

Preparing for data transparency requirements of the new EU CTR

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ABSTRACT

The EU Clinical Trial Regulation (Regulation (EU) No 536/2014) (“EU CTR”) is set to become applicable in January 2022. A key objective of the EU CTR is to strengthen transparency of clinical trial data. Organisations must take steps now to ensure readiness for the application of the EU CTR. In this article, we review transparency requirements and provide perspectives from a contract research organisation (CRO) in preparing for the enhanced clinical trial data transparency requirements arising from its implementation.

Introduction

Publicly disclosing information about clinical trial data and results, regardless of outcome, can benefit patients, healthcare professionals, researchers and the public. Such information can improve decision-making related to potential recruitment for a trial, improve collaboration across the research community to better align research and medical goals, avoid duplication of unsafe or unsuccessful trials, drive efficiencies in trial design and conduct to save time and money, and provide greater insight for trial participants and the public to support better informed personal healthcare decisions while enhancing trust between patients, regulators and sponsors.

Ethical principles for transparency of clinical trial data are outlined in the Declaration of Helsinki.¹ National requirements for clinical study registration, reporting results and data sharing, currently vary between regions/countries and are constantly evolving. In recent years there has been a drive to improve clinical data transparency by both industry and regulatory authorities (RAs). For example, since 2014 the European Federation of Pharmaceutical Industries and Associations (EFPIA) and its member companies have taken measures beyond legislative requirements to share clinical trial data on request via individual member portals.²

In 2018, the US FDA enacted the ‘Final Rule’,³ clarifying legal requirements and penalties for failing to disclose trial results, following the 2007 FDA Amendments Act (FDAAA), which required result disclosure within 12 months of study conclusion, with certain exceptions.⁴ In March 2019, Health Canada released new guidance aimed at making clinical information in drug submissions and medical device applications publicly available for non-commercial purposes.⁵ In the EU, clinical data transparency requirements are currently established across multiple governing documents. In 2014 the EU Clinical Trial Regulation (536/2014) (“EU CTR”) was adopted and entered into force. A key objective of the EU CTR is to improve transparency of clinical trial data. Broadly speaking, all trial information entered into the Clinical Trial Information System (CTIS) will be publicly accessible unless its confidentiality can be justified. Prior to Brexit, the UK was heavily involved in the preparations for the EU CTR. Currently in the UK, information regarding clinical trials of medicines are automatically registered into a public registry. A public registry is defined as any register on the World Health Organization (WHO) list of primary registries or the International Committee of Medical Journal Editors (ICMJE) list of registries, such as the International Standard Randomised Controlled Trial Number (ISRCTN), ClinicalTrials.gov or the EU

Clinical Trials Register. However, certain clinical studies, such as those for medical devices, surgery, public health and behavioural interventions, are expected to be registered by sponsors. In reality, this is not always occurring. Due to the UK’s departure from the EU, an updated Integrated Research Application System (IRAS) is being developed to mimic the EU CTIS through which submissions will occur via the ‘Combined Ways of Working’ pilot programme. A transparency functionality of the IRAS has been released as part of the UK’s Health Research Authority’s (HRA) transparency strategy to ensure information, such as the registration of a study and results, is shared and trial participants are informed.⁶ In future, the HRA will register clinical trials on behalf of sponsors, using data that sponsors submit for their clinical trial to be authorised, unless a sponsor has been granted permission to defer registration. Future transparency goals are also expected to involve the appropriate sharing of data for observational studies, studies involving questionnaires and studies using patient data or human tissue data.⁶

In this article we focus on the clinical trial data transparency requirements arising due to the EU CTR and steps to be taken now to ensure readiness for its application.

The EU Clinical Trial Regulation

The EU CTR was adopted and entered into force in 2014 with the proviso that the timing of its application would occur six months after the European Commission (EC) published notice in the *Official Journal of the European Union* confirming full functionality of the CTIS as verified by independent audit. In December 2015 the European Medicines Agency (EMA) management board endorsed a delivery timeframe anticipating that application of the EU CTR would occur in October 2018.⁷ The CTIS go-live date has repeatedly been delayed due to technical difficulties during development, but the EMA has indicated the delivery model has improved since June 2019.⁸ At its March 2021 management board meeting the EMA’s board agreed to a revised CTIS go-live date of 31 January 2022, and on 21 April 2021 the EMA confirmed that the CTIS is fully functional and meets the functional specifications, following an independent, successful audit.⁹ Once applicable, the EU CTR will repeal the existing EU Clinical Trial Directive (2001/20/EC) (“the Directive”) and national legislation implementing the same.¹⁰ However, a three-year transition period will commence on application: during the first year sponsors can choose to submit trial applications under the EU CTR or the Directive but, at the end

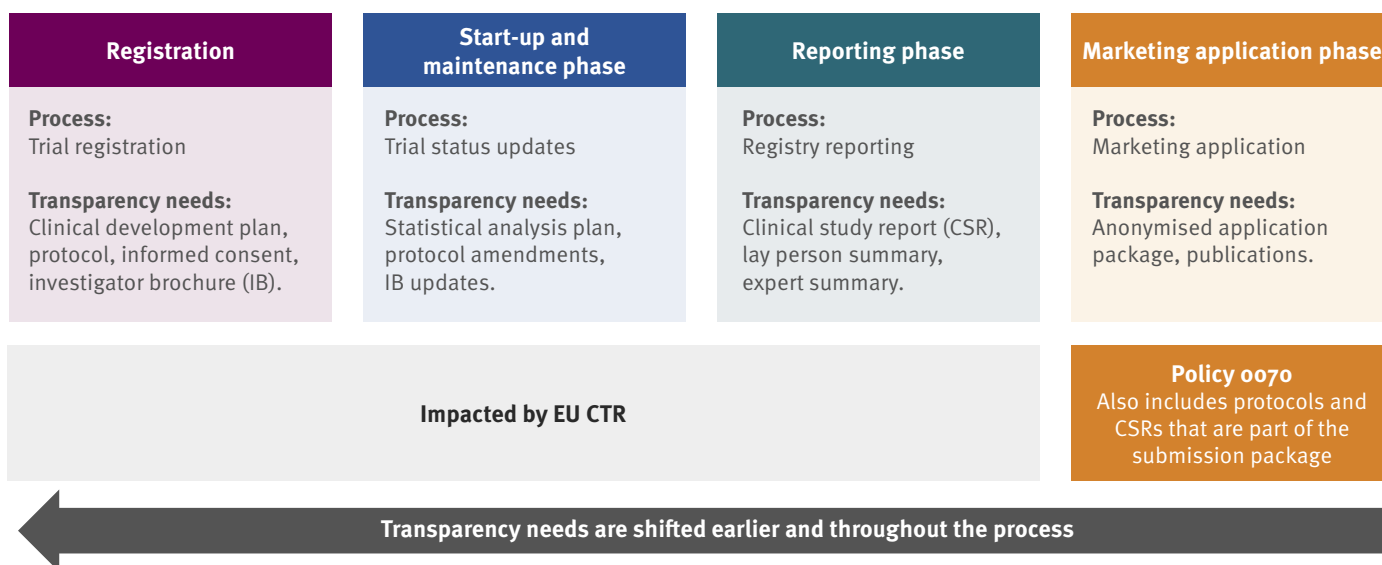
FIGURE 1

Current landscape for data transparency in the EU

Legislation/Policy	Details
EU Clinical Trial Directive (2001/20/EC)	Article 11 establishes EudraCT database where authorities (not sponsors) must share information on most CTs conducted wholly, or partially, in the EU.
Paediatric Regulation (1901/2006)	Articles 31 & 41 establish that the EudraCT database should be utilised to make publicly available all ongoing, prematurely terminated, and completed paediatric studies conducted within the EU and third countries.
Regulation 726/2004 (Centrally authorised products)	Article 57(1)(L) establishes publicly accessible database (EudraPharm) for approved medicinal products, including those authorised for children.
Policy 0043 (EMA/729522/2016)	Establishes framework for request of documents from the EMA, defining documents as “any content whatever its medium (written on paper or stored in electronic form or as a sound, visual or audio-visual recording) concerning a matter relating to the policies, activities and decisions falling within the EMA sphere of responsibility”.
Policy 0070 (EMA/144064/2019)	Applies to all clinical data included in a centralised marketing authorisation application (MAA), eg, clinical overviews, clinical summaries, clinical study reports, appendices to the CSRs. Applies to all products approved by the European Commission since 2015.

FIGURE 2

Overview of disclosure during clinical development



of the three-year period, the EU CTR will apply to all trials regardless of whether they were authorised under the EU CTR or the Directive.

Impact of the EU CTR on data transparency requirements

In the EU, data transparency requirements are currently established across multiple governing documents including Directive 2001/20/EC, the Paediatric Regulation (Regulation (EC) No 1901/2006) and Regulation (EC) No 726/2004, in addition to EMA Policy 0043, and EMA Policy 0070. Summary details for the EU data transparency landscape are set out in Figure 1.

The regulatory landscape for clinical trial data transparency in the EU is complex and unharmonised, which results in only limited information being made publicly available. For example, Regulation (EC) No 726/2004 and Policy 0070 only apply to products assessed via the centrally authorised procedure coordinated by the EMA, regardless of approval outcome. Both Policy 0043 and Policy 0070 do not apply to documents held by national RAs, many of which hold differing positions on disclosure requirements.

Among its goals, the EU CTR aims to harmonise and strengthen clinical trial data transparency requirements. These requirements will apply to all EU members states, for all clinical trials conducted in the EU and registered in the CTIS, in addition to paediatric trials conducted outside the EU that are part of paediatric investigation plans. Thus, the EU CTR will mandate transparency throughout the clinical trial lifecycle, as depicted in Figure 2.

Essentially, the CTIS should be viewed by clinical trial sponsors as a source of public information, from the assessment of the initial clinical trial application (CTA) through to trial decision, as well as end-of-trial activities and inclusion of trial results in the CTIS. However, certain data may be exempt from disclosure if their confidentiality can be justified on the basis of the following criteria set out by the European Commission:¹¹

- Protection of commercially confidential information (CCI)
- Protection of personal data
- Protection of confidential communication between EU countries
- Ensuring effective supervision of clinical trials by EU countries.

FIGURE 3

Navigating the disclosure requirements of EU CTR

Note: The following will generally not be made public:

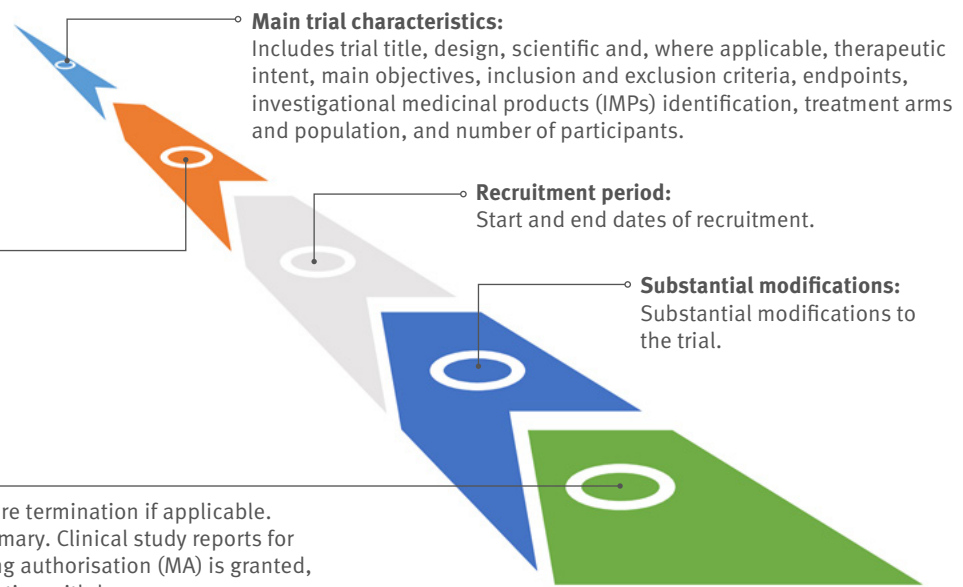
- Information on applications for assessment of Part I only (Article 11)
- Information on applications which are not validated or are withdrawn before a decision is made.

Trial decision:

Conclusion of the assessment and decision on the trial.

End-of-trial notifications:

Date of end of trial, reasons for premature termination if applicable. Summary of results and lay person summary. Clinical study reports for trials on medicines for which a marketing authorisation (MA) is granted, the procedure completed, or MA application withdrawn.



Furthermore, information on applications that are only submitted to enable assessment of part I of the dossier (EU CTR Article 11 applications), and those applications that are not validated or are withdrawn before a decision is issued will not be made public. In exceptional circumstances, such as overriding public interest in disclosure, these items may be made available. According to EMA document EMA/129363/2015 this would occur via manual override in the CTIS.¹²

Another consideration here is that sponsors will have an option to defer publication of results under certain circumstances. This request for deferral must be made at the time of initial submission and include justification. In the European Commission Q&A (latest update February 2021), an explanation is provided to address how sponsors can request a deferral for the publication of some trial information.¹³ The eligibility criteria for deferral and associated timelines, in addition to all currently available disclosure rules under the EU CTR, is set out in EMA guidance document EMA/228383/2015.¹⁴ A summary of all details that will be disclosed for all trials in the CTIS is provided in Figure 3.

Preparing for the EU CTR data transparency requirements

Many organisations have instated or re-instated initiatives to prepare for the EU CTR becoming applicable in early 2022. Next, some recommendations for organisations preparing for this change:

Cross-functional preparation. Addressing clinical trial data transparency requirements requires cross-functional collaboration across organisations. For this reason, it is recommended to establish a transparency workstream as part of any initiative preparing the organisation for the EU CTR with members from different functional units. Many organisations have now introduced transparency programmes that may support this workstream. A typical transparency workstream would assess the EU CTR transparency requirements, perhaps in conjunction with those of other regions to identify trends and commonalities to support internal efficiencies. Collaboration with data protection officers (DPOs) is recommended, particularly involving those in ex-EU regions (in addition to EU) to support expertise in all aspects of privacy affecting clinical studies. Maintaining awareness of the evolving data transparency landscape, particularly initiatives by industry associations

such as EFPIA, different functional PHUSE, the European Federation of Statisticians in the Pharmaceutical Industry (EFSPI) and other relevant associations is another important area. In addition, it is recommended to involve experts in data anonymisation and de-identification to ensure personal data and CCI are protected in files intended to be made publicly accessible.

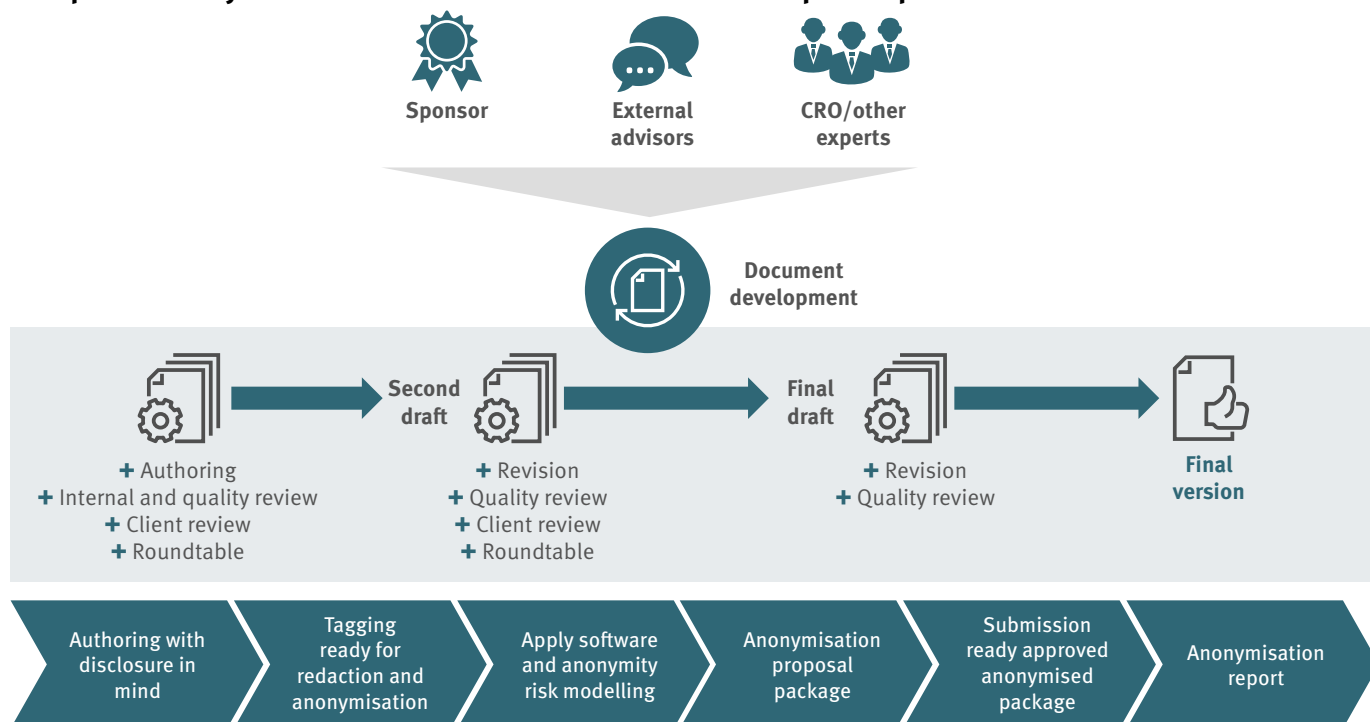
Protecting personal data in accordance with GDPR. The General Data Protection Regulation (GDPR) (EU) 2016/679¹⁵ will apply simultaneously with the EU CTR. The GDPR applies to organisations established in the EU that process personal information. In certain circumstances, organisations based outside the EU also are covered by this law, particularly those that process personal information on EU residents. In a clinical trial setting, the sponsor is the “controller” (responsible party) in respect to personal information collected via case report forms (CRFs) and which forms part of the research results. These data are pseudonymised or key coded, with subjects’ direct identities remaining at site. These key coded data are still regulated personal data because of the risk of re-identification if the data were to be shared with a motivated third party. To ensure compliance with the principles of data minimisation, security and confidentiality contained within the GDPR, sponsors seeking to fulfil their transparency obligations under the CTR, are required to ensure that research data are effectively anonymised before release. This is a statistical process that involves the data being depersonalised, so that any attempt by a motivated party to re-identify individuals will very likely fail.

Anonymisation of personal data and CCI. It will be the responsibility of the sponsor or submitting party to ensure reports or documents loaded to the CTIS have been appropriately anonymised to protect personal data and CCI. The EMA has advised that the requirements will be set out in a separate guidance and consistent with those developed for EMA Policy 0070 unless alternative anonymisation methodologies are permitted for some elements.¹⁴ The EMA has already provided some practical advice to support sponsor readiness, for example, the investigational medicinal product dossier (IMPD) should be separated into the Quality, Safety and Efficacy sections to facilitate different publication rules to each. Similarly, this applies to the protocol synopsis and the protocol.¹²

Several options are available to anonymise information. Figure 4

FIGURE 4

Example of anonymisation in the clinical document development process



outlines a generic example of this process. The procedure is complicated, and errors may result in serious consequences (eg, release of personal data), therefore inexperienced companies are strongly recommended to use an expert external service provider.

The following are important considerations related to anonymisation of information:

- **Data anonymisation:** Turning data into a form that does not identify individuals and where identification is unlikely to take place. In this case, preservation of scientific utility is important to ensure usefulness of anonymised clinical trial data. Removal of direct identifiers is key, and consideration should be given to indirect identifiers, including the intentional introduction of “noise” and generalisation techniques to reduce the likelihood of re-identification of individual subjects. By combining multiple indirect identifiers, it is reasonably possible to re-identify a subject. Therefore, a careful assessment must be made of the whole database by experts or specialised software to ensure the data are transformed sufficiently to protect individual patient data.
- **Data transformations:** Replacement of subject and site identifiers with random (validated) values. In this case, variables that contain potentially identifying information could be dropped/blanked or replaced by ranges (eg, for age or height, which is particularly relevant for extreme values). Verbatim terms that have coded/preferred-term companion variables are always dropped. When transforming dates, two approaches exist: (1) convert dates to study days from a reference date (eg, study start); or (2) apply participant-level random offsets to all dates. The goal here is to preserve the temporal relationship between events, findings and interventions.
- **Anonymisation of trial data for rare disease indications and small populations** presents a challenge and these types of data may potentially not be sufficiently anonymised for public dissemination.
- **Anonymisation is complex** and regulators are increasingly moving toward the need for quantitative risk-based modelling for this process.

Posting study results. Regardless of the trial outcome, the sponsor will be required to submit a summary of the trial results within one year of the end of the trial in all member states concerned, unless scientific reasons justifying a delay are described in the protocol. In the latter case, the results should be submitted as soon as possible, no more than 18 months after the original due date or at the time of the marketing authorisation if it is earlier, and the protocol should indicate the submission timeline.¹⁴ A layperson summary is also required (see below.) The content for the study summary is outlined in Annex IV of the Regulation. It is not dissimilar to the current requirement for result disclosure in the EU but goes further, for example, by requiring transparency of information on global substantial modifications, global interruptions and re-starts, as well as potential concerns in the overall results of the clinical trial relating to efficacy of the investigational medicinal product (IMP) and a declaration of the accuracy of the submitted information.

Requirement for layperson summary. The EU CTR (Article 37) introduces a requirement for sponsors to submit a summary of the results trials, regardless of their outcome, in a format understandable to laypersons within defined timelines and in all the EU languages in which the study was conducted. The content of the summary (10 elements) is set out in Annex V of the EU CTR and includes details such as trial identifiers, sponsor name, general trial information such as main objectives, information on the trial population, description of the IMPs, and adverse reactions, as well as overall results and comments on the outcome. For adult trials these must be loaded to the CTIS within 12 months of the end of the trial, and for paediatric trials, within six months.

Transitioning from the Directive to the Regulation. As mentioned earlier, a three-year transition period will commence on application of the EU CTR. During year one, sponsors can choose to submit trials under EU CTR or the directive but at the end of the three-year period the EU CTR will apply to all trials regardless of whether they were authorised under the EU CTR or the Directive. At this time the EU CTR disclosure rules will apply to new trials authorised under EU CTR and trials authorised under the Directive that are still ongoing at the three-year milestone. Therefore, it is recommended

that sponsors make provisions to transition these trials to ensure relevant information is entered into the CTIS ahead of the three-year timeframe.

Discussion

Clinical trial data transparency is important for patients, researchers, healthcare professionals, clinical trial participants and the public for the numerous reasons noted herein. Following its application, the EU CTR is expected to achieve its goal of strengthening trial data transparency requirements for clinical trials in the EU. Those outside the EU that are part of paediatric investigation plans because of the link to the CTIS will essentially disclose all information available in the CTIS, albeit with applicable exceptions. This effectively brings the current focus on transparency of clinical trial information much earlier in the process to a study level rather than a product approval level, further enhancing the industry's desire to increase transparency within the drug development process.

The timing of EU CTR application will remain closely watched by the industry, but at present it is expected to occur in early 2022. Based on the circumstances, sponsors and CROs are recommended to take actions now to introduce or develop transparency programmes incorporating the new transparency requirements. The factors listed here are not exhaustive but some of the aspects are raised from a CRO perspective in preparing the organisation for the wide-ranging impacts of the EU CTR.

Conclusion

Transparency in trial data should always follow legislation or regulatory guidances (as applicable in the region). Efforts to strengthen transparency by RAs, pharma/biotech companies and industry associations have progressed well in recent years. However, in the EU this remains a complex and somewhat fragmented area. Many companies have taken positive

steps on data transparency beyond current legislative/regulatory guidance. More harmonisation in this regard, which the EU CTR is expected to bring, should be the common goal. ■

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