

Recent and upcoming regulatory changes in the European region: Opportunities for medical writers

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Abstract

The European regulatory landscape for clinical trials and medical devices is in the midst of major transformation. Older policies are giving way to new regulations that emphasise more harmonised and streamlined processes for document submittal, greater public transparency of documents, and the creation of plain language summaries of clinical trials for easier understanding by the general public. This article provides an overview of important new regulations and policies, including some new guidances regarding research related to the COVID-19 pandemic. This article also discusses opportunities for medical writers working in the context of a new regulatory environment that requires balancing increased public disclosure of information and greater privacy protections for individuals.

Introduction

In Europe, the conduct of clinical trials has been regulated and harmonised across all EU Member States through the Clinical Trials Directive. Nevertheless, over the past few years, healthcare providers have witnessed major changes to the dynamic EU regulatory landscape. The much

talked-about Clinical Trials Regulation (EU CTR 536/2014) to replace the directive is likely to be implemented in 2023. It is expected to increase the transparency requirements as it will streamline the process of multi-country EU trials through a single portal for all applications. Along with EU CTR 536/2014, the regulatory landscape of devices and drug-device combinations is also changing, as the new EU Medical Device Regulation is scheduled to be implemented in May 2021. The new regulation imposes new requirements, which will require changes in document preparation for devices. This article provides details about such new requirements, changes in preparation of clinical document processes, and associated opportunities for medical writers.

A main objective of the EU Clinical Trials Regulation 536/2014 and other transparency policies is to establish a European database that will serve as a central electronic communication platform for member states, sponsors, investigators, and ethical committees.^{1,2} Once EU CTR 536/2014 replaces the directive, there will be new requirements for disclosure of clinical documents at a much earlier point along the timeline. The database will house all relevant clinical information related to a clinical trial – protocol, scientific summary, clinical study report, and safety report, which may have been publicly disclosed as per registered clinical trial application (CTA), results reporting, and EMA Policy 0070 and EMA Policy 0043.^{2,3} In addition to this, a plain language summary (PLS) of clinical trial results, following health literacy and numeracy principles, will also need to be posted on the portal, detailing in lay language how the trial was conducted and its results.⁴

By now, medical writers are likely to be familiar with the General Data Protection Regulation (GDPR), enacted in May 2018, which has resulted in major changes to informed consent

processes, data collection, and data reporting.⁵ Because of GDPR, trial subjects now have a better control of their data. However, given the current epidemic situation from COVID-19, there are also some special considerations related to privacy, making it especially important that medical writers stay informed as new guidances are issued.

Furthermore, the EU has also witnessed a considerable refurbishment of the regulatory system for medical devices to create a centralised and transparent procedure of assessment that can be implemented across the member states. In recent years, the EU MDR Medical Device Regulation (MDR, 2017/745) and the In Vitro Diagnostic Medical Device Regulation (IVDR, 2017/746) have been enacted.⁶ Medical device companies are required to submit clinical documents for approval of new and existing products following these regulations. The following sections present the key changes in the EU regulatory landscape and the importance of

these changes for medical writers.

EU CTR 536/2014

The EU CTR 536/2014 is based on a comprehensive technology platform known as Clinical Trial Information System (CTIS).¹ CTIS will serve as a portal for clinical trial sponsors to upload trial-related documents for all the key activities throughout the entire lifecycle of a clinical trial, e.g., during submission stage, maintenance of clinical trial documents beginning from the time of decision on authorisation of a trial by EMA and its member states, and through to the study completion stage. Prior to submission on CTIS, sponsors will need to anonymise personally protected data (PPD) and any commercially confidential information in the clinical documents, CTA submissions, CTA / substantial modifications, study results, and ad-hoc reports.

Given the current epidemic situation from COVID-19, there are some special considerations related to privacy, making it especially important that medical writers stay informed as new guidances are issued.

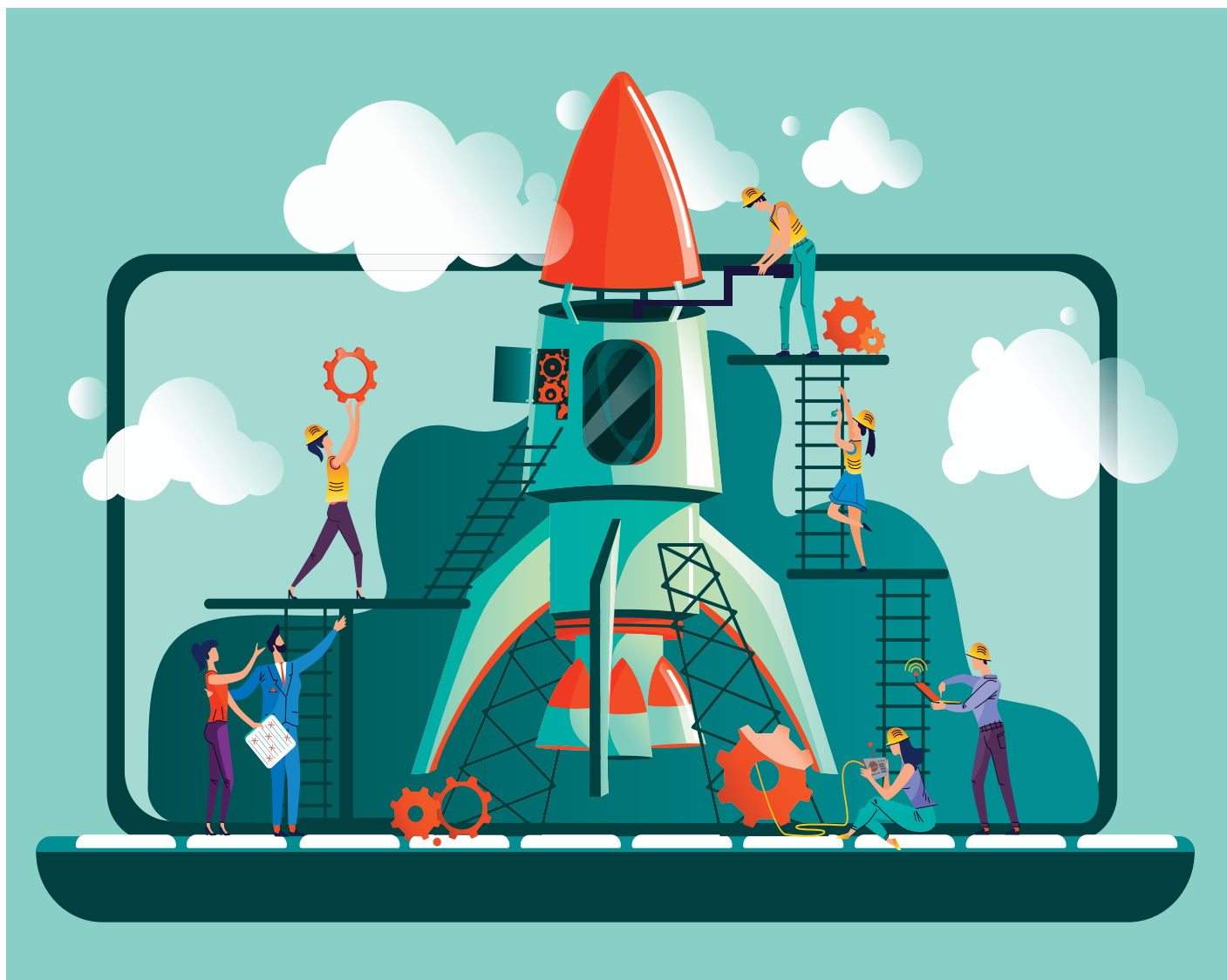


Figure 1 shows the timeframe of EU CTR activities and the clinical study document categories.

EU CTR 536/2014 has also created deferral provisions for the publication of clinical documents based on the clinical trial phase (Table 1). The information like protocol, Investigator brochure, efficacy and safety sections of the investigational medicinal product are allowed for waivers based on categorisation of clinical trial.²

However, deferral rules will not be of significant benefit to the sponsors, as other platforms such as the EU Clinical Trial Register and regulations such as EMA Policy 0043 and EMA Policy 0070 will continue to request protocol information, clinical study reports, and clinical and safety modules to be put in the public domain irrespective of the clinical phase.

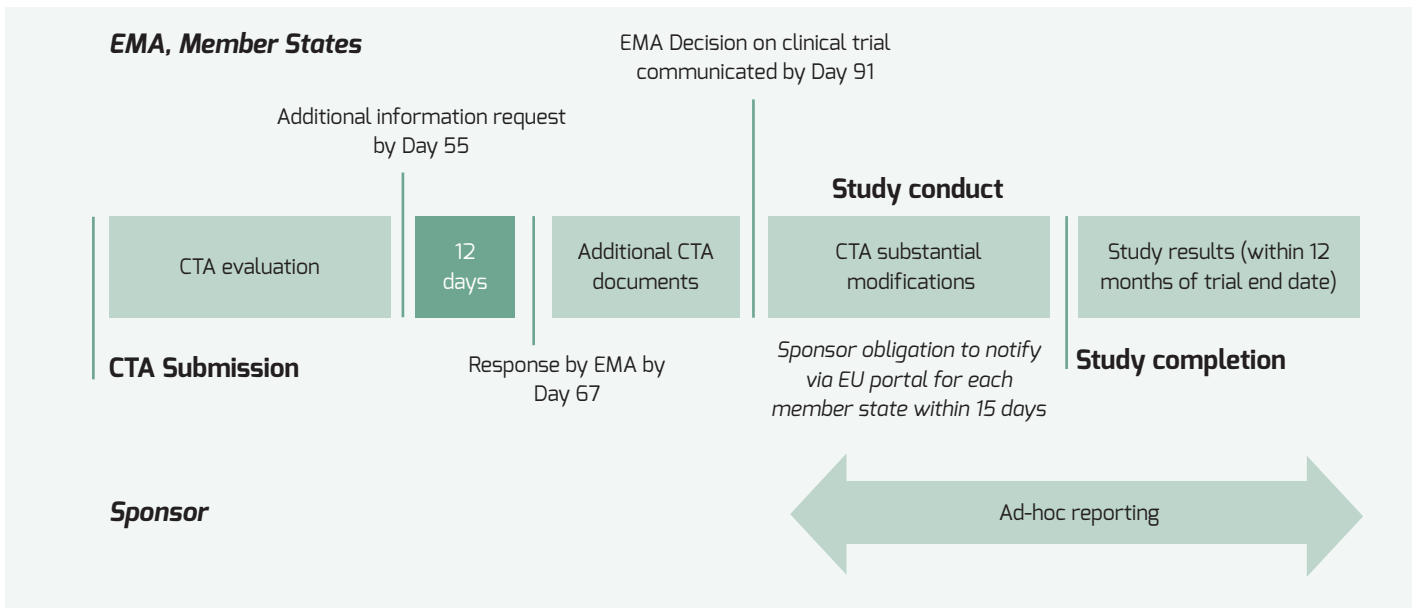
With the requirements to disclose various

clinical documents at regular intervals during a clinical trial, there are a number of points medical writers should consider:

- **The preparation of disclosure-ready clinical documents:** By beginning with the end in mind, writing disclosure-ready clinical documents is imperative in making disclosure activities efficient. Lean, concise writing of these documents will ensure that redaction or anonymisation is only needed in limited sections.
- **The integration of consistent redaction/anonymisation processes:** Sponsors will need to incorporate new processes or streamline existing processes to ensure that redaction/anonymisation strategies are consistent across clinical documents and are performed proactively to meet the new disclosure obligations. Furthermore, it is

imperative to prepare documents in a manner that will require minimal work to anonymise them. To better prepare for the transparency requirements of EU CTR, medical writers should assess PPD and commercially confidential information within the documents and prepare consistent anonymisation. Sponsors will also need to identify any in-scope documents prepared in local languages and require redaction prior to uploading to CTIS. Such documents may necessitate back-translation to English first, to ensure efficient redaction.

- **Anonymisation of clinical documents:** Some sponsors are considering creating a secondary-use CSR using the anonymised dataset. This will eliminate the need to anonymise the CSR for public disclosure. CORE Reference also suggests preparing



CTA submission	CT Substantial modifications	Study results	Ad-hoc reporting
EU Clinical Trial Application Form	Receipt of confirmation of EudraCT number	Interim Results Report	Report of urgent safety measures
EU Active Substance Code Details		CSR Synopsis	
List of countries and status	Cover letter	Clinical Study Report	Report of serious breaches
Legal representative agreement letter		Pop PK and PK/PD reports	
Data Protection	Protocol and substantial modifications	Plain language summary	Inspection reports responses
Recruitment Arrangement		Safety reports	
Certificate of Analysis	Scientific advice letters	EU Clinical trial results registry	Unexpected events
Investigator CVs and other related details		Statistical Analysis Plan	
Facilities details		Case report forms	Study notification reason

Figure 1. A snapshot of EU CTR activities, timeframe and type of documents required



Table 1. Deferral Rules of EU CTR 536/2014 for clinical documents²

Category	Clinical phase	Deferral term	Deferral allowed for document
Category 1	Phase I, Phase 0, Bioequivalence, Bioavailability	Deferral up to the time of marketing authorisation for Investigational Medicinal Product (IMP) used in the trial or 7 years from end of trial, <i>whichever is earlier</i>	Protocol, Subject information sheet, changes to previously public information or documents, Investigator brochure, IMP dossier (IMPD) Safety and Efficacy (S and E) sections
Category 2	Phase II, III	Deferral up to the time of marketing authorisation for IMP used in the trial or 5 years from end of trial <i>whichever is earlier</i>	Protocol, Subject information sheet, changes to previously public information or documents, IMPD S and E
Category 3	Phase IV, Low interventional clinical trial	None	Protocol may be deferred for publication till the time of summary results reporting if a suitable justification is provided by sponsor to prove the novelty of trial design and hypothesis

“primary” and “secondary” use CSRs separately.⁷

- **Timely availability of the interim reports and CSRs:** Because clinical trial results

summary will be needed 12 months from the intermediate data analysis date, it is important to finalise the interim data analysis report so that this new disclosure obligation can be

met. As the main source document for preparation of the PLS, the CSR would need to be written as soon as possible after clinical trial completion. For paediatric studies, the

timeline for results' disclosure is even stricter (6 months from global end of trial date). Therefore, to meet the suggested timelines, availability of source documents for disclosure preparation is key.

- **Translation requirements and PLSs:** The master PLS (in English) will need to be translated into local languages for the region where the trial is conducted. The English and translated PLSs will need to be posted on the portal 12 months after the end of trial. To increase efficiency, medical writers may also consider finalising the sections of the PLS that are not data-dependent at the same time of the CSR shell stage, leaving only the data-dependent sections to be completed at the time of CSR finalisation.
- **Clinical trial results summaries format:** It is likely that during the first phase of EU CTR 536/2014 implementation, the format required for the clinical trial results summary for the intermediate analysis and end-of-trial analysis will be similar to a clinical study synopsis or disclosure synopsis. In such a case, the disclosure efforts for preparing the clinical trial results summary in EudraCT will be reduced because the requirement of full data sets may phase out. This may change in the future as new functionalities are added to the EU portal.
- **Developing PLS writing skills:** Medical writers preparing PLSs will need to learn new skills of writing for patients or a non-scientific audience, such as applying health literacy and numeracy principles in PLS preparation. A medical writer will also need to learn to summarise results in a clear, concise, correct, and complete manner, along with considering the appropriate length of the PLS. They may also be required to attain skills to create simple visuals to explain trial results or collaborate with illustrators or designers to create custom visuals/graphics for these documents.

EMA Policy 0070 and GDPR

EMA Policy 0070 provides for the disclosure of anonymised clinical documents while protecting personal data of trial participants. For compliance, marketing authorisation holders must anonymise PPD by adopting a mix of various anonymisation strategies, followed by a thorough assessment of risk of re-identification.³ While disclosure of documents is an ethical obligation and clinical trial transparency initiatives have significantly enhanced public access to evidence-

based clinical information, it is important to understand the GDPR implications to prevent any privacy-protection related issues. GDPR came into force on May 25, 2018, replacing the EU Data Protection Directive, with an objective to protect personal information under "right to privacy", i.e., the rights of individuals to have reasonable control of their data and be better informed about how their data are being used.⁶ GDPR applies to the EU, EEA, and any data controller or processor located outside of the EU. Failure to comply with GDPR may lead to monetary penalties and dissolute reputation. To remain compliant with GDPR, data being disclosed should be rendered completely anonymous.

With the evolving EU transparency requirements, pharmaceutical organisations have a greater responsibility for ensuring compliance with GDPR. Although these regulations and policies have been well received by the healthcare industry, they do bring certain challenges:

- While EMA Policy 0070 and EU CTR 536/2014 significantly enhance public access to evidence-based clinical information, the GDPR warrants that personal data are adequately protected. These conflicting regulations lead to underreporting of data (redaction vs transformation techniques), data abuse, privacy risks, and compromise on commercially confidential information.
- Redaction-only methodology decreases data utility, thus different anonymisation strategies must be considered during PPD anonymisation. Re-identification risk assessment should be done by considering three criteria (whether it is still possible to single out an individual, link records for an individual, or infer information about an individual) or a quantitative risk assessment, as recommended by Article 29 Working Party.⁸
- Due to the movement of clinical data across borders, the impact of GDPR on data usage, processing and storage is evident, and pharmaceutical organisations must adapt their processes and systems to maintain GDPR compliance.
- Sponsors also need to ensure consistency

of the publicly disclosed information for scientific integrity.

Because medical writing teams are tasked with activities related to EMA Policy 0043, Policy 0070, and data disclosure, it is imperative that medical writers understand policy requirements and GDPR implications. Medical writers should evaluate collected data for potential risks, be able to categorise information as direct- or quasi-identifiers, and understand anonymisation rules. Organisations should also make resources aware on GDPR requirements to ensure adherence to data privacy policies and to address accidental breaches.

Guidance during the COVID-19 pandemic

The COVID-19 pandemic has relentlessly affected every aspect of human fraternity across the globe. The healthcare industry is under constant pressure to find an appropriate treatment or vaccine, while responding to rapid challenges related to disruptions in R&D activities, supply chain, and manufacturing.

To help contain the spread of the novel coronavirus, EMA has issued specific guidance on the conduct of clinical trials in EU

member states. In April 2020, the European Data Protection Board issued "Guidelines 03/2020 on the processing of data concerning health for the purpose of scientific research in the context of the COVID-19 outbreak" to reconcile privacy and public safety.⁹ It is clear that organisations must be legally obliged to ensure the lawful processing of personal data.

Europe and many countries including India, Singapore, Taiwan, South Korea, Iran, and Israel are tracking their citizens using mobile data through invasive applications¹⁰ (e.g., DiAry and allertaLOM in Italy, GeoTrace in Europe, CovTrack in Romania, Arogya Setu in India, Trace Together in Singapore) for the purpose of medical and administrative interventions. The collected data is anonymised before being shared with health agencies in line with data privacy laws. GDPR Articles 6(e)¹¹ and 9(g)¹² also have provisions related to the processing of personal data, necessary in the public interest, without consent of individuals during public health

A medical writer will also need to learn to summarise results in a clear, concise, correct, and complete manner, along with considering the appropriate length of the PLS.



emergencies. However, once this situation is over, the previous rules will need to be enforced to ensure judicial use of data and maintain sufficient data protection.

Medical writers should keep themselves abreast of updates made in the guidance and policies by the EMA, while preparing clinical documents. As the COVID-19 crisis has affected site monitoring, patient visits, and data collection activities, amendment to protocols (including informed consents) and trial conduct are inevitable, and these changes need to be properly addressed during results disclosure.

Medical devices and drug-device combinations

The EU MDR (2017/745) and the IVDR (2017/746) were adopted in April 2017 by the EU Council and the Parliament and entered into force in May 2017.^{13,14} The EU MDR did not provide clear regulatory information for devices. Therefore, Article 117 of MDR needed to be amended to provide specific requirements regarding drug-device combinations.¹⁵ This has

changed the legal framework in EU for medical devices, introducing new responsibilities for EMA and for national competent authorities. These regulations replace the three existing directives (93/42/EEC, 98/79/EC, and 90/385/EEC) for medical devices. The MDR has a transition period of 4 years and will fully apply from May 26, 2021. The IVDR has a transition period of 5 years and will fully apply from May 26, 2022.¹⁶

Article 117 of the MDR introduced a new requirement – inclusion of CE certificate (*Conformité Européene*, which means “European Conformity”) for the device in its marketing application.¹⁵ It requires that the marketing authorisation applications for an integral drug-device combination should include a declaration of conformity, or relevant certificate, issued by a notified body (NB). EMA now has three key roles within MDR – it provides consultation on certain medical devices and drug-device combinations, and opinion on borderline products.¹⁷

With the MDR, the risk classification for

medical devices categories remains identical compared to the directive for Class I, Class IIa, Class IIb, and Class III. Class III covers the highest risk products. However, MDR reclassifies certain devices and extends the scope to devices that are left out in the directive. New devices included under the scope of MDR are:¹⁸

- Products without an intended medical purpose
- Devices manufactured utilising non-viable human tissues or cells
- Devices incorporating or consisting of nanomaterial

Manufacturers now need to demonstrate that their medical device meets the revised rules for the classification of MDR. New compliance requirements should be evaluated due to reclassification under the scope of MDR. In the current scenario, many devices will be reclassified to a higher device class, affecting their clinical data requirements and require involvement of NB. A clinical evaluation report, previously based on an analysis of literature,



might require clinical investigation and/or post market clinical follow-up. This will need involvement of medical writers for preparation of clinical investigational plan and report.

The regulation has now created a more patient-friendly environment where transparency, patients' information, and patient preferences are of utmost importance. The regulation mandates the establishment of a comprehensive EU database on medical devices (Eudamed) that will cover the lifecycle of all products available on the EU market. Much of this information will be made publicly available. The following are some of the transparency requirements:

- Registration of clinical investigational studies (Article 73.1); the registration information will be publicly accessible through Eudamed (Article 73.3).
- Publishing of clinical investigational studies results within 1 year of the end of the clinical investigation or within 3 months of the early termination or temporary halt, irrespective of the outcome, including summary of results that can be understood by the intended user (similar to PLSSs)
- Preparation of a summary of safety and clinical performance for all Class III and implantable devices. This summary will need to be updated annually.

- Public disclosure of documents that are part of technical documentation such as the clinical evaluation plan and report, clinical investigation protocols and results, and summary of safety and clinical performance.
- Clinical evaluation application documents will include Clinical Investigation Application (CIP), Clinical Investigation Plan, Investigator's Brochure, CIP must also describe policy on the publication of results.
- A clear policy for publishing investigation results, with an emphasis on evaluating available literature for clinical evaluation process will also be needed. For publication of results, the International Committee of Medical Journal Editors' Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals¹⁹ should be followed.

Dossiers prepared for medical devices include documents similar to those submitted for medicinal drugs, however the content requirements are slightly different, e.g., a clinical evaluation report is equivalent to a CSR written for drugs. Periodic safety update reports, written for drugs, are nonetheless a new requirement for devices according to the MDR.

Conclusion

Considering the increasing requirements of transparency initiatives in Europe, there are numerous opportunities for medical writers. Several national competent authorities have already updated their processes and systems to be compliant with the regulations. We understand that Eudamed and CTIS both are delayed due to technology-related challenges. However, it is well beyond just an IT-driven initiative, as organisations have to prepare for these changes. As of now, the impact of CTIS on EMA Policy 0070 full data summaries is still being explored. The delay has resulted in some organisations following an observational approach, while many other organisations have started preparing their processes to be ready for the transition. Medical writers should take the opportunity now to organise and plan their writing activities accordingly, given the significant impact of the regulations on internal processes and operational activities.

Conflict of interest

The authors do not have any conflict of interest.

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