

The emerging transparency paradigm for clinical trials in Europe

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Differences in transparency requirements for interventional clinical studies between Europe and the US have become more pronounced since the implementation of the EU Clinical Trials Regulation (EU CTR) in 2022. The latter mandates public disclosure of EU trial application data and documents, setting a new norm for global transparency standards. This article outlines how to practically navigate the EU transparency rules within the global context and achieve a balanced, holistic approach, which aligns the need for transparency with data privacy and protection of confidential information.

Keywords – clinical trial application, clinical trial transparency, ClinicalTrials.gov, CTIS portal, EU CTR

Introduction

On 31 January 2022, the EU CTR (EU/536/2014) came into effect within the European Union.¹ The regulation replaced the Clinical Trials Directive (2001/20/EC)² and aims to improve interactions between sponsors, national regulatory agencies, and ethics committees when submitting clinical trials in Europe and to increase trial transparency. Under the EU CTR, a new EU database – the Clinical Trials Information System (CTIS) – provides a single entry point for submitting, assessing, authorizing, supervising, and reporting a clinical trial in all member states in the EU and European Economic Area.³ (**Table 1** on page 2 provides a glossary of terms and details specific term usage in this article.) To increase transparency, the EU CTR requires that all information in the CTIS is publicly available once the trial is approved unless there is adequate justification by the sponsor to keep it confidential.

The EU CTR transparency requirements are part of the overall policy of the European Medicines Agency (EMA). Starting in 1995, the EMA published

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Table 1. Glossary of terms^a

Topic	Explanation
Article 57	Refers to Article 57(2) of Reg (EC) No. 726/2004 ⁶ and covers all products with a valid marketing authorization, irrespective of the route of authorization. Information is collected/maintained and included in the XEVMPD. Data are published via an Excel download.
Centralized procedure	In the EU, drugs may be authorized through: <ul style="list-style-type: none"> • National procedures (decentralized procedure, mutual recognition procedure, single-country national procedure), leading to one or more national licenses (1 per participating country); or • The centralized procedure, leading to a single EU license, issued by the European Commission and valid in all member states.
Clinical study or clinical trial	The EU CTR distinguishes between a clinical study (broad term) and a clinical trial (narrower term). A clinical trial is defined as a clinical study that fulfills the indicated criteria and is classified as interventional or low-intervention. The EU CTR applies only to clinical studies that fulfill the criteria of a clinical trial. Although this distinction is used only in the EU, for the purpose of this article, to remain consistent with EU terminology, we have consistently used the term <i>clinical trial</i> .
European Medicines Agency	The EMA is a centralized agency of the EU, responsible for the scientific evaluation, supervision, and safety monitoring of medicinal drugs in the EU. It is a coordinating body and has contacts with thousands of experts across Europe who work for the various scientific committees. The EMA does not assess clinical trials.
European Union and European Economic Area	The EU currently comprises 27 member states in Europe. The European Economic Area comprises the 27 EU countries plus Norway, Iceland, and Liechtenstein, which adhere to EU pharmaceutical legislation. For this article, when mentioning EU, this refers to EU and the EEA countries.
Extended EudraVigilance medicinal product dictionary	The XEVMPD is also known as the Article 57 database. It contains information on product name, active substance, route of administration, authorization details, product information, and the contact details of the marketing authorization holder. To ensure a high-quality database, only trained personnel are allowed to submit data.
Member states	Under the EU CTR, a clinical trial application is assessed and approved by one or more member states (the national competent authority for scientific review and the ethical committee). If a trial runs in more than one member state, one member state is appointed as the reporting member state and the other member states are referred to as “member states concerned.” For this article, this distinction is not relevant, and the term <i>member state(s)</i> is used throughout.
Policy 0070	Policy 0070 is the policy on the publication of clinical data for medicinal products for human use. ⁴ The EMA publishes the clinical data submitted by pharmaceutical companies to support their requests for marketing authorization, which are assessed by the CHMP. This comprises publication of clinical overview and clinical summaries; trial reports on individual clinical trials, including the protocol; the sample case report form for recording information on an individual patient; and documentation of the statistical methods for analyzing the data.
Reg (EC) No 45/2001 and Reg (EU) 2016/679 (GDPR)	<ul style="list-style-type: none"> • Reg 45/2001 ensures uniform and consistent protection of natural persons with regard to processing of data and applies in those situations where the GDPR is not applicable. • Regulation 45/2001 has been adapted to the principles and rules of the GDPR to ensure uniform and consistent protection.
SPOR	Portal providing data management services for substances, products, organizations, and referentials ensuring delivery of quality data to support EU regulatory activities.

CHMP, Committee for Medicinal Products for Human Use; **CTR**, clinical trials regulation; **EEA**, European Economic Area; **EMA**, European Medicines Agency; **GDPR**, General Data Protection Regulation; **SPOR**, substances, products, organizations, and referentials; **XEVMPD**, extended EudraVigilance medicinal product dictionary.

^aRows highlighted in gray detail specific term usage in this article.

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European public assessment reports for initial marketing authorizations (MAs) and subsequent variations approved under the centralized procedure.

Over time, this publication policy was gradually expanded to include committee meeting agendas and minutes, as well as protocol summaries and trial results in the European Union Clinical Trials Register. In 2016, the EMA started to publish clinical data submitted by companies to support their MAs assessed through the centralized procedure.⁴ In summary, the EU CTR can be seen as the latest development in the evolving transparency landscape in Europe.⁵

Sponsors submitting studies in the EU have seen a large impact on their working processes due to the heightened transparency requirements of the EU CTR, as early involvement of regulatory experts is now needed in an area that was traditionally the domain of regional clinical and operational colleagues. This article provides an overview of the changes in disclosure triggered by the requirements in the EU CTR and their practical consequences. Practical feedback is based on early experience of a single company. The article also compares clinical trial disclosure activities in the EU with those in the US and identifies the key steps needed to support harmonization efforts.

Understanding and navigating the transparency requirements

The EU CTR makes it a core provision that any data submitted as part of a clinical trial application (CTA) in any EU member state will be made public unless there is a justification not to do so. Thus, the EU transparency requirements are now globally the most stringent of any regulatory system. An overview of the disclosure mechanisms that are currently applicable in the EU around data sharing from clinical trials is given in **Table 2** (p. 4). As shown in **Figure 1** (p. 4), CTA documents and structured data are submitted by the sponsor through a portal to a database hosted by the EMA, creating the “data pool” that is then used to populate the publicly available database.

Under the EU CTR, a CTA can thus only be submitted via CTIS. Clinical trial sponsors need to perceive CTIS as a public information source, starting from the evaluation of the initial CTA and continuing through the trial, concluding with end-of-trial activities and the inclusion of trial results in CTIS. According to Article 81(4) of the regulation, some exceptions for the sponsor’s data publication in the public database can be made. The following reasons directly affect sponsors and are most relevant to this article:

- Protecting personal data in accordance with applicable regulations,^{11,12} and
- Protecting commercially confidential information (CCI), in particular through taking into account the status of the marketing authorization for the medicinal product, unless there is an overriding public interest in disclosure.

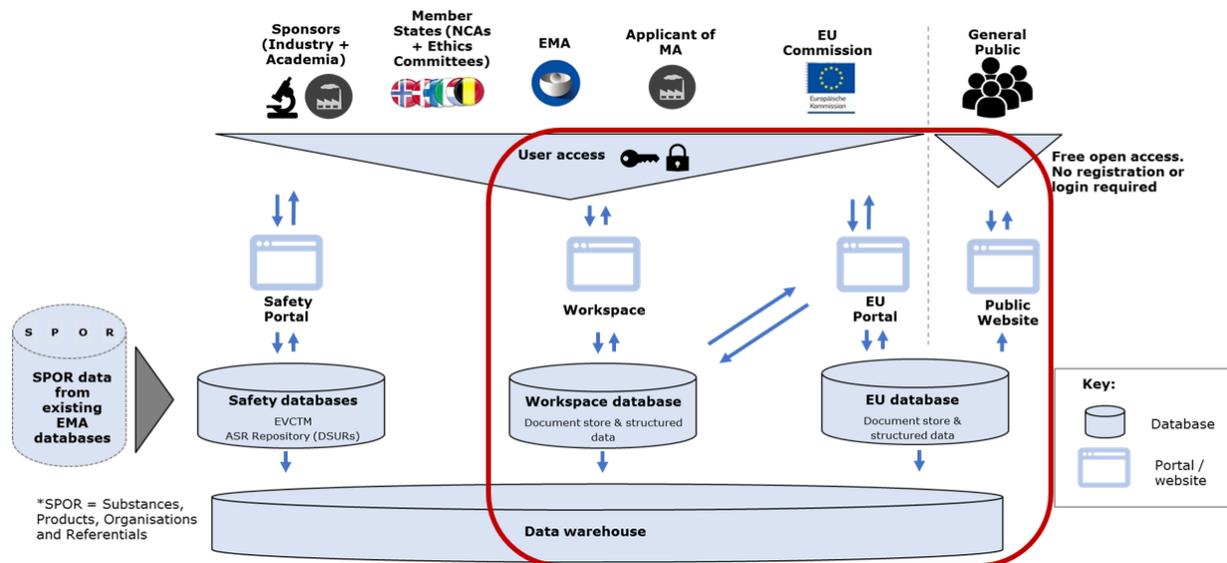
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Table 2. Clinical data access at the European Medicines Agency

Feature	Type of information			
	European public assessment reports	Access to documents	Clinical data publication	EU CTR
Legal basis	Reg (EC) 726/2004 ⁶	Reg (EC) 1049/ 2001 Policy 0043 ⁷	Policy 0070 (2015) ⁴	Reg (EC) 536/2014 ¹
What information is provided	Scientific grounds for whether an MAA has been approved	Any documents held by the EMA	Clinical reports supporting an MAA for human medicines via central authorization	Data on EU interventional clinical trials
When the information is available	By EMA at the end of the marketing authorization assessment process	Upon request	Proactively	Proactively
Where the information can be found	EMA website ⁸	Provided upon request through a secure system	CDP portal (since 2016) ⁹	CTIS portal (since 2022) ¹⁰

CDP, clinical data publication, CTIS, Clinical Trials Information System, EU CTR, EU Clinical Trials Regulation; EMA, European Medicines Agency; MAA, marketing authorization application.

Figure 1. Overview of the infrastructure of the EU portal and database



ASR, annual safety report; DSUR, development safety update report; EMA, European Medicines Agency; EU, European Union; EVCTM, EudraVigilance clinical trial module; MA, marketing authorization; NCA, national competent authority; SPOR, substances, products, organizations, and referentials.

Adapted from European Medicines Agency

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Protection of personal data

It is crucial to protect personal data when deciding to disclose information in the EU due to the application of the General Data Protection Regulation (GDPR).¹² However, the GDPR cannot be used to withhold clinical trial information entirely. CTIS therefore facilitates the submission of both “for publication” (redacted, unreadable personal data) and “not for publication” (unredacted) versions of documents containing personal data.¹³

The responsibility to protect the data is a joint responsibility of all CTIS users,¹⁴ with each party taking care of the documentation they have submitted. At the time of submission via CTIS, the authorized user is required to verify that EU data protection legislation has been adhered to.

As a general principle, only personal data that are strictly necessary for the assessment of the trial should be provided. Such data can be provided in a version of the document in the CTIS marked “not for publication.” The default version is marked “for publication” and should always be provided and uploaded first, immediately followed by the version that is not for publication, when required. Special attention should be given to the content of the structured data fields in CTIS because no redaction is possible for those data fields. It is the responsibility of the sponsor to ensure that no personal data or only redacted personal data of clinical investigators, sponsor employees, or other personnel working on the trial are included in documentation submitted with a CTA or in the clinical trial report. **Table 3** summarizes recommendations and redaction needs for frequently encountered roles in clinical trials.

The sponsor also has an obligation to protect the rights of trial participants. Article 81(7) of the EU CTR sets out that no personal data of trial participants may be made publicly accessible. This may be enforced by monetary penalties in the event of disclosure.

Table 3. Summary of practical recommendations and redaction needs for frequently encountered roles in clinical trials

Role	Recommendation	Redact
Principal investigator at the clinical site(s)	Use template to structure information and curriculum vitae (at least name and surname)	Name and surname: No Other information: Yes
Other clinical investigator(s)	Use template to structure curriculum vitae	Yes
Other sponsor employee(s)	Avoid as much as possible	Yes
Sponsor contact person for information on the trial	Use functional role	No
Head of the clinic/institution or other responsible person issuing the statement of suitability of the facility	At least name and surname	Name and surname: No Other: Yes
Sponsor legal representative	Omit signatures	No
Person(s) signing the clinical trial reports	Omit signatures	No

The EU CTR does not specify any particular method for anonymizing personal data of participants in clinical trials, recognizing that each anonymization technique has its own advantages and disadvantages.¹⁵ The choice should be based on a thorough quantitative approach to risk assessment for the specific trial and, quite possibly, a combination of more than one method may be necessary. It is crucial to emphasize that maintaining the usefulness of data in the public version of the documents is equally important while ensuring adequate anonymization.

Protection of CCI

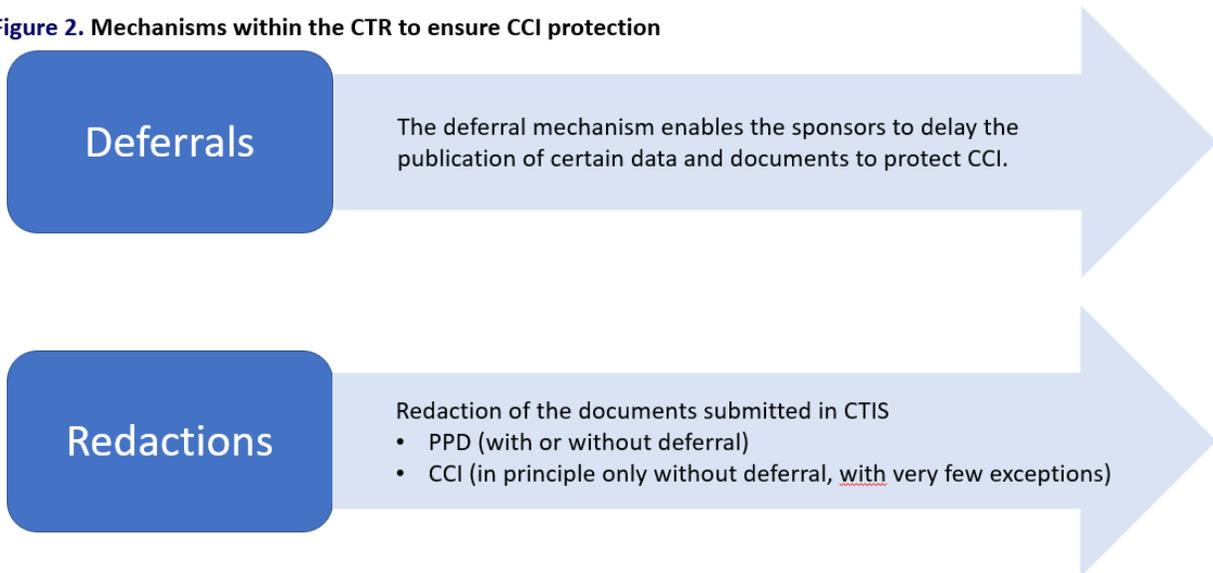
The term *commercially confidential information* refers to any information included in the CTA or shared throughout the trial lifecycle that could potentially harm the legitimate economic interests or competitive position of the sponsor (or later the applicant/holder of the marketing authorization) of the trial. It is up to the sponsor to determine what qualifies as CCI, within the framework of EMA guidance and built-in behaviors of the CTIS system, and it depends on factors such as the phase of the trial and the development status of the investigational medicinal product being used. In summary, the determination of what can or cannot qualify as CCI is a complex exercise and requires an expert cross-functional team looking at safeguarding patentable information at the current development stage but also with regard for the future.

To safeguard CCI, the EU CTR has introduced two mechanisms (**Figure 2**, p. 7). Documents can either be submitted for publication with CCI redacted or a deferral of publication of a subset of the trial documents can be applied for. The length of the deferral of publication depends on the phase of the trial. It is assumed that by the time the deferral period ends, the majority of the information will no longer qualify as CCI, and redaction of deferred documents is therefore not needed or expected. However, the guidance indicates that in certain exceptional circumstances, some pieces of information (e.g., the quality data in the protocol) could still be considered CCI after the deferral period has elapsed and can still be redacted from the documents that will be published on public domain once the deferral is elapsed.¹³

The recently released draft EMA guidance recommends that sponsors follow a two-step process to facilitate a consistent identification of CCI.¹³ In the first step, it is important to rule out the possibility that a particular piece of information is already publicly available. If this is not the case, then the information should be assessed, in collaboration with relevant subject matter experts, to determine whether disclosure of the information may undermine the legitimate economic interest or competitive position of the sponsor. **Figure 3** (p. 7) shows a decision tree for assessing whether a CCI redaction is needed.

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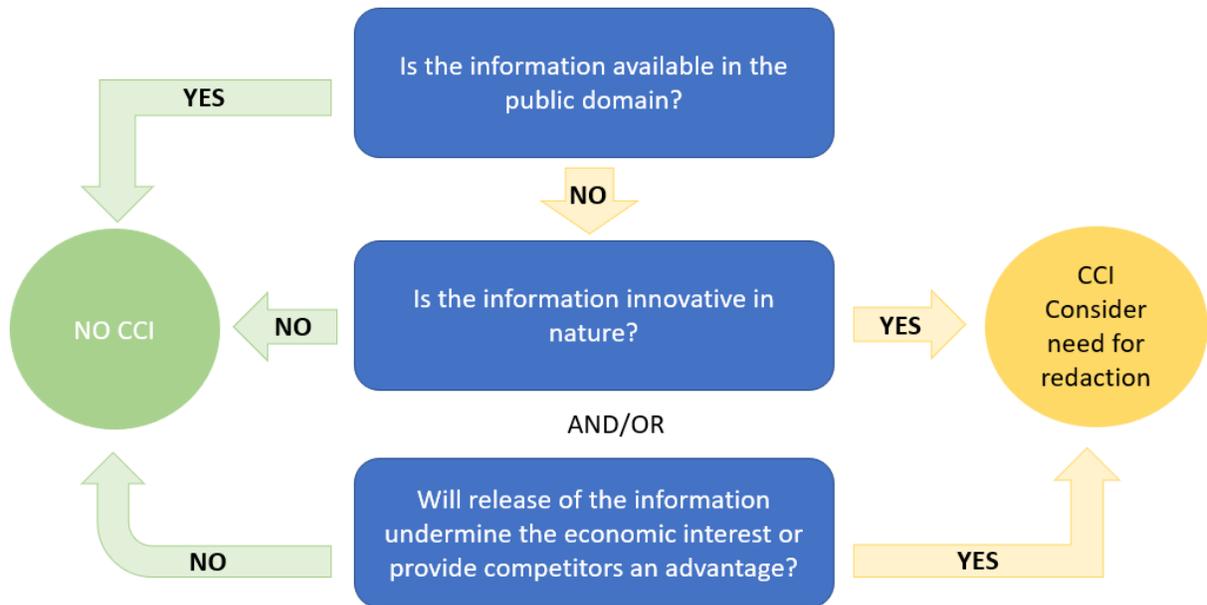
Figure 2. Mechanisms within the CTR to ensure CCI protection



CCI, commercially confidential information; CTIS, clinical trials information system; PPD, protection of personal data.

Source: EMA/212507/2021¹³

Figure 3. Decision tree for assessing need for CCI redaction



CCI, commercially confidential information

Source: Adapted from EMA/212507/2021¹³

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The guidance offers examples of possible CCI and what should not be considered as CCI.¹³ But these lists are not definitive classifications. CCI redaction should align with program-level disclosure policies, decreasing over time with product development phases, in line with time-dependent patent applications.

EU CTR deferral mechanism and associated publication rules

Decisions on whether to defer depend on the phase of the clinical trial, as well as the marketing authorization status of the product indications, pharmaceutical forms, and routes of administration under investigation. To facilitate an automated process, CTIS requires that when each CTA is submitted, the trial is allocated to one of three EMA-determined categories (**Table 4**).¹⁶ The category is selected by the sponsor at the time of the CTA; however, the member states reviewing the application may recommend an alternative category if they disagree with the sponsor. The final agreed category will be part of the final conclusion of the CTA.

The timing of (automated) publication of data and documents is based on the trial categorization and is determined in relation to key milestones of the clinical trial (decision on the trial, end of the trial, 12 months after the end of the trial). For certain types of information, sponsors have the option to request and justify deferral of publication for a limited period of time. A high-level overview of the timing and publication of data and documents and the associated options for deferrals in CTIS are summarized in **Table 5** (p. 9).¹⁷

It should be noted that the deferral mechanism applied upon trial approval is not absolute. The member states concerned may decide to make data or documents public earlier if “an overriding public interest in disclosure” prevails.^{1,13} A sponsor will have to provide a written justification for the requested deferral, which will be included in CTIS as structured data. This justification consists of two parts – one part will be made public immediately,

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Table 4. Categorization of clinical trial rules and criteria¹⁶

Trial category	Description	Examples
1	Pharmaceutical development clinical trial	Phase 1 trials in healthy volunteers or patients, bioequivalence and/or bioavailability trials, biosimilarity trials, and other trials without therapeutic or prophylactic intent
2	Therapeutic exploratory and confirmatory clinical trial	Phase 2 and Phase 3 trials
3	Therapeutic use clinical trial	Phase 4 trials and low-intervention trials

Table 5. High-level overview of deferral rules for CTA content by trial category¹⁷

Type of information ^a	Category 1 Phase 1	Category 2 Phases 2 & 3	Category 3 Phase 4
Main characteristics of the trials	Publication of a final summary of results	No deferral	No deferral
Notifications	Publication of a final summary of results	No deferral	No deferral
Subject information sheet	Up to 7 years after the end of the trial in the EU	Up to 5 years after the end of the trial in the EU	No deferral
Protocol (incl. synopsis)	Up to 7 years after the end of the trial in the EU	Up to 5 years after the end of the trial in the EU	Publication of a final summary of results
IMPD S&E sections, ^b investigator's brochure, MIA/GMP certificates, QP declarations, content of the labeling of the IMPs	Up to 7 years after the end of the trial in the EU	Up to 5 years after the end of the trial in the EU	Publication of a final summary of results
Responses to Requests for Information	Up to 7 years after the end of the trial in the EU	Up to 5 years after the end of the trial in the EU	Publication of a final summary of results
Clinical trial results summary for an intermediate data analysis planned in the protocol	1. Default up to 12 months after the interim analysis date. 2. Option to further defer a maximum of 18 months after due date or until the time of the marketing authorization (if earlier). Does not apply to trials that include pediatric patients.	No deferral	No deferral
Clinical trial results summary and layperson summary	1. Default up to 12 months after the end of trial date in the EU; 6 months for trials including pediatric patients. 2. Option to further defer a maximum of 18 months after due date or until the time of the marketing authorization (if earlier). Deferral does not apply to trials including pediatric patients.	No deferral	No deferral
Clinical trial report	30 days after the marketing authorization decision (authorization or refusal of MAA) or 30 days after withdrawal of the application. Deferral is not possible for clinical trials that are part of an EU Pediatric Investigation Plan or that include pediatric patients (<18 years of age).		

CTA, clinical trial application; **EEA**, European Economic Area; **GMP**, good manufacturing practice; **IMP**, investigational medicinal product; **IMPD S&E**, Investigational Medicinal Product Dossier Safety & Efficacy [sections]; **IMPD-Q**, Investigational Medicinal Product Dossier-Quality [section]; **MAA**, marketing authorization application; **MIA**, manufacturing and importation authorization; **QP**, qualified person.

^aThe sponsor is the owner of the information. ^b IMPD-Q is not published under CTIS.

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and the second part, providing more detail, will be made public at the same time as the investigator’s brochure for that trial (**Figure 4**).

Hands-on company insights: Dealing with transparency realities

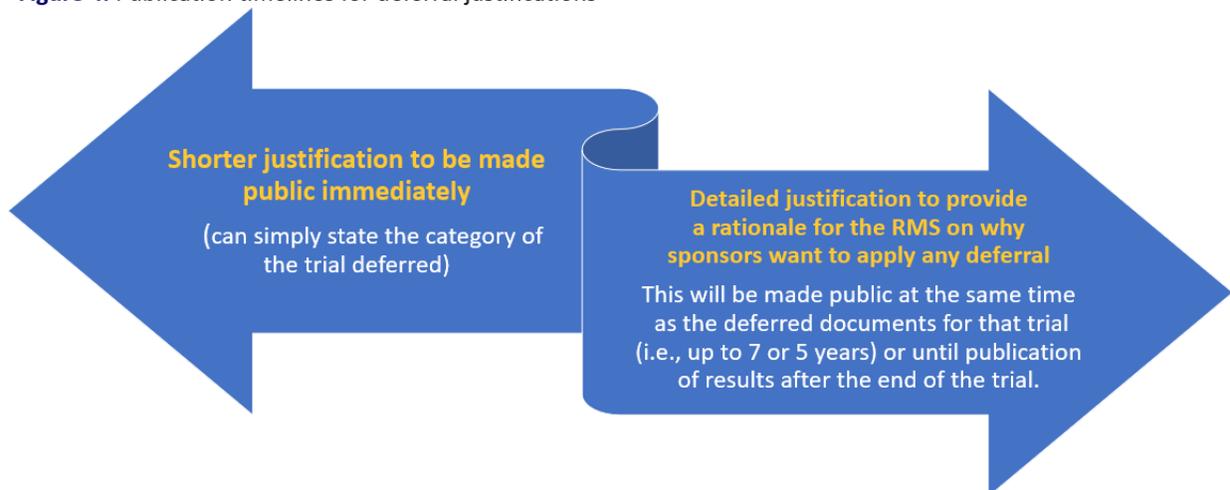
The transparency rules introduced by the EU CTR are unprecedented and have a big impact on company internal processes, affecting not only EU trials but also global submission strategies. The newly introduced processes must be adhered to and consistently applied starting with the first clinical trial that includes an EU trial site and continuing throughout development, subsequent authorization, and postapproval development. **Table 6** (pp. 11-12) provides an overview of important considerations and decisions to be made at an early development stage.

From the table, it is clear that the EU CTR transparency impacts timing of global actions (e.g., ClinicalTrials.gov submissions)^{18,19} and necessitates early engagement of colleagues. The legislation has triggered the introduction of entirely new techniques and ways of working. Early involvement of a patent attorney in deferral discussions is advantageous, along with educating stakeholders on deferral options and justifications.

In addition to the timing of the activities around ClinicalTrials.gov, it is important to be aware that other documents such as the IB are also shared between jurisdictions. As the EU requirements are the most stringent, they will need to be considered whenever global documents are being drafted, and checkpoints

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Figure 4. Publication timelines for deferral justifications



RMS, reporting member state

Source: Appendix to EMA/42167/2014¹⁷

Table 6. Internal adaptations due to the new EU CTR transparency rules

Topic	Decision	Rationale
Cover letter	Template cover letter, wherever possible, contains only core information approved for public disclosure to outline the study, avoids additional details or refers to Part I documentation, and omits personal signatures.	Avoid the need to redact the cover letter content.
Structured data fields in CTIS	Limit to main objectives, key inclusion/ exclusion criteria, primary/secondary endpoints; consider whether nonmandatory tertiary or exploratory endpoint fields are required, aligning with ClinicalTrials.gov posting.	Keep information globally aligned. Team needs to start early with the ClinicalTrials.gov drafting to meet the CTIS submission timeline.
Request for deferral	<ul style="list-style-type: none"> • Start ahead of time and engage key stakeholders (regulatory professionals, clinical trial transparency experts, clinical and patent attorneys) to discuss deferral category, duration of deferral, and adequate justification. • Overview of planned transparency deliverables helps define the deferral duration. • Allocate responsible lead author and reviewers for the deferral request text. 	Ensure an aligned deferral approach taking all necessary elements into consideration.
Publication of documents after deferral	The latest version of the document per submission application (including substantial modifications) is published in the public portal after deferral expires.	It is crucial to highlight and redact pertinent PD and CCI in the initial submission of documents to CTIS, as all versions will become publicly accessible at the end of the deferral period.
Version control of redacted documents	Robust quality control is needed while uploading the version “for publication” and the version “not for publication” to avoid unintended disclosure of data at point of submission.	It is not possible to upload redacted versions postapproval, so it must be ensured that the final submitted documents are correctly uploaded to the relevant location in CTIS.
Redactions	Involve clinical trial transparency colleagues early in the trial submission strategy to plan redactions. Ensure early training of subject matter experts on: <ul style="list-style-type: none"> • The redaction process itself and the transparency guidelines, and • What is considered PD and what can be redacted as CCI. 	Overall redactions should be kept limited to maintain a balance between commercial confidentiality and public interest in disclosure.
Create awareness about CTIS transparency aspects	Education/training at functional level to streamline redaction (CCI) at a project level.	Efficient CCI redaction review.
Create a culture of mindfulness when generating core trial documents to exclude as much PD/CCI content as possible	Brainstorming session and training with relevant lead authors and subject matter experts to limit inclusion of PD and CCI to what is absolutely necessary for the regulatory assessment.	Reduce: <ul style="list-style-type: none"> • The extent of redactions, • The operational workload, and • Member state RFIs.

Table 6 continued on following page

Table 6 (cont.) Internal adaptations due to the new EU CTR transparency rules

Topic	Decision	Rationale
Redline documents	It is not required to include track changes/redline documents for substantial modifications.	Reduce the operational workload.
Document metadata	Before finalizing the redacted version, remove document metadata from the “for publication” version.	Metadata may contain PD.
Response procedure	Separate IMPD-Q related responses from the non-quality-related topics to enable them to remain confidential. A separate response document to member state questions is to be created and uploaded for IMPD-Q-related questions.	Quality responses are never disclosed within the scope of CCI protection if uploaded to the IMPD-Q location in CTIS; in contrast, the non-quality-related responses will be made public.

CCI, commercially confidential information; **CTIS**, Clinical Trials Information System; **IMPD-Q**, Investigational Medicinal Product Dossier-Quality [section]; **PD**, personal data; **RFI**, request for information.

^aThe information in this table is based on company choices and experience.

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should be introduced along the creation pathway to identify potential personal data and CCI and establish agreement on how best to manage these aspects.

It is also important in this early stage of implementation for internal processes to remain flexible, as for several crucial aspects (e.g., naming conventions), the necessary guidance was not yet available when the trial documentation was initially being prepared. In addition, the EMA’s policy regarding the mechanisms to avoid publication of CCI has shifted from allowing both redaction and deferral to now emphasizing one approach or the other. The policy could be expected to evolve further as an outcome of the ongoing EMA consultation of transparency requirements with stakeholders.²⁰

Another transparency reality is that CCI that is included in CTA documentation may also carry through into the member state assessment report. The sponsor has no possibility to review the assessment report content prior to publication by the member state. The EU transparency guidance recognizes this, and to minimize the potential for unintended inclusion of CCI when preparing the assessment report, it is recommended that the sponsor flag in the CTA document version “not for publication” which data should be redacted in the matching “for publication” version. This will allow the member states to exactly align their redactions in the assessment report to the sponsor’s request.^{13,21} However, this will be an additional operational workload on top of creating a redacted “for publication” version, and it remains to be seen how carefully this will be implemented by the member states when creating the assessment report.

A welcome development, and of particular importance for trials that have an integrated Phase 1/Phase 2 design, is that since May 2023, the transparency guidance^{13,21} identifies the details of the maximum daily dose allowed and maximum total dose allowed for the investigational medicinal product as potential CCI for early phase trials. The sponsor will need to provide justified grounds in the cover letter about why this may be patentable information that is not yet in the public domain. If this justification can be provided, it permits redaction of this information that would not otherwise apply for a Category 2 trial.

A point of concern yet to be resolved is that in July 2022, the EMA became aware that information on some trials with agreed deferrals approved in CTIS had been prematurely published.²² As a mitigating measure, clinical trials with a decision issued after mid-August 2022 that have deferrals of any type in the application form are currently not published on CTIS. This is a temporary measure until the functionalities of the public portal are fully restored.²²

Global harmonization of transparency at the trial level

An overview of the transparency requirements for EU submissions in CTIS under the EU CTR and trial disclosure in the US is given in **Table 7** (p. 14).

The overview shows that the disclosure rules in the EU and the US are not aligned for any of the trial phases. This applies to the type of information that has to be disclosed, the timing of the disclosure of the information (e.g., distinction between primary completion date and completion date), and the extent of public disclosure of information. In addition, the disclosure rules in the EU encompass many documents that may contain personal data and will require redaction to ensure they are never disclosed publicly. Although the need for redaction cannot be fully avoided, it can be limited by taking this aspect into consideration from the first draft document version and carefully considering where and how personal data are included.

By taking this approach, the need for redaction can be made more predictable and less extensive. Early involvement of regulatory affairs colleagues in the preparation of clinical trial–related documentation is needed to ensure EU and US transparency aspects are considered in the trial submission strategy and planning, thus reducing the final redaction workload. Because of the different trial information disclosure timepoints, it is also important to align at the program level so that all published information remains consistent across regions.

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Table 7. Transparency requirements for clinical trial submissions in the EU and US by trial phase

US ClinicalTrials.gov portal	EU CTIS portal
<i>Study start-up phase</i>	
<i>Regulatory framework:</i> Clinical trials registration and results information submission to meet transparency and disclosure requirements are in addition to the IND regulatory application. Along with an IND application, the sponsor has to provide information on trial design and submit the results for public disclosure on ClinicalTrials.gov in accordance with laws and regulations outlined in the FDAMA of 2017 ^{18,23} and Section 801 of the FDAAA of 2007. ^{19,24}	<i>Regulatory framework:</i> Transparency requirements must be integrated into the trial application submitted to the regulatory authorities in the selected member states, thereby making transparency considerations an essential component of preparation before conducting a trial in EU. Entering information through the CTIS public portal is the only way to submit a CTA for regulatory approval, which ensures that trial documentation is automatically published in the public domain based on the approved trial documentation as per the transparency specification outlined in regulation (EU) No. 536/2014. ¹
It requires that the responsible party registers an applicable clinical trial not later than 21 calendar days after enrolling the first human subject. Information on trial design should be published before the first patient is enrolled (applicable to Phases 2 to 4 interventional trials).	Publication of trial design at authorization (i.e., before the start of trial; defined as first act of recruitment of a potential subject) in EU and EEA (Phases 1 to 4 interventional trials).
<i>Data disclosure:</i> Public disclosure of the main characteristics of the trial – primarily endpoints, trial milestones, inclusion and exclusion criteria, high-level overview of trial drug and dose administration, and site locations including details at the time of registration of the trial.	<i>Data disclosure:</i> Public disclosure of the main characteristics of the trial is mostly similar to the US but in addition: investigational medicinal products identification including administration details (max daily dose, drug strength, and total daily dose). XEVMPD data on the investigational medicinal products are also disclosed on a public portal. ^a
No document disclosure at the time of registration of the trial.	Document disclosure (option to redact PD and CCI before submitting for public disclosure): <ul style="list-style-type: none"> • Clinical trial documents (redacted), including but not limited to protocol, protocol synopsis, summary of scientific advice, pediatric investigational plan opinion, data safety monitoring committee charter. • Product-related documents: IMPD (only safety and efficacy sections) and IB, MIA/GMP certificates, QP declarations, labeling.^b
<i>During trial conduct</i>	
Changes in the trial data fields, including but not limited to trial start date, trial completion date, primary completion date, overall recruitment status, substantial amendment (including changes of the planned number of patients) shall be released to ClinicalTrials.gov within the specified (15 or 30 calendar days) timelines.	Obligation to submit notifications including trial timepoint-related details (e.g., site initiation visits, start of recruitment, end of recruitment, end of trial, global end of the trial).
<i>After trial completion</i>	
Tabulated summary of trial results to be submitted 12 months after primary completion date for clinical trials registered on ClinicalTrials.gov. Document disclosure: redacted protocol (including all amendments) and statistical analysis plan.	Clinical trial results summary, layperson summary, and clinical trial report (redacted) to be uploaded 12 months after the end of the trial (defined as last subject's last visit) in EU. ^c

CCI, commercially confidential information; **CTA**, clinical trial application; **CTIS**, Clinical Trials Information System; **XEVMPD**, extended EudraVigilance medicinal product dictionary; **IMPD-Q**, Investigational Medicinal Product Dossier–Quality [section]; **EEA**, European Economic Area; **FDAMA**, Food and Drug Administration Modernization Act; **FDAAA**, Food and Drug Administration Amendments Act; **GMP**, good manufacturing practice; **IMPD**, Investigational Medicinal Product Dossier; **IND**, investigational new drug; **MIA**, manufacturing and importation authorization; **QP**, qualified person.

^aThese data are published at the time of the decision on the trial; however, publication of the data can be deferred for certain types of trials. See article section *EU CTR deferral mechanism and associated publication rules* for more information. ^bDefault is publication at the time of the decision on the trial; however, publication of these documents can be deferred for certain types of trials (see *EU CTR deferral mechanism and associated publication rules*).

^cDefault is 12 months after the end of trial; however, publication of the information can be deferred in some cases – for example, up to 30 months after the end of trial for Phase 1 trials (see *EU CTR deferral mechanism and publication rules*).

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Conclusion

The regulatory landscape for interventional studies in the EU and US could not be more dissimilar in terms of the interplay between transparency requirements and regulatory submissions. The EU CTR has prompted emphasis on transparency as a subject demanding meticulous attention from global regulatory affairs teams from the very inception of the submission strategy and planning for any interventional CTA. However, in the US, transparency is managed as a separate consideration after submission of the investigational new drug application. The increased transparency obligations in the EU pose a considerable operational burden if not managed effectively and need to be factored into the resource and timeline considerations when planning new study applications under the EU CTR. This aspect also needs to be considered for transitioning studies that are ongoing under the Clinical Trials Directive into CTIS before the deadline of 31 January 2025. Several key aspects, such as the availability of harmonized or consolidated trial documentation (including protocols, IB, IMPD), as well as redacted versions for public disclosure, must be considered for a smooth and timely transition into CTIS. Overall, while both the EU and US emphasize transparency to enhance public trust and promote informed decision making, the specific mechanisms, databases, and legal frameworks they employ vary, reflecting their distinct regulatory approaches.

To avoid unintended disclosure of personal data and CCI when submitting documents in CTIS in the EU, sponsors must have at their disposal the available redaction tools to ensure that data sharing in CTIS does not compromise the legal or legitimate confidential interests of the sponsor. Deferral of publication without the additional option of some redaction under certain circumstances may not always be practicable. Redaction and deferral serve distinct purposes and can be used to safeguard personal data and CCI within documents or data submitted. Using redaction alone to protect CCI allows for earlier document disclosure, but it reduces the information available to the public. On the other hand, using the deferral mechanism alone to protect CCI delays public access to data and/or documents but leads to more complete data availability upon publication, although it can disclose information that remains confidential even after the deferral period has elapsed. Neither option is inherently more transparent than the other. Also, the deferral mechanism is crucial for safeguarding CCI in documents such as assessment reports, issued by member states, which may contain sensitive data. Hence, both mechanisms used in conjunction are essential for complying with transparency rules in the EU CTR while ensuring the protection of sponsors' confidential knowledge and intellectual property.

Ideally, the best possible approach from a transparency perspective (for patients and the public) would be the generation of clinical documents that are largely free of personal data and CCI so that they could be published at a very early stage of clinical development. However, since this is not always possible,

stakeholders should concentrate only on the redaction of sensitive confidential information and personal data contained in those documents to promote transparency while maintaining data integrity in clinical development. The evaluation of a recent public consultation on transparency requirements by the EMA will provide more insights into the needs of all stakeholders and help to inform changes that can reduce the burden of sponsors but also ensure that the public has access to the clinical trial information that they think is important.²⁵

The disclosure of clinical trial result summaries and lay summaries under the EU CTR plays a pivotal role in enhancing transparency and accountability. To achieve consistency, alignment with the requirements for posting results on ClinicalTrials.gov is essential. By harmonizing the format, content, and timing of trial result disclosure (to the extent possible) between the EU CTR and ClinicalTrials.gov, we could establish a cohesive and standardized approach to disseminating vital trial information in the public domain, including patients. The industry is very supportive of measures to make information on clinical trials readily available to the public in a format that is easily accessible and understandable.

The implementation of EMA Policy 0070 and Health Canada Public Release of Clinical Information in recent years has enabled sponsors to proactively address the transparency mandate of the EU CTR.^{5,26} This involves creating a foundation of optimal approaches through streamlined documentation (limit inclusion of personal data or CCI from the start of writing) and risk-focused data anonymization procedures. As a result, sponsors are better positioned to smoothly transition into the transparency provisions outlined in the EU CTR framework. There is talk of collaboration between the EMA and Health Canada to standardize transparency practices between EMA Policy 70, Health Canada Public Release of Clinical Information, and the EU CTR. Aligning anonymization practices across these regulatory frameworks promotes transparency while safeguarding confidential data and reducing the operational burden on the sponsors. This will ensure a seamless and cohesive global approach to transparency and reduce regional barriers to accessing vital information on clinical research.

Abbreviations

CCI, commercially confidential information; **CTA**, clinical trial application; **CTIS**, Clinical Trials Information System; **EU CTR**, EU Clinical Trials Regulation; **EEA**, European Economic Area; **EMA**, European Medicines Agency; **GDPR**, General Data Protection Regulation; **IMPD**, Investigational Medicinal Product Dossier; **MAA**, marketing authorization application; **NCA**, national competent authority.

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References

All URLs for references were verified on 4 October 2023.

1. 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. Accessed 17 October 2023. <https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32014R0536>
2. 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. Accessed 17 October 2023. <https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32001L0020>
3. European Medicines Agency. Clinical Trials Information System. Not dated. Accessed 17 October 2023. <https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trials-information-system>
4. European Medicines Agency. Clinical data publication. Not dated. Accessed 17 October 2023. <https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/clinical-data-publication>
5. European Medicines Agency. Transparency. Not dated. Accessed 17 October 2023. <https://www.ema.europa.eu/en/about-us/how-we-work/transparency>

6. Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency. Accessed 17 October 2023. <https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32004R0726>
7. Regulation (EC) No 1049/2001 of the European Parliament and of the Council of 30 May 2001 regarding public access to European Parliament, Council and Commission documents. Accessed 17 October 2023. <https://eur-lex.europa.eu/legal-content/en/TXT/?uri=CELEX%3A32001R1049>
8. European Medicines Agency. Medicines. Not dated. Accessed 17 October 2023. <https://www.ema.europa.eu/en/medicines>
9. European Medicines Agency. Clinical data. Not dated. Accessed 17 October 2023. <https://clinicaldata.ema.europa.eu/web/cdp/home>
10. Clinical trials in the European Union. Not dated. Accessed 17 October 2023. <https://euclinicaltrials.eu/>
11. Regulation (EU) 2018/1725 Regulation (EU) 2018/1725 of the European Parliament and of the Council of 23 October 2018 on the protection of natural persons with regard to the processing of personal data by the Union institutions, bodies, offices and agencies and on the free movement of such data. Accessed 17 October 2023. <https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32001R0045>
12. Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation). Accessed 17 October 2023. <https://eur-lex.europa.eu/eli/reg/2016/679/oj>
13. European Medicines Agency. Guidance document on how to approach the protection of personal data and commercially confidential information while using the Clinical Trials Information System (CTIS) [draft guidance]. Dated 7 April 2022. Accessed 17 October 2023. https://www.ema.europa.eu/en/documents/other/draft-guidance-document-how-approach-protection-personal-data-commercially-confidential-information_en.pdf
14. European Medicines Agency. Joint controllership arrangement with regard to the Clinical Trials Information System (CTIS): Annex II Data protection notice regarding personal data processing in the Clinical Trials Information System (CTIS). Dated 7 December 2021. Accessed 17 October 2023. https://www.ema.europa.eu/en/documents/other/joint-controllership-arrangement-regard-clinical-trials-information-system-ctis_en.pdf
15. [EU] Data Protection Working Party. Opinion 05/2014 on anonymisation techniques. Adopted on 10 April 2014. Accessed 18 August 2023. https://ec.europa.eu/justice/article-29/documentation/opinion-recommendation/files/2014/wp216_en.pdf
16. European Medicines Agency. Annex I to the guidance document on how to approach the protection of personal data and commercially confidential information while using the Clinical Trials Information System (CTIS) Version 1.1;2023:1-28. Accessed 17 October 2023. https://accelerating-clinical-trials.europa.eu/system/files/2023-07/annex-i-guidance-document-how-approach-protection-personal-data-commercially-confidential_.pdf
17. European Medicines Agency. Appendix, on disclosure rules, to the “functional specifications for the EU portal and EU database to be audited – EMA/42176/2014.” Dated 2 October 2015. Accessed 17 October 2023. https://www.ema.europa.eu/en/documents/other/appendix-disclosure-rules-functional-specifications-eu-portal-eu-database-be-audited_en.pdf

18. Food and Drug Administration. FDAAA certification to accompany drug, biological product, and device applications or submissions. Dated 28 March 2018. Accessed 17 October 2023. <https://www.fda.gov/regulatory-information/food-and-drug-administration-amendments-act-fdaaa-2007/fdaaa-certification-accompany-drug-biological-product-and-device-applications-or-submissions>
19. 42 CFR Part 11. PART 11. Clinical trials registration and results information submission. Current as of 25 October 2023. Accessed 17 October 2023. <https://www.ecfr.gov/current/title-42/chapter-I/subchapter-A/part-11>
20. European Medicines Agency. Review of transparency rules for the EU Clinical Trials Information System (CTIS). Dated 3 May 2023. Accessed 18 August 2023. <https://www.ema.europa.eu/en/news/review-transparency-rules-eu-clinical-trials-information-system-ctis>
21. European Medicines Agency. Q&A on the protection of commercially confidential information and personal data while using CTIS. Version 1.2. Dated 16 May 2023. https://accelerating-clinical-trials.europa.eu/system/files/2023-06/questions-answers-protection-commercially-confidential-information-personal-data-while-using-ctis_en.pdf Accessed 17 October 2023.
22. European Medicines Agency. EU CTR update: Year 1. Not dated. Accessed 18 August 2023. https://phuse.s3.eu-central-1.amazonaws.com/Deliverables/Data+Transparency/EU+CTR+Blog+Update_Year+1.pdf
23. US Congress. Food and Drug Administration Modernization Act of 1997. Dated 21 November 1997. Accessed 17 October 2023. <https://www.govinfo.gov/content/pkg/PLAW-105publ115/pdf/PLAW-105publ115.pdf>
24. US Congress. Food and Drug Administration Amendments Act 2007. Dated 27 September 2007. Accessed 17 October 2023. <https://www.govinfo.gov/content/pkg/PLAW-110publ85/html/PLAW-110publ85.htm>
25. Gonzalez-Quevedo R, et al. European Medicines Agency seeks stakeholders' views on future transparency measures for clinical trials. Br J Clin Pharmacol. Published 22 June 2023. Accessed 17 October 2023. <https://doi.org/10.1111/bcp.15825>
26. Health Canada. Public release of clinical information: Guidance document. Dated 12 March 2019. Accessed 17 October 2023. <https://www.canada.ca/en/health-canada/services/drug-health-product-review-approval/profile-public-release-clinical-information-guidance/document.html>