ACRO Innovate Advocate Collaborate

6 June 2024

Good Clinical Practice Inspectors Working Group (GCP IWG)
European Medicines Agency
Domenico Scarlattilaan 6
1083 HS Amsterdam, The Netherlands

RE: EMA Final Guideline on *Computerised Systems and Electronic Data in Clinical Trials:* Unintended Consequences of the Guideline's Application to Electronic Medical Records (EMRs)

Dear members of the GCP Inspectors Working Group,

The Association of Clinical Research Organizations (ACRO) represents the world's leading clinical research and clinical technology organizations. Our member companies provide a wide range of specialized services across the entire spectrum of development for new drugs, biologics and medical devices, from pre-clinical, proof of concept and first-in-human studies through post-approval, pharmacovigilance and health data research. ACRO member companies manage or otherwise support a majority of all biopharmaceutical sponsored clinical investigations worldwide and advance clinical outsourcing to improve the quality, efficiency and safety of biomedical research.

ACRO welcomes the EMA final Guideline on Computerised Systems and Electronic Data in Clinical Trials. However, we would like to raise a major concern relating to the discussion and treatment of electronic medical records (EMRs) which ACRO members have encountered while trying to operationalize and implement the Guideline's recommendations.

Introduction

At the time ICH GCP was first issued in 1997, the requirement for direct access to records applied primarily in an environment dominated by *paper* records. Direct access was interpreted as the ability to physically review the subject notes. Over time, more and more institutions have moved towards the use of EMRs as part of the modernization of their health systems. While EMRs play a key role in clinical research, the ownership and control of EMR systems may lie outside of clinical research, as recognized by EMA. The EMA *Guideline on Computerized Systems and Electronic Data in Clinical Trials* clearly acknowledges that the computerized systems used by investigators and sites for holding and managing data may – or may not – be under the ownership and control of the investigator and site, as indicated in the bolded language below (emphasis added):

> *4.2. Responsibilities*
> *Roles and responsibilities in clinical trials should be clearly defined. The responsibility for the conduct of clinical trials is assigned via legislation to two parties, which may each have implemented computerized systems for holding/managing data:*

- *Investigators and their institutions, laboratories and other technical departments or clinics, generate and store the data, construct the record, and may use their own software and hardware* ***(purchased, part of national or institutional health information systems, or locally developed).***
- *Sponsors that supply, store and/or, manage and operate computerised systems (including software and hardware) and the records generated by them. Sponsors may do this directly, or via service providers, including organisations providing e.g. eCOA, eCRF, or IRT that collect and store data on behalf of sponsors.*

EMR digital systems utilized in clinical trials that are part of a national health information system meet national requirements. These national/institutional EMR systems are used in day-to-day routine healthcare settings and are therefore considered the "digital standard of care." The EMA Guideline adds an additional layer of compliance that is impossible for sites and sponsors to verify when such national/institutional EMRs are used because the site and sponsor are not the system owners and, therefore, do not have the system access that is necessary to ensure compliance with the Guideline. Please note that we have included an Appendix in this letter which details specific examples of impossible compliance requirements contained in the Guideline. In those instances where the site does not own the system and is, therefore, unable to access the computerized system for the purpose of verifying compliance with the Guideline, the national "digital standard of care" should be considered an adequate and satisfactory alternative to the Guideline for the purpose of validating computerized systems used in clinical trials.

The Problem

Variability in site-based computerized systems used in clinical trials – such as EMRs – presents challenges for both sites and industry to meet the expectations of Annex 6 of the EMA Guideline. These challenges fall into two main categories:

- the adequacy of the EMR functionality
- the ability of sites to provide direct access to monitors, auditors and inspectors

In situations where the EMR (or other computerized system) is owned by an entity outside the direct control of the research site (e.g. a national or regional EMR system), research sites may be limited in their ability to verify compliance with the EMA Guideline on *Computerized Systems and Electronic Data in Clinical Trials.* Moreover, in those instances where shortfalls are identified, neither the site – nor the sponsor – have any scope to influence remediation. This inability of sites to address deficiencies in systems they do not own (and the resulting inability to verify compliance) risks the following:

- Most importantly, rigid implementation of the Guideline and its impossible compliance requirements may lead some sites to exit from research. Fewer available sites could prolong the already lengthy drug development process and delay patients' access to clinical trials which may benefit them. This is counter to the EMA's ACT EU Initiative, which includes the objective *"to transform how clinical trials are initiated, designed and run to further promote the development of high quality, safe and effective medicines, and to better integrate clinical research in the European*

health system." Moreover, the potential reduction in research sites and disincentives to use new sites may thwart clinical trial diversity and inclusion goals.

- Sites may adopt high-risk "workaround" solutions such as the creation of duplicative, trial-specific paper-based notes or the use of alternate monitoring strategies, such as sites printing and 'certifying' notes. Not only do both of these workarounds take time away from core, patient-focused activities, but they are often not GCP compliant as the CRA may not be provided with the 'true' source of information for review. In addition, this may result in important information being omitted from the subject's overarching medical record, impacting their overall care. These workarounds in themselves lead to data integrity risks.

An internal survey by an ACRO member company helps illustrate these concerns. The company conducted an informal global survey of their CRO staff across 54 countries, and 32 staff responded that at least some sites were unable to provide direct access to the EMR and therefore certified copies were in use. Additionally, 5 countries in Eastern Europe/Baltic states indicated that the EMR did not meet the requirements of the EMA Guideline and therefore paper printouts were used.

- In Asia Pacific, staff in most countries reported an issue at less than 20 percent of sites; the one exception was Hong Kong where all sites indicated the use of certified copies
- In EMEA and LATAM, staff identified 10 countries in EMEA and 5 in LATAM for which the majority of sites (more than 70 percent) used certified copies and in some cases this was estimated to be in excess of 90 percent of sites
- Even in the USA, where use of EMR is well-established, staff estimated that approximately 10 percent of sites have restrictions on CRA access to their EMR systems.

Proposed Solution and Recommendations

The Guideline imposes an impossible compliance requirement on sites that use EMRs that are part of national or institutional information systems – and may result in those sites utilizing paper source data or paper certified copies, or even exiting research altogether. ACRO recommends a risk-proportionate, pragmatic approach – which is supported by the opening paragraph of Annex 6 which notes: *"the general approach towards computerized systems used in clinical practice is that the decision to use a system in a clinical trial should be risk proportionate and justified".* This approach would incorporate the following requests:

1. We suggest that EMA state that – in those instances where the site does not own the system and is, therefore, unable to access the computerized system for the purpose of verifying compliance with the EMA Guideline – the national "digital standard of care" for collection and management of clinical trial data is an adequate and satisfactory alternative to the EMA Guideline for the purpose of validating computerized systems in clinical trials.

2. We suggest that EMA provide examples of acceptable workarounds for systems which may not be fully compliant. We include two proposed examples here. First, in the case where a system cannot limit access to trial subjects only, an audit trail print out or statement from the investigator site that the monitor only accessed trial subject data would be sufficient. Second, in a situation where CRA access to the EMR cannot be limited to 'read-only,' appropriate mitigation might be for the site to provide a printed report or statement confirming that the site monitor has not made any additions or changes to the data (unless local requirements, Clinical Trial Agreement or institution's policy indicate this is not necessary). Additional, practical examples such as those provided by MHRA in this blog[1] would be welcome.

3. ACRO members are concerned about the prospect that auditors and EMA inspectors might retrospectively apply a rigid interpretation of the requirements and challenge the use of alternative methods of source data review. Retrospective application of this Guideline to any clinical trial data captured before the Guideline was implemented in September 2023 would adversely impact those trials in three ways:
    - Reduction of the opportunity for patients to be involved in trials of new treatments, which is counter to the industry drive to increase accessibility
    - Unintentional introduction of bias through post-hoc exclusion of sites
    - Loss of statistical power of the trial due to exclusion of sites

    These potential impacts would affect the equity of access to clinical research and the ability of research sites to be involved in future research and development programs. Therefore, we suggest EMA state that the Guideline will not be applied retrospectively – specifically, the Guideline will not be retrospectively applied to sites activated prior to September 2023, when this Guideline came into force. Moreover, we ask for a grace period for application of the Guideline to new sites, understanding that they may not have direct influence over the functionality of institutional or national medical record systems.

4. In the situation where a site's EMRs do not meet minimum EMA Guideline requirements (or it is impossible to verify compliance with the EMA Guideline), we ask that the Guideline permit the use of monitoring via 'over the shoulder' or 'certified copy print outs.' We recommend that this option is available in order that a diversity of sites is available to ensure representativeness for clinical trials. However, use of sites in this circumstance should be accompanied by a documented process for monitors to follow to verify they are being provided with all necessary information.

[1] https://mhrainspectorate.blog.gov.uk/2019/07/23/electronic-health-records/

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We request the opportunity to meet with you, remotely via Zoom, to further clarify ACRO's concerns and recommendations and answer any questions.

Sincerely,

Karen A. Noonan
Senior Vice President, Global Regulatory Policy

Attachments: Appendix

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Appendix

This table includes some examples of the Guideline's impossible compliance requirements. Sponsors, CROs, and investigators face challenges in the application of these requirements to systems outside of their control. If the national/institutional "digital standard of care" is not an acceptable compliance standard, the risk is that stakeholders will regress to pen-and-paper processes since documentation and evidence to confirm compliance with this Guideline may not be accessible to the site or Sponsor/CRO, even if the system is compliant.

Section	Text	Issue
A6.1 Purchasing, Developing or Updating Computerized Systems by Site	*To ensure the system requirements related to GCP compliance (e.g. audit trail for an electronic medical record) are addressed, experienced clinical trial practitioners should be involved by the institution in the relevant steps of the procurement and validation process'*	As acknowledged in section 4.2 of the Guideline, in some countries, systems are developed at a national level with a primary focus on provision of healthcare (without consideration of clinical trial research). These EMRs that are implemented at an institutional, regional or national level are outside of the sphere of influence of the investigator.
Section A6.2 Site Qualification by the Sponsor	*If the systems do not fulfil the requirements, the sponsor should consider whether to select the investigator/institution. The use of systems not fulfilling requirements should be justified, either based on planned implementation of effective mitigation actions or a documented impact assessment of residual risks*	This overly broad language is open to widely varying interpretation by inspectors and auditors. To mitigate this uncertainty, we ask for the adoption of ACRO's recommendations in this letter.
Section A6.4 Documentation of Medical Oversight	*The systems should allow the investigator to document the assessment and acknowledgement of information entered into the system by others*	As acknowledged in section 4.2 of the Guideline, in some countries, systems are developed at a national level with a primary focus on provision of healthcare (without consideration of clinical trial research). These EMRs that are implemented at an institutional, regional or national level are outside of the sphere of influence of the investigator.

Section 4.4 Source data	*This process should be validated to ensure that the source data generated/captured is representative of the original observation and should contain metadata, including audit trail, to ensure adherence to the ALCOA++ principles (see section 4.5.). The location where the source data is first obtained should be part of the metadata.*	It may not be possible for sites/Sponsors to dictate what metadata, e.g. audit trail, location, must be collected in national/institutional systems. As acknowledged in section 4.2 of the Guideline, in some countries, systems are developed at a national level with a primary focus on provision of healthcare (without consideration of clinical trial research). These EMRs that are implemented at an institutional, regional or national level are outside of the sphere of influence of the investigator.
Section 4.10 Validation of systems	*Documentation (including information within computerised systems used as process tools for validation activities) should be maintained to demonstrate that the system is maintained in the validated state. Such documentation should be available for both the validation of the computerised system and for the validation of the trial specific configuration or customization.*	System validation and documentation of the validation may not be accessible to the site/Sponsor for national/institutional systems. As acknowledged in section 4.2 of the Guideline, in some countries, systems are developed at a national level with a primary focus on provision of healthcare (without consideration of clinical trial research). These EMRs that are implemented at an institutional, regional or national level are outside of the sphere of influence of the investigator.
		Training on national/institutional systems may be directed by the national/institutional requirements, which are outside the scope of the sponsor. As acknowledged in section 4.2 of the Guideline, in some countries, systems are developed at a national level with a primary focus on provision of healthcare

Section 5.3 Training	*All training should be documented, and the records retained and available for monitoring, auditing, and inspections.*	(without consideration of clinical trial research). These EMRs that are implemented at an institutional, regional or national level are outside of the sphere of influence of the investigator.
Section 6.2.1 Audit trail	*Audit trails should be visible at data-point level in the live system, and it should be possible to export the entire audit trail as a dynamic data file to allow for the identification of systematic patterns or concerns in data across trial participants, sites, etc. The audit trail should show the initial entry and the changes (value – previous and current), specifying what was changed (field, data identifiers), by whom (username, role, organisation), when (date/timestamp) and, where applicable, why (reason for change).*	Not all national/institutional "digital standard of care" may have audit trails visible at the point of entry nor the ability to export the entire audit trail as a dynamic file. The specific content of the audit trail in the national/institutional "digital standard of care" may not meet the exact specifications described.
Section 6.8 Backup of data	*Disaster mitigation and recovery plans should be in place to deal with events that endanger data security. Such plans should be regularly reviewed. Disaster mitigation and recovery plans should be part of the contractual agreement, if applicable.*	For national/institutional "digital standard of care" it may not be possible to incorporate disaster mitigation and recovery plans into site/Investigator contractual agreements, since the site/Investigator may have no direct control or even insights into this aspect.