Protecting Commercially Confidential Information (CCI) While Complying with the European Union Clinical Trials Regulation 536/2014

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Revision History

Version	Date	Summary
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1. Overview: Purpose of this document

This White Paper aims to provide clinical study sponsors with practical insights and actionable strategies for effectively identifying, managing, and protecting their Commercially Confidential Information (CCI) within clinical study documentation that must be submitted with Clinical Trial Applications (CTAs) in the European Union (EU) or European Economic Area (EEA), and are subject to public disclosure requirements under the EU Clinical Trials Regulation (CTR) 536/2014. The Clinical Trials Information System (CTIS) disclosure framework represents a cornerstone of the transparency initiative mandated by the CTR. By systematically publishing CTA documents at key stages of the trial's lifecycle, CTIS promotes transparency in clinical research, strengthens protection of public health, and fosters innovation in medical research. Through practical guidance, this White Paper will help sponsors navigate the balance between adherence to regulatory transparency requirements while legitimately protecting CCI.

2. Scope

This White Paper focuses on the identification, management, and protection of CCI within clinical study documents that are submitted in Part I or Part II of an EU CTA and are subject to public disclosure through EU CTIS.

While this paper focuses on solutions for the protection of CCI, it is important that sponsors also consider approaches to protect personal protected data (PPD) in documents that will be made public. Additional PHUSE resources focused on the protection of PPD can be found here: 'Protection of Personal Data in Clinical Documents- A Model Approach';[1] 'De-identification and Anonymization of Individual Patient Data in Clinical Studies - A Model Approach';[2] 'Recommendations for GDPR Compliancy';[3] 'De-identification Standard for SDTM 3.2 Version 1.0';[4] 'Data Anonymisation and Risk Assessment Automation (DeID Toolkit)';[5] 'PHUSE Good Transparency Practice'.[6]

This paper does not seek to address downstream data reuse or secondary research access; its focus remains on transparency at the CTA phase and the principles governing CCI protection therein.

3. Definitions

Commercially Confidential Information (CCI): Any information contained in the clinical reports submitted to the European Medicines Agency (EMA) by the applicant/marketing authorisation holder (MAH) which is not in the public domain or publicly available and where disclosure may undermine the legitimate economic interest of the applicant/MAH.[7]

European Union Clinical Trials Regulation 536/2014 (EU CTR): a comprehensive legislative framework adopted by the European Parliament and Council that governs the conduct, authorization, and supervision of clinical trials on medicinal products for human use across the EU and EEA.

Clinical Trials Information System (CTIS): the centralized EU portal and database established under the EU CTR that serves as the single-entry point for submitting, assessing, and supervising clinical trial applications across the EU/EEA

Disclosure: The mandatory process of publicly releasing clinical trial information, data, and documents through the CTIS to increase clinical trial transparency and promote scientific integrity. The strategy for disclosure under EU CTR is based upon the category of the clinical trial.[8]

- Category 1: Pharmaceutical development clinical trials including phase I in healthy volunteers or patients, phase 0, and bioequivalence and bioavailability
- Category 2: Therapeutic exploratory and confirmatory clinical trials including phase I/II integrated, phase II, and phase III
- Category 3: Therapeutic use clinical trials including phase III/IV integrated, phase IV, and low interventional

4. Problem Statement

The EU CTR mandates public disclosure of specific CTA documents when sponsors initiate a study within the EU/EEA. This transparency obligation creates a multifaceted challenge for sponsors who must simultaneously fulfil regulatory transparency obligations while protecting CCI contained within these documents. While navigating this challenge, sponsors may face operational hurdles such as the:

- Need to extensively redact protocols and corresponding documents
- Need to translate and redact country-specific part II documents (e.g., ICF)
- Lack of an established CCI redaction process during initiation of trial and during the Request for Information (RFI) process
- Lack of CCI libraries and processes for library maintenance
- Absence of robust technology enabled redaction tools

5. Background

History of document disclosure

Document disclosure has evolved into a foundational requirement within the pharmaceutical regulatory landscape. Multiple global regulatory authorities mandate clinical trial document disclosure based on their specific jurisdictional requirements, including the European Medicines Agency (EMA), the US Food and Drug Administration (FDA), Japan's Pharmaceuticals and Medical Devices Agency (PMDA), and Health Canada. These diverse disclosure frameworks, which vary in scope and implementation, collectively form a comprehensive global transparency ecosystem that clinical trial sponsors must navigate effectively. Table 1 below provides a comparative overview of these major disclosure requirements, highlighting key differences in scope.

Table 1: Document Disclosure by Different Regulatory Authorities[9–16]

	PMDA	EMA	FDA	Health Canada
Regulatory Requirement / Policy/ Procedure	Access to Information Held by Administrative Organs (Act. No. 42 of 1999) Procedures for public release of information on review of applications for new drug. PMDA Notification No. 0325004	EMA policy on access to documents (Policy 0043) EMA policy on publication of clinical data for medicinal products for human use (Policy 0070) EU CTR 536/2014	FDA Amendment Act (2007) US 42 CFR Part 11, NIH Final Rule	Health Canada Public Release of Clinical Information
Effective Date	25 March 2013	**EMA Policy 0043:** 30 November 2010 **EMA Policy 0070:** 2 October 2014 **EU CTR 536/2014:** 31 January 2022	18 January 2017	12 March 2019
Documents Published/ Released	Module 1 (1.5-1.10, 1.12) and Module 2 (2.2-2.76)	**EMA Policy 0043:** All written requests for access to any document originated, received or held by EMA **EMA Policy 0070:** Module 2.5 and 2.7 (clinical overview, clinical summaries), Module 5.3 (CSRs, protocols, SAPs, CRFs) **EU CTR 536/2014:** For each trial: Protocols and its synopses, PLPS, patient-facing documents, scientific and plain language summary of results, CSRs (if part of an MAA)	Protocol and SAP of each trial, with the results of each trial	Module 2 (clinical overview, clinical summaries), Module 5.3 (CSRs, protocols, SAPs, CRFs)

Abbreviations: PMDA = Pharmaceuticals and Medical Devices Agency; EMA = European Medicines Agency; FDA = Food and Drug Administration (United States); SAP = Statistical Analysis Plan; CRF = Case Report Form; CSR = Clinical Study Report; MAA = Marketing Authorization Application

In addition to the publication of study and marketing authorization documents, numerous jurisdictions also release comprehensive assessment reports or detailed product reviews that provide insight into the regulatory decision-making processes. These include the EMA Public Assessment Report (EPAR),[17] the Australian Public Assessment Report (AusPAR),[18] EMA Paediatric Investigation Plan Opinion,[19] and the Japanese PMDA assessment report.[20] Furthermore, authorities have established formal mechanisms for members of the public to request access to documents that support clinical trials and marketing authorizations. Examples include EMA Policy 0043[11] and the US Freedom of Information Act (FOIA),[21] which create additional pathways for document disclosure beyond established publication requirements.

In addition to the above regulatory requirements, an increasing number of scientific journals now require the publication of clinical study protocols and statistical analysis plans as supplementary information accompanying manuscript submissions.

Documents that are disclosed under these various policies and procedures often contain CCI. CCI encompasses any information that, if publicly disclosed, could negatively impact the economic interests or competitive position of its owner. Consequently, sponsors must approach these disclosure requirements with careful consideration, ensuring compliance with transparency mandates while simultaneously implementing strategic safeguards to protect their legitimate CCI.

Disclosure Requirements Under EU Clinical Trials Regulation No. 536/2014

The EU CTR was introduced to harmonise and streamline the processes for conducting clinical trials across the EU/EEA. It replaced the Clinical Trials Directive (2001/20/EC)[22] and came into effect on 31 January 2022.

The legal basis for transparency in the EU CTR is outlined in Articles 80 and 81.[13] These provisions govern disclosure and transparency requirements and exempt PPD and CCI from publication.

The CTIS is designed to increase transparency and accessibility of clinical trial information across the EU. The transparency timeline for CTIS disclosure is structured to ensure that stakeholders, including participants, healthcare professionals, and the public, have timely access to critical information about clinical trials.

As of 31 January 2025, all ongoing clinical trials in the EU are required to comply with the CTR and be registered in CTIS. This date signifies the conclusion of a three-year transition period that commenced when the CTR was implemented in the EU.[23]

Upon initial implementation, CTIS transparency rules required sponsors to publicly disclose numerous clinical documents (Appendix 1). However, during a public consultation from 3 May 2023 to 28 June 2023 to review and refine the initial CTIS transparency rules, stakeholders (clinical trial sponsors, academic institutions, patient advocates, and regulatory bodies) provided their feedback and opinion on these rules.[24] The key concerns raised by these stakeholders included complexity of the current transparency framework, short timelines, operational difficulties, heavy administrative workload, and an increased risk of error, which hindered clinical trial registration in the EU. Non-sponsor groups raised concerns about the delay in publishing essential documents such as the trial protocol. This prompted a compelling call for rule simplification to effectively balance transparency requirements with the essential protection of PPD and CCI.

In response, the EMA conducted a comprehensive review of the feedback and finalised its revised transparency rule proposals. This response showed that the stakeholders concerns played a crucial role in the revised transparency rules.

Revised CTIS Transparency Rules

The revised CTIS transparency rules[8] were adopted in October 2023, introducing significant updates to improve public access to clinical trial information. These updates included a revamped CTIS portal[25] that was launched on 18 June 2024. The revisions have created a balanced approach between transparency and the protection of CCI. The revised rules require publishing of the documents that are relevant to trial participants. Furthermore, significant changes were made to the earlier publication of clinical trial data and documents during the clinical trial lifecycle. This change benefits participants, healthcare professionals, and the public by ensuring timely access to critical information. Additionally, the revised rules simplify the publication process, making it more user-friendly for sponsors and stakeholders. The streamlined procedures within the CTIS now enable smoother submission workflows and more efficient access to information. Appendix 2 provides a comparison of the initial rules vs. the revised rules.

Another significant change was the removal of the deferral mechanism that previously allowed sponsors to delay the publication of certain data and documents depending on the clinical trial category. This change ensures that stakeholders have access to the clinical study protocol, protocol synopsis, country-level informed consent forms (ICFs), and patient-facing documents immediately following Member State assessment. The revised rules brought an operational ease due to reduced workload on documents requiring redaction, as fewer documents are subject to publication.

Additionally, after the implementation of the revised transparency rules, fewer structured data fields are publicly available compared to the initial transparency requirements. Detailed information on the structured data can be found in the following EMA documents: 'CTIS Application Fields'[26] and 'Notifications and Results'.[27]

Table 2 summarises the timing of publication of the documents in-scope of the revised CTIS transparency rules.

Table 2: Revised CTIS Transparency Rules - Publication timelines[8,28–30]

CTIS Documents	Category 1 Paediatric or Paediatric Investigation Plan (PIP) Trials	Category 1 Adult Trials	Category 2 and 3 Trials
Protocol with protocol synopsis (synopsis recommended in plain language),[30] patient facing documents	Upon results submission	30 months after the end of trial in EU/EEA	First MSC decision
Summary of medicinal product characteristics (SmPC)	Not published	Not published	First MSC decision
Informed consent form, Subject information sheet	Not published	Not published	Respective MSC decision
Recruitment arrangements, including advertising materials	Not published	Not published	
Interim summary of results (or intermediate data analysis)	Not published	Not published	Not published
Final summary of results	As soon as submitted	Submitted in CTIS secure domain (12 months after the end of trial in EU/EEA) and published 30 months after the end of trial in EU/EEA	As soon as submitted
Layperson summary of results (Plain Language Summary)	As soon as submitted	Submitted in CTIS secure domain (12 months after the end of trial in EU/EEA) and published 30 months after the end of trial in EU/EEA	As soon as submitted
Clinical Study Report (CSR)	As soon as submitted (i.e. within 30 days from marketing authorisation decision)		

- The study protocol, protocol synopsis, and patient-facing documents related to trial endpoints will be publicly accessible for all trials. For Category 1 paediatric or PIP trials, public disclosure will occur at the time of summary results submission. For Category 1 trials in adults, this will happen 30 months after the end of trial in the EU/EEA. For Category 2 (Phase II, Phase III, including Phase I/II) and Category 3 (Phase III/IV, Phase IV) trials, public disclosure will take place at the first MSC decision on the CTA submission.
- Translations of patient facing documents related to clinical trial endpoints (usually submitted under Part I) are not published as they are now submitted under Part II application - compliance with national requirements on data protection.
- Subject information, informed consent forms, recruitment arrangements, and SmPC will be publicly accessible only for Category 2 and 3 trials, upon MSC decision on the CTA submission.
- Layperson summaries of results, summary results, and CSR (if applicable) will be made public as soon as they are submitted to CTIS. The exception is Category 1 trials in adults, which will be made public 30 months after the end of trial in the EU/EEA. However, for regulatory purposes, such documents need to be submitted to CTIS within 12 months of end of trial in the EU/EEA.

CCI in the Context of the EU CTR and the Revised Transparency Rules

The revised transparency rules have established an unprecedented level of transparency in clinical document disclosure. For the first time, critical documents, such as the study protocol and country-level ICF, are now publicly accessible at the onset of a clinical trial in the EU. Additionally, clinical study results are disclosed in the form of structured results and Clinical Study Reports. This fundamental shift in the timeline and scope for transparency necessitates sponsors to reevaluate their strategies for identifying and safeguarding CCI. The reassessment must occur prior to initial CTA submission to avoid any significant implications for intellectual property protection and competitive positioning.

Two primary categories of CCI commonly found in CTA documents published under EU CTR are patentable information and information that, if disclosed, could compromise a sponsor's competitive advantage. Table 3 provides examples of these two categories of CCI. Conversely, information that cannot be considered CCI includes data already in the public domain, known methodologies, and other general information (Table 4).[26]

Table 3: Types of CCI and Potential Examples Relevant to Initial CTA Submission

Patentable Information	Information That May Jeopardize Competitive Advantage if Disclosed
· Details of investigational product chemical name, molecular formula, molecular mass	· Future development plans (planned studies, analysis, strategies)
· Information on dosage and treatment regime	· Detailed information on innovative analytical methods, novel biomarkers
· Details of medicines: release properties (immediate release, sustained release etc.), method of manufacture (dry granulation, spray dried)	· Specific vendor of interest (niche laboratory for exploratory end point analysis)
· Novel approach designed by the applicants, including statistical and strategic information	· Adaptive trial design (screening and retention dates, stopping criteria)
· Information on exploratory endpoints and associated parameters	· Future biomedical research that will be using the novel approach.

Table 4: Examples of Information That Are Not Considered CCI at Initial CTA submission

Examples of Information That Are Not Considered CCI at Initial CTA Submission
· Information already available in the public domain in this context e.g., on ClinicalTrials.gov (countries, D codes, milestones, primary and key secondary endpoints, total number of participants enrolled, key inclusion and exclusion criteria, study population age range)
· Information that is not innovative in any way (well-known methods, name of known cell line)
· Information typically not CCI, unless innovative (storage conditions, stability criteria, statistical methods, pharmacokinetics parameters)
· File paths
· Confidentiality statement
· Drug concentration units of measure
· Study numbers or trial identifiers
· Information disclosed in public assessment report e.g. European Public Assessment Report (EPAR) such as Summary of Product Characteristics (SmPC) and Risk Management Plan (RMP)

While the examples in Table 3 illustrate the types of information that may qualify as CCI in a CTA application, it is recommended that CCI is assessed on a case-by-case basis. CCI classification varies by sponsor, by study, and throughout the dynamic lifecycle of a molecule, as the nature of CCI evolves with the progression of development stages.

In the early stages of product development, a broader range of information is often considered CCI due to the molecule's innovative and proprietary nature. This includes dosage details and rationale, dose scheduling, clinical outcome assessments (COAs), tertiary/exploratory endpoints, unpublished research findings, and future development plans. Much of this information serves as a basis for future patent applications, which are typically filed later in the development process. Consequently, CTA documents supporting early phase trials (e.g., Phase I and Phase I/II), often contain substantially more CCI than those for later phases (Phase II or III).

Early-stage development program / initial trial phases: More information may be considered CCI (e.g., drug dosage)

Late-stage development / later trial phases: Information that was previously considered CCI no longer CCI due to patent, product authorisation, or publication (e.g., drug dosage no longer considered CCI after patent filed)

As the product progresses through development and becomes patented and authorised, the scope of CCI narrows. At this stage, CCI may be limited to specific, detailed information, such as suppliers of raw and starting materials, excipient compositions and formulation specifics, bioanalytical methods, or qualitative and quantitative manufacturing information.

Throughout all stages of development, information related to partner organizations, risk management plans, financial strategies, and business methodologies may be subject to confidentiality agreements, proprietary protections, or classified as trade secrets. Depending on the scenario, these elements may maintain their CCI status regardless of the product's development phase.

Therefore, documents disclosed on CTIS as part of a CTA prior to the marketing approval may contain a broader range of CCI due to the innovative and proprietary nature of early-stage development data. This represents a distinct difference from other transparency requirements that apply following Marketing Authorisation (e.g., EMA Policy 0070), where regulatory agencies enforce stricter transparency standards, and significantly less information is accepted as CCI. This progressive tightening of transparency requirements across the product lifecycle reflects the balanced approach of regulatory authorities; in protecting innovation during development while maximizing public access to information one a product reaches marketing authorization. This shift underscores the need for sponsors to implement meticulous, phase-appropriate management of sensitive data throughout the development and regulatory journey of a pharmaceutical product.

Figure 1 below provides a practical framework for assessing whether information may qualify as CCI, based on key principles reflected in the regulatory guidance.[34, 36] It guides reviewers through sequential questions on whether the information is non-public, proprietary or commercially valuable, whether it reveals future strategy or confidential methods, and whether disclosure could reasonably harm the sponsor's competitive position. The outcome should be documented with an item-specific rationale and supported by appropriate subject matter expert input where needed.

NOTE: This decision tree is an illustrative aid only; it should not replace a case-by-case assessment or be interpreted as official regulator-approved content.

Figure 1: Decision Tree Example for CCI Assessment

Decision Tree	Identify the information proposed for redaction.
1. Is it public or general?	**Yes →** Generally not CCI. Disclose information that is public, standard, general, pharmacopoeial, or already reflected in regulatory/public sources. **No →** Continue.
2. Does it reveal clinical or regulatory strategy?	**Yes →** Potential CCI if it discloses non-public development plans, ongoing or planned studies, submission timing rationale, non-EU regulatory advice, formal authority correspondence, unresolved label discussions, or strategy for special designations, rare diseases, ADCs, NMEs, or new indications. **No →** Continue.
3. Does it reveal proprietary study design or analytical know-how?	**Yes →** Potential CCI if it includes innovative study designs, novel analytical or bioanalytical methods, company-specific assays, immunogenicity assays, sample-size drivers, endpoint variability, measurement precision, or screening/retention assumptions. **No →** Continue.
4. Does it reveal detailed quality, manufacturing, or product development information?	**Yes →** Potential CCI if it includes detailed active substance, formulation, manufacturing, test procedures, validation, synthesis routes, by-products, degradation products, polymorphism, particle size, strain constructs, cloning strategy, operating parameters, or specific material requirements. **No →** Continue.
5. Does it reveal detailed specifications or acceptance criteria?	**Yes →** Potential CCI if it includes detailed company assay specifications, quantitative composition, active substance or finished product specifications, quantitative acceptance criteria, or detailed characterization methods, unless the information is pharmacopoeial, public, or general. **No →** Continue.
6. Does it concern future or non-finalised developments?	**Yes →** Potential CCI if it relates to new formulations, novel packaging, medical device aspects, future developments, pending applications with other authorities, or not yet approved uses or indications not yet in the public domain. **No →** Continue.
7. Would disclosure undermine the company's economic interest or competitive position?	**Yes →** Treat as potential CCI if supported by a specific, substantiated justification. **No →** Generally not CCI.

Table 5 illustrates how borderline CCI categories may be assessed in practice. Key considerations include whether the information is novel, proprietary, commercially valuable, and whether disclosure could reasonably harm the sponsor's competitive position.

NOTE: These fictional examples are for illustrative purposes only; they do not represent regulator-accepted CCI nor guarantee that similar information will automatically qualify as CCI.

Table 5: Fictional Examples of CCI

Category	Fictional Example	Likely CCI?	Detailed Justification
Exploratory Endpoints	The study includes evaluation of the sponsor-developed NeuroResponse Composite Index (NRCI), which combines 18 biomarkers using a proprietary weighting algorithm to identify treatment responders.	Yes	Disclosure would reveal a proprietary scale developed through substantial internal research and investment. The proprietary weighting algorithm constitutes commercially valuable know-how that is not publicly available and is intended for use in ongoing and future development programs. Competitors could use the information to replicate, validate, or adapt the endpoint, thereby reducing the sponsor's competitive advantage and diminishing the value of its investment in endpoint development.
Adaptive Design Elements	Dose selection during the study is governed by a sponsor-developed Bayesian adaptive model integrating efficacy, safety, and exposure data using confidential decision thresholds.	Yes	The adaptive algorithm represents proprietary trial-design methodology developed by the sponsor. Disclosure would provide competitors with access to unique development strategies and operational know-how that could be used in future programs without incurring equivalent research and development costs. The competitive value resides in the specific decision framework rather than the general concept of adaptive design.
Novel Clinical Outcome Assessments (COAs)	Patient benefit will be assessed using the sponsor-developed Digital Cognitive Fatigue Score generated from continuous wearable sensor data processed through a proprietary machine-learning model.	Yes	The clinical outcome assessment (COA) is an internally developed asset that may support future regulatory submissions, qualification activities, and lifecycle management opportunities. Disclosure would reveal innovative measurement approaches and potentially enable competitors to develop similar tools or infer future development strategies.
Vendor-Specific Methodologies	Biomarker data will be processed using Vendor X's proprietary multi-analyte classification platform employing confidential signal-normalization algorithms and proprietary prediction models.	Yes	The methodology incorporates trade secrets and confidential technical processes. Disclosure would reveal commercially valuable information regarding analytical methods that are not publicly available and could undermine the sponsor's competitive interests.
Future Development Plans	If predefined biomarker thresholds are achieved, the sponsor intends to initiate registrational studies in pediatric patients and expand development into autoimmune indications beginning in the next development phase.	Yes	Disclosure would reveal confidential business strategy, lifecycle planning, indication expansion plans, and future regulatory intentions. Competitors could use this information to anticipate market positioning, accelerate competing programs, or adjust commercial strategies, resulting in potential competitive harm.

Current Mechanisms for Protection of CCI in CTIS

Under the revised transparency rules of the CTIS, redaction serves as the primary method for clinical trial sponsors to safeguard CCI and PPD in CTA submission documents slated for publication. This approach aligns with Article 81(4)(b) of the CTR.[8,13]

Redaction entails a meticulous evaluation and obscuring of sensitive text (either CCI or PDD) within a document prior to its upload to the CTIS. The CTIS system allows users to upload both a 'for publication' and 'not for publication' version of a document within a specific application. This dual upload and submission feature ensures that sensitive information remains confidential in the redacted "for publication" version of a document while allowing Member State access to the unredacted versions of documents necessary for regulatory evaluation.

Despite the acceptance of redaction as a method to protect CCI, over redacted documents (e.g., documents containing entire paragraphs or pages that have been redacted) may offer limited value to stakeholders and fail to meet the transparency objectives of EU CTR. Such documents risk rejection by Member States, who review redacted and unredacted CTA documents, necessitating revision of the redaction strategy by sponsors during the brief RFI period. Additionally, an emerging challenge is that Member States may be inconsistent in their review of redactions and have differing opinions on the extent of what is acceptable for redaction. It is therefore recommended that sponsors exercise caution regarding the extent of redaction applied within a document and adhere to EMA's guidance of only redacting specific words or numerical values that are deemed confidential. This approach will increase the likelihood that redactions will be accepted by all Member States.

As noted above, it is acknowledged that documents supporting Phase I studies are likely to contain more CCI and sensitive information compared to those from other study phases. Consequently, documents for Phase I studies conducted in the adult population, categorised under a subset of Category 1 trials, are published on the CTIS 30 months post-trial completion in the EU/EEA. This default delay in publication provides an additional safeguard for sponsors in protecting CCI.

Sometimes written agreements between the sponsor and the third-party provider do not allow copyrighted information to be disclosed in the public domain. This includes patient facing documents containing COAs. In these cases, the sponsor can upload a placeholder document in the 'for publication' section explaining why the patient-facing document cannot be disclosed. The full document should still be uploaded in the 'not for publication' section for the Member State(s) assessment.

Additionally, it is worth noting that, the EU CTR allows sponsors to upload redacted versions of documents without requiring a justification for each redaction. This differs significantly from EMA Policy 0070 or Health Canada's PRCI which require Marketing Authorisation Holders to provide a detailed, specific, and robust justification for each proposed CCI redaction, highlighting the innovative features of the information and how disclosure would undermine legitimate economic interests. Such justification is subject to strict evaluation under these other transparency mechanisms, and insufficient or irrelevant justifications are frequently rejected, with redaction only permitted in limited circumstances.

Risks of Inadvertent Disclosure of CCI and Potential Consequences:

Unintentional disclosure of CCI through the CTIS during the CTA process can have several serious repercussions for sponsors. Primarily, such disclosure can result in the loss of a sponsor's competitive advantage. If proprietary information that provides a company with a market edge is inadvertently revealed, competitors may gain access to this sensitive information, potentially undermining the company's competitive position. This could include novel components of trial design, innovative exploratory endpoints, or unique strategies that differentiate a sponsor's development program.

Additionally, unintended disclosure of CCI can jeopardise intellectual property rights, complicating the protection of patents or trade secrets. Recent legal cases concerning patent invalidity have underscored that if CCI is publicly disclosed before a patent application is filed, it can lead to later loss of patent protection, as the information may render certain patent claims obvious and therefore invalid. The financial implications of such scenarios are also significant, as they may require sponsors to take costly legal actions. Additionally, companies could face legal liabilities from partners, stakeholders, or other entities affected by the disclosure of CCI. To mitigate these risks, it is crucial for sponsors to carefully manage and protect CCI throughout the CTA process.

The EMA permits the retraction of documents that have been inadvertently disclosed to the public through CTIS and contain CCI. This process is designed to protect sensitive information that should not have been made public. To initiate a retraction, a sponsor must submit a request, often referred to as a "ticket," to the EMA. The agency will then review the request and either approve or decline it. If approved, the document will be updated during the next substantial modification cycle.

It is important to note that retractions should be considered rare exceptions rather than routine corrections. Sponsors should exercise extreme caution in their initial submissions to minimise the risk of accidental disclosures, as the CCI will remain publicly accessible until the retraction is processed, which could result in irreversible damage to IP rights or competitive positing.

6. Solutions and Recommendations for Protecting CCI in EU CTA Submissions

Draft CTA Documents with the End (i.e., Disclosure) in Mind: A Proactive Approach to CCI protection

i. Clinical Study Protocol

While drafting the clinical study protocol for submission under the EU CTR, sponsors should consider adopting a "disclosure-first" mindset. Rather than authoring documents and then subsequently performing extensive CCI redaction, the most effective approach is to draft with public disclosure as a foundational consideration. Specifically, sponsors can focus on strategically shifting their mindset to focus on including only the necessary information within the study protocol, rather than including exhaustive details that might contain CCI.

Practical implementation techniques to ensure clear, compliant, and disclosure-ready study protocols include collaborative development that involves legal teams during the drafting process and establishing clear guidelines for content inclusion/exclusion. To effectively minimize the inclusion of CCI in the protocol, stakeholders must first understand what CCI entails and fully comprehend the EU CTR disclosure requirements. Structural considerations should also be made to minimize Chemistry, Manufacturing, and Controls (CMC) information in the protocol, to cross-reference non-public study results to the relevant Investigator's Brochure sections, and to exclude certain COAs from the protocol with appropriate references. Once the document is stable, CCI reviewers, including legal representatives, can ensure compliance.

When CCI must be included in the protocol, referencing it just once and using cross-references throughout the document, employing more generalised terms, such as dose designations (e.g., dose 1, dose 2), are effective practices for strategically managing content. Examples of such unavoidable CCI inclusion include innovative tests, dosing details, biomarkers, and exploratory endpoints. It is recommended to consider the justification for redaction of these types of information during the drafting phase and have this available when engaging with Member States during the RFI process.

Protocol templates that include explicit guidance regarding public disclosure requirements can serve to remind teams that the protocol will be publicly accessible, that the inclusion of CCI should be limited, and that certain content (e.g., training material) may not be able to be redacted at different stages of the development lifecycle.

Standardised templates, such as those developed by TransCelerate [31] can facilitate drafting the protocol with disclosure in mind and minimize the need for extensive redaction. However, achieving consistency and standardization can be challenging when working across multiple diverse therapeutic areas with different sensitivity profiles, when working with numerous research collaborators, and in balancing disclosure requirements with the need for scientific explanation.

Advanced technology-enabled protocol drafting tools may also assist in minimizing the inclusion of CCI; however, it is important to recognize that even when these technologies are used, expert review is still a necessary component in the writing and disclosure process.

ii. ICFs and Other Patient Facing Documents

Patient-facing materials such as ICFs, PLPS, and participant brochures contain clinical content that parallels information in the protocol. The most effective approach is to completely exclude CCI from these documents whenever possible. This strategy focuses on providing information essential for patient understanding and informed decision-making without revealing proprietary details, thereby minimizing the need for redaction. This preventative approach is particularly crucial considering these documents often require translation into local languages, with each translation potentially needing separate redaction.

Sponsors should be particularly vigilant about how information is translated between technical protocol language and participant-friendly terminology. The same underlying CCI may be expressed differently in patient-facing documents due to audience considerations, creating potential disclosure risks that might be overlooked. For example, a novel mechanism of action described in technical terms within the protocol might be simplified in participant materials but still reveal proprietary information. This variation in expression may require sponsors to conduct parallel CCI reviews across document types rather than assuming that redactions in one document will address all instances of the same information.

To implement these approaches effectively, sponsors should develop distinct drafting guidelines specifically for patient-facing materials, create standardized template language that conveys necessary information without including CCI, establish dedicated review processes focused specifically on eliminating CCI from these documents, and provide specialized training to medical writers on techniques for accurately translating protocol content into participant-friendly language while protecting proprietary information.

Establish and Manage a Redaction Process

For clinical trial sponsors, creating and managing an internal redaction process is essential to consistently protect CCI in EU CTA documents and mitigate disclosure risk. Since complete exclusion of CCI in CTA documents is unlikely, establishing a systematic process for key stakeholders to identify CCI for redaction will help to ensure consistency and mitigate the risk of inadvertent disclosure.

i. Determine the Stakeholders to Involve

Developing a robust redaction process requires engaging appropriate stakeholders who will be responsible for executing each step of the process.

For example, sponsors may find it useful to identify the functions who will be responsible for:

- identifying documents for redaction
- initiating the redaction process
- developing and maintaining a CCI library
- identifying CCI for redaction
- approving CCI for redaction
- applying redaction to documents
- tracking timelines for redaction
- uploading redacted versions of documents into CTIS

Document ownership and management responsibilities vary across organizations. For example, certain CTA documents may be drafted and managed by internal teams (e.g., protocol) whereas others may be the responsibility of external partners or CROs (e.g., country-level ICFs). Creating a visual process map that includes these steps alongside responsible stakeholders can help illustrate workflow and clarify handoff points between different functional areas and external stakeholders.

Although the roles involved in the redaction process vary by sponsor, the list below outlines potential roles to engage in the process. These roles are suggested due to the expertise in the study methodology and scientific conduct, product development program, and/or information that may serve as a basis for a patent application. It is suggested to identify the role and responsibilities for each stakeholder. It is also important to note that a greater number of stakeholders may be required while the initiating a study or development program, relative to the number of stakeholders that are involved in following study completion or marketing authorisation application.

Stakeholders to consider including in a sponsors redaction process

- Program Management
- Clinical Development
- Regulatory
- Statistics
- Medical Writing
- Pre-clinical
- Clinical Drug Supply
- Safety/Pharmacovigilance
- Chemistry, Manufacturing, and Controls
- Legal/Patents
- Medical Affairs
- Clinical pharmacology/CPMS
- Pharmacometrics

ii. Consider the Role of Partners and Collaborators

Collaborations with partner companies in therapeutic development are governed by confidentiality agreements and established working guidelines that protect sensitive information and ensure regulatory compliance. However, aligning with partners for Health Authority submissions presents unique challenges, particularly for submissions requiring public disclosure under the EU CTR.

Each collaboration may require a tailored approach, depending on the partner's SOPs and the agreements in place between the two companies. For example, one partner may impose stringent requirements for data handling and redaction, while another may adopt a more flexible approach. This variability can create challenges in harmonising processes.
To ensure alignment during submissions, partners and collaborators should be integrated as key stakeholders in the CCI identification and redaction process, requiring careful planning, open communication, and a shared commitment to safeguarding CCI while fulfilling regulatory obligations.

iii. Consider EU CTR Timelines

The assessment timeline for an initial application is between 60 to 106 days.[23] The trial can only be initiated after the application has been approved. To avoid delays, sponsors are recommended to establish internal timelines to prepare redacted documents to align with the EU CTR requirements. Sponsors may benefit from identifying and involving stakeholders early, developing the CCI library, and initiating redaction of documents during the drafting stage. This approach is particularly advantageous when the number of authors is limited, and the drafting timelines are flexible. However, sponsors should carefully consider the scope of documents subject to publication via CTIS, as these documents may be authored by different functions within the organisation. For instance, protocols, country-level ICFs, and patient-facing documents, might involve different functional areas, complicating consistent execution of this approach. Even if CCIs are identified during the drafting stage, sponsors must still establish a process for implementing redactions to the final versions of documents submitted through CTIS.

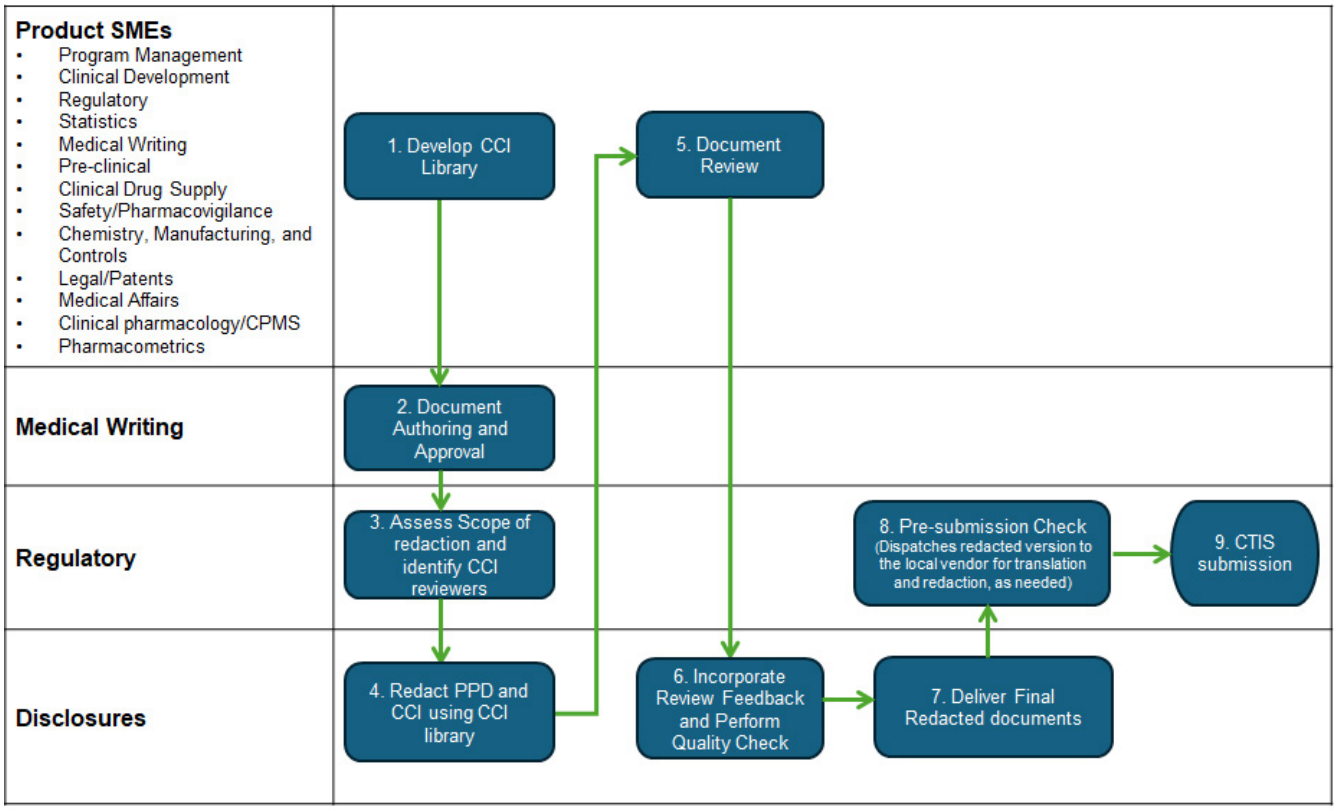
Alternatively, sponsors facing tight timelines or involving numerous contributors to the document may prefer to identify CCI during the authoring process. This method allows stakeholders to have a clear understanding of the CCI and allow the identification early.

It is crucial for sponsors to consider the time required for the redaction process, especially under strict Request for Information (RFI) response timelines, where documents like protocols may need to be updated and redacted within a 12-calendar days or shorter timeframe.

iv. Map the Process

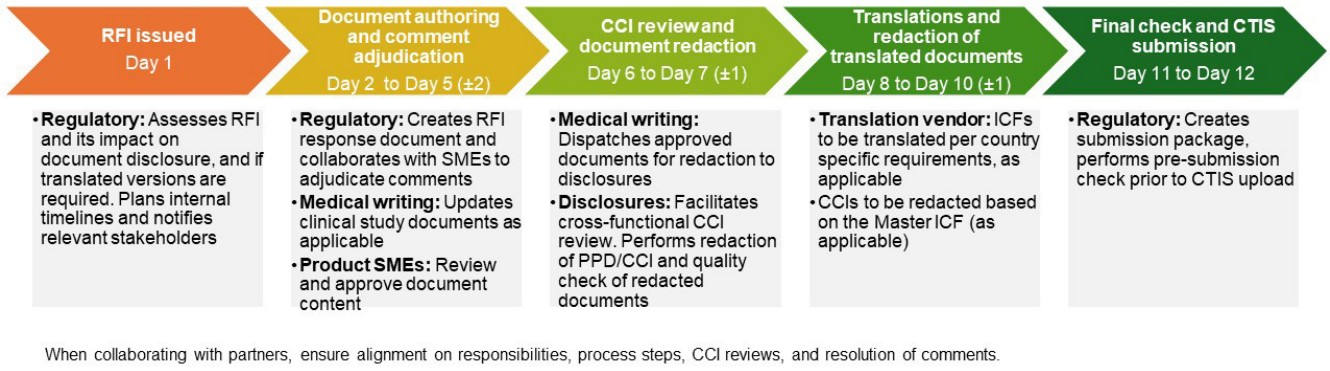
Once the stakeholders involved in the CCI identification and redaction process are determined sponsors should map out a comprehensive process. This process should detail each step, the stakeholders involved, the tools used, and the timelines to be followed. Figure 2 and Figure 3 provide an example of a high-level redaction process that sponsors might consider for managing documents submitted with an initial CTA and in response to an RFI, respectively.

Figure 2: Potential Redaction Process for an Initial CTA submission



When collaborating with partners, ensure alignment on responsibilities, process steps, CCI reviews, and resolution of comments.

Figure 3: Potential Redaction Process for RFI Submission



When collaborating with partners, ensure alignment on responsibilities, process steps, CCI reviews, and resolution of comments.

After implementation, it is suggested to continually monitor and evaluate the redaction process and incorporate feedback from stakeholders to improve. Sponsors may benefit from establishing key metrics and checkpoints to evaluate the effectiveness of their redaction process and conduct assessments of the process to help identify potential issues or bottlenecks before they occur.

As trial documents undergo amendments, sponsors may need to revise CCI redactions. This could mean either removing previously redacted content or adding new CCI. As trials progress, information once identified as CCI may lose its confidential status due to the publication of information throughout the clinical trial lifecycle. Re-evaluating CCI requires effective management of internal timelines, awareness of regulatory requirements, and proactive planning. A well-organised process will avoid unnecessary redactions as well as lapses in CCI.

Create and Maintain a CCI Library

To facilitate writing with disclosure in mind and streamline the redaction process, sponsors can develop a centralized library of CCI identified throughout the product and study lifecycle. This library can serve as a valuable resource for identifying potential CCI that should be excluded during the drafting of documents or flagged for redaction when preparing documents for publication. However, simply creating the library is not enough; it is equally critical to maintain and update this library throughout the development lifecycle. Global (or centralized transparency team) and local affiliates should establish clear governance for the CCI library, with defined ownership, update responsibilities, and communication pathways to ensure the CCI library is maintained consistently and remains accessible for use by all relevant functions. Depending on the sponsor's operating model, ownership may reside with the Transparency/Disclosure function, Legal/IP, Clinical Operations, Medical Writing, or another designated cross-functional governance body.

Sponsors should track publication dates of when CCI was released into the public domain. Additionally, the library should document the CCI that need to be redacted and when specific information ceases to qualify as CCI (i.e., when it becomes publicly available, such as through patent applications, conference presentations, publications, or registries). This tracking ensures that such information is no longer treated as CCI in future disclosure activities.

By the time sponsors prepare anonymized Clinical Study Reports (CSRs) for submission, the CCI list should be thoroughly refined to include only genuinely sensitive information, with clear justification for why its protection remains necessary. For global sponsors managing EU CTR, EMA Policy 0070, and Health Canada PRCI simultaneously, consistency in CCI determinations is not merely a best practice, it is a strategic imperative. A shared CCI library directly addresses this need and an example CCI library structure is depicted below (Figure 4)

Figure 4: Example CCI Library Structure

Document name and version	Section no./Heading	Page no. and Line no.	Proposed CCI	Published? If yes, provide link. If no, move to the next columns	Rationale	Responsible Function
Protocol v1.0	Section X: Physical, Chemical and Pharmaceutical Properties of the Formulation	Pg. 23, Line 17	ABC	No	Information was collected through an innovative assay method developed in-house, which is yet to be validated. The present information is exploratory in nature.	CMC

Review/ Discussion date	Decision on CCI (Y/N)	Reviewer and Review date	Approver and Approval date	Proposed date until when the information remains CCI	Next planned review date
17-Mar-23	Y	Name and Date	Name and Date	15-Jun-26	15-Jul-24

Use AI and Large Language Models for CCI identification

Large Language Models (LLMs) and Generative AI technologies can support the identification and redaction of CCI in clinical trial documents, though implementation requires careful security controls and validation in regulated environments. Unlike traditional rule-based systems that rely solely on pattern matching or keyword lists, LLMs can provide contextual analysis of unstructured text, potentially supporting detection of complex CCI patterns such as manufacturing processes, dosing regimens, product formulations, and exploratory endpoints. Advanced LLM implementations can be trained on domain-specific pharmaceutical language to recognise implicit references to proprietary information that might otherwise be missed by conventional methods. However, sponsors must recognise that no AI technology is perfect, and point-in-time considerations are critical when it comes to CCI; therefore, any AI-generated recommendations require human verification.

For pharmaceutical sponsors and CROs, implementing LLMs for CCI identification can reduce manual redaction effort while maintaining human oversight. LLM-assisted redaction can help ensure consistency across document sets while adapting to varying formats, writing styles, and scientific conventions found in clinical study protocols, CSRs, and related reports. When properly validated and implemented with appropriate security controls, LLM integration may support auditable decisions that align with regulatory compliance requirements for EMA Policy 0070, EU CTR, and Health Canada PRCI. While AI and LLM tools offer meaningful efficiency gains in identifying and flagging potential CCI, their outputs serve as a starting point for, not a substitute for, the informed judgment of experienced transparency professionals.

7. Conclusion

The EU CTR has revolutionised clinical trial transparency by mandating early public disclosure of CTA documents through CTIS. While this regulatory framework fosters public trust, it presents sponsors with unprecedented challenges in in protecting CCI. The removal of deferral mechanisms has elevated redaction to the primary safeguard for sensitive proprietary data in CTA documents.

A critical complexity sponsors now face is the need to disclose the same document at multiple trial stages to meet numerous jurisdictional requirements, making it impossible to maintain a single set of redacted documents. As CCI evolves throughout the product lifecycle, sponsors must implement proactive, strategic, and technology-driven practices to manage disclosure. Sponsors should consider as best practice while drafting documents to review with disclosure in mind. Also, this includes maintaining robust processes, standardized templates, early engagement of appropriate stakeholders, and fostering collaboration with cross functional teams.

To navigate this evolving landscape, sponsors should consider adopting these strategic approaches:

- Deploy a proactive “disclosure-by-design” mindset when drafting CTA documents, minimizing CCI inclusion from the onset
- Establish a systematic redaction process to drive consistency and mitigate CCI disclosure risk across document types
- Build and maintain dynamic CCI libraries that evolve with the product lifecycle and regulatory expectations
- Invest in secure, AI-enabled solutions to streamline redaction workflows
- Educate and align cross-functional teams around a unified strategy for transparency and CCI protection
- Engage proactively with regulators and industry peers to shape future standards and best practices

As the clinical trial disclosure landscape continues to evolve toward increased transparency, regulatory harmonisation, and digital transformation, sponsors may proactively embrace these practices to lead in responsible clinical trial disclosure. This forward-thinking approach ultimately serves the dual purpose of protecting legitimate commercial interests while advancing the broader goals of scientific progress and public trust in clinical research.

8. Disclaimer

The opinions expressed in this document are those of the authors and should not be construed to represent the opinions of PHUSE members; respective companies/organisations or Regulator's views or policies. The content in this document should not be interpreted as a data standard and/or information required by Regulatory Authorities.

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12. Appendices

Appendix 1: Initial CTIS Transparency Rules - Publication timelines[32,33]

CTIS data and documents	Category 1	Category 2	Category 3
Main Characteristics*	· Date of decision · Up to publication of final summary of results	Date of decision	Date of decision
Notifications*	· As soon as submitted · Up to publication of final summary of results	As soon as submitted	As soon as submitted
Subject information sheet	· Date of decision · Up to 7 years after the end of trial in EU/EEA	· Date of decision · Up to 5 years after the end of trial in EU/EEA	Date of decision
Protocol, Protocol synopsis, Scientific Advice, IB, IMPD S&E sections, Responses to RFI	· Date of decision · Up to 7 years after the end of trial in EU/EEA	· Date of decision · Up to 5 years after the end of trial in EU/EEA	· Date of decision · Up to publication of final summary of results
Interim summary of results (intermediate data analysis)*	· As soon as submitted · Up to 12 months after interim analysis date · Up to 30 months after the end of trial in EU/EEA	As soon as submitted	As soon as submitted
Final summary of results, Lay person summary of results*	· As soon as submitted · Up to 12 months after the end of trial date in EU/EEA · Up to 30 months after the end of trial in EU/EEA	As soon as submitted	As soon as submitted

*Not permitted for paediatric trials or paediatric investigational plan (PIP) trials

Appendix 2: Comparison of Initial versus Revised CTIS Transparency Rules[8,28,29,33,34]

	Initial CTIS Transparency Rules	Revised CTIS Transparency Rules
Timelines	The initial CTIS transparency rules were applicable from 31 January 2022 until 17 June 2024.	The revised CTIS transparency rules were adopted by the EMA Management Board on 5 October 2023 and implemented on 18 June 2024 with the launch of the revamped CTIS portal.
Deferral Mechanism	The deferral mechanism allowed sponsors to delay the publication of certain data and documents based on trial category, for up to a maximum period of 7 years after the end of trial in EU/EEA.	The deferral mechanism was removed to facilitate access to key clinical trial information at an early stage. Classification of trials under one of the three applicable categories is retained but no longer linked to the use of deferrals.
CCI protection	The deferral mechanism was the preferred tool to protect CCI, redactions were less emphasized. Redaction-related RFIs were issued if the documents were extensively redacted while deferrals were simultaneously applied.	Redaction is the only tool to protect CCI, significantly reducing the likelihood of receiving redaction-related RFIs.
Publication of Documents	Many documents were published, except for quality related documents. The timing of publication of data and documents for historical trials (CTAs submitted before 18 June 2024) was based on the agreed deferral.	Key documents most relevant for the public, participants, and researchers are published early. For historical trials only limited structured data will be made publicly available across all trial categories. Documents submitted 'for publication' before 18 June 2024 will not be publicly accessible. However, certain CTA updates may trigger the publication of documents in-scope of the revised CTIS transparency rules.
Stakeholder Impact	Increased workload on documents requiring redaction as large number of documents were subject to publication	Reduced workload on documents requiring redaction, as fewer documents are subject to publication.