

Retention of Clinical Trial Records, Medical Records and Essential Documents:

Will the Implementation of the GCP CT Directive Help to Harmonize This Process?

Good management and long-term control of clinical trial documents and medical records containing data relating to patients' participation in a clinical trial are fundamental to meeting statutory requirements for marketing authorizations. The main problem for records management groups in the pharmaceutical industry is that in the Good Clinical Practice (GCP) environment these records are scattered among several partners involved in the research, and each is subject to specific but different regulations and guidelines in respect of retention requirements.

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Maintaining records under such diverse conditions increases the complexity of two key issues:

- Protecting records, which may be stored in a diverse range of media, against accidental or intentional loss or premature destruction
- Ensuring that records are retained for long enough to guarantee their availability in the event of a subsequent regulatory inspection, or to help in the case of litigation

This article reviews some of the practical problems associated with maintaining clinical documents and medical records in this complex regulatory environment. It also addresses variations in these retention requirements and highlights areas where some harmonization in archiving practice may enhance the record-management process in clinical research.

European Union regulatory framework

Ever since a medicinal product was first defined in 1965 by European Union (EU) Directive 65/65/EEC [1], all subsequent related directives have added some element or condition to the necessity to produce and retain documentation to support the claims of an application for a marketing authorization.

More precise rules on records retention will be needed to meet the new regulatory framework, which also includes other recent directives with direct impact on the drug development process

One directive—91/507/EEC [2]—requires that all clinical trials undertaken in order to gather data for drug registration and marketing authority purposes within the EU must be conducted according to the principles of Good Clinical Practice (GCP) [3].

The International Conference on Harmonisation (ICH)–GCP principles agreed to by the EU, USA and Japan in 1997 have been integrated into the EU “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” [4]. As these principles become translated into national law in the EU member states over the next

2 years, further guidance from the commission on their interpretation by regulatory authorities is expected. More precise rules on records retention will be needed to meet the new regulatory framework, which also includes other recent directives with direct impact on the drug development process, such as data protection (95/46/EC [5]), electronic signatures (99/93/EC [6]) and the integration of Good Manufacturing Practice (GMP) for drug supplies in clinical trials [7].

Types of documentation

The documentation required to support the clinical aspects of an application for a marketing authorization is generally defined as either study documentation held by the sponsor in the trial master file, or source documentation (e.g. patient records) held by the investigator, hospital or clinical institution. The ICH guideline (1997) further refined this definition to include essential documentation for both sponsor and investigator, establishing a core element of clinical documents that must be available in the trial master file and the investigators' site files [8].

Study and essential documents

There are several disparate groups with responsibility for retaining all or part of the study documentation required to support a marketing authorization. The principal participants are the sponsor, the investigator and the hospital or clinical institution. If the sponsor is to be assured of the integrity of all the data required to support an application then control of documentation should be subject to formal cooperation between these groups. This is particularly important from the sponsor's viewpoint because it is the sponsor who has ultimate responsibility for the quality and integrity of the trial data, even where

sponsor obligations are transferred in writing to a third party such as a contract research organization or subcontractor. It is frequently the case that the sponsor's in-house study files are divided among several functions (e.g. data management, drug safety and clinical operations), are not always at the same site or even in the same country, and are managed according to local, autonomous practices and procedures, thus complicating the final assemblage of study documentation into a single integrated archivable file.

Retention of sponsor documents

One apparent anomaly in EU Directive 2001/20/EC [4] concerns the requirement to retain all production, control and

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distribution records for medicinal products for at least 1 year after the expiry date of the batch. Records of active pharmaceutical ingredients with retest dates are retained for at least 3 years after the batch is completely distributed [7]. This would

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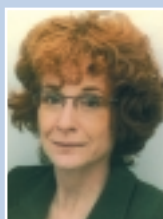
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appear to conflict with the ICH (1997) definition for record retention, which states that records should be kept until 2 years after the last approval in an ICH region or the formal discontinuation of the clinical development program [8].

Retention of investigator-site documents

Another anomaly arises with regard to investigator-site file retention. Is the investigator also required to retain the investigator-site file for “2 years after last approval in an ICH region?” This imposes an additional obligation on the sponsor to notify the investigator of when such documents may be destroyed. In practice, the decision concerning retention times is indeed transferred to the sponsor, a measure that could, in effect, lead to indefinite retention. On the other hand, in the USA investigators are permitted by law to destroy records 2 years after the date of an approved marketing application or, if no approval is obtained or sought, then 2 years after discontinuation of the investigation (21 CFR 312.62 [9]). Although source documents have clear retention periods defined by national laws, such clarity is lacking for investigator-site copies of case report forms, protocols and other trial master files documents.

Source documents

Source documents constitute the patient files, records, charts and laboratory reports that are kept by the hospital or clinical institution.

Retention of hospital/institution documents

Patient files and other source data must be kept for the maximum time permitted by the hospital, institution or private practice, but not for less than 15 years [3]. However, the subsequent ICH–GCP [8]

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Table 1. Document retention timelines specified by European Union (EU) directives and ICH Good Clinical Practice (GCP) guidelines.

Participant	Document retention timelines of the EU–GCP directives (1991) [3]	Document retention timelines of the ICH–GCP guidelines (1997) [8]
Sponsor	All documents must be retained for the lifetime of the product. The final report must be held for 5 years longer than that	All documents must be retained for 2 years after the last approval in an ICH region or the formal discontinuation of the clinical development program
Investigator	Patient identification codes must be retained for 15 years	Essential documents must be kept according to applicable regulatory requirements and protected against premature loss or destruction
Hospital/institution	Source data must be retained for the maximum time permitted, which should not be less than 15 years	Essential documents must be kept according to applicable regulatory requirements and protected against premature loss or destruction
Ethics committee	Not specified	All records (approvals, membership list and written working practices) must be retained for at least 3 years after the completion of the trial to which approval was given

guideline is more pragmatic as it recognizes that there will be variations in the practices of record keeping standards by European national health authorities. Retention times for health records are generally governed by legislative requirements, but limits can be anything from zero—that is, either the records are not retained or are destroyed immediately—to an unlimited amount of time, although the general consensus appears to be 15–20 years minimum. However, without adequate protection or control some records could potentially be lost to destruction almost immediately after they have been generated. The European Forum for Good Clinical Practice (EFGCP) Records Management and Archiving Working Party’s “Guidelines for Retention of Clinical Trial Records at Investigator Study Sites” [10] discusses these issues further.

Rules that govern retention and storage of these documents are determined by national legislation or regulation of each respective country and are administered

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by national health departments, which oversee the management of national health services. How long hospital medical records departments must keep records and under what conditions may also be specific to the nature of the illness or disease (e.g. records for cancer patients are often kept for 50 years).

The differences that exist between the European directives and the ICH–GCP guidelines with regards to document retention are summarized in Table 1.

Data storage

Archived data may be retained as paper or electronic records. If paper records are retained as scanned images then it must

be possible to produce a hard-copy backup if required. Despite the potential problems of legal admissibility, best practices may emerge where only the most important documents will be kept as paper originals (such as contracts with original signatures). While a court of law would demand the paper document if it existed, if it were an organization's declared policy to retain only the electronic version then this should be acceptable provided that there was a good audit trail leading to its production. Standards such as the British Standards Institute's "Code of Practice for Legal Admissibility and Evidential Weight of Information Stored Electronically" [11] provide guidance on the legal admissibility of electronic records.

Electronic data

Electronic records (including laser disk and computer files) may be either directly captured, where no prior paper version exists, or scanned from an original paper source. In the former case, where data are captured electronically at the source, it would be considered unacceptable to create (that is, to print) a paper document for the purpose of retention as an 'original' because it could not be considered a source document. Electronic storage can alleviate the problem of restricted storage space, permit rapid retrieval and reduce the potential for loss or deterioration of data, but can place an obligation on the data owner—for example an investigator—to ensure that the data and systems comply with any relevant regulations, such as 21 CFR Part 11 [12]. A further issue is that of ensuring that data can be retrieved from any electronic storage media, which entails maintaining systems in the long term or, where migration occurs, ensuring compatibility.

A document-management plan could provide a central point of control for the sponsor of an application for a marketing authorization, enabling them to be aware of the status of supporting documents

Data protection

Acceptable storage of records requires adequate archival space and qualified staff. All access to records needs to be carefully controlled to ensure protection of patient data and confidentiality. Accessibility is determined by control and ownership and will therefore be dependent on a formal agreement between all parties holding records for an understood purpose.

The archive plan

One solution for records managers and archivists might be to produce a document-management plan for each type of GCP document or source record, and adapt it to specific projects where necessary. This should identify the following information clearly:

- The nature of the document
- The person or body who retains the document during and after the trial, e.g. the sponsor, investigator, hospital or other body
- The medium, e.g. paper original, scanned electronic (plus audit trail) or electronic only (direct capture)
- The time when documents should be transferred to file or archive
- The method by which documents should be transferred to file/archive and under what circumstances
- Who may access, review and copy archived documents and for what purpose
- The time when documents may safely be destroyed

Implemented at trial startup, this could provide a central point of control for the sponsor of an application for a marketing authorization, enabling them to be aware of the status of supporting documents. It would facilitate agreement between the sponsor and other parties such as investigators, hospitals and health authorities, and would help ensure that records are available and reasonably readily retrievable in the event of a regulatory inspection. It would assist the sponsor in fulfilling obligations regarding maintaining the quality and integrity of the data, while all parties would be in a position—ideally contractually obliged—to keep each other informed of any change in the status of all required documentation. This would include

There needs to be a clear understanding between sponsor, investigator and hospital/institution (and health authority) as to which records need to be maintained and the purpose and duration of this retention

the physical movement to another storage area or migration to another medium.


Conclusion

For all archiving systems, compliance with such a diversity of retention times and conditions of storage, in terms of who may have access and when, how the access may be granted and for what purpose and reason, is an ongoing potential source of organizational, logistic and financial problems.

For retention and accessibility of medical records, there are particular issues, most of which center around protection of patient confidentiality in an international healthcare market.

There needs to be a clear understanding between sponsor, investigator and hospital/institution (and health authority) as to which records need to be maintained and the purpose and duration of this retention. An open dialogue between all parties to identify problems—whether real or perceived—is the only way to achieve this.

In conclusion, while it must be recognized that the EU Clinical Trial Directive provides a guiding framework for a legal minimum standard, its interpretation into national legislation will always be subject to local record retention needs and the requirements of the health authorities in evaluating local health issues. We can expect continued diversity in medical record retention requirements throughout the EU. In the wider global healthcare market, the potential for diversity in medical record retention is even greater. This was demonstrated by the recently introduced law in Canada requiring all medical records to be kept for 25 years. Reducing record retention times from 'the lifetime of the product' is undoubtedly a

step in the right direction, but there still needs to be vigilance and awareness on the part of the record manager who is charged with the responsibility of ensuring availability of documents to support and defend marketing authorizations around the world. 

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Further information

The Good Clinical Practice Records Managers Association (GCP-RMA) is an organization dedicated to the development of best practice for the management of Good Clinical Practice (GCP) records across all media. Originally a Working Party of the European Forum for Good Clinical Practice (EFGCP), it is now an independent group comprising records managers and associated professionals working in the area of GCP records management in Europe. It prides itself on the active participation of all members in meetings and discussions, based on trusted

and confidential sharing of practices, ideas and interpretations of guidelines and legislation. It has amongst its objectives the development of European industry standards for the management of GCP records.

The inaugural meeting of the GCP-RMA was held in Paris, France, on February 28–March 1, 2002 to discuss “Electronic Records: Current Practice and Future Trends”. Further details about GCP-RMA, its mission, aims and aspirations can be found by visiting the association’s web site: www.gcp-rma.org