DOCUMENT HIS

Investigator's signature on electronic Case Report Forms (eCRFs)

Best Practices

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Author: eClinical Forum Principal Investigators' Signature Team

The eClinical Forum Principal Investigators' Signatures team included expertise from these companies: Abbvie, Amgen, Astellas, Boehringer Ingelheim, Bristol Myers Squibb, CSL Behring, Eli Lilly, Establishment Labs, Ferring IPC, Gilead Sciences, Lilly Deutschland GmbH, Memorial Sloan Kettering Cancer Center, Merck, MSD, Novo Nordisk, Pfizer, Viedoc.

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Date	Revision	Author	Changes
20-Nov-2017	MR1	eClinical Forum – PI Signature Task Force	First release to eCF members only
7-Apr-2022	MR2	eClinical Forum –Principal Investigators' Signature Team	• Clarified scope and objective of this document within section 2. • Adding new input to risk approach in section 4 (transcription vs direct entry). • Adding ability to pre-define time points as recommended functionalities in section 6. • Removed ability to sign on batches and added different levels of application in section 6. • Adding new section (7) for other data collection tools. • Adding section "Next Steps".
9-May-2022	MR2.1	eClinical Forum –Principal Investigators' Signature Team	• Updated 2022 eCF member companies
01-OCT-2022	PR2.1	Public release of MR2.1	Changed the cover page for the public release

Contents

1 ABOUT THE ECLINICAL FORUM

The eClinical Forum (eCF) is a global not-for-profit and non-commercial, technology independent group representing members of the pharmaceutical, biotechnology, and allied industries. The eClinical Forum's mission is to serve these industries by focusing on those systems, processes and roles relevant to electronic capture, management and submission of clinical data. For further information visit the website at www.eclinicalforum.org .

The eClinical Forum has sought out opportunities to promote electronic capture since its inception in 2000. The cross-industry forum has a broad view of research with members - Sponsors, Contract Research Organizations (CROs), Technology vendors (both clinical research and healthcare), Academia, and Investigators - and with invited outreach opportunities with global Regulatory representatives.

The eClinical Forum is firmly committed to promoting electronic data in all areas of clinical research. The eClinical Forum endeavors to ease the pain of change by providing clear rationale on implications of regulatory guidance in this area.

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The information presented in these works draws upon the combined current understanding and knowledge of the eClinical Forum on this topic and is provided as an aid to understanding the environment for electronic clinical research. While the information provided has been guided and reviewed by members of the eClinical Forum representing all areas of the pharmaceutical and associated support industry, the opinions of the author(s) and the eClinical Forum do not necessarily reflect the position of individual companies. Users should assess the content and opinions in the light of their own knowledge, needs and experience as well as interpretation of relevant guidance and regulations.

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2 INTRODUCTION

There is increased scrutiny by regulatory agencies on the collection of investigator's signature as evidence of the overall oversight on the eCRF data reported to the sponsor.

Due to different interpretation on the timing and frequency for the collection of the investigator's signature, an eCF Task Force has been formed to identify best practices that are based on the compliance to regulatory requirements and on risks such as reputation, credibility, legal liability of the data being used by the sponsor.

The intent of this document is to provide a framework for individuals' risk-based decisions and best practices for implementing solutions for investigators' signature collection on data reported to sponsor.

For the purpose of this document, data that are not collected in the eCRF cannot be considered in scope of the investigator's signature. This is because of the fundamental requirement that an

electronic signature should be linked to the records being signed to ensure that the signature cannot be excised, copied or otherwise transferred (See 21 CFR Part 11.70).

Note: Considering the clinical research evolution and the incremental use of different data sources, section 7 has been created for data collection tools different from eCRF.

3 REGULATORY REQUIREMENTS

Principles from existing regulatory guidelines apply, irrespective of the type data collection format (paper or electronic). This document is based on regulatory requirements reinforcing expectations on collection of investigator signatures in EDC solutions:

- In September 2013, **FDA** published the **Guidance for Industry on Electronic Source Data in Clinical Investigations**, and indicated that to comply with the requirement to maintain accurate case histories, clinical investigator(s) should review and electronically sign the completed eCRF for each subject before the data are archived or submitted to the agency. If changes are made to the eCRF after the clinical investigator(s) has already signed, the changes should be reviewed and electronically signed by the clinical investigator(s).
- **ICH E6 R2** section 4.9.1 indicates that the investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the eCRFs and in all required reports. In addition, section 8.3.14 requires the maintenance of the signed/dated and completed eCRF, at site and at sponsor, to document that the investigator or authorized member of the investigator's staff confirms the observations recorded.
- **J-GCP Art. 47** does not allow the delegation of the signature on the eCRF. (*"The investigator shall inspect the case report forms prepared by the sub-investigator and upon confirming the content thereof, should sign and seal them"*).
- The **China FDA** has also established requirements for the use of electronic signatures in their "Technical Guidelines on Electronic Data Capture for Clinical Trials". Once data entry has been completed and queries closed, it is required that researchers add their electronic signatures to the eCRF within the Electronic Data Capture (EDC) system and after such signatures, the EDC system should generally no longer allow data changes. Where such changes are made any previous electronic signature should become invalid. Additionally, the presence of electronic signatures on eCRFs should be verified before the trial database is locked, to confirm that eCRF data is complete and accurate.
- **EMA homepage: Q&A: Good clinical practice (GCP)** has published under GCP matters #13 requirements for investigators' review and sign-off data. The investigators are responsible for data entered into eCRFs and other data collection tools and those data should be reviewed and signed-off. The acceptable timing and frequency for sign off needs to be defined for each trial by the sponsor on risk-based manner. Timely review and sign-off is important prior to interim and final analysis, for important data (e.g., reporting of SAEs), and for data that are entered directly into the CRF as source. The design of the EDC system should be laid out to support the signing of the data at the defined timepoints.

4 GENERAL REQUIREMENTS

An electronic signature consists of at least two distinct identification components, such as an identification code and password and should clearly indicates all the following:

- The name of the signer
- The date and time when the signature was executed
- The meaning (such as creation, confirmation, or approval)
- Electronic signatures are permanently linked to their respective record(s).

For investigator's signature meaning on eCRF data, it is recommended to indicate that the electronic signature is equivalent to that of a handwritten signature and when executed it is done to confirm that eCRF data is accurate and complete.

Unless otherwise required by local regulatory requirements (e.g. J-GCP Art. 47), the signing of the eCRF data can be delegated to an appropriately qualified person of the investigator's staff. The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated these trial-related duties, including the signing of the eCRF data (ICH E6 R2, 4.1.5).

5 RISK-BASED APPROACH

The sponsor should mitigate risks to critical processes and data, ensuring that all aspects of the clinical trial are operationally feasible, without adding unnecessary complexity. These principles apply to the collection and controls of investigator's signature on the eCRF data.

Even if there are other records at investigator sites that may demonstrate investigator's supervision, some regulators see the investigator signature as an indicator of the overall oversight of the trial rather than just an attestation of the accuracy and completeness of the eCRF data being submitted to the sponsor.

When a more frequent collection of the investigator's signature is required, it is recommended that such intervals are established, documented and clarified with the investigators prior to starting the eCRF data collection.

To identify the frequency/timing of the investigator's signature collection, it is recommended to use a risk-based approach that considers:

- the investigator's accountability on the accuracy/completeness of the data as per regulatory requirements and ability to demonstrate oversight on the clinical trial data;
- the identification of data that is critical to ensure human subject protection and the reliability of trial results;
- the transcription of data versus data directly entered in the eCRF, as source;
- the methods used by the sponsor to assure and control the quality of the data, which are proportionate to the data risks and the importance of the information being collected;
- the intended use of the collected data by the sponsor, such as, but not limited to:
    - interim or final analysis for regulatory submission,
    - regulatory discussion,
    - other external exposure to data (e.g. adjudication),
    - sharing of data for transparency initiatives,
    - publications and posters,
    - Institutional Review Board (IRB) data listings,
    - final archival;
- how missing signatures will be addressed based on the potential impact to data integrity for the intended use of the data (see above). The following missing signature classifications should be considered:
    1. eCRF never signed by investigator,
    2. eCRF signed by investigator but subsequent change(s) to data require re-signature,
    3. eCRF have been signed by investigator but background activities that did not impact the eCRF data (e.g. validation rules, query management etc.) invalidated/broke the signature.

NOTE: For the first and second categories, it is strongly recommended that the investigator signature is obtained before proceeding, for example, with database lock. For the third category, while ideally the investigator should re-sign the eCRF, if this is not done, it is recommended to document the justification to not recollect the investigator's signature (e.g. a memo kept with the database lock documentation). If possible, evidence that no data has changed should also be provided (e.g. a report of changed data).

6 RECOMMENDED FUNCTIONALITIES

To facilitate the collection and the monitoring of the investigator's signature on the eCRF data, the following EDC functionalities are recommended:

- Ability to configure the meaning of the electronic signatures;
- Ability to invalidate or break the electronic signature on the eCRF data when data changes are made by the investigator staff;
- Availability of audit trail data of the signature events for reviews and copying;
- Ability to easily identify the time-zone used;
- Ability to provide a listing of data changes that occurred between initial and subsequent signatures;
- Visibility of unsigned eCRFs for immediate identification;
- Ability to link one electronic signature to all the eCRFs data associated with an individual subject or to sign at the eCRF page level;
- Ability to collect the electronic signatures any time during the clinical trial;
- Ability to support the signing of the data at pre-defined time points;
- Ability to define if electronic signatures can be applied at form level, at visit level and at subject level (e.g. casebook);
- Ability to review an investigator's access to ensure they routinely log into the eCRF system;
- Ability to review the time between eCRF entry and investigator's signature.

7 OTHER DATA COLLECTION TOOLS

Most of the above-mentioned practices are applicable to other data collection tools, such as eCOA tools or novel digital health technologies, if used in a clinical trial under the supervision of the investigators.

In the current environment, with the increased use of new technologies (e.g. connected devices, BYOD etc.), the investigator's evidence of supervision might have a different weighting, and its meaning might be better associated with the assessment/evaluation of clinical data, instead of the accuracy and completeness of the collected data.

Whenever there are technical limitations, alternative methods might replace the use of electronic signatures, as readable and enduring evidence of supervision.

Alternative evidence of oversight might be demonstrated using (but not limited to):

- Workflows;
- Confirmation dialog boxes;
- Custom buttons;
- Audit trail;
- Access logs.

8 ABBREVIATIONS

Abbreviation	Meaning
21 CFR Part 11	Code of Federal Regulations Title 21 Part 11 (Electronic Records; Electronic Signatures)
BYOD	Bring Your Own Device
eCRF	Electronic Case Report Form. A CRF is a printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject (ICH E6 R2, 1.11)
eCOA	Electronic Clinical Outcome Assessment
EDC	Electronic Data Capture
EMA	European Medicines Agency
FDA	Food and Drug Administration (United States of America)
GCP	Good Clinical Practice
ICH E6 R2	International Conference on Harmonization E6 – Guideline for Good Clinical Practice – R2 Integrated Addendum
J-GCP	Japan GCP

9 NEXT STEPS

Critical thinking - keep on disciplined evaluation for application of regulatory requirements, by:

- continuous monitoring of regulatory expectations;
- sharing members' experience on implementation and regulatory findings (if any);
- brainstorming for an industry definition of the "meaning" of signature on data reported to sponsors during both traditional and non-traditional clinical investigations.

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