# Complying with ICH E6 (R2)

## *WHAT YOU SHOULD KNOW ABOUT RISK-BASED EVALUATION BEFORE DESIGNING THE ECLINICAL SYSTEM FOR YOUR CLINICAL PROGRAM: PART 2*

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# COMPLYING WITH ICH E6 (R2)

## What You Should Know About Risk-based Evaluation Before Designing the eClinical System for Your Clinical Program

*A two-part series from YPrime*

"Risk" is the watchword for sponsors working to comply with ICH E6(R2), the 2016 revisions to the International Council on Harmonisation's guideline on good clinical practices. At the heart of these changes is the imperative to manage the risks to patient safety and data integrity that are posed by eClinical tools and electronic data processes.

In this two-part series, YPrime presents:

*Part 1. An Overview of the ICH E6(R2) Guideline*

*Part 2. Risk Mitigation in eClinical Design Requirements*

### Part 1. Summary

In *Part 1. An Overview of the ICH E6(R2) Guideline*, we summarize the key changes of the revised guideline which requires sponsors to adopt risk-based approaches in centralized monitoring, clinical monitoring and software validation. We outline the components of a quality management system and sponsor responsibilities for software and system validation.

### Part 2. Summary

In *Part 2. Risk Mitigation in eClinical Design Requirements,* we outline the risks posed by eClinical systems to patient safety and data integrity and discuss what sponsors should do to comply with ICH E6(R2) requirements to mitigate these risks prior to and during the development of an electronic data capture system.

# PART 2. RISK MITIGATION CONSIDERATIONS IN ECLINICAL DESIGN

As clinical researchers adopt the risk-based thinking mandated by the 2016 revisions of the ICH E6(R2) guideline on good clinical practices, the U.S. Food and Drug Administration advises sponsors to begin risk mitigation by asking three basic questions[i]:

- What might go wrong?
- What is the likelihood that it will go wrong?
- What are the consequences if it does go wrong?

"Risk" is anything that could go wrong, or has gone wrong, in the process of collecting, overseeing, recording and reporting clinical trial data. Level of risk (severity) is gauged by potential harm to study patients and impact on data integrity. In this context, risk mitigation is conducted in a quality risk management process designed to assess, control and review risk events.

In the design of eClinical systems, the hallmarks of regulation-compliant risk mitigation are transparency, traceability, and documentation. *"eClinical providers should partner with sponsors early on to implement this new, proactive mindset. Risk management should always be an integral part of eClinical system design," says* Jaime Cook, Executive Vice President, YPrime.

## What Might Go Wrong? Common Risks Posed by Electronic Systems

Failure to build in correct, protocol-specified requirements in EDC, IRT and eCOA systems can result in serious risks, including the enrollment and treatment of unqualified patients, dosing errors, and failure to capture primary endpoint data. The following scenarios do not represent an exhaustive list but describe the most common potential risks.

**Risks to Patient Safety.** Errors in the design of IRT and eCOA platforms, which manage patient screening, randomization and drug dispensing, pose the highest level risks to the safety of patients and can also impact data integrity.

*Screening, Randomization and Patient Eligibility*. If criteria for study participation are not built correctly into the IRT system or eCOA platform, there is potential for enrollment of unqualified patients who may be at risk during study participation. Even subtle errors in criteria for randomization can pose serious harm by exposing unqualified patients to inappropriate treatment. In addition, data from unqualified patients can skew results and make study findings unreliable.

It is vital in IRT system and eDiary design to:

- Develop algorithms and calculations in close collaboration with the sponsor's clinical and biostatistics team to ensure that all relevant points are represented and data are logged in a manner conducive to the planned statistical analysis. It is also useful to create a static web report that displays results of the eligibility calculation for reference so that eligibility can be confirmed at any point in the future.
- Present results in simple format to facilitate accurate interpretation by investigative staff.
- Train Investigative staff sufficiently to interpret and act on results of algorithms and calculations.

*Drug Dispensing*. Accurate information is absolutely critical for eClinical systems' management of drug dispensing operations. Again, the IRT platform poses the biggest risk. An error in the protocol or an incorrect algorithm can result in the system directing the wrong drug to be dispensed to a study arm, or in failure to dispense drug at appropriate times and correct doses. Complex and cross-treatment study designs pose increased risk, as patients move into different study arms that require different drug or placebo and different doses.

*Adverse Event Reporting*. eCOA systems capture symptom data that may be reviewed by investigative staff for identification and report of safety signals to appropriate pharmacovigilance stakeholders. Safety signals must be integrated with EDC. It is vital for the safety of all study patients that eCOA capabilities effectively support pharmacovigilance practice. Vendors need to understand the pharmacovigilance process in order to provide relevant, accurate data to sites so that investigators can meet regulatory reporting deadlines.

**Risks to Data Integrity.** From the capture of endpoint data through data recording, storage, transfer and reporting, eClinical systems introduce risk to data integrity that must be managed by documenting eClinical data processes and by making them transparent and traceable through audit trails. YPrime advises sponsors to give special attention to the following common points of risk.

*Data capture*. Risks arising from data capture begin with the possibility that the eClinical system design fails to capture key endpoint data. An important consideration in the course of data collection is differences between IRT and EDC systems. Typically, IRT data are available first; but EDC data, which undergo more review and data cleaning, are considered to be more reliable. EDC data serve as the master version of the data and widely regarded as the "single source of truth."

*Site and patient usability*: Trends toward patient-centric research are driving industry to include more patient input and PRO data in clinical trials. Sponsors are seeking patient input on endpoint selection to align research objectives with patient-perceived clinical needs, and on study protocols and designs to reduce patient burden and encourage research participation. Patient-centric study designs that enable home-based remote data collection rely on sensors and devices that capture information in the course of the patient's everyday activities. Patient-centric designs and technologies pose additional risks. Study data are not reliable if sites and patients fail to operate data-collection devices or follow procedures correctly. Complex technologies and poorly designed systems can result in missing data. Insufficient site and patient training is a huge issue—in some cases resulting in more missing data than patient related noncompliance.[ii]

*On-device data storage*. Remote data collection devices can pose security risks. IRT and EDC study data are likely encrypted in vendor databases but may not be encrypted. on remote devices such as smart phones. Ideally, data stored on remote devices should be uploaded in near real-time.

*Methods of data editing*. Data integrity may be seriously compromised by unauthorized and poorly tracked data changes. The data governance plan should should stipulate who may request data changes or initiate data change forms. Authorized investigative staff must be sufficiently trained to understand the data and potential impacts on study results, and an approval process must be satisfied prior to implementing data edits.

*Data transfer*. Risks may arise from the transfer of data from one eClinical system to another—from EDC or collection devices to the study database, from database to collection device. These are primarily due to failures in, or lack of, encryption.

*Database integrity*. Risk stems from database construction and user access. The biostatistics team should be involved in database construction to ensure that appropriate endpoints are captured. User controls focus on prescribing who has read/write access to the database—who is authorized to see the data and change the data.

*Data transfer to trial sponsor*. Transferring data from the eClinical system provider to the sponsor can pose risks related to the roles of those who view the data. Sponsors must be sure, for example, that blinded data are not viewed by sites and investigators. Data transfer from the eClinical system provider to other vendors poses similar risks and requires "chain of custody" documentation.

## Where to Begin: Upfront Considerations for eClinical Risk Management

"The best way to make sure things don't go wrong is to anticipate these problems long before you build your eClinical system and put plans in place to solve them," says Cook. "Your system can actually help manage risk when the design incorporates tools that indicate risk for each function and how those risks can impact patient safety and data integrity."

**Begin with the Protocol.** At the annual CBI Conference on ePRO/eCOA in 2017, former FDA Compliance Officer and conference co-chair Jonathon Helfgott noted that a well-articulated protocol functions as the blue print for a high-quality clinical trial: sponsors should consider endpoints first and technology second.[iii]

eClinical system designers work on the assumption that the protocol captures everything necessary to conduct the trial—that all endpoints and functions that touch patients are complete, accurate and clearly defined ahead of time.

**End-to-end audit trails are essential.** Audit trails are the single most important component of an eClinical system to ensure data integrity. Audit trails must document when and where data come from, who made changes to the data and why. Audit trails must be accessible via reports or other pre-approved mechanisms. To ensure accuracy, audit trails must be in protected format, such as PDF 1. Audit trails can be massively voluminous and hard to interpret. Vendors should work with sponsors upfront to determine important information and mutually-agreed data points to include in a human readable audit trail report that should be reviewed at routine intervals

As Helfgott explained, "It comes down to transparency with data integrity assessments." He advised sponsors to put controls in place to answer these essential questions: Who tracked the data? Why? Can you reproduce it? Is the chain of custody available? Using the raw data, can you come up with the same conclusion?

**Data governance is the roadmap.** Data governance is an essential component of a quality management system and the foundation for risk management in eClinical system design. Data governance typically defines:

- Key endpoints for data capture.
- Who owns the data.
- Who is permitted to see what data: roles authorized to view blinded data.
- Who is authorized to change data: editing procedures, approvals, tracking.
- What tertiary systems are to be used (IRT, eCOA)
- When and how data are to be updated.
- Error remediation processes.

## Special Challenges of Data Integration: Risks Posed by Disparate Data

Data integration is one of the most critical functions of an eClinical system and one of the most challenging for risk management practice. The average clinical trial conducts operations using between eight and 10 electronic systems. Management of siloed data across diverse systems is not only inefficient; it introduces massive risk to data integrity due to system overlap, potential for data loss, and versioning control--the inability to identify the single source of truth in terms of source data. Constant monitoring is necessary to flag anomalies and ensure data integrity.

Integration of disparate data streams is a well-recognized challenged. Sponsors should work closely with technology partners to design data integration plans upfront, including procedures to actively manage data integration processes. YPrime recommends the following key considerations to inform your risk management initiative.

*Data governance*. Has a data governance plan been established to determine who owns and who consumes each type of data? This will guide design decisions concerning the need for integrations and authorization to view data. It should also prescribe procedures for risk remediation and error correction.

*Design*. Where does the data come from—IRT, EDC, eCOA, a laboratory system? Keep in mind that EDC typically serves as single source of truth. Design will designate which data are to be integrated, where they are to be sent, and for what purpose. It is important to ask whether an integration is needed at all. Are the data essential for trial operations and decision-making by the recipient, or merely a point of interest? To answer this question, consider each endpoint--its relative importance to the study, and the roles and needs of recipients to conduct the trial. The time required to build an integration is another factor to consider. Depending on complexity, time required for a single integration can range from three to seven days.

*Transfer mechanisms*. How and when will the data be transferred? Unless transfer is conducted in off-line mode, data may be exposed to unauthorized viewing. Controls are necessary to ensure encryption during transfer from a collection device to the study database and from the database to the device. There are numerous options for transfer mechanisms, including: CSV files for real-time data; transfer of delta data or a Web API transfer of data any time it is collected. The choice of mechanism depends on factors including: the type and use of the data; timeliness (is real-time view necessary?); efficient match for the sponsor's capabilities; and the number of vendors involved. Smaller companies tend to have more vendors, all using different transfer mechanisms.

*Security*. What do your integrations expose, and to whom? An integration takes data from inside a secure firewall to outside the firewall where unauthorized viewers can intercept them. Sponsors need to be certain that the entire transmission is encrypted.

*Blinding*. Does the integration unblind a trial patient? Sending unblinded data to unauthorized viewers can threaten the integrity of the entire study. Sponsors should give careful attention to identifying the roles of authorized viewers to minimize risks for unintentional unblinding. For example, investigators and site personnel are roles authorized to view blinded data only, while medical monitors and pharmacists are roles authorized to view unblinded data.

*Error remediation*. What happens when things go wrong? Common integration errors include:

- Missing parent data. For example, adding a patient for a site that does not yet exist in the system.
- Business rules. For example, adding a patient visit date in the future.
- Invalid data. For example, sending a status that does not exist in the system.

Sponsors should be sure that data governance puts a plan in place to direct how integration errors will be resolved. The data governance plan serves as the blueprint for risk-based eClinical planning and design to ensure that the technology implements the study objectives.

## Our Risk-Based Future

Clinical studies continue to grow in size and complexity, and risk-based thinking must become an inherent practice in the design and implementation of eClinical technologies. Expanding sources and types of data are driving the future of clinical research in applications of Big Data, artificial intelligence and cloud technologies. In addition to traditional clinic-based trials, remote data collection sensors and smart devices are advancing real-world studies capable of generating unprecedented volumes of data as patients pursue everyday activities. Managing the risks posed by eClinical systems will be increasing important in this environment and will continue to be a focus of evolving regulation.

### References

[1] Leister SM, 2018. Risk management in clinical trials. The new ICH E6 focus. *FDANews Report*.

[2] Basch et al., 2017. Feasibility of patient reporting of symptomatic adverse events via the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) in a chemoradiotherapy cooperative group multicenter clinical trial. *International Journal of Radiation Oncology*Biology*Physics*, 98:2, 409-418.

[3] Helfgott, J, 2017. Explore New FDA Guidelines for New Clinical Outcome Assessment Qualification Programs. Presented at the CBI eCOA/ePRO Annual Conference.