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White Paper

ePRO Regulatory Inspections:

Best Practices for Smooth and Successful Outcomes

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Introduction

Across the globe, inspections by regulators are a common component of the review process of an application for registration of a biopharmaceutical product. Companies that have made such submissions exert significant effort to ensure these inspections proceed well, and do not have a negative impact on the review of their submission.

The primary purpose of these regulatory inspections is to ensure the quality and integrity of the data that was captured in the clinical trials of the product development program. An appropriate global standard for biopharmaceutical companies is the International Conference on Harmonization (ICH) Good Clinical Practices (GCP). In the European Union, following ICH GCP is a regulatory mandate. In the United States, the Code of Federal Regulations (CFR), Part 21 has a number of requirements for the development and evaluation of biopharmaceutical products. Together, these regulations, along with local regulations and guidance from individual countries around the world, provide the framework for the review of clinical data in support of a biopharmaceutical submission.

This regulatory framework also applies when technology is used to collect data in clinical trials. For example, if patient reported outcomes (PRO) - data reported directly by patients - are captured with electronic devices (ePRO), the same regulatory framework is used to evaluate the quality and integrity of the data. Given that ePRO data is still relatively new when compared to the longstanding history of using paper PRO, the challenge for many biopharmaceutical companies is how to prepare for an inspection of ePRO data.

This paper addresses the challenge of an ePRO inspection from a regulatory agency. Based upon our experience of supporting companies through such inspections across the globe, we outline here the process and procedures that will facilitate a successful outcome. Our experience suggests that while each inspection is different, we have witnessed some common themes and collaborated with sponsors on responses that have worked successfully in answering regulators' questions.

The Situation

The notification of inspection from a regulatory agency can send shockwaves through an organization. Are you ready? If ePRO was collected and part of the regulatory submission, what can the sponsor expect? Based on some recent inspections, focusing on a few basic areas will help in evolving your strategy for success.

What to Expect

In our experience, sponsors who have considered the inspection early in their pivotal (Phase 3) trials have had fewer surprises when they received the announcement of an inspection. In order to anticipate the challenges a sponsor may face, attention to certain factors through the life of the pivotal trials should be considered. The following reflects the most common themes we have observed during regulatory inspections in the US, EU, and Japan.

How is the system to be designed and validated?

To prepare for questions around validation of the ePRO system, sponsors should ensure that their validation documentation meets the requirements of the regulations and guidance and request access to this evidence. Universally, inspectors request a demonstration of the system procedures and validation evidence; and actual outputs such as device transmission records and proof that the correct software was placed on subject devices.

How is site staff to be trained and qualified on all ePRO system-related procedures? How will subjects learn to use the ePRO device's protocol-specific and general features?

ICH GCP requires that all those responsible for trial conduct be given the necessary training to execute their given role. Participation in trial execution can only be granted after the training requirements have been fulfilled. The same requirements are true for trial subjects.

Who has responsibility for the source data? How are the data to be captured, viewed, edited, extracted, archived, and retained?

Source data maintenance, accessibility, and retention are topics that require explanation in order for inspectors to assess data reliability. Sponsors can provide details regarding the point at which the source data was collected, who was responsible for maintaining it, and where the source is located at the time of inspection.

How will trial conduct be assessed and what are the key stakeholder responsibilities for its execution? If errors are detected, does the quality system support proper root cause analysis and follow up to ensure corrective actions are implemented and can be evidenced?

An area of increasing interest during inspections is how the sponsor maintained proper oversight of trial conduct. The sponsor can provide evidence of the processes utilized, the responsibilities for, and outputs created to support appropriate controls.

Providing evidence to support questions in these areas can help significantly increase the likelihood of a successful outcome.

Preparing Yourself

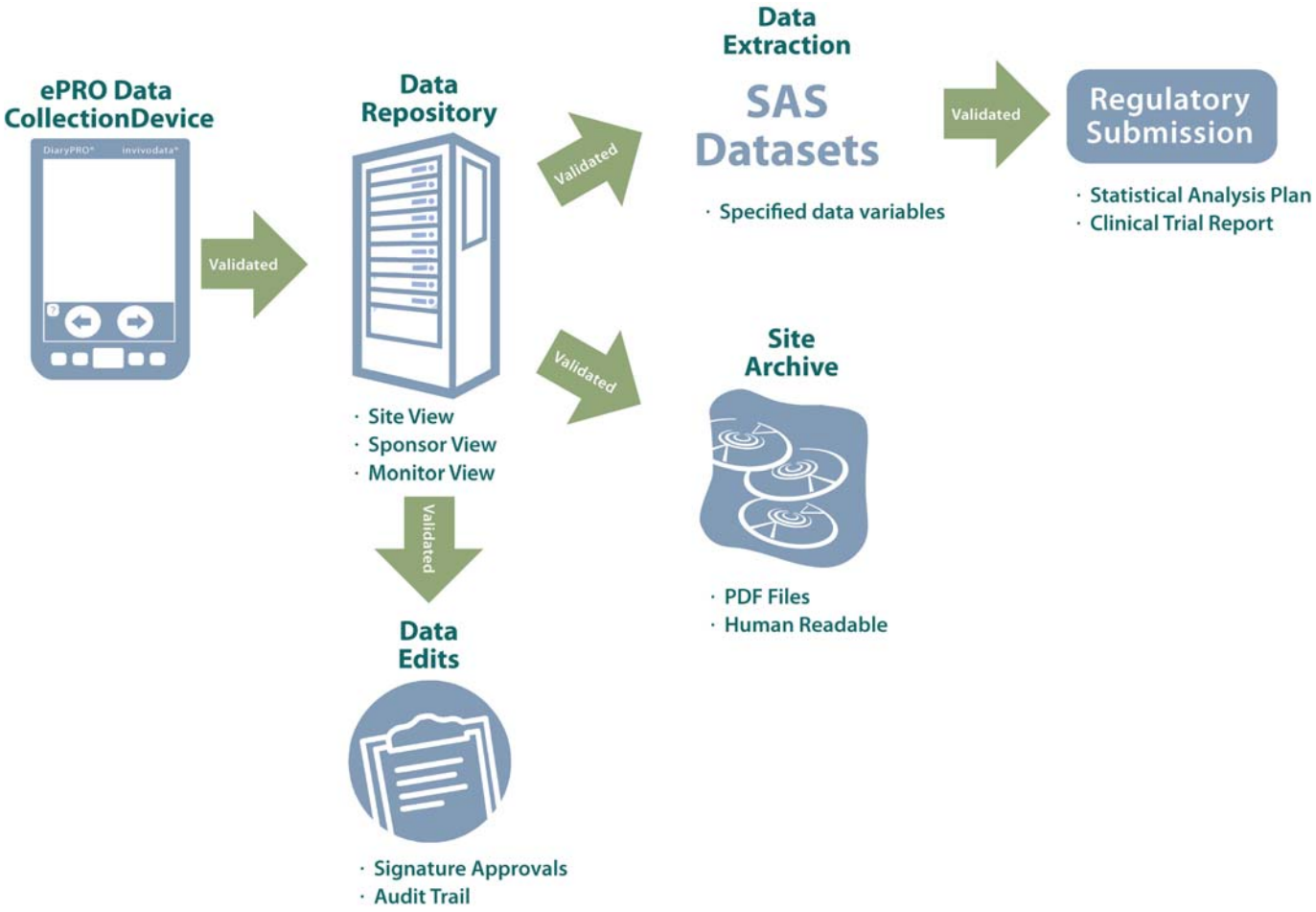
As regulatory agencies advance their knowledge about clinical technologies, they have increased their vigilance in inspecting ePRO systems. They are requesting ePRO system information be provided as part of the registration submission review to gain insight prior to the inspection. Therefore, sponsors are best served by having a good understanding of how their ePRO system was built and utilized to collect subject data in accordance with applicable regulations and guidance. In this way, the sponsor can direct the inspector to the appropriate trial stakeholder (e.g., investigative site, ePRO provider, etc.) to obtain the most accurate understanding of the ePRO system and the eSource data process.

Inspectors commonly perform source data tracing through the system - from the point of entry by the subject, to the statistical datasets submitted to regulatory agencies. The goal is to ensure data integrity. Sponsors who have a working knowledge of the ePRO system, and are equipped to represent the systems and services used to collect ePRO data in the clinical trial can successfully support this approach. This begins with being able to provide an awareness of the validation of systems utilized to design, build, collect, report, and retain ePRO in the regulated environment.

Figure 1 is an example of a system used to collect ePRO data. Demonstrating how the data flows through the system and being prepared to provide the documentation that supports the validation effort will give the inspector confidence that the sponsor was in control of overseeing the trial and data.

ePRO data collection begins when the subject enters data on an ePRO Data Collection Device. The subject-entered data is then transferred to a Data Repository to provide reporting to sites, monitors, and the sponsor. Depending on how the ePRO system is used, Data Edits are performed in a controlled manner in the system and at the direction of the site. This provides audit trails and electronic signature approvals. At agreed upon intervals, Data Extractions from the data repository occur and are delivered to the sponsor in a specified format. Once the trial is complete and the database is locked, ePRO data are extracted from the data repository and provided in the Site Archive in a human readable format. In addition, the ePRO data are provided to the sponsor for Regulatory Submission.

Figure 1: Example of ePRO Data Flow



Sponsors can demonstrate data integrity by asking and answering the following questions:

1. **ePRO Collection Device: Source data entry point**

   How are the data collected and does the software work? Providing the protocol and showing how its requirements are outlined in the software design is a good place to start. Evidence of this tracing can be accomplished with process descriptions, design requirements, software testing, and detailed information on how software changes are implemented. If the activity is outsourced, a sponsor can demonstrate that they conducted an appropriate level of user acceptance testing in order to verify the system design against the requirements of the protocol.

2. **Data Repository: View of ePRO collection device-entered-data on secure system**

   Where are the data stored and how are they viewed? Sponsors can offer visibility into how data are viewed during the active trial by the investigative site, monitors, and the sponsor through live access

to the data repository. Controls over the source can be verified through records on access availability and roles, the data views provided, edits made to subject data, and the data delivered during the trial and with the data archive at the end of the trial.

3. **Data Edits: Data changes through electronic signature with audit trail**

   How are data edited and protected against unauthorized changes? An explanation of the type of data edits and how edits are executed can be given to the inspector. Examples of data edits include changes to subject identifiers (e.g. date of birth, subject initials) or device identifiers (e.g. serial number). Successful execution of the process is substantiated with examples of edits to subject data that required action by the investigative site staff through 1) the electronically signed approval of the investigative staff prior to changes to subject data and 2) the audit trail record of the data edit including the person making the change, the date/time, and the reason for the change. All editing systems should ensure that any changes, deletions, or additions to the subject data record leave the previous data untouched.

4. **Data Extraction: Extraction of data from server in SAS dataset or other format dictated**

   How were the data pulled from the data repository and provided to the sponsor during the trial? How were the data introduced into the clinical trial database? Sponsors can provide evidence of validation that the extraction of the data produces an accurate and complete copy of the source data retained in the data repository, and in turn, how that extraction was then introduced into the clinical trial database. Verification of the integrity of the process can be shown with a comparison between the extracted record and that which is stored in the clinical trial database.

5. **Site Archive: Extraction of data from data repository (final data delivery for archive by investigative site and sponsor)**

   How are data delivered to support requirements for retention? Sponsors can expect to demonstrate that the data have been under the control of the investigative site at all times. Both sites and sponsor should make available an accurate and complete copy of all of their subjects' data, along with the complete audit trail of any changes in a human readable format. This is the archived version of the source data that existed on the data repository during the trial and is to be maintained by the investigative site. Verification of data integrity may be exhibited through a comparison of the site archive data with a view of the records on the data repository and the records stored in the clinical trial database.

6. **Regulatory Submission: Compilation of data from the clinical trial database supplied by sponsor to regulatory agency**

   How are the data prepared for submission to the agency? Sponsors can demonstrate the process used for submission of the ePRO data. The statistical analysis plan and clinical trial report should describe how the ePRO data were managed and summarized, and the process leading to its presentation to the regulatory agency. Verification of data integrity can be shown with a comparison of the site archive data to the submission.

7. **Training of System Users: Investigative site personnel and subjects**

   How was user-training executed and comprehension measured? Materials used for training, assessment of comprehension (e.g. exams), and training certification records will be requested during an inspection. Subject training materials and a record of subject training can be presented as part of the electronic data stream for each participant.

8. **Oversight by the Sponsor: Management of the trial conduct**

   Below are some specific questions the sponsor should be prepared to answer when discussing their management of the ePRO system with an inspector:

   a. What is the process for assignment of user levels of access and granting of access in a controlled manner? (e.g. access requirements, validation of system access controls)

   b. Where is the evidence of how devices were distributed and attributed to subjects? (e.g. subject identifiers, device identifiers, device initiation records)

   c. Where is the evidence of the type of data edits that were carried out, that they did not obscure previous records, that they were fully audit-trailed and if there was any consistency in the type of edits being performed from a system and site perspective? (e.g. data clarifications, audit trails)

   d. What evidence documents that issues were reported in a consistent and controlled manner? (e.g. help desk tickets)

   e. What updates to the software were effectively validated and distributed to users? (e.g. software testing, software build numbers released to subject devices)

   f. Where is the proof within the system that demonstrates how data were viewed and archived? (e.g. data report views, data archive records)

g. Does the system provide evidence that the sites and monitors were appropriately fulfilling their duties? (e.g. system access reports, requests and approval of data edits)

h. How do we show that the investigator had control of the data through to data archive? (e.g. data archive receipts, database lock record)

i. Is there analysis to support the impact of issues to the ePRO data, how root cause was determined, and that the corrections that were implemented worked effectively? (e.g. CAPA system records)

j. What were the oversight controls of outsourced activities? (e.g. sponsor audit records, partner procedures, sponsor approval of design, UAT documentation)

Working with Your Technology Partner

The above provides the foundation for demonstrating and supporting the integrity of the ePRO data. Now the focus turns to the day of the inspection. Will you need your ePRO provider to support you? Collaborating with your partners can be valuable during an inspection.

Developing a communication plan ahead of time with your partners will lessen the stress level of the team. Sponsors are best served by setting expectations with partners about impending inspections, collaborating on how to manage questions, and providing responses with supporting evidence.

Partners can assist you in ensuring appropriate data retention; granting accessibility to the data repository; providing an accurate description of processes utilized; accessing the materials used for training of site and sponsor staff; producing data queries requested by the inspector; and maneuvering through the validation evidence for the ePRO system.

We propose the following "Do's" for inspection preparation:

1. Conduct a pre-audit of investigative sites prior to the regulatory inspection so that you can identify any issues and prevent any surprises beforehand. Some sponsors elect to conduct a mock inspection in advance of the scheduled inspection.

2. Confirm that the investigative site has retained and has access to the data archive, the record of its receipt, as well as all training materials and certificates.

3. Provide "refresher training" to site and sponsor personnel if necessary.

4. Review the data archive and how to navigate it, so that you and the site will be able to easily maneuver through it with the inspector.

5. Reactivate view access to the website to "bring it back to life".

6. Ensure your partner knows important dates for your trial, such as First Patient In, Last Patient Out, Database lock, etc.

7. Have your validation documentation ready, particularly for sponsor inspection, in order to prove how the data were managed.

8. Know your areas of risk. Specifically, if you had challenges with any of the sites, know which sites they were and what type of issues they had so that you can explain the level of risk and any impact it had on your trial.

9. Be able to articulate the different views of the data that were provided during the life of the trial and as part of the data archive.

10. Develop a communication strategy with your ePRO provider and any other partners involved in the clinical trial. Identify how you will manage questions, how you are going to document those questions and who your point people are and how to reach them. Set expectations for what you need from your partners so that they can be in the best position to support you.

Conclusion

Begin with the end in mind. Inspectors evaluate compliance to requirements of the regulations using ePRO data. Advanced planning on the part of the sponsor and with your ePRO provider can aid in easing inspection anxiety. By gaining an understanding of the ePRO data, systems, and areas of interest with regard to data integrity, you can be comfortable and confident in responding to questions about the ePRO data collected in your trial.

We have observed a number sponsors successfully meet the expectations of regulatory inspections, resulting in market approval of new medical products using ePRO data.