**White Paper**

# An Assessment of the Impact of Regulation EU 536/2014 on GCP Records Management

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Scientific Archivists Group

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Promoting excellence in records management

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## 1. Introduction

The new EU clinical trial regulation (Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC) ("the Regulation") was published in the Official Journal of the European Community on the 27th May 2014. "The Regulation" replaces the European Clinical Trials Directive (2001/20/EC) and aims to harmonise requirements for the conduct of clinical trials of medicinal products in all member states.

The first notable change is the change in legislative status: being a regulation rather than a directive, the requirements of "the Regulation" will automatically be directly binding in all EU Member States once it comes into force without the need for any national legislation to be implemented. This will ensure that the underlying rules for conducting clinical trials are identical throughout the EU, so minimising differences in the application of clinical trial requirements across all Member States.

In this publication, the Scientific Archivists Group looks at the key changes and implications for GCP Records Managers and Archivists.

## 2. The EU Clinical Trial Portal and Database

Perhaps the most fundamental change in "the Regulation" is the introduction of a harmonised, simplified and more efficient clinical trials application process. "The Regulation" requires that sponsors will submit a single electronic application regardless of the number of participating Member States. This will also result in a single decision on a clinical trial, replacing the current separate approvals given by each Competent Authority in each Member State.

In order to achieve this, the European Medicines Agency (EMA) is responsible for the development of a new "EU Clinical Trial Portal and Database" ("the Database") to be used for the submission, authorisation and supervision of trials in the EU.

As well as streamlining the applications process, "the Regulation" also aims to improve the transparency of results reporting by making it a legal requirement for clinical trial results to be made publically available via "the Database", which will serve as the central source of information for the public on clinical trial applications and clinical trials being

conducted in the EU. This means that the public will now have access to regulatory approvals and the full results of a clinical trial.

The criticality of "the Database" means that "the Regulation" cannot come into effect until "the Database" is fully functional (estimated to take at least 2 years) and so the earliest date for implementation of "the Regulation" will be 28th May 2016. Implementation will be delayed, however, if "the Database" is not available by 28th May 2016.

## 2.1. Impact on Records Management

Harmonisation and simplification of the application process will impact on the filing of applications documentation in the following ways.

### 2.1.1. Country-level vs Study-level Filing

Most sponsors currently file clinical trial authorisations at country level. In future, this information will more likely be stored at study level, except where there are country-specific applications e.g. for non-EU countries.

### 2.1.2. Regulatory Applications (New Document)

With notifications of start, end, temporary halt and early termination of a clinical trial also being made via "the Database"[1], it is anticipated that sponsors will need to maintain their own record of these notifications. This is likely to result in the creation of a new document type, though equivalent to the correspondence that is currently sent to regulatory agencies.

### 2.1.3. Legal Representation (New Document)

The requirement for a non-EU sponsor to have a legal representative in the EU[2] implies that the trial master file should include an official document that identifies the legal representative.

### 2.1.4. Definition of Clinical Trial Start

"The Regulation" defines the start of a clinical trial as "the first act of recruitment of a potential subject for a specific clinical trial, unless defined differently in the protocol"[3]. The start of a clinical trial is often used to help define which documents need to be retained if the trial ends prematurely. Currently, if a trial is deemed "not to have started" but aspects of subject recruitment have begun, for example, it is often the case that no documentation is retained. This practice may need to be reconsidered if the clinical trial start is now defined with reference to subject recruitment.

### 2.1.5. Notification of Start of a Clinical Trial and of End of Recruitment (Time Limits)

The requirement for sponsors to notify each Member State of the start of a clinical trial and of the end of recruitment in each Member State within 15 days[4] has an impact on data/document collection. Evidence of compliance with this time schedule needs to be maintained in the TMF and study tracking tools need to be sufficiently sophisticated and up-to-date to comply with this reporting requirement. Tracking systems need to provide assurance of compliance with these deadlines.

### 2.1.6. Clinical Trial Application Withdrawal (New Document)

"The Regulation" allows a sponsor to "withdraw the application for authorisation of a clinical trial …and submit a new application for authorisation of a clinical trial following a withdrawal"[5]. The TMF index or metadata associated with a TMF needs to accommodate a "clinical trial application withdrawal" document, although the nature of this document is not specified in "the Regulation".

### 2.1.7. Regulatory Notifications (New Document)

The requirement that each Member State "shall notify the sponsor through the EU portal as to whether the clinical trial is authorised, whether it is authorised subject to conditions, or whether authorisation is refused"[6] suggests that there will be a need for a record of the decision to be included in the TMF, possibly via "print decision" option in the portal, although the nature of this new document is not clear.

### 2.1.8. Clinical Study Report Table of Contents

It is not clear whether a PDF file with a simple table of contents will meet the requirement for a Clinical Study Report (CSR) that is "easily searchable"[7] or whether the CSR content will need to be text searchable. It should also be noted that the content of a CSR may appear differently when viewed using different software tools. CSRs often contain hyperlinks to assist navigation but it is recommended that hyperlinks should only link to locations within the open CSR and not link to other documents or locations within other documents.

### 2.1.9. Clinical Trial Summary Report (New Document)

"The Regulation" requires the creation of a clinical trial summary report, which must be submitted within one year from the end of the clinical trial in all Member States concerned irrespective of the outcome of a clinical trial[8]. It is expected that this report will be held in the TMF, and so the indexing system needs to accommodate this.

### 2.1.10. Clinical Trial Summary Report for Laypersons (New Document)

"The Regulation" requires that sponsors must produce a version of the clinical trial summary report that is in plain language and understandable to "laypersons"[8]; this must be submitted within one year of the end of the trial (irrespective of the outcome of the trial). It is expected that this report will also be held in the TMF.

### 2.1.11. Management of the EU Clinical Trial Portal and Database

After a period of public consultation the EMA Management Board has endorsed the functional specification of the EU portal and EU database. However, uncertainties remain regarding the potential risks posed by "the Database" It is unclear, for example,

- whether uploaded records will fall outside of the control of the sponsor;
- who will be responsible for records retention, archiving, and preservation;
- which mechanisms will be in place to control access and management rights;
- whether "the Database" will be compatible with Member States' own IT systems; and

- whether "the Database" will be sufficiently robust in terms of security, usage, data volumes, and back up/recovery.

# 3. Clinical Trial Master File (TMF)

"The Regulation" includes the requirement to comply with the principles of Good Clinical Practice referred to in ICH E6 Guideline[9]. This includes GCP requirements regarding the TMF so long as they are compatible with "the Regulation" and no other specific guidance applies.

## 3.1. Impact on Records Management

### 3.1.1. Single TMF

"The Regulation" refers throughout to "the clinical trial master file", whereas previous directives, guidelines and regulations have made reference to "clinical trial master files" (in the plural). There is, however, reference to the "clinical trials master file kept by the investigator and that kept by the sponsor [which] may have a different content if this is justified by the different nature of the responsibilities of the investigator and the sponsor"[10]. It is uncertain as to whether or not "the Regulation" requires there to be a single "trial master file" (paper or electronic) containing all required content. SAG recommends that the sponsor trial master file and investigator master file continue to be treated and managed as distinctly separate records due to their differing content, purpose, and nature of the responsibilities of sponsors and investigators.

### 3.1.2. TMF Availability

"The Regulation" requires that the TMF "shall at all times contain the essential documents relating to that clinical trial" and "shall be readily available and directly accessible upon request to the Members States"[10]. This reinforces the expectation made in the 2013 "EMA Reflection Paper on GCP Compliance in relation to Trial Master Files" that the TMF is maintained contemporaneously. This may require a change of practice in some organisations where construction of the TMF occurs only periodically during the course of the trial or at predetermined event(s).

### 3.1.3. Traceability of TMF Alterations

The requirement to ensure traceability of alterations to TMF content is included only in the article on long-term archiving[11]. By inference (and implicitly), there is not a requirement for the same level of traceability for systems holding "live" TMF content. However, SAG recommends that it is good practice also to ensure the traceability of alterations to "live" TMF content.

### 3.1.4. Batch Certification

The requirement to ensure that batch certification by the Qualified Person "shall be made available by the sponsor at the request of the Member States concerned"[12] implies that this documentation is expected by default to be stored in the TMF.

### 3.1.5. Use of Summary of Product Characteristics as Investigator Brochure (New Document)

"The Regulation" states that "If the investigational medicinal product is authorised, and is used in accordance with the terms of the marketing authorisation, the approved summary of product characteristics (SmPC) shall be the [Investigator Brochure] IB"[14]. Where an SmPC is deemed to be equivalent to an IB, it will be necessary to document that decision as well as the mechanism(s) employed to track the use of SmPCs. This is especially relevant when electronic content management systems are used. Whilst this is not a new requirement within the Regulation, the wording helps to clarify some of the current ambiguities with regards to what documentation is expected to be held in the TMF.

### 3.1.6. Investigational Medicinal Product Dossier

The "Regulation states that "the [Investigational Medicinal Product Dossier] IMPD may be replaced by other documentation which may be submitted alone or with a simplified IMPD"[15]. If a simplified IMPD is used, version control and tracking of its use is important and there will need to be documented mechanisms in place to track its use. Again, whilst this is not a new requirement within the Regulation, the wording helps to clarify some of the current ambiguities with regards to what documentation is expected to be held in the TMF.

## 4. Clinical Trials and Low-interventional Studies

"The Regulation" differentiates between a "clinical trial" and "non-interventional study", both being categories of "clinical studies"[16]. "The Regulation", including records management and archiving requirements, applies only to "clinical trials".

Furthermore, "the Regulation" introduces the concept of low-interventional studies (i.e. studies involving the use of an Investigational Medicinal Product (IMP) that is covered by a marketing authorisation or "where the intervention poses only a very limited additional risk to the subject compared to normal practice"[17]) which are "subject to less stringent rules as regards … requirements for the contents of the trial master file…"[17].

### 4.1. Impact on Records Management

These relaxed rules suggest that a risk-based approach[17] should be adopted, although it should also be noted that there is frequent emphasis throughout "the Regulation" on the importance of "data reliability and robustness". The relaxed rules imply that some documents that might otherwise be expected in a TMF for a clinical trial might not be expected in a "low intervention clinical trial" and there is likely to be an impact the "master TMF index" that many sponsors maintain.

## 5. Co-Sponsorship

Current regulations require a single sponsor to be identified as having responsibility for a clinical trial. "The Regulation", though, introduces the concept of co-sponsorship permitting a clinical trial to have one or several sponsors[18]. All co-sponsors will in principle assume full regulatory responsibility for the entire clinical trial unless the co-

sponsors agree otherwise through a written contract detailing their respective responsibilities[18].

### 5.1. Impact on Records Management

#### 5.1.1. New Agreements

The option to have co-sponsors[18] may require additional contracts, agreements, task ownership documents and other related documents to be created. Whilst these are likely to be filed and managed as "agreements", there is potential to impact on metadata/indexing requirements for TMF systems.

#### 5.1.2. Wording of Agreements

Moreover, if agreement(s) between co-sponsors[18] are not sufficiently well-worded, there is a risk that records management and archiving responsibilities are not adequately defined; this could result in ambiguity and the adoption of poor practice, leading to an inability to (readily, if at all) produce the documentation required for a regulatory inspection.

#### 5.1.3. Establishment of Responsibilities for TMF

It is not clear from "the Regulation" which parts of the TMF should be held by which co-sponsors and this may have implications for managing and archiving records.

## 6. Subject / Data Protection

"The Regulation" requires sponsors to "apply appropriate technical and organisational measures to protect information and personal data against unauthorised or unlawful access, disclosure, dissemination, alteration, or destruction or accidental loss"[19] but does not specify the technical or organisational methods to be employed.

### 6.1. Impact on Records Management

There may be some expectation that electronic TMF (eTMF) functionality is able to provide this protection. It is unclear what is meant by "system access" or how this might be defined and controlled. In any event, it is difficult to protect against the unauthorised disclosure or dissemination of data solely through the use of technology and so there will be significant reliance on the use of policies and procedures to ensure compliance. This report recommends the adoption of a practical and pragmatic approach to complying with these requirements rather than trying to implement "heroic measures".

## 7. Safety Reporting

Until recently sponsors were required to report all pharmacovigilance information to the Competent Authorities of each Member State. However, "the Regulation" affirms sponsors' obligations to report adverse reactions and other events so that rather than submit individually to each Member State:

- there is the possibility to submit to Eudravigilance Clinical Trial Module a single safety report on all IMPs used in a clinical trial for a clinical trial involving more than one IMP; and

- "unexpected events which affect the benefit-risk balance of the clinical trial"20 will be reported via the Eudravigilance Clinical Trial Module

### 7.1. Impact on Records Management

#### 7.1.1. Pharmacovigilance Reporting (New Document)

While "the Regulation" streamlines the previous system by sparing sponsors the burden of submitting largely identical information separately to authorities within each Member State, overall it appears to increase reporting obligations by extending the scope to cover "unexpected events which affect the benefit-risk balance of the clinical trial"[20]. This is likely to constitute an additional "artefact" type to be added to the TMF inventory.

#### 7.1.2. Pharmacovigilance Reporting Timeframes

The requirement for sponsors and investigators to report on safety matters within agreed reporting timeframes has an impact on data/document collection.

## 8. Recruitment and Informed Consent

"The Regulation" states that in the event that clinical trial subjects are unable to read or write that the informed consent "may be recorded through appropriate alternative means, for instance through audio or video recorders."[21]

### 8.1. Impact on Records Management

It is unclear what file format requirements there are for these records, if any. It is noted that these files (particularly video files) can be extremely large and can prove onerous to preserve. Advertising is also often effected via social media channels (e.g. Facebook, Twitter), yet it is unclear what needs to be retained for these advertising forms and how such records would be extracted and filed in the TMF.

## 9. Records Retention

"The Regulation" mandates a new minimum retention period for the trial master file of 25 years after the end of the clinical trial"[11] which establishes a more specific time period than with internationally accepted practice of ICH GCP.

### 9.1. Impact on Records Management

#### 9.1.1. Retention of Electronic, Audio and Audio-visual Records

This extended retention requirement will have a significant impact on storage requirements, particularly for electronic records and data; this must be taken into consideration when designing / acquiring eTMF systems and archive solutions for use by both sponsor and investigator.

"The Regulation" also establishes that subject informed consent may be obtained by using audio or video recorders[21]. If media is checked for degradation or obsolescence, there will be a need to maintain a record of these checks.

The requirement to ensure traceability of alterations to TMF content is included in the article on archiving[11]. This requirement has a significant impact on the Records Manager/Archivist who must ensure this is achievable throughout the duration of the retention period.

## 10. Archiving

The term "Archivist" does not appear in "the Regulation". Rather it states that the "sponsor shall appoint individuals within its organisation to be responsible for archives"[10] yet no mention is made of the responsibility of the investigator or any other party to appoint the same.

### 10.1. Impact on Records Management

This requirement implies that it is the sponsor that must have an Archivist within its organisation with accountability for the archives, wherever those archives are located and even if the physical storage of records (in hard-copy or electronic) is delegated to a third party.

## 11. Conclusion

The European Federation of Pharmaceutical Industries and Associations (EFPIA) has called "the Regulation" "an important step towards a much needed simplification and standardisation of clinical trials administration". However, it is noted that "the Regulation" does not set specific rules for medical device trials. It is therefore assumed that national laws will continue to apply for these trials.

"The Regulation" sometimes resorts to some vague concepts such as "normal clinical practice", which leaves room for interpretation and therefore inconsistency in application by Member States. There are questions raised in this assessment that need to be carefully considered. On the whole, however, "the Regulation" seeks to introduce clarity and improve upon existing practices in some elements of the clinical trials arena (such as records retention).

If "the Regulation" is to succeed in delivering its intended aims, Records Managers and Archivists will need to continue to engage with all parties involved in clinical trials to ensure that there is continued effective learning and so ensure that the overarching ambitions of "the Regulation" can be mutually understood, appropriately applied and achieved.

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http://sagroup.org.uk

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## References to EU Regulation 536/2014

[1] Art 36; [2] Art 74; [3] Art 2 (25); [4] Art 36 (1); [5] Preamble (21); [6] Art 8 (1); [7] Art 2 (35); [8] Art 37 (4); [9] Preamble (43); [10] Art 57; [11] Art 58; [12] Art 62; [13] Annex 1 D17w; [14] Annex 1 E28; [15] Annex 1 G37; [16] Preamble 3; [17] Preamble 11; [18] Preamble 59; [19] Art 56; [20] Art 53; [21] Preamble 30


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**Scientific Archivists Group Ltd**
Registered Office Berkeley Townsend,
Hunter House, 150 Hutton Road,
Shenfield, Essex, CM15 8NL.
Registered in England & Wales,
Company Number: 07614340