, a description of how informed consent was obtained from study subjects, a description of how the study was monitored, et cetera.

Many of these items typically are included in other parts of the submission and they don't need to be provided multiple times, but rather, simply cross-

referenced to demonstrate that the required supporting information was included for all applicable studies.

The final rule also indicates that the required supporting information is based on the level of risk subjects were exposed to during that investigation. All required elements must be submitted for significant risk investigations, a subset for NSR investigations, and for IDE exempt studies, no information needs to be submitted, although some must be made available to us if we ask for it.

The sponsor or applicant must also maintain documents that explain their risk determination for the investigation, and we can request those if we need to.

So the final rule provides regulatory flexibility for complying with the requirements. For example, it does not specify a single GCP standard that all investigations must comply with, but rather, it provides a definition of GCP that must be met for the standard that is chosen. We believe that conducting clinical investigations according to such a GCP standard will help ensure the integrity and quality of the data and the protection of subjects, similar to FDA's GCP regulations for investigations conducted inside the United States.

You may submit non-compliant investigations, and we may accept the data from those investigations for regulatory decision making, if you explain the steps taken to ensure the results are credible and accurate, and that the rights, safety, and well-being of subjects were adequately protected during the investigation.

Another example of regulatory flexibility is that, if you are planning an OUS or multinational investigation, and compliance with the regulation is a concern, you can discuss your concerns with the appropriate FDA review

division before conducting the investigation. If appropriate for your study, you may request a waiver for one or more of the requirements before beginning that study.

So to conclude this part of the presentation, here's a summary of the key provisions in the final rule. The provisions apply to investigations that begin on or after February 21, 2019, and that are included to support an IDE, 510(k), De Novo, PMA, HDE, or PDP.

For US investigations, a statement of compliance with 21 CFR Parts 50, 56, and 812 is required, or a rationale for noncompliance with those regulations. If the investigations are conducted solely outside the United States, a statement of conformance with GCP as defined in the regulation is required, and in addition, supporting information to demonstrate conformance is required. Alternatively, for OUS investigations, a rationale for noncompliance can be provided, or a waiver of one or more of the GCP requirements can be requested. Finally, for multinational investigations, the US requirements apply to the US sites, and the OUS requirements apply to the OUS sites.

And now for the last part of the presentation I will turn it over to my colleague (Jayna Stohlman).

(Jayna Stohlman): Hello, good afternoon, my name is (Jayna Stohlman). I will be speaking to you about implementation of the final rule, including recommendations and resources to help you comply with the rule.

I will first describe updates we have made to 510(k) and PMA Acceptance Review guidances and checklists. We've revised these documents to include a new section that is meant to capture whether compliance with GCP is

addressed for each supporting clinical investigation included within a premarket submission.

These updated guidances are currently available and can be found by following the links provided on this slide. The new section that has been added to address these requirements is similar between both the 510(k) and PMA guidances, and this is because these requirements are now the same across device marketing application and submission types.

Here we will use the 510(k) version as an example to briefly go over how this new section is organized. Each checklist addresses the new requirements in three parts. The first part describes the scope and applicability of this new section.

The second part is a question applicable to any US investigations falling under the scope. And the third is a question which is applicable to any OUS investigations falling under the scope. I will go over each part in more detail in the following three slides.

This first part outlines the scope and defines the applicability of the subsequent questions. It references the effective date of the final rule and also describes how or when the subsequent questions apply for US, OUS, or multinational investigations. Finally, a link to the guidance associated with the final rule is also provided for more information. This part outlines whether the next two parts are applicable.

This next part is a question that is applicable for any clinical investigations that were conducted at US sites. It asks whether, either a statement of compliance with Parts 50, 56, and 812, or a brief statement of the reason for noncompliance with these regulations has been provided for each US clinical

investigation. These two options are requirements specifically outlined in the final rule and can be found in the amended regulations.

This last part is applicable for any clinical investigations conducted at OUS sites. It asks whether, either a statement that the OUS clinical investigations were conducted in accordance with GCP as described in 812.28(a), or a waiver in accordance with 812.28(c), or a brief statement of the reason for not conducting the investigation in accordance with GCP, and a description of the steps taken to ensure the integrity of data and protection of human subjects, has been provided for each OUS clinical investigation. Again, these provided options are requirements specifically outlined in the final rule and can be found in the amended regulations.

Now I'll walk a bit more through waiver requests. A provision in the final rule was created to allow for sponsors or applicants to request a waiver to any applicable requirements for clinical investigations conducted outside of the United States. These requests can be prior to, or within, an IDE or marketing submission or application, or in an amendment or supplement to one of these submissions.

Examples of when a waiver request may be appropriate or necessary would include, when a clinical investigation is being conducted in a country where the foreign laws do not permit disclosure of source documents, such as medical records, which might be needed to verify clinical data, or when sharing of IEC member qualifications, a supporting information requirement, is prohibited.

As outlined in the regulation, a waiver request is required to include at least one of the following: an explanation of why compliance with GCP in accordance with 812.28(a) is unnecessary or cannot be achieved, a description

of an alternative course of action that satisfies the purpose of the requirements, or other information justifying the waiver.

As said before, these waiver requests may be submitted as part of an IDE or marketing application or submission, or in an amendment or supplement to one of these submissions. However, waiver requests may also be submitted prior to and outside of a premarket submission, which I will refer to here as a standalone waiver request.

When submitting a standalone waiver request we suggest the submission should include the information outlined in the previous slide, and be submitted to the Document Control Center with a cover letter that clearly identifies that the submission is a waiver request in accordance with 21 CFR 812.28(c). This should help ensure that the submission is correctly and efficiently processed and reviewed.

This slide summarizes how and when we will be communicating with sponsors or applicants about any submitted waiver requests. Here we have organized waiver requests into two categories. In general, ones that will have a formal letter sent to the sponsor with the decision of Grant or Deny on the waiver request, and then those that will not have a formal letter sent.

The waiver requests that we do not intend to issue a formal decision on are those that come in within a marketing application or submission, or in an IDE for investigations supporting the report of prior investigations. Waiver requests coming in with these submissions, would be applicable to investigations that have already been completed and included to support those submissions.

Whereas the information submitted to support a waiver request within one of these submissions will be reviewed, the decision on one of these waiver requests will not necessarily be communicated outside of normal review of the subject submission, unless a deficiency letter references the waiver request.

For those waiver requests that are submitted and applicable to investigations conducted prior to submission of a marketing application or submission, or an IDE -- referred to here as Other Waiver Requests -- these types will have a formal decision communication, as the intention for these waiver requests is to seek waiving of requirements before the clinical data are included in a future IDE, or marketing application or submission. Also note that acceptability of waiver requests is determined on a case by case basis.

Now I will present some recommendations we have for any premarket submission with clinical data. In order to help facilitate review of these submissions, clearly identify in the cover letter whether the submission contains data from clinical investigations conducted outside the United States that are subject to 21 CFR 812.28.

Further, explicitly cite where the FDA can find all the requirements under 812.28, either within the subject submission, or cross-referenced from previously submitted materials, with section and page number references to the respective clinical investigation reports, and other applicable information.

It is also recommended to state if the submission includes any statements for not conducting the clinical investigations in accordance with GCP, or if any waiver requests are included as part of the subject submission or have been previously granted for the applicable OUS clinical investigations.

We also wanted to draw your attention to the pre-submission guidance shown here. This guidance will provide you with more information about getting feedback from the FDA for any specific questions you may have about a future submission.

For example, you can request a study risk determination for a clinical investigation conducted solely outside the United States, in order to determine the supporting information that would be required for submission in support of your future IDE, or marketing application or submission.

You may also submit a pre-submission request for feedback on specific questions pertaining to your future IDE, or marketing application or submission. More information about how to organize and submit these types of submissions can be found within this guidance.

In summary, for studies beginning on or after February 21, 2019, the final rule helps to provide clarity and consistency in FDA requirements for acceptance of clinical data from device clinical investigations submitted to support all premarket submissions and applications.

As we've gone over in detail, the final rule requires that data from clinical investigations submitted to support premarket submissions be from investigations conducted in accordance with GCP. Therefore, it is FDA's intention that quality data are being used to support IDEs, and marketing submissions and applications, as well as ensuring that the rights, safety, and well-being of subjects have been adequately protected.

We would like to point you to these document references, which can provide more information about Good Clinical Practices and the requirements of the final rule. We are also including the email address for the CDRH Clinical

Evidence mailbox. If you should have any additional questions about the final rule requirements, please feel free to contact us here.

Otherwise, you may contact the Division of Industry and Consumer Education for more general assistance or information, and you may access this presentation, transcript, and recording at the links provided.

Irene Aihie: We will now take questions.

Coordinator: Thank you. At this time if you would like to ask a question please press star one from your phone, unmute your line, and record your first and your last name clearly when prompted. One moment as we wait for our first questions.

(Jayna Stohlman): Hello, this is (Jayna Stohlman) again. We wanted to address a couple of points of clarification concerning the applicability of the final rule and the new requirements for acceptance of clinical data while we're getting organized.

One important point is when the required statements of compliance and submission of supporting information, in the case of OUS conducted sites from a given clinical investigation, should be submitted for an IDE.

To clarify, for IDE submissions these requirements apply to data submitted as part of the report of prior investigations. The required statements and information are not required to be submitted, for example, in progress report updates submitted for an active study under an IDE.

However, if and when the data from a clinical investigation that was conducted under an IDE comes in to support a future IDE, or marketing application or submission, applicability of the rule should be evaluated to

ensure that the required information is included with that future submission or application, and the sponsor should submit information about compliance with GCP accordingly.

Another important point of clarification we hope will be helpful involves use of leftover, de-identified human specimens for certain in vitro diagnostic, or IVD, applications. The FDA intends to continue its enforcement discretion policy regarding the requirement for informed consent under certain circumstances outlined in the FDA guidance entitled, “Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens That Are Not Individually Identifiable.”

When applicable, applicants may cite this policy as the reason for noncompliance with the requirement for informed consent, and other requirements, such as those related to IRBs, still apply.

Irene Aihie: We'll take our first question.

Coordinator: Thank you. Our first question comes from (Ingrid Oakley). Your line is open.

(Ingrid Oakley): Hello. Yes, I was just interested in finding out if you were going to share the links for those of us who are just on the phone? If those could be sent to the emails of record that would be great.

Irene Aihie: I'm sorry, can you repeat your statement?

(Ingrid Oakley): Yes. So for those of us who are on the phone, we can't see the links on the screen. So I'm just wondering if those can be sent to the emails for the people who registered?

Irene Aihie: Sure thing.

(Ingrid Oakley): That will be great, thank you.

Coordinator: Thank you. Our next question comes from (Gail Gasory). Your line is open.

(Gail Gasory): Hello. I believe you've already answered the question in your recent clarification that you just talked about, in the context of FDA intending to continue to enforce their discretion on requiring informed consent for leftover specimens.

Would you please clarify, if a sponsor intends to point to that guidance as rationale, should that be addressed in the pre-sub process? Or is it not necessary to address it in the pre-sub process and merely document it in the submission?

(Jayna Stohlman): Hi, this is (Jayna Stohlman). I would say that it's good practice to communicate with your review team ahead of time, if you have the opportunity, so that it's clear before going into your premarket submission. However, it's not necessary or mandatory that you do so -- you can come in with a reason for noncompliance, and that is an acceptable reason.

(Gail Gasory): Okay, thank you.

Coordinator: Thank you. As a reminder if you would like to ask a question please press star one from your phone, unmute your line, and record your first and your last name clearly when prompted. One moment as we wait for any additional questions.

Okay, one moment. Okay, this question comes from (John). Your line is open.

(John): Yes. I'm trying to figure out, does this apply to simulated use data that's generated for usability testing? And or actual use evaluations for human factors testing?

Irene Aihie: Can you repeat your question?

(John): Does this apply directly to human factors evaluations - whether they be simulated use or actual use studies?

(Soma Kalb): I think it would be helpful - hi, this is (Soma Kalb). Thanks for that question, it's a good one. And I think it would be helpful if you can provide more information specifically about the studies that you're describing so that we can understand whether it falls within the scope.

There are a lot of different uses of those terms. And whether it actually would be one of the types of investigations that fall within the scope of the rule, we would be happy to look at. I would suggest that you can send that question to the mailbox that is on the screen here.

Alternatively, you could send it to CDRHClinicalEvidence@FDA.HHS.gov. And we could go into a little bit more detail about your specific studies.

(John): Okay. That would be great, thank you.

(Soma Kalb): Sure.

Coordinator: Thank you. There are no other questions in queue at this time.

Irene Aihie: Thank you. This is Irene Aihie. We appreciate your participation and thoughtful questions.

Today's presentation and transcript will be made available on the CDRH Learn web page at www.fds.gov/training/CDRHLearn by Wednesday, March 27. If you have additional questions about today's presentation, please use the contact information provided at the end of the slide presentation.

As always, we appreciate your feedback. Following the conclusion of the webinar please complete a short, 13-question survey about your FDA CDRH webinar experience. The survey can be found at www.FDA.gov/CDRHwebinar immediately following the conclusion of today's live webinar.

Again, thank you for participating. This concludes today's webinar.

Coordinator: Thank you for your participation in today's conference. All participants may disconnect at this time.

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