



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

09 June 2010
EMA/INS/GCP/454280/2010
GCP Inspectors Working Group (GCP IWG)

Reflection paper on expectations for electronic source data and data transcribed to electronic data collection tools in clinical trials

Adoption by GCP Inspectors Working Group for release for consultation	14 June 2007
End of consultation (deadline for comments)	31 April 2008
Adoption by GCP Inspectors Working Group	09 June 2010
Date for coming into effect	01 August 2010

Keywords	<i>Source data, electronic, eCRF, eSource, ePRO, Clinical trial</i>
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1. Glossary

The following definitions are taken from the section 1 (Glossary) of the Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95)¹:

1.9 Audit Trail

Documentation that allows reconstruction of the course of events.

1.11 Case Report Form (CRF)

A printed, optical, or electronic document designed to record information to be reported to the sponsor on each trial subject.

1.51 Source Data

All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

1.52 Source Documents

Original documents, data, and records (eg., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

The following definitions are provided in order to facilitate the review of the reflection paper. A reference is provided with each definition, as applicable:

Audit Trail

A process that captures details such as addition, deletions or alterations of information in an electronic record without obliterating the original record. An audit trail facilitates the reconstruction of the history of such actions relating to the electronic record. [after ICH E6, CSUICI] (CDISC Clinical Research Glossary Version 8.0, DECEMBER 2009)².

Certified Copy

A copy of original information that has been verified as an exact (accurate and complete) copy having all of the same attributes and information as the original. The copy may be verified by dated signature or by a validated electronic process (CDISC Clinical Research Glossary Version 8.0, DECEMBER 2009)².

Validation

Process of establishing suitability to purpose for software and systems, establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes. (CDISC Clinical Research Glossary Version 8.0, DECEMBER 2009)².

Transcription

Process of transforming dictated or otherwise documented information from one storage medium to another. NOTE: often refers explicitly to data that are manually transcribed from source docs or measuring devices to CRFs (i.e. Transcribed Data). (CDISC Clinical Research Glossary Version 8.0, DECEMBER 2009)².

2. Executive Summary

Collection of accurate clinical trial data is essential for compliance with Good Clinical Practice (CPMP/ICH/GCP/135/95)¹. With increasing use of information technology in pharmaceutical development there is a need to have clear guidance on the use of electronic source data and transcribed data and the principles that should apply to them. This is necessary in order to ensure that the processes can be used and accepted with confidence when such requirements are complied with, and that the benefits that these systems offer can be fully utilized.

This reflection paper outlines the current opinion of the EU GCP Inspectors Working Group on the use of electronic data capture in clinical trials and on related inspections

3. Introduction

Computers are being used increasingly in the conduct of clinical trials. This is already a well-established practice for data management, analysis and reporting at the sponsor or CRO site. Computers are also widely used in laboratories, and are an increasing feature of medical records. They are being used more and more for the capture of clinical data, at the study site, as an electronic (e)CRF, for patient diaries or other forms. These activities use a variety of software and hardware, and in particular several categories of system – PC, LAN, WAN, mobile devices, email transmission, web-based systems, Interactive Voice Response Systems (IVRS), Interactive Web Response System (IWRS). The fundamental issues to be demonstrated remain common in many cases to both paper and electronic systems (e.g. traceability, change-control...), though electronic systems present additional challenges in providing an adequate level of confidence in the data and should be validated.

Source data and transcribed data have traditionally been recorded in paper documents. Many requirements and expectations have been developed in this context. The principles underlying these expectations and requirements are largely applicable to electronic media but their practical application is different.

Electronic source data can be described in a number of ways. It is important to consider who is providing and controlling the electronic tool being used. Broadly, there are two important groups who may provide these, in the context of clinical trials:

- ❑ Investigators and their institutions, including their laboratories and other technical departments or clinics, generate 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, supplying, and / or, managing and operating electronic recording systems (including software and instruments) and the records generated by them. The sponsors may do this directly, or via Contract Research Organisations (CROs), such as service providers, ePRO, eCRF, or IVRS specialists, or 3rd party data vendors that collect and store data on behalf of sponsors or other service providers.

At each stage of the electronic data capture and handling in the clinical trial database, the responsibilities of the investigator and the sponsor as defined in GCP should be applied, in order to ensure the reliability of the data.

The use of electronic records for clinical data results in new issues as well as a need to reiterate established principles in this context.

The GCP Inspectors Working Group has noted the CDISC (Clinical Data Interchange Standards Consortium) e-SDI Group publication “CDISC Standards and electronic Source Data Within Clinical Trials 20 November 2006”³. In particular the CDISC publication includes a set of 12 user requirements for source data, irrespective of the media or technology used to hold the data. These requirements describe a group of high-level principles, which, when they are adhered to, provide a good basis for the acceptability of source data. These principles should be internationally applicable – an important consideration given the global nature of clinical trials. They provide a good reference for sponsors or investigators establishing such systems, and for monitors and auditors or regulatory inspectors reviewing them. The group has, therefore, chosen to centre this reflection paper on these 12 user requirements, knowing also that they have been prepared on the basis of the ICH GCP¹ and other requirements.

In this context the reflection paper has categorised these 12 requirements into five topics and discusses issues relating to each. This does not imply endorsement of other concepts or details in the CDISC publication³, which contains an extensive discussion of the issues involved, although they could also apply.

The requirements of Directive 95/46/EEC of the European Parliament, the Council of 24 October 1995⁴ on the protection of individuals with regard to the processing of personal data and on the free movement of such data and the considerations set out in this paper should be followed.

Clear requirements for electronic source and transcribed data need to be stated in a way that the processes can be used and accepted with confidence when such requirements are complied with, and the benefits that these systems offer can be fully realised.

This paper outlines the current expectations of GCP inspectors. Any departure from this paper would need to be justified. The GCP Inspectors Working Group considers that a reflection paper on the issues is appropriate at this stage.

4. Scope

The scope of this reflection paper is electronic systems, (including instruments, software and services) used in clinical trials in the creation/capture of electronic clinical data, such as:

- ❑ Electronic Case Report Forms (e-CRFs) e.g. laptop/desktop, mobile device based programs or web based tools, which may contain source data directly entered, transcribed data by re-keying from other sources, or both.
- ❑ Electronic patient data capture devices used to collect Patient Reported Outcome (PRO) data– e.g. mobile devices supplied to patients to record observations, rating scales, IMP use. This can be primary efficacy or supportive data.
- ❑ Instruments supplied to investigators for recording clinical data either by data entry or by automated capture of events such as biometric measures (e.g. blood pressure, respiratory measures, ECG monitoring etc).
- ❑ Instrumentation or electronic systems to capture, generate, manipulate or store data in an environment where analysis, tests, scans, imaging, evaluations, etc. are performed in support of clinical trials.
- ❑ Electronic Health Records.

5. Legal Basis

This document is a Reflection paper (reference to Guideline on Guidelines) of the GCP Inspectors Working Group. The paper is intended to cover the creation/capture of electronic clinical data in all clinical trials in the EU/EEA or in third countries in case the clinical trial reports are submitted as part of Marketing Authorisation Applications to EU/EEA regulatory authorities. The requirements have their basis in Directive 2001/20/EC⁵ and Directive 2005/28/EC⁶, and in the Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95)¹.

6. Principles

6.1. General Principles

The elaboration of general principles to be adhered to is of importance since it allows the preparation of guidance that can then be adapted to the specific situation of a particular electronic data capture instrument or to the context in which it is used. The basic concept of source data is that it permits not only reporting and analysis but also verification at various steps in the process for the purposes of confirmation, quality control, audit or inspection. A number of attributes are considered of universal importance to source data and the records that hold those data. These include that the data and records are:

- Accurate
- Legible
- Contemporaneous
- Original
- Attributable
- Complete
- Consistent
- Enduring
- Available when needed

Section 5.5 of the Note for Guidance on Good Clinical Practice (CPMP/ICH/GCP/135/95)¹ describes standards for the use of electronic trial data handling and/or remote electronic data systems. GCP requires that sponsors operating such systems validate the system, maintain SOPs for the use of the system, maintain an audit trail of data changes ensuring that there is no deletion of entered data, maintain a security system to protect against unauthorized access, maintain a list of the individuals authorized to make data changes, maintain adequate backup of the data, safeguard the blinding of the study and archiving of any source data (i.e. hard copy and electronic). If data are transformed during processing, it should always be possible to compare the original data and observations with the processed data. The sponsor should use an unambiguous subject identification code that allows identification of all the data reported for each subject. Sponsors are responsible for ensuring compliance with the requirements outlined above when tasks are subcontracted. There should be no loss of quality when an electronic system is used in place of a paper system.

6.2. Specific Requirements

The 12 requirements stated in the CDISC standard are categorised into five topics and related issues are addressed below. The CDISC requirements specifically relate to source data, however, the interpretation is also applicable to transcribed data.

Topic 1: Creation and modification of systems

- ❑ An instrument used to capture source data should ensure that the data are captured as specified within the protocol. (Requirement 1, ICH GCP 2.6 and 6.4.9)

An instrument used to generate, capture, transfer, manipulate or store data (e.g. Case Report Form (CRF), patient diary, site-designed worksheet) should be an accurate representation of the protocol ensuring that the data as specified within the protocol can be captured correctly and that the investigator or subject response is not biased by default values present within the instrument. Where applicable, the availability of an optional free text field for investigators to record additional information is encouraged.

The instrument should be created in a controlled manner to ensure that it conforms to the protocol and is validated. In addition, appropriate change control as part of ongoing validation is needed, in cases where protocol amendments require changes to the instrument. Records of system validation including requirements, design, installation, access and security, testing (e.g. user acceptance testing, installation, operational and performance testing), training and controlled release for use should be maintained.

Topic 2: Creation, modification and transfer of data

- ❑ Source data should be Accurate, Legible, Contemporaneous, Original, Attributable, Complete and Consistent. (Requirement 2, ICH GCP 1.51, 1.52, 4.9.1 and 6.4.9)

Accurate: The use of such instruments/systems should ensure that the data are at least as accurate as those recorded by paper means. The validity of the data capture process is fundamental to ensuring that high-quality data are produced as part of a trial. The process needs to ensure that all data required are captured and that data are captured in a consistent manner. The coding process which consists in matching text or data collected on the CRF to terms in a standard dictionary, thesaurus or tables (e.g. units, scales, etc.) should be controlled. The process of data transfer between systems should be validated.

Legible: Readable at the input and output stage in a form meaningful to an independent reviewer i.e. a human being should be able to read it, not encrypted, coded or in programmed language.

Contemporaneous: The recording of a clinical observation is made at the same time as when the observation occurred. If this is not possible the chronology of events should be recorded. An acceptable amount of delay should be defined and justified prior to trial recruitment.

Original: This must be the first record made by the appropriate person e.g. ePRO record produced by the subject and not the investigator or the first acceptable result generated in an environment where analysis, tests, scans, imaging, evaluations, etc. are performed in support of clinical trials.

Attributable: The person undertaking the action should be recorded by the system. Unique user identification is necessary (login, username, password, PIN etc.), and this needs to account for the fact that many trials are conducted at multiple locations, and permit entries to be consolidated into a central database. As with hard copy paper data, it is important that electronic data are time/date

stamped when the data are created/generated. Reasonable controls should be established to help assure that user identification truly represents that individual (i.e. there is no identity theft).

Completeness and consistency: can be assisted by the use of features such as drop-down lists, online edits, check boxes and branching of questions or data entry fields based on entries. The individual (investigator site staff, study subjects, caregivers or others) capturing the data need to have documented training in the correct use of the instrument and the electronic data capture document. In addition, when considering data from an environment where analysis, tests, scans, imaging, evaluations, etc. are performed in support of clinical trials, it should be possible to fully reconstruct the activities performed.

Electronic checks do not automatically remove the need for review of data by the investigator or other experts, or by the monitor / data manager depending on the nature, purpose and importance of the items involved. Data should be traceable and an unambiguous subject identification code should be used to allow identification of all data reported for each subject.

A procedure should be in place to address the situation when a study subject or other operator capturing data, realises that he/she has made a mistake and wants to correct the recorded data. It is important that original electronic entries are visible or accessible (e.g. in the audit trail) to ensure the changes are traceable.

Any transfer from paper to electronic CRF should be subject to quality control and the level of control should be justified.

- ❑ An audit trail should be maintained as part of the source documents for the original creation and subsequent modification of all source data. (Requirement 3, ICH GCP 4.9.3 and 5.5.4)

The maintenance of an audit trail is essential to ensure that changes to the data are traceable. Secure, computer-generated, time-stamped audit trails (or alternative methods that fulfil the audit trail requirements) should be used to independently record the date and time of operator entries and actions that create, modify, or delete electronic records. Such audit trail documentation should be retained as long as the subject electronic records. Audit trails need to be readable and changes to audit trail data should be prevented by the system. The responsible investigators, sponsors and inspectors should be able to review the audit trail. The audit trail will record changes made as a result of data queries or a clarification process. The clarification process for data entered by trial subjects should be documented and it should be clearly stated where changes to data entered by subjects will not be made.

- ❑ The location of source documents and the associated source data should be clearly identified at all points within the capture process. (Requirement 11, ICH GCP 6.4.9)

The protocol should identify any data to be recorded directly into the CRFs that is considered to be source data. A detailed diagram and description of the transmission of electronic data should be provided in the protocol. The source data and their respective capture methods should be clearly defined prior to trial recruitment (i.e. in the protocol or study specific source data agreement). The sponsor should describe which data will be transferred, the origin and destination of the data, the parties with access to the transferred data, the timing of the transfer and any actions that may be triggered by real-time review of those data.

There should only be one source defined at any time for any data element.

Considering the electronic source data environment it is accepted that the earliest practically retainable record should be considered as the location of the source data and therefore the source document. In this case the process should be clearly documented and the protocol should state which data recorded on the instrument will be used as the official source data.

There is a need to capture the logical location (e.g. a folder) of the source data. When data are created, copied or transferred the final location and identification (source, copy or back-up) should be documented.

Topic 3: Control

- ❑ The investigator should maintain the original source document or a certified copy. (Requirement 5, ICH GCP 2.11, 5.15.1)
- ❑ Source data should only be modified with the knowledge or approval of the investigator. (Requirement 6, ICH GCP 4.9.3, 4.9.4 and chapter 8)
- ❑ The sponsor should not have exclusive control of a source document. (Requirement 10, ICH GCP 8.3.13)

The fundamentals of clinical research include that patient rights, safety and well-being are the most important considerations and the integrity of the reported data must be confirmable. To this end all data generated in a clinical trial relevant to patient care must be made available to the investigator at all times during and after the trial and all data held by the sponsor that has been generated in a clinical trial should be verifiable to a copy not held (or that has been held) by the sponsor.

The requirements above are not met if data are captured in an electronic system and the data are stored on a central server under the sole control of the sponsor. This is because the investigator does not hold an independent copy of the data and therefore the sponsor has exclusive control of the data. In order to meet the requirements a contemporaneous certified copy of the data should be retained at the investigator site in addition to the record maintained on a central server.

The requirement 10 above is not met if data are captured in an electronic system and the data are stored on a central server not under the control of the sponsor, but eventually are transferred to the sponsor. This is because the sponsor has exclusive control of the data. In order to meet the requirements a certified copy of the data should be created before the transfer to the sponsor and retained at the investigator site. The method of transfer should be validated

The sponsor of a study remains ultimately responsible for the quality of the study data and for ensuring that procedures, system controls and contracts/agreements are in place to protect this quality. The investigator should ensure the accuracy, completeness, legibility and timeliness of the data reported to the sponsor in the CRFs and in all required reports (ICH GCP 4.9.1). Part of the processes in place to achieve this could be the use of service providers that furnish the hardware and may manage the software and data capture receipt and storage. A service provider collecting or storing data should be a separate legal entity from the sponsor and from the investigator. A detailed contract should be in place defining the duties of the service provider, enabling the sponsor and/or investigator to transfer some of their tasks, but to retain control of their responsibilities.

The contracts/agreements with the sponsor and with the investigator will need to make clear the role of the service provider and to what extent this relates to the specific responsibilities of the investigator and those of the sponsor.

The method by which it is ensured that the investigator is informed about and/or approves of modifications to the data should be clearly established, and this control by the investigator should be demonstrable. Any changes to the data should be captured by the audit trail (see requirement 3). This includes any modifications arising from data query or clarification processes. The investigator should have access to review the data on an ongoing basis.

- ❑ Source documents should be protected against unauthorized access. (Requirement 9, ICH GCP 2.11, 5.15.1)

Source documents need to be protected in order to maintain subject confidentiality. Changes or deletion by unauthorised individuals, either accidental or deliberate, should be prevented. Authority checks should be used, as these could ensure that only authorised individuals have access to the system, or the ability to enter or make changes to data.

Records of authorisation of access to the systems, with the respective levels of access clearly documented (e.g. individual user accounts) should be maintained. Audit trails should record changes to user access rights. There should be documented training on the importance of security including the need to protect and not share passwords as well as enforcement of security systems and processes. The system users should confirm that he/she accepts responsibility for data entered using their password. Security systems should prevent unauthorised access to the computer system and to the data in the electronic record. Procedures should be in place to avoid/prevent unauthorised access when a workstation is vacated. There should be timely removal of access no longer required, or no longer permitted.

Topic 4: Copying

- ❑ The source document should allow for accurate copies to be made. (Requirement 8, ICH GCP 1.51)
- ❑ When source data are copied, the process used should ensure that the copy is an exact copy preserving all of the data and metadata of the original. (Requirement 12)

It is a fundamental requirement that a source document and data can be copied and that there is a practical method of copying that is complete and accurate, including relevant metadata. When required, it should be possible to print the source document/data for review, audit or inspection purposes.

Accurate and complete copies for certification should include the meaning of the data (e.g. date formats, context, layout, electronic signature and authorisations), as well as the full audit trail. The investigator site should have the ability of reviewing the data and generate copies. Where certified copies are made the process for certification should be described, including the process for ensuring that the copy is complete and accurate and for identifying the certifying party and their authority for making that copy. The process of making a "certified copy" needs to be validated.

Topic 5: Storage

- ❑ The storage of source documents should provide for their ready retrieval. (Requirement 4, ICH GCP 2.11, 5.15.1)

Source documents and data should always be available when needed to authorised individuals to meet their regulatory obligations. Whilst a trial is active and after its conclusion, existing source data should be readily available to the investigator and others such as monitors, auditors and inspectors. Direct access to the system should be provided by the sponsor and/or investigator to monitors, auditors and inspectors.

- ❑ Source documents and data should be protected from destruction. (Requirement 7, ICH GCP 4.9.3, 4.9.4 and chapter 8)

Source data should be protected from destruction, either accidental or deliberate. Regular backups should be made. Suitable archiving systems should be in place to safeguard the data integrity for the periods established by the regulatory requirements including those in any of the regions where the

data may be used for regulatory submissions, and not just those of the country where the data are generated. Checks of accessibility to archived data, irrespective of format, including relevant metadata, should be undertaken to confirm that the data are enduring, continue to be available, readable and understandable by a human being.

6.3. Electronic Health Records

Clinical trials can be conducted at institutions that use electronic health record systems. In that case the sponsor must assess the systems in use by investigators to determine how well they meet the requirements of GCP including those detailed above. The assessment should include consideration of the potential harm to trial subjects and patient rights and to the data integrity of the trial. If the systems do not meet the GCP requirements then mitigating actions should be taken as necessary prior to trial site initiation. Examples where the above requirements may not be met are discussed below:

- Investigator controls may be absent in systems where non-trial healthcare professionals at the investigator site or other location may alter the health records. In this instance the sponsor assessment on the impact to the trial should include whether there is an audit trail of changes made. If there is an audit trail, then a chronological assessment of what was known at the time of a trial decision is possible and therefore the absence of investigator control may have little impact. However, if an audit trail is not available, additional process controls, such as a signed and dated print outs, will have to be introduced to maintain the information. (Requirement 6).
- The monitor, auditor and inspector should have direct access to trial subjects' entire electronic health records whilst the trial site staff should ensure that the medical records of patients who are not trial subjects should not be accessible. (Requirement 4).
- Whenever copies of electronic health records are provided for the purpose of monitoring/auditing/inspecting the monitor/auditor/inspector should be able to verify that this copy is a complete and accurate copy of the electronic health record.

7. References (scientific and / or legal)

1. Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) Volume 3C Efficacy, Rules Governing Medicinal Products in the European Union.

2. CDISC (Clinical Data Interchange Standards Consortium) Clinical Research Glossary Version 8.0, DECEMBER 2009

http://www.cdisc.org/stuff/contentmgr/files/0/be650811feb46f381f0af41ca40ade2e/misc/cdisc_2009_glossary.pdf.

3. CDISC e-source standard requirements-CDISC (Clinical Data Interchange Standards Consortium) Version 1.0 20 November 2006.

4. Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data (*Official Journal L 281, 23.11.1995, p. 31–50*).

5. Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (*Official Journal L 121, 1/5/2001 p. 34 - 44*).

6. Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products (*Official Journal L 91, 9/4/2005 p. 13 - 19*).