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Webinar Q&A

Inspection Preparation With a Risk-Based Approach Consistent with ICH E6 (R2) Requirements

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Questions submitted by audience participants.
Responses provided by Steve Whittaker, Grace Crawford, Irene Michas, and Karin Daun.

Q1) From my experience of two MHRA inspections with different companies, they have had a huge focus on data flows, data integrity, and awareness of their Data Integrity Guidance. Are the other agencies releasing their own data integrity guidance to your knowledge and is there a standard for what should be included in a data flow diagram or an example template available?

A) Data flows are highly recommended; however, highly variable per sponsor, study, etc. It is important that the diagram include all data from source (including sites, external vendors, etc.) through to the generation of the tables/listings and any other format that goes into the CSR.

Below are key references on data integrity from the FDA, EMA, WHO, and MHRA:

FDA: DRAFT Guidance for Industry Data Integrity Compliance with cGMP, April 2016: https://www.fda.gov/downloads/drugs/guidances/ucm495891.pdf

EMA: EMA/15975/2016, Good Clinical Practice Inspectors Working Group (GCP IWG), DRAFT Guideline on GCP compliance in relation to trial master file (paper and/or electronic) for content, management, archiving, audit and inspection of clinical trials, 31March2017: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2017/04/WC500225871.pdf

WHO: Guidance on Good data and Record Management Practices, Annex 5, Sept. 2015: http://apps.who.int/medicinedocs/documents/s22402en/s22402en.pdf

MHRA: GxP Data Integrity Guide, March 2018: https://www.gov.uk/government/publications/guidance-on-gxp-data-integrity

Q2) Have there been any audits of sponsors who've implemented the Avoca oversight tools? Have they been found acceptable?

A) A case study was presented by Alexion during the 2015 Avoca Quality Consortium Fall Members' meeting regarding an agency inspection of their pharmacovigilance quality management system. They had used Avoca leading practices. Upon completion of the inspection, the inspector indicated that it was the most effective management system he had seen. This case study is available to all AQC Members on the AQC online Knowledge Center. Other examples are available upon request.

Q3) What is the best practice for certifying a document in an eTMF?

A) A well-defined process must be in place with defined individuals qualified and assigned to generate a copy, verifying (certifying) that it is identical to the original and signing for accuracy. There must also be internal organizational audit verification that copies are consistent with originals.

Q4) When asked about the SAE reports in the TMF, is it acceptable to document in the TMF and respond to the inspector that the Safety Database is the central repository of safety data and all SAE reports and related documents are archived in the safety database? Do we also need to enter all SAE information in the TMF if everything is archived in?

A) Yes, it is acceptable to reference in your TMF index the location of source safety data and direct an inspector to the Safety Database as the central repository for safety data. Guided access is acceptable for certain data records within an eSystem in addition to TMF system direct access (and examples include, in addition to safety databases, audit trails (eCRF/CTMS, eCRF, CTMS). This is due to the technical nature of some of these systems, for example those containing data rather than documents.

Q5) What are best practices for filing emails in the TMF? What constitutes contemporaneous?

A) Emails that contain relevant and important information concerning the conduct of a clinical trial, decisions made that affect patient safety or data integrity, or key risks for the trial, and any documentation of actions taken for these items, should be retained in the TMF.

Having said this; however, best practice is not to document these items within emails, but rather to document them in actual team or study documents such as meeting minutes, trip reports, monitoring reports, analysis reports, etc.

Contemporaneous means within a time relevant period (e.g., 30 days) of the time that the email was generated.

The references above are useful with respect to terminology for ALCOA- C +.

Q6) How do inspectors typically want to view an eTMF's audit trail? Do they want access to the system's back-end, or is an export of the audit trail accepted?

A) The approach differs by agency, and certainly the MHRA are known to request access to TMF metadata, including audit trail. If/where there is particular reason for which access to system back-end is not available, provision of exported audit trail can be negotiated- provided it is reliable, i.e., from validated system.

Q7) When an eTMF is in a hybrid model (paper/electronic), sponsor documents are paper files and the CRO has an electronic eTMF. How are these audited with the EMA or MHRA?

A) The MHRA and EMA have a strong preference to directly access eTMFs for their inspections. If a sponsor TMF is paper and the CRO used for trials is an eTMF, then the sponsor is accountable for the entirety of all documents that support the conduct of the clinical trial, patient safety, and data integrity. The sponsor's QMS should clearly articulate how the paper-based TMF and eTMF operate together to complete the necessary complete TMF. Additionally, the contract or other document or procedure agreed between all parties should outline the arrangements for the TMF (which should include how the TMF would be made available if either party were to be inspected).

Q8) For an eTMF and certified copy requirement, in a scenario where the site process is to retain original essential docs (i.e., 8.2, 8.3, 8.4 - site) and they do not have a process to send in certified copies for filing an eTMF, how practically do you deal with this?

A) It is common for sites to retain their original (wet ink signed) documents. Sites either send copies to the monitoring organization, post a scanned copy of the original in the eTMF, or the site monitors collect it for filing to the TMF/eTMF. Since the site will have the original documents in the Investigator Site File which are verified by the site monitor, it is not typically expected that a certified copy process (since the monitor verification step covers this) is implemented.

Q9) What is your recommendation in terms of certification of original documents. Is it acceptable to do a manual certification if the eTMF system does not provide such feature?

A) Based on references and guidance above, certification can be done manually (e.g., dated signature) or through validated process.

Q10) What is the expectation for CROs to keep hard-copy documents once they are uploaded into the eTMF. Once they are uploaded and QC'd to ensure image correctness/quality, can the hard copies be destroyed or should they be kept by the CRO until the eTMF is transferred to the sponsor at the end of the study (at which time the CRO can destroy the hard-copies)?

A) This is usually based on the risk level acceptable to the CRO and sponsor. In concept, once a document has been certified via a validated and documented approach, paper copies may be destroyed. Section 5.2 "Destruction of original paper after digitization" of the Draft EMA Guideline on GCP compliance in relation to trial master file (paper and/or electronic) for content, management, archiving, audit and inspection of clinical trials outlines several relevant points for consideration when making this risk based decision.

Q11) As a CRO we are seeing quite a bit of variability as to how our customers are determining which TMF content requires a certified copy. What is the perspective of MHRA?

A) Based on the references above, the general principle is that original documents that are required for TMF (e.g., ICH essential documents and/or other documents that are pertinent to the study) need to be transferred to an electronic format for the purpose of eTMF filing. The process of transfer should be validated and undergo regular quality control checks in order to ensure that the information will not be lost or altered. Per EMA/15975/2016 definition (aligned with ICH), a certified copy is a paper or electronic

copy of the original record that has been verified (e.g., by a dated signature) or has been generated through a validated process to produce a copy having the exact content and meaning of the original.

Q12) Are there recurring cases where inspectors are not willing to take required training before receiving access to a system such as EDC or eTMF?

A) Yes, MHRA, and sometimes EMA, expect that the eTMF will be straight-forward in terms of use such that they should not require training. They request direct access with minimal orientation.

Q13) Do you have any experience with MoH/ANMAT/ANVISA in Latin America?

A) The AQC has not yet collected Member experiences with Latin American agencies. It will be considered for potential future enhancements.

Q14) What is BIMO?

A) BIMO is the FDA's Bioresearch Monitoring Program. You can find out more here: https://www.fda.gov/scienceresearch/specialtopics/runningclinicaltrials/ucm160670.htm

Q15) Has the FDA begun inspecting against ICH E6 (R2)? If so, what have their focus areas been?

A) Interviews with AQC Member companies have indicated that the FDA has not yet inspected companies against ICH E6 (R2) since most studies being inspected occurred prior to implementation of the new guidance. Inspectors have; however, requested to see sponsor risk plans and QMS documents or procedures to indicate that they are implementing new studies according to the guidance.

Q16) Please define the process or provide an example of what the agencies are looking for in "Certified Copies".

A) ICH E6 (R2) definition of certified copy:

1.63 Certified Copy

A copy (irrespective of the type of media used) of the original record that has been verified (i.e., by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.

Q17) Did you see any sign that actual inspectors did not accept the risk-based approach for certain aspects of a trial? We received critical(!) finding from EMA recently for mistakes in 2 CSR listings. These listings were classified as "low risk" by our stats team. I still stand puzzled as the finding was that we had mistakes in two listings and not that the risk rating was wrong. The "low risk" listings were QC'd of course but not double-programmed like the high-risk listings/tables.

A) We have received anecdotal comments from Member companies that individual inspectors may still identify findings within inspection reports even when the issue had been identified within the risk plans as low risk and therefore not managed by risk plans. These seem to be inspector specific and not a broad trend.

Q18) What about ostriches who have not dealt with sponsor oversight – leaving it to CROs, or not having enough people or a commitment to sponsor oversight? Will there be a grace period for sponsors who have not addressed the sponsor QMS, risk-based documentation, documented oversight, risks at early stages (Phase I) lack of oversight procedures and records?

A) The regulations apply to all sponsors, investigators, and providers who support the conduct of clinical trials. These regulations place accountability with the sponsor and with the investigators. One specifically documented accountability is that sponsors retain accountability for activities outsourced to CROs and providers to ensure quality, data interpretability, and patient safety.

Some, but not all, agencies have formally designated the date(s) by which they will hold sponsors accountable to be operating consistently with new regulations. For ICH E6 (R2), some agencies designated this date as June 2017. Regulations suggest using risk-based approaches for Quality Management Systems. These risks frequently relate to patient safety and data integrity/interpretability, but may include other risks. It is notable that patient safety and data interpretability risks do exist for early phase (e.g., Phase I) trials, so regulations apply to those studies as well as late phase trials. Each regulatory agency uses differing criteria (see the AQC Knowledge Center) that trigger inspections. Some focus on market authorization applications which tend to focus on later phase trials; however, some agencies focus on other risk criteria or factors and may inspect early phase trials.

Q19) What is the approach to using KRI in Phase Ib/IIa studies?

A) Key Risk Indicators (KRIs) are appropriately used for all phases of clinical research. For shorter duration Phase Ib/Iia trials with fewer patients, the risk triggers and metrics need to be selected in a fashion to permit early detection of appropriate thresholds.

Q20) Do all agencies publish inspection reports on an annual basis?

A) Many agencies such as the FDA and EMA do publish annual reports, but some agencies do not.

Q21) Should we prepare a Phase I site for inspection even though we are not sure if we will use the data to support the registration application?

A) This should be part of your risk-based plan as you determine the likelihood of an inspection and the potential implication for your product, market approval application, or other factors should the site actually be inspected. Please note that some agencies inspect for reasons other than market authorization application.

Q22) It sounds like you are expecting audit trails to capture also ACCESS (e.g., just reading records), and not the create/change/delete of Part 11.

A) The expectation is that access is controlled, visible in the audit trail, and checked (via reviews/interrogations of audit trails) IN ADDITION to checking/reviewing the standard expectations regarding ALCOA/Part 11 control of records (appropriate creation/changes/deletions, etc.). Non-audit trail evidence of oversight may also suffice; however, the presentation covered actual inspection scenarios and without full context, the intent was to raise awareness of this possibility. Arrangements for oversight of the quality control/quality assurance of the TMF by the sponsor and how this would be documented (e.g. audit reports, QC reports) should be included in study agreements and/or plans.

Q23) Do you have examples of a vendor oversight plan that you could send us?

A) The AQC Knowledge Center has a jQMP template as well as other oversight plan documents. All AQC Member companies may access these tools via the website. If your company is not a member of the AQC, and you would like information about membership, please contact caryn.laermer@theavocagroup.com.

Q24) Are the inspectors already expecting to see certified copies and for which documents are these demanded?

A) Inspectors are requesting certified copies and verification of processes for certification. These are required for all essential documents, which now can include not only trial specific clinical study data, but also some process documents such as risk plans, decision documents, etc.

Q25) For the finding against sponsor for the CRO's inadequate audit report; what agency was this from and what predicate rule, regulation or guidance document was cited?

A) The inspection experience shared was an EMA PV inspection (which also included an IT track and DMKA (Danish Medicines Agency) GCP Inspection with safety focus) – 10 inspectors for 5 days. The inspection at the sponsor included a review of "the systems" which included the CSV package and the expectations were:

- Immediate and full access to all documentation (even outside sponsor's scope).
- Immediate access to experts at vendor (and the ePROs/eCOAs were delegated to the CRO. CRO subcontracted the ePRO/eCOA vendor).

They identified deficiencies with PI access and constant readable audit trail and linked the observation to inadequate audit of the vendor performed by the CRO which ultimately fell under the responsibility of the Sponsor.

EMA Q&A: Good clinical practice (GCP) "GCP Matters":
What are the pitfalls to be aware of regarding contractual arrangements with vendors for electronic systems in connection with clinical trials?

(see answer under Audits and inspections)…

"It is sometimes not stated that the sponsor should have access to conduct audits at the vendor site and that the vendor site could be subject to inspections (national and international authorities) and shall accept these."
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000016.jsp

Useful ICH references related to this topic:

ICH-GCP 5.2.2
The sponsor should ensure oversight of any trial-related duties and functions carried out on its behalf, including trial-related duties and functions that are subcontracted to another party by the sponsor's contracted CRO(s).

ICH-GCP 5.5.3
The sponsor should base their approach to validation of such systems on a risk assessment that takes into consideration the intended use of the system and the potential of the system to affect human subject protection and reliability of trial results.

Q26) Previously FDA had not accessed systems directly (in breach of their insurance) with the preference to request the documents or driven review. Has this now changed?

A) The FDA has continued to predominantly request that documents be brought to them; however, they are shadowing EMA and MHRA and gaining awareness and interest in potentially accessing eTMFs directly.

Q27) For the Effect a Risk-based Approach to Inspection Readiness slide, what is White Paper referring to in the examples section?

A) A white paper is an approach similar to a storyboard; however, it is prepared with the intent to share it with a regulatory authority (whereas a story board is not). An example of a scenario where a sponsor has written and used a white paper is when a laboratory test that was originally exploratory became important (i.e., included in a submission). The sponsor created a white paper to describe the control measures that were in place for the testing (since there was no formal qualification or validation documentation) supporting the validity and integrity of the lab data.

Q28) Why do we need storyboards when we have eTMF? How will these storyboards benefit? Is it recommended to have this?

A) Storyboards do not duplicate or conflict with what is stored in eTMFs. They are used to address an identified gap or issue by employees or via an internal audit (either by a sponsor study team, a provider, or an investigative site) whereby it is recognized that, should an inspector identify the gap or issue, it would be beneficial to have a pre-developed response explaining the situation, indicating if it did or did not have a material impact on patient safety or data integrity, and what was done to minimize the risk or implication.

Storyboards are extremely useful for proactive inspection readiness or when preparing for an impending inspection. They keep everyone on the same page (various functions, sponsor, CRO, and other vendors) so that when it comes time to explain the situation during an inspection, there is a consistent story that is told with confidence.

Q29) What is the overall trend with the use of notes-to-file or storyboards and how are they received during an inspection?

A) The use of notes-to-file is not recommended for compliance to industry standards. Storyboards, as described in answers above are becoming utilized frequently as internal prep documents for inspections.

Use of Note to Files should be limited, and they should only be used when they are comprehensive (for example, provide a full justification with the explanation and a description of why there was no or low impact). They should often include a summary of the corrective/preventive action plan that was carried out.

Q30) Do you share the storyboards with inspectors?

A) Storyboards are usually for internal use only to prepare for inspections.

If your company is not a member of the Avoca Quality Consortium and you would like information about membership, please contact caryn.laermer@theavocagroup.com.