

MHRA GCP Stakeholder Engagement
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Electronic Systems in Clinical Trials

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Disclaimer

- The data and information contained in this presentation have been obtained from a number of Pharmaceutical companies and CROs for the specific purposes of this meeting.
- The views expressed in this presentation are a collation of the comments volunteered from the above companies; they are neither my own personal views nor do they represent the position of my employer.

Introduction

- In recent years, the use of electronic systems in clinical trials has steadily increased such that most commercial and many non-commercial sponsors now utilize electronic systems for most aspects of a trial.
- These systems may be hosted and managed by vendors, CROs and sponsors, and their complexity has added challenges to the management and oversight of clinical trials.
- In the next slides, I will present some examples of 3 areas where RQA members have found challenges for which the solutions are not always easily determined from current regulations and guidance. We welcome the opportunity to discuss with MHRA and to understand the expectations in these areas.

1. Validation of vendor software

- Sponsor uses vendor software, which is then further configured by sponsor. Configured aspects are validation tested against functional specification, and sponsor is responsible for ensuring full system validation has been performed.
- It is unclear how far the sponsor should go in determining and documenting what was conducted by the vendor. Options could be (in ascending order of rigour):
 - a) Treat vendor validation as a “black box” and accept validation evidence without detailed review
 - b) Sponsor requests vendor to provide traceability report to show how testing maps to system requirements, and status of testing
 - c) Sponsor audits vendor validation documentation in detail against functional specification, to trace back all system requirements to the validation documentation

1. Validation of vendor software (cont.)

RQA would like clarification / advice on what is acceptable:

- Is it acceptable for vendor to provide a traceability report to demonstrate that the system requirements have been tested (Option b)?
- For both options (traceability documentation, Option b, or detailed audit, Option c) can a risk-based approach be taken to limit the activity to key system requirements, rather than verifying the entire system requirements?
- How much of the vendor validation documentation needs to be retained by the sponsor?
- When limited study-specific changes are made (e.g. adding fields to EDC system), is “Option b” acceptable to demonstrate validation of the changes?

1. Validation of vendor software - guidance

- MHRA GXP Data Integrity Guidance, March-2018, Section 6.19:
 - “ .. The acceptance of vendor-supplied validation data in isolation of system configuration and users intended use is not acceptable. Functional verification demonstrates that the intended required information is consistently and completely presented. Validation for intended purpose ensures the steps for generating the custom report reflect those described in ... SOPs ... ”
- MHRA Grey Guide, 14.5.2.2 provides a list of the minimum validation documentation expected:
 - Approved specification
 - Testing documentation for developers and users
 - Signed validation report (confirming specifications met and UAT bugs resolved)
 - User instructions and user training
 - Documented release (from testing to production)

2. Electronic Patient Reported Outcomes (ePRO)

Scenario 1: ePRO completed by subject via a portal, reviewed by site staff at each visit.

Subjects entered 2 types of data:

- **Subjective (free text): locked and could not be edited by site**
- **Objective (e.g. dosing details + symptoms selected from drop-down list of terms): not locked, so could be edited by site**
- **It is clear that the CRO/sponsor should not have access to change ePRO data, but site staff do have access edit rights for objective data:**
 - **Is the ePRO audit trail sufficient to document changes made by site staff, or should the justifications also be captured in subject source records?**
 - **If the site has source data (e.g. dosing details) that show the ePRO data are incorrect, is this a self-evident change that can be made? Or should the change be made only with subject input?**
- **If site has read-only access (e.g. to review subjective subject data):**
 - **does this review need to be captured in subject source records?**

2. Electronic Patient Reported Outcomes (ePRO)

- **Scenario 2: ePRO data goes directly to Sponsor; ePRO device is not retained by site, and is a data capture device only. The device could be:**
 - (a) BYOD or
 - (b) ePRO that is wiped and re-used per visit or per subject
- Site staff do not generate, review or sign-off the ePRO data. PI is sent a copy of the data by secure e-mail, but does not retain control of the data, as subject is the source, not site
- MHRA Guidance (next slide) needs clarification and/or interpretation:
 - Grey Guide (2012) requires audit trail functionality for ePROs
 - MHRA GXP Data Integrity Guidance, March-2018 allows for alternatives when audit trail functionality not possible or not available
- How can Sponsor demonstrate the integrity of the PRO data?
 - Would appropriate validation and testing of transfer (ePRO-to-Sponsor database), plus robust Sponsor procedures, controls and audit trails be adequate to demonstrate integrity of ePRO data?
 - Another approach is for site and sponsor to have access to an ePRO portal with access to the data at all times. The portal is considered the source rather than the device and contains the audit trail. At end of study, the site receives the archival CD with the data and audit trail.

2. ePRO - guidance

- MHRA Grey Guide, Section 8.2.7 contains a number of requirements for ePROs, including:
 - ePRO device should be validated in relation to the protocol requirements
 - Source data should be available to the site
 - Must be an audit trail to record changes to diary data
- MHRA GXP Data Integrity Guidance, March-2018:
 - Section 6.8: Data transfer should be validated. There should be an audit trail for this process
 - Section 6.13: Where relevant audit trail functionality does not exist ... an alternative control may be achieved, for example defining the process in an SOP. Alternative controls should be proven to be effective
- SI 2004/1031, Schedule 1, Part 2:
 - (10) All clinical trial information shall be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification

3. MHRA remote access to sponsor systems during OBIs

- **GCP Symposium Sept-2018, Paula Walker presented on Office Based Inspection (OBIs)**
- MHRA conducts OBIs, not only pre- and post-inspection, but also “in parallel”
- Efficient and cost effective approach for MHRA
- Industry is now seeing requests for remote access to electronic systems other than eTMF, for example ePRO portals, eSOP Systems
- Industry is not geared up to provide controlled, remote access to all its e-Systems, for example infrastructure changes would be required to allow remote access
 - Changes are very costly and take time to develop, implement and test
 - Security considerations need to be taken into account
 - Training needs to be adapted
- We would like to discuss expectations regarding direct, extended, remote access to sponsor systems