Guidance for
electronic trial data capturing of clinical trials

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Japan Pharmaceutical Manufacturing Association

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1. Background

The method of collecting electronic clinical trial data in institutes, which to say, Electronic Data Capture (hereinafter ‘ EDC’) is now becoming widespread use in western countries as the method to shorten time to get improvement in quality and fixing clinical trial data.

When 2000’s begins, EDC also spreads slowly domestically, and now is becoming practical option in collecting clinical trial data.

In addition, regarding documents related to marketing approval of drugs which only had been accepted by ‘paper form’, after starting of Law concerning Electronic Signatures and Certification Services, the law has improved to enable electronic data use.

Especially using electronic case report form was approved by MHLW Ministerial Ordinance No.44 Established as of March 25, 2005. In addition, the guidance for using Electronic Records/Electronic Signature concerning approval of drugs (Notification No. 0401022 0f the PFSB as of April 1, 2005) became effective. (Commonly called ‘ERES (Electronic Records/Electronic Signature) guideline)

Also, it is increased that electric data are transferred from central laboratories to sponsors directly.

As stated, now that sponsors get more chances to capture electronic clinical trial data, so that regulated companies had better to share requirements of using such data (electric data), and to operate them on common concept.

In case capturing electronic clinical trial data which had been captured by paper operation in the past, you need to employ controls in advance so that they aren’t inferior to paper Case Report Form (hereinafter ‘CRF’) in terms of quality and quality assurance of data.

Though guiding document for these cases is ERES guideline, this guideline describes general requirements in using electronic data, so when you apply this guideline to specific case such as case report form, more specific requirements shall be considered.

Under these circumstances, the Drug Evaluation Committee of JPMA considered as self guidance and issued this guidance to improve above requirements.

2. Purpose

The purpose of this guidance is describing conditions that following electronic data described 1 & 2 can be using for NDA submission (namely electronic records are identified original) regarding data created by EDC systems or obtained electronic data from central laboratories.

1. Electronic data within EDC system
2. Electronic data transferred to another electronic media after data was fixed

3. Scope

This guidance assumes that the data flow showing the chart in the last page.
There are many clinical trial data such as data captured by institutes, direct transferred data from the central laboratories to the sponsor, random allocation table (so called key code) and patients' dairy.
The scope of this guidance is the data entered to the EDC system in the institutes and electronic data reported by central laboratories.
The process of data transferring from electronic medical chart system to EDC system is not scope of this guidance, but the data captured by the EDC system is in scope.
And also query information, code value, calculated data and SDV records are not scope of this guidance.
But things to keep in mind are described due to query information and calculated data have a close connection to clinical trial data.

4. Requirements of capturing electronic clinical trial data

4.1 Requirements for entered data by institutes

If you comply with ERES guideline and following requirements (4.1.1. - 4.1.3.1.), the data stored in the EDC server which is entered (including direct entry and capturing partial institutes' electronic data via electronic media) by investigator, co-investigator (here after 'investigators') and CRC using EDC system is identified the original electronic case report form.
Original includes entered data including investigators' evaluation, audit trail and electronic signature information (if you use electronic signature).
After data transferred from EDC server, if you comply with 4.1.1 - 4.1.3.1 before transferred and "4.1.3.2. Requirements of storability of permanent electronic CRF after transferred", data stored another media from the server can be identified as original.
But, original electronic case report form should be predefined each stage of using EDC system and after transferred from EDC server.
On the assumption that the EDC system is ensured its reliability by computerized system validation (here after CSV) according to your CSV policy, it must be noted that following things.

- CSV shall include not only for developing and implementing phase, but also operating, revising and retirement phase.
- During the documents' retention period, sponsor shall explain the CSV policy, process and deliverables which were applied to the EDC system.
- Sponsor has the responsibility of ensuring the quality of entrusted business for vendors and CROs.

4.1.1 Requirements for authenticity of electronic records

1) The EDC system shall have an ability to grant access rights according to the user's responsibility, and has controls that intended data is entered correctly according to the granted access rights.

- User management and access rights grant are conducted according to the predetermined rule appropriately.
- Identify of the user is secured when access to the system. (ID and password are operated appropriately)
- Operation shall be adequate and compliance shall be ensured by training. (i.e. Prevent from spoofing, stealing password and so on.)
- Entered data shall be recorded correctly just as the user intended.
- Entered data shall be confirmed by the display.
- Audit trail shall be recorded automatically. (i.e. The EDC system is designed to permit data changes in such a way that the data changes are documented and that there is no deletion of entered data.)
- Audit trail shall not be modified by anyone.
- If sponsor would like to capture certain electronic data in institute via electronic media, sponsor shall make clear the scope of responsibilities of quality assurance provision of transferring electronic data in a contract, and shall ensure its quality by checking of data.
- Sponsor shall check compliance of quality management agreement at institutes.
  - ✓ Sponsor shall check quality of provided data.

2) Employ procedures and controls designed to ensure the security

- The ability to investigate of operator, content and timing of input/modify of data.
- The ability to prevent alteration, divulgation and repudiation of fact of operation.
- The ability to prevent unauthorized access. (take a measure of malware and security hole, management and prevent of leaking of ID and password, user management)
- The ability to detect any unauthorized access. (monitoring of access, alert, access logs)
- The ability to ensure the authenticity, integrity, and, as appropriate, the confidentiality of electronic records.

3) Process of creating electronic CRF shall be ensured as same quality level as paper CRF by management and operation in accordance with GCP.

- Meet with GCP and related laws requirements.
- Ensure conformity of data by sponsor's SDV in case of source documents exists.
- In case of source document does not exist (i.e. data of electronic CRF is source document), employ controls to identify the data creator clearly, such as functionality of control of access rights to the EDC system. If you employ procedures partially instead of controls, source documents shall be identified in protocol and prepare briefing paper which describe

how to create and modify the data in advance. In that case check and ensure the process has been conducted appropriately.

- Sponsor shall provide electronic CRF copy to investigators, and confirm they are maintained appropriately.
- The electronic CRF copy which is maintained by investigators shall meet following requirements.
  - ✓ The electronic CRF copy is exported directly or converted automatically (which shall be qualified in advance) from the original data in the server.
  - ✓ The electronic CRF copy shall be comparable to the original.
  - ✓ The electronic CRF copy shall be identified
  - ✓ Be able to identify the time point of copy from the original.
  - ✓ In the institutes, authority and investigators are able to check the data of CRF at anytime within the retention period.
- Records of creating CRF and investigators' signature are managed as follows.
  - ✓ The account list which mentions personnel access rights shall be created and operated instead of handwriting signature list.
  - ✓ As GCP requires, in case of using signature for creating and modifying CRF on the EDC system, you shall do follows.
  - ✓ The ability to identify of operator's ID and input time of each data by log (i.e. audit trail).
    - ✧ Note that signature shall not be requested for every data input.
    - ✧ But, the operator shall be identified for every data input.
  - ✓ The investigator shall check and confirm the created or modified electronic CRF and put electronic or handwriting signature on it.
  - ✓ The signature (including handwriting signature) and CRF is linked properly.
  - ✓ If there are some amendments after investigator signed, the investigator shall check and confirm the modified electronic CRF and put electronic or handwriting signature on it again.
  - ✓ The ability to confirm the audit trail on the display by the investigator.

4) Electronic signatures are operated properly according to ERES guideline.

- Employ account management rule for electronic signature, and operate it properly.
- Training record of every related people shall be maintained.
- The EDC system shall clearly specify the signature time, intended data and meaning of signature. And ensure that the signatures cannot be excised or copied. Signed electronic records shall contain information such as signer, the date and time when the signature was executed and meaning of signature.

- When using handwriting signature, ensure that the link between intended electronic records and handwriting signature is certainty.
- Clearly identified signature time and intended electronic records and if electronic records are modified, electronic signature shall be executed on the modified records.

5) Backup of CRF data and EDC system (including users list, access rights information, and so on) is performed appropriately.

- According to the documented procedures, latest electronic CRF data, audit trail and electronic signatures are backup periodically. In case of emergency, CRF data shall be recovered in accordance with predetermined procedures. In this case the original 'data set' shall be uniquely identified.
- In terms of recognizing that the recovered data is original, recovering procedures shall be tested and qualified in advance.
- In case of H/W or S/W incidents, the environments shall be recovered in accordance with predetermined procedures.

6) During operating period, if the EDC system is revised, the revising operation shall be performed appropriately.

- The revised system shall be ensured its quality by CSV in accordance with CSV policy. The 'revising' means followings,
  - ✓ EDC system's version up. (Program change such as functionality addition, modification and elimination to the system, and environment change.)
  - ✓ Revising input form of electronic CRF. (In case of protocol amendments or bug fix.)
  - ✓ Program addition, modification and elimination due to automatically query output.
- In case of data migration due to revising of EDC system, the original data shall be exported directly or converted automatically (which shall be qualified in advance) and keeping their contents and meaning. And also readability of data (including audit trail) is ensured.
  - ✓ Validation deliverables shall be maintained that ensure the data is converted or exported according to the qualified procedures and the data is in consistency with original data.
- In case of revising of related records such as validation deliverables, change control procedures shall be predetermined, and creation or change history of validation deliverables shall be maintained and traceable in chronological order.
- After new EDC system has gone live, if you discard previous EDC system, related records such as validation deliverables shall be maintained and ensure adequacy of all documents produced by previous EDC system.

4.1.2 Requirements of readability for electronic records

1) The ability to generate output for display and printouts of every input/modified data and audit trail (including electronic signature) for human readable format at anytime.
2) Readability means that not only human readable format but also legible and easy to teat. Poor display functionality such as users are obliged to trace many tables according to some kind of key code is not met with readability requirements. All information shall be integrated when users display or print out.

4.1.3 Requirements of storability for electronic records

4.1.3.1 Requirements of storability for electronic records (electronic CRF data, audit trail and electronic signature) on the EDC system

1) Maintain method of electronic records are assessed according to its appropriate risk and documented in advance. (prepare for SOP)
2) Electronic records shall be managed as well as paper original. (assign manager)
3) Electronic records on the EDC server shall be ready retrieval by authority's inspection throughout the records retention period.

4.1.3.2 Requirements of storability of permanent electronic CRF after transferred

When you transfer electronic data from EDC server to another electronic media, there are following requirements.

A. Requirements for clinical trial data storability

1) In case of data (original) transfer, the data shall be exported directly or converted automatically (which shall be qualified in advance) and keeping their contents and meaning.
2) Appropriate document format for permanent electronic CRF
    - Document format can be using throughout the records retention period. (i.e. open format such as PDF, XML, SGML are preferable)
    - Officially admit document format for long term retention. (i.e. ISO)
    - Searchable format.

3) Appropriate electronic media for permanent electronic CRF
    - Enough warranty periods for not data missing throughout the records retention period.
    - Method for checking quality of data on the electronic media periodically.
    - Not be able to amend and delete. (i.e. optical disk)

B. Requirements for keeping EDC system

1) In case of not maintain EDC system after data transfer, necessary records should be maintained.
    - In case of not maintain EDC system after data transferred to permanent electronic CRF, validation deliverables such as system requirements specification deliverables, design specification deliverables and qualification deliverables are to be maintained for inspection.
2) Readability shall be ensured if the EDC software is migrated for new computer system.
    - After data transfer, if you intend to preserve EDC software and re-install it in any occasion, readability shall be ensured on the new computer environment.

4.2 Requirements for capturing electronic data from central laboratories

This section describes handling data when medical institutes don't conduct clinical laboratory test but ask it of central laboratories for analysis results.

Analysis results (source documents) from central laboratories are normally reported to the institutes which ask laboratory test.

The accuracy of the analysis results should be assured by central laboratories because no evaluation or discretion of investigators is included.

On the other hand, sponsors should ensure that investigators make clinical judgment on analysis results from central laboratories, assure examinee's safety and reflect their observation to clinical trial assessment.

In the other words, even if the data was measured by central laboratories, it should be assured that investigators make clinical judgment under recognizing accuracy of these data, and analysis results and data for clinical judgment, including their relationship, should be guaranteed their authenticity.

If sponsors get clinical data directly from central laboratories not via institutes, and import them into sponsors' server or EDC server, sponsors should have primary responsibility to assure identity of the data and data reported from central laboratories to institutes.

In consequence, sponsors need to make measures to assure identity of data reported to institutes and data which sponsor imported directly from central laboratories by contracts with central laboratories.

There are some cases that analysis results are included in electronic case report form or not, but in both case authenticity , readability and storability are should be guaranteed and complied with 4.1.1～4.1.3.1.

Followings are additional requirements of and specific to analysis results from central laboratories.

4.2.1 Authenticity

1) Assure reliability of analysis results, and transfer and import data properly.
   - Make articles that central laboratories should comply with by contract documents to ensure scope of responsibilities for quality of transferred electronic data and reliability of data.
     - ✓ Central laboratories shall assure accuracy of analysis results and ensure that laboratory reports to institutes correspond with electronic data sent to sponsors.
     - ✓ Arrange procedures of handling electronic data and scope of responsibilities in central laboratories.
   - Define reporting procedure of clinical data among institutions, central laboratories and sponsors and input methods in protocol.
   - Create operation in advance procedures for data acceptance/acceptance confirmation, and data import/import confirmation at sponsors' side.
   - Reliability, repeatability and security should be assured in methods of data import.
   - Records should be maintained to make sure that operations of both sponsors and central laboratories are done as procedures

2) Sponsor shall confirm reliability through whole process.
   - Confirm laboratory reports regarding as source documents stored in institutes are correspond with electronic data transferred to sponsors.
   - Confirm patients' ID and date by SDV, and also confirm consistency with other source documents.
   - Confirm that investigators shall make clinical judgment on analysis results, assure examinee's safety and reflect their observation to clinical trial assessment.
   - In case analysis results are modified, monitor shall confirm by records that investigators make evaluation on fixed analysis results and it is reflected on data entered.
   - Confirm by records that procedures are maintained and all operation is conducted on them in central laboratories.

4.2.2 Readability

1) Clinical data captured can be displayed on screen or printed on paper as forms or inventory for each clinical case

4.2.3 Storability

Requirements for data storability is same as 4.1.3.

There are many difficulties to maintain original computer systems which used to data clean up for long term. In case of store data in long term without maintaining systems, to assure authenticity,

following requirements should be complied in addition to 4.1.3.

2) Identify original documents stored in long term.
3) Store documents regarding procedure and scope of responsibilities mentioned in 4.2.1. 1), and records and documents related to CSV system in use.
4) Store copy data from central laboratories and records of transferring data
5) Store operation records in importing data and transferring original data
6) Store audit records.
7) Store documents about backup of fixed data, methods of decompression procedures and to confirm successful decompression

5. Remarks for related information out of CRF

5.1 Query information

In case of using query information (monitoring and questionnaire) via EDC system, ensure authenticity, readability and storability of electronic records on the EDC server according to the ERES guideline.

Sponsor shall predetermine that if you collect and maintain query information by EDC system or not.

And also sponsor shall predetermine the method in case of data amendment after EDC system removal from institutes. (For example, using paper format)

5.2 Calculated data

The calculated data (i.e. BMI, sum etc.) may be displayed on the EDC system, they are not necessary to include CRF original.

6. Definitions of terms

Terms used in this guidance are shown below.

Terms	Definitions
Electronic Data Capture （EDC）	In this guidance, it mentions systems that sponsors capture clinical trial data (including clinical trial after production and distribution) electronically instead of existing paper CRF. Following data are scope of this guidance. 1) Data that investigator, co-investigator and CRC manually enter source documents and investigators' evaluation to computer systems directly on definition of protocol. 2) Laboratory data reported to sponsors directly from central laboratories which conduct test.
Electronic CRF	In this guidance, it mentions data that investigator, co-investigator and CRC manually enter source documents and investigators' evaluation to computer systems directly on definition of protocol and electronic documents consisted of audit trail. If any comments, memo, and signature information related data are existed, they are included. Investigators must check the content of electronic CRF and confirm that there's no problem before placing a seal or signing . On the other hand, case data which its source is in central laboratories not in institutes is not included in electronic CRF, and there are some cases that central laboratories transfer direct report to sponsors.
Paper CRF	In this guidance, it mentions Paper CRF in the past. (In addition, in Paper CRF, there are various transactions about laboratory data reported from central laboratories, such as the case investigator, co-investigator and CRC transcribe source data, posting list of laboratory data, and not posting it .)
Original of Electronic CRF, Paper CRF	Electronic CRF before data was fixed is entered by computer system, and the data on the server is identified as the original. After CRF data was fixed, by copying data on server to other media, data of same contents as the original can be copied to other media. Using this procedure makes multiple data consists of information same as the original exist, but original have to be unique, it is necessary to identify the original in advance in case of multiple data same as the original exist. And also change over of original have to be conducted according to predetermined procedure. On the other hand, paper CRF in the past, original is always fixed uniquely as the signature written or seal placed by investigators.
Permanent Electronic CRF	This guidance define it as "Electronic document including audit trail, that are displayed as meaningful value in case of input data or coded data, and/or also displayed almost input form when final data value of Electronic CRF input" There are cases that electronic signatures are included, and signatures are done on stored media or documents stored at the same time. No matter EDC system is operative or removed, it indicates electronic CRF identified as original electronic CRF.

Terms	Definitions
Computerized system validation (CSV)	GCP operating notification mentions that validation is "ensure and document that the electronic data processing system(s) conforms to the sponsor's established requirements for completeness, accuracy, reliability, and consistent intended performance".That is CSV is the ongoing process of establishing documented evidence which assure that a system will consistently perform according to its predetermined specifications(user requirements and use purpose).Documents include various requirements specification, operating organization and structure, and documented procedures. The scope covers overall life cycle of computer systems from planning to retirement(or stop of use)
Query	General inquiries about contents of CRF from sponsors to investigators, co-investigators and CRC. They are established to correct mistakes, to confirm and solve flaws and discordances, and for remainder.
Calculated Data	Secondary data calculated from CRF data by prescribed algorithm.
Central Laboratories	Inspection institutes which perform clinical laboratory tests intensively. Sometimes they are called central labos, or centering measuring institutions.
SDV (Source Data Verification)	Checking CRF and source documents when important records and reports are investigated, analyzed, confirmed and copied to evaluate clinical trial (source document verification)
Audit trail	A sequence of operation records with accurate time stamp (that computerized systems put automatically).It is basically used Japan Standard Time for time stamp. But if other standard time is used or clinical trials are conducted at the same time in several countries or regions using different standard time, it is necessary to have function to define which standard time is applied. The operation records shows histories that people create, alter and delete electronic records on computerized systems and record time and date of operation, operators, operating contents by time-series. This guidance includes CRF data, comments and memos related with CRF, input data related with signature information, time and date of alternation or modification, data before and after alternation, operating users information, operation type such as input, alternation and signature and the reason of important alternation or modification.Key operation to call screen is out of audit trail And also transactions performed by computerized systems automatically (operation and calculation) aren't included in audit trail. In addition, time adjustment function is to link time stamp directly, therefore it should be included a part of audit trail when systems has automatic time adjustment function.
Electronic Signatures	Signatures on electronic records as same as handwritten signatures or seals and data coded electronically a series of meanings such as creation, adoption, confirmation and approval of individuals or companies.
Data management system	The computerized system to support data management work. It is also called (clinical data management system(CDMS)).

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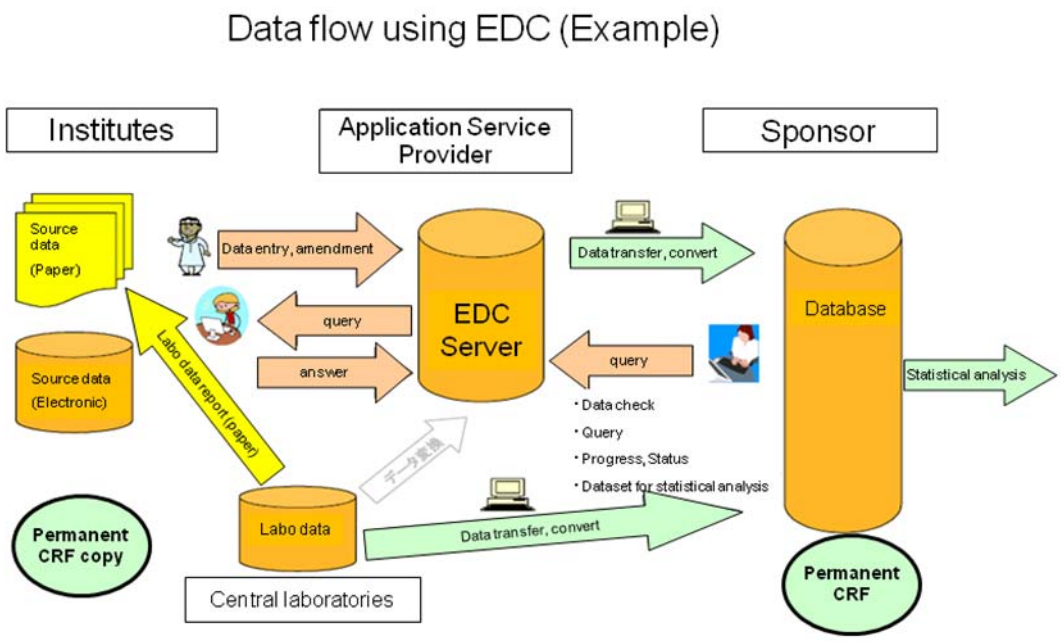

Target data of EDC

– Direct data entry by Investigator, Co-investigator and CRC.

– Data from central laboratories, direct captured data from device (ECG, etc.).

Computer systems for EDC

– Institutes and sponsor access via network.

Business assignment

– Institutes, Application service provider, Sponsor and central laboratories.

(Remarks: If EDC server locates in sponsor site, there are some differences regarding CSV scope and deliverables.)