MULTI-REGIONAL CLINICAL TRIALS
THE MRCT CENTER OF BRIGHAM AND WOMEN'S HOSPITAL and HARVARD

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Good Clinical Practice in Practice: Implementing ICH E6(R3)

Q&A Fact Sheet for Webinar

1. Why are equipment, its calibration, performance checks not involved in the case?

The case study was intended to be illustrative of the key concepts of Data Governance in ICH E6(R3) but it is not an exhaustive analysis. Certainly it would be important to ensure that equipment used in the collection and management of critical to quality data are fit for purpose and that necessary performance oversight measures are in place.

2. Can you please share any practical tips on how to avoid the CTQFs to become one more document which is filed in the TMF before the trial starts?

It is important that clinical trial oversight activities are prioritized to focus on the data and processes that are critical to quality. Therefore, documentation within which these factors and their related risks are identified should serve as an important input to support the development of downstream operational/quality management plans (i.e. monitoring plans, data management plans, pharmacy manuals, etc).

Moreover, critical to Quality factors should not be thought of as just another document to file. When identified early and used effectively, they can make a trial easier to run. They play an essential role in streamlining the protocol, identifying what data truly needs to be collected, reducing unnecessary complexity and risk. And by focusing attention on the aspects that matter most, participant protection and the reliability of trial results, they help teams prioritize where effort and oversight are most needed. Since Critical to Quality factors need to be considered at the protocol development stage anyway, there is also a strong case for including them directly in the protocol.

3. I'm surprised to hear the emphasis on some vs other eligibility criteria. Each criteria selected is specific to the desired patient population. What might seem minor, ie a lab value, could turn out to be critical. Also, if there is ever an FDA audit and even one criteria is missed, that subject potentially becomes ineligible and all that patient data can potentially be eliminated from the trial. Now a subject has been subjected to all the tests and procedures of the trial almost for nothing. This is not putting subject safety first.

What was presented during the panel discussion should not be understood as suggesting that compliance with inclusion and exclusion criteria is optional. Every criterion exists for a reason, and sponsors and investigators are expected to meet all of them. That has not changed.

The point being made was a narrower one about quality management and oversight of the trial. In practice, not all criteria carry the same level of risk to participant protection or the reliability of trial results. Some criteria are critical to quality, meaning that failure to meet them, or inadequate documentation of compliance, could directly impact participant safety or the integrity of the trial results. Other criteria, while still required, carry a lower level of risk in that context. A risk-based quality management approach recognizes these different levels of criticality. It does not mean that some criteria can be ignored or that non-compliance is acceptable. It means that the intensity of the management, oversight, and verification efforts applied should reflect the relative criticality of each criterion to participant protection and the reliability of the trial results.

When applied correctly, a risk-based approach actually strengthens compliance and inspection readiness, by ensuring that the criteria with the greatest potential impact on participant safety and trial integrity receive the most rigorous attention and documentation. From an FDA inspection standpoint, what we want to see is evidence that sponsors have thought carefully about which criteria are most critical, have put proportionate oversight and verification measures in place, and have maintained robust documentation throughout. That kind of thoughtful, well-documented approach to eligibility criteria is precisely what holds up best under inspection scrutiny.

4. How much of E6 (R3) does apply to Natural History studies?

Natural history studies are non-interventional by design. They observe the natural course of a disease without any intervention, and as such, ICH E6(R3), including Annex 2, does not apply to them directly. GCP, as described in E6(R3), is a standard for the design,

conduct, and oversight of interventional clinical trials, and natural history studies fall outside that scope.

However, where natural history study data are subsequently used as a historical or external control group in an interventional clinical trial, the picture changes. At that point, those data are being incorporated into an interventional trial as a secondary use of data, and Annex 2 would apply related specifically to how the sponsor of that interventional trial manages, accesses, and ensures the fitness for purpose (i.e., relevance and reliability). So it is not the natural history study itself that falls under Annex 2, but rather the sponsor's use of data from that study within the context of an interventional trial.

5. **How do you foresee AI to impact the Quality by Design creating not only list of CTQFs but rather creating the environment with historical data and intelligence to build the better trials?**

While the process of designing quality into a new clinical trial may benefit from Artificial Intelligence and the use of other tools to gather historical data/intelligence, its important to avoid discounting the necessary impact of critical thinking and the incorporation of input from interested parties. The best solutions will likely be a combination of these approaches.

6. **What is the pragmatic approach to overseeing the computerized systems used in a clinical trial by sponsors, vendors and investigators as foreseen by ICH E6R3? It is complex to have the full list of the systems; will it be acceptable to focus only on DATs?**

ICH E6(R3) takes a risk-based, proportionate approach to the management of computerized systems used in clinical trials. The guideline does not require an exhaustive, one-size-fits-all management approach of every system involved in a trial. Rather, it expects sponsors to apply management and oversight that is proportionate to the role the system plays in participant protection and the reliability of trial results.

To your specific question about whether it is acceptable to focus only on data acquisition tools, the answer is that it depends on the individual trial, its objectives, design and the systems being used to support the trial conduct. However, it is possible that focusing exclusively on DATs would likely be insufficient. While DATs are an important category of systems used in trials, there are other systems used in clinical trials that fall outside of this category but can still have a meaningful impact on the reliability of trial results (e.g., safety

databases, statistical programming and analysis systems, trial master files, clinical trial management systems). The risk-based management framework should account for the full range of systems involved in the trial, not just those that directly acquire data

That said, the depth of management and oversight applied to any given system should reflect its criticality to the trial. A pragmatic approach could be to start by mapping the systems involved in the trial against the trial's critical to quality factors, and then calibrating the oversight effort, accordingly, focusing the most intensive attention on the systems where failures would have the greatest potential impact on participant protection or data reliability.