EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Inspections Office, Quality and Safety of Medicines Department

Notice to sponsors on validation and qualification of computerised systems used in clinical trials

Introduction:

The integrity, reliability and robustness of data generated in clinical trials, e.g. data submitted to support marketing authorisation applications (MAAs), are essential to regulators. Most clinical trial data supporting MAAs are now collected through computerised data acquisition tools, e.g. electronic case report forms (eCRFs) and electronic patient reported outcomes (ePROs). In addition, a wide range of computerised media and systems are used in the conduct of a trial, such as safety databases, systems for electronic interactive response technology (eIRT), clinical trial management systems (CTMSs) etc., the use of which will increase in the future.

Given recent inspection findings and the implications they have had on the integrity, reliability, robustness and acceptability of data in the context of MAAs, the GCP Inspectors Working Group (IWG) in cooperation with the Committee for Medicinal Products for Human Use (CHMP) sees the need to emphasize requirements for sponsors/vendors providing computerised systems or services as well as for the qualification and validation of computerised systems used to manage clinical trial data.

Legal and regulatory background:

- Regulation (EU) No 536/2014, Recital 51, Articles 2 (30), 2 (31), 47, 71
- ICH Guideline for good clinical practice E6(R3), (EMA/CHMP/ICH/135/1995 Revision 3) principle 9, annex 1 sections 3.16.1 (d), 3.16.1 (x) (ii), 4 (b), 4.3 (including 4.3.4).

Regulation (EU) No 536/2014 contains the provision that regardless whether a sponsor delegates all or part of the clinical trial related activities to an individual or an organization, the ultimate responsibility with regards to the clinical trial conduct — in particular related to the safety of subjects and the integrity, reliability and robustness of the data generated in the clinical trial — remains with the sponsor.

The EU legal framework requires that the sponsor of a clinical trial and the investigator ensure that the clinical trial is conducted in accordance with the protocol and with the principles of GCP. Furthermore, the legislation also defines the process of GCP inspection by a competent authority and the coverage of such inspections. Finally, it contains provisions that the information generated should be recorded, handled, and stored adequately for the purpose of ensuring effective inspection by Member States.

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Validation and qualification of computerised systems:

ICH E6(R3) requires that sponsors operating computerised trial data handling or computerised data systems, amongst others, shall validate these systems, maintain an audit trail for initial entry of data and any subsequent changes, maintain a security system to protect against unauthorized access and maintain a list of the individuals authorized to create, access, modify or delete data. Sponsors should set up these computerised systems in such a way that the blinding of clinical trials, when applicable, is maintained. In addition, ICH E6(R3) requires that "The quality and amount of the information generated in a clinical trial should be fit for purpose and sufficient to provide confidence in the trial's results and support good decision making" (principle 9.1), that "Systems and processes that aid in data capture, management and analyses, as well as those that help ensure the quality of the information generated from the trial, should be fit for purpose, should capture the data required by the protocol and should be implemented in a way that is proportionate to the risks to participants and the importance of acquired data" (principle 9.2), and that "Computerised systems used in clinical trials should be fit for purpose (e.g., through risk-based validation, if appropriate), and factors critical to their quality should be addressed in their design or adaptation for clinical trial purposes to ensure the integrity of relevant trial data" (principle 9.3).

Data integrity, reliability and robustness will depend on the design and the validation status of the computerised systems used. Failure to document and therefore demonstrate the validated state of a computerised system is likely to pose a risk to data integrity, reliability and robustness, which depending on the criticality of the affected data may result in a recommendation from the GCP inspectors to the CHMP not to use the data within the context of an MAA.

The term qualification is used in this notice to describe verification of system functionality. The term validation is used to describe the process of establishing and documenting that the specified requirements of a computerised system can be consistently fulfilled from design until decommissioning of the system or transition to a new system, i.e. it operates to defined specifications and defined procedures (SOPs) by a trained user.

Lack of documentation (or access to documentation) of qualification activities:

Recent inspection findings relating to the qualification and validation of computerised systems are of concern, as some sponsors have not been able to provide adequate documentation of the required qualification and validation activities for computerised data collection tools/software during inspections. Computerised systems used in clinical trials can be built by the sponsor but are more typically purchased from a vendor either under a license to use software or as part of a service purchased, which could also include e.g. trial specific builds, hosting of trial data, etc. Qualification activities would consequently be performed by the vendor, by the sponsor or by shared efforts.

The sponsor is ultimately responsible for the validation of the computerised system and for providing adequate documented evidence on the validation process.
Sponsors shall be able to provide the GCP inspectors of the EU/EEA authorities with access to the requested documentation regarding the qualification and validation of computerised systems irrespective of who performed these activities.

The sponsor may rely on qualification documentation provided by the vendor, if the qualification activities performed by the vendor have been assessed as adequate. However, the sponsor may also have to perform additional qualification (and validation) activities based on a documented risk assessment. The conditions for a sponsor to rely on a vendor's qualification documentation are described in the Guideline on computerised systems and electronic data in clinical trials published on the EMA website: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-computerised-systems-and-electronic-data-clinical-trials_en.pdf (EMA/INS/GCP/112288/2023). If the sponsor chooses to perform its own full qualification of a system purchased from a vendor, the sponsor should ensure access to the vendor's system requirement specifications to perform its own appropriate qualification of the system. This is necessary, because otherwise the sponsor would not know all the built-in system functionalities and would consequently risk unknown functionalities/actions with unknown impact on their data. Considering the relevant version and configuration of a system, qualification and validation activities should be performed on the basis of all the requirement specifications the system was initially built on and any updates.

Insufficient contractual arrangements:

Clear, written agreements should be in place to document any arrangements between the sponsor and the vendor with regards to qualification and validation. The sponsor remains responsible for ensuring that the conduct of the trial and the final data and data that are submitted to support an MAA comply with relevant legislation.

Guidance regarding contractual arrangements with vendors of computerised systems used in clinical trials is available in annex 1 of the guideline mentioned above.

In the framework of a particular MAA, IT vendors could be inspected when they contractually assume clinical trial sponsor-related duties/activities and/or the contract between the sponsor and the vendor contains provisions for inspections/audits of duties/functions performed by the vendor.
According to Article 2(31) of Regulation (EU) No 536/2014, inspectors should be able to inspect third parties who have trial-specific relevant documentation. As qualification documentation of a generic software (a software without trial-specific functionalities or features) does not necessarily fall into this category, the sponsor should ensure access for GCP inspectors in case any such activities are delegated to the vendor, i.e. if the sponsor relies on the vendor for documentation of system requirement specifications, test documentation, etc.

It is not acceptable to use computerised systems in clinical trials for which the validation status is not confirmed or for which appropriate documentation on system validation cannot be made available to GCP inspectors.
If appropriate contracts cannot be put in place, e.g. because a vendor does not allow provision of adequate measures as listed above (access to system requirements specifications, pre-qualification audits, access for GCP inspectors, etc.), systems from such a vendor shall not be used in clinical trials. This is irrespective of the number of sponsors making use of or having used the systems, the number of years such systems have been on the market etc., as serious GCP non-compliances and risks to data integrity, reliability and robustness could exist unnoticed if auditors and GCP inspectors are not allowed access as well as if potential serious breaches are not escalated appropriately by the vendor.