Introduction

The new EU Clinical Trial Regulation (Regulation (EU) No 536/2014) (EU CTR) became effective on 31st January 2022, repealing Clinical Trials Directive 2001/20/EC. The Clinical Trials Regulation harmonizes the processes for assessment and supervision of clinical trials throughout the EU. It does not apply to non-interventional studies.

One 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 without the need for any national legislation to be implemented. This ensures that the underlying rules for conducting clinical trials are identical throughout the EU, so minimizing differences in the application of clinical trial requirements across all Member States.

Another notable change is the introduction of the Clinical Trials Information System (CTIS). This enables sponsors to submit one online application via a single online platform for approval to run a clinical trial in several European countries, making it more efficient to carry out such multinational trials. CTIS also aims to improve the transparency of results reporting by making it a legal requirement for clinical trial results to be made publicly available via CTIS which will serve as the central source of information for the public on clinical trial applications and clinical trials being conducted in the EU.

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.

EU CTR Workshop

The Trial Master File Reference Model (TMF RM) group held a workshop in April 2022, bringing together around 70 people across multiple companies to discuss the impact of the EU CTR on the content of the TMF. This workshop was run by Karen Roy (Phlexglobal), Martina Duevel (Bayer) and Russell Joyce (Heath Barrowcliff Consulting). A recording of the workshop can be found here: https://youtu.be/ZhAAgc-HNWc.

During the workshop, we ran a poll, the responses to which were:

1. 73% of attendees had assessed or were in progress of assessing the impact of the EU CTR on TMF management
2. 27% had in depth awareness; 65% had basic awareness
3. 20% had used CTIS, 32% had resource dedicated to CTIS management and 26% had a process in place

EU CTR Comments on TMF

- *Article 57*
- **Clinical trial master file**
- The sponsor and the investigator shall keep a clinical trial master file. The clinical trial master file *shall at all times contain the essential documents* relating to that clinical trial which allow verification of the conduct of a clinical trial and the quality of the data generated, taking into account all characteristics of the clinical trial, including in particular whether the clinical trial is a

low-intervention clinical trial. It shall be readily available, and *directly accessible upon request*, to the Member States.
- The clinical trial master file kept by the investigator and that kept by the sponsor may have a different content if this is justified by the different nature of the responsibilities of the investigator and the sponsor.

- **Archiving of the clinical trial master file**
- *Unless other Union law requires archiving for a longer period, the sponsor and the investigator shall archive the content of the clinical trial master file for at least 25 years after the end of the clinical trial.* However, the medical files of subjects shall be archived in accordance with national law.
- The content of the clinical trial master file shall be archived in a way that ensures that it is readily available and accessible, upon request, to the competent authorities.
- Any transfer of ownership of the content of the clinical trial master file shall be documented. The new owner shall assume the responsibilities set out in this Article.
- The sponsor shall appoint individuals within its organisation to be responsible for archives. Access to archives shall be restricted to those individuals.
- The media used to archive the content of the clinical trial master file shall be such that the content remains complete and legible throughout the period referred to in the first paragraph.
- Any alteration to the content of the clinical trial master file shall be traceable.

Overall Opinion

The overall view from the group was that, whilst the EU CTR is the greatest change in the management of clinical trials in EU for a long time, and that there were significant process changes, the outcome is similar and therefore the document types are similar. It was felt that the 'new' document types could mostly be mapped to the TMF Reference Artifacts, with possibly new sub-artifacts being required.

A key factor on TMF content was the company process for the storage and tracking of CTIS documents. A survey showed a wide range of places being used to store the documents:

- Trial Master File (TMF) 16%
- Regulatory Information (RIM) system 6%
- TMF & Document Management System (DMS) 6%
- TMF & RIM 18%
- TMF, DMS & RIM 8%
- Other 12%

If the CTIS documents are stored and tracked in the TMF, this would naturally increase the volume of documents in the TMF. If the entire CTA is filed in the TMF, this would have a significant impact as well.

The Regulation reiterates that a TMF must be readily available and directly accessible upon request as per previous guidance documents. Note that these requirements apply irrespective of the status of the TMF meaning that an archived TMF must also be readily available and directly accessible.

The transparency rules of the Regulation require that information submitted to CTIS (with some justified exceptions) is published. Protected personal data needs to redacted to ensure that there is no leakage of confidential information. This can result in the creation of a "for publication" version of a document which will be uploaded along with the full version. Company confidential information can also be protected by redaction in the "for publication" version and or request of deferral of publication.

Due to the requirement to potentially have redacted and non-redacted versions of documents available, it was felt this could drive duplication in the TMF, if both versions were stored in the TMF. Nothing in the Regulation states that the redacted versions need to be stored in the TMF.

Source documents to support the CTIS application (e.g., data field information collation sheet) could also produce extra documents that could be filed in the TMF, depending on Company processes.

Some of the documentation will apply at a regional (EMA) level, rather than study or country level. Whilst the TMF Reference Model supports regional filing, this may need to be incorporated into eTMF systems.

The retention period for CTIS is unknown so Sponsors should not rely on CTIS for archiving purposes.

Specific Document Types:

1. **Regulatory Submissions, Approvals and Notifications**

There is a significant change in regulatory submissions – no longer one per EU country, but one overall. This would mean that the regulatory submission and approval documents may be filed at a regional or even study level, rather than at a country level.

There will be significantly more submission evidence and so it is proposed to have a new sub-artifact in 3.1.1 Regulatory Submission.

Each Member State is required to notify the sponsor through the EU portal as to whether the clinical trial is authorized, whether it is authorized subject to conditions, or whether authorization is refused.

With all notifications of start, end, temporary halt, and early termination of a clinical trial also being made via CTIS within 15 days, it is anticipated that sponsors will need to maintain their own record of these notifications. There will be notifications both to and from CTIS and so it is proposed to add new sub-artifacts in 3.1.1 Regulatory Submission and 3.1.2 Regulatory Authority Decision. Sub-artifacts should be generic and not system specific.

Note that CTIS does not provide email notifications; instead, notifications will need to be extracted from the system.

There is also the concept of Request for Information and response to RFI. It is assumed that these are treated as correspondence if they are stored in the TMF.

The Regulation allows a sponsor to withdraw the application for authorization of a clinical trial and to submit a new application for authorization of a clinical trial following a withdrawal. This could be a new sub-artifact in 3.1.1 Regulatory Submission as well.

2. Lay-person Documents

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. This can be filed in the sub artifact Clinical Study Report Synopsis in 2.3.1 Clinical Study Report.

The Regulation specifically calls for a Protocol Synopsis and Clinical Trial Summary Report for Laypersons to be produced. These versions must be in plain language and understandable to laypersons. Following discussion about adding these to information given to subjects, it was agreed that they should be filed as follows, with definitions being expanded:

- Protocol Synopsis for Laypersons – new sub artifact in 2.1.3 Protocol Synopsis
- Clinical Trial Summary Report for Laypersons – new sub artifact in 2.3.1 Clinical Study Report

3. Batch Certificates

Batch certificates are called out to be stored in the TMF. The discussion concluded with the documents being stored with 06.02.04 Batch Records.

4. Investigator Brochure and IMPD

Although this is not new, it has been clarified that a summary of product characteristics (SmPC) can be used instead of an Investigator brochure for trials where the investigational medicinal product is authorized and is used in line with the terms of the marketing authorization. A sub-artifact for SmPC could be added to 02.01.01 Investigator's Brochure.

The Regulation specifically states that there could be two versions of the IMPD – one for quality and one for safety and efficacy. There was discussion to add two specific sub-artifacts. The Regulation does make it clear that the IMPD should be stored in the TMF.

5. Safety Documents

There is a new requirement to report on unexpected events which affect the benefit-risk balance of the clinical trial. This could potentially be added as a new sub-artifact to 07.02.02 SAE Report or 07.02.04 Special Events of Interest.

6. **Compliance with Biological Samples**

There is a new document requirement for Compliance with use of biological samples. It was agreed this should go in Zone 8, possibly as a new artifact or a sub-artifact in 08.02.03 Sample Storage Condition Log.

7. **Auxiliary Medicinal Products**

Zone 6 is for IP and Trial Supplies, this includes Non-IP documentation. Auxiliary medicinal products are not IP, but documentation around them should be able to be filed in Zone 6.

8. **Compliance for Data Protection**

To prevent publication of confidential information personal protected data (PPD) or company confidential information (CCI) in the public space of CTIS versions of documents need to be created in which these data are redacted. The "for publication" versions are uploaded to CTIS along with the full versions. The suggestion of the participants is to file them together with the full version if they are to be stored in the TMF.

9. **Non substantial Modifications**

Non substantial modifications (NSMs) will have to be recorded in the Trial Master File and made available on request for inspection purposes as appropriate. There is a sub-artifact for the justification in 2.1.4 Protocol Amendment, this may need to be extended to include the NSM itself.

10. **Site Suitability**

Site Suitability is called out in the Regulation. Post the workshop, there has been discussion on the filing of these documents. It as suggested that they be filed in 05.01.03 Feasibility Documentation, possibly as a new sub-artifact.

Other TMF Impacts

1. **Archiving**

Long term storage of the TMF is significantly affected by the Regulation. The greatest impact is the change to archiving requirements, retention now mandated to be 25 years from the end of the Clinical Trial, although the end date is for each organization to define. It should be noted that

- for low-interventional studies (see 4 below), records should continue to be retained in accordance with existing guidance i.e. for "at least five years after final report or first publication of study results, whichever comes later." [ISPE Guidelines for Good Pharmacoepidemiology Practices VII]).
- for advanced therapy IMP clinical trials some records should continue to be retained in accordance with existing guidance i.e., for a minimum of 30 years after the expiry date of the product, or

longer if required by the Commission as a term of the marketing authorization [Regulation (EC) No 1394/2007 & EMA Guideline on GMP for ATMPs, Nov 2017].

The extended 25-year retention period under Reg EU536/2014 has a particularly significant impact 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 highlights that differing formats will need to be archived and may require additional considerations e.g., it is acknowledged in the Regulation that subject informed consent may be obtained using audio or video recorders, a media that must be periodically checked for degradation or obsolescence throughout the retention period in order to remain accessible, viewable and usable.

The Regulation reinforces the requirement to ensure traceability of changes to archived documents throughout the retention period.

The start of a clinical trial is often used to help define which documents need to be retained if the trial ends prematurely. The Regulation now 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". If a trial is deemed "not to have started" but aspects of subject recruitment have begun, documentation will now need to be archived.

2. 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".

It is clear from this that there needs to be one overall TMF plan, even if the documents are stored in separate locations.

3. 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. 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. Whilst this will not create new document types, there will need to be segregated identification of the different sponsors for their specific documents such as additional contracts, agreements, task ownership documents etc. In addition, it will need to be defined which of the co-sponsors hold the TMF or if it is split.

4. Low Interventional Studies

The Regulation introduces the concept of low-interventional studies (i.e., studies involving the use of an Investigational Medicinal Product that is covered by a marketing authorization or "where the intervention poses only a very limited additional risk to the subject compared to normal practice".

Low interventional studies are "subject to less stringent rules as regards … requirements for the contents of the trial master file". Consequently, it may be that the Real World Study Master File Index could be used.

A specific document referred to as the justification of low interventional clinical trial is required for CTIS submission

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Acknowledgements

An Assessment of the Impact of Regulation EU 536/2014 on GCP Records Management - The Scientific Archivists Group (Now The Health Sciences Records and Archives Association) GCP Records Special Interest Group (May 2015).