10 July 2023
EMA/212507/2021
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) Version 1.1

Table of contents

1. General information

1.1. Introduction

The European Clinical Trials Regulation (EU) No 536/2014[1] (hereinafter 'the Clinical Trials Regulation' or 'CTR') repeals Directive 2001/20/EC on clinical trials[2] (CTs) and establishes a harmonised approach to the submission, assessment, supervision, and reporting of clinical trials information with the implementation of consistent rules throughout the European Union (EU)/European Economic Area (EEA) Member States (MSs).

The Clinical Trials Regulation aims to foster innovation through harmonised content of clinical trial applications submitted to Member States for assessment, to increase collaboration between the Member States on the assessment of clinical trial applications, and to increase transparency and availability of information on clinical trials and their results. Publicly available information foreseen by the CTR should contribute to protecting public health and fostering the innovation capacity of European medical research, while recognising the legitimate economic interests of sponsors and protecting personal data.

In accordance with Recitals 66 and 67 and Articles 80 and 81 of the Clinical Trials Regulation, the Agency, in collaboration with the Member States and the European Commission (EC), has the obligation to set up and maintain an EU Portal as a single-entry point for the submission of data and documents relating to clinical trials, and an EU Database containing the data and documents submitted via the EU Portal. The EU Clinical Trials Portal and Database are jointly referred to as the EU Portal and Database (EUPD).

To ensure transparency of clinical trials, the EU Database should be publicly accessible and data should be presented in an easily searchable format.

The EU database is a key instrument to ensure transparency of clinical trial information. The database serves as the source of public information on assessed clinical trial applications, from the time of decision until the submission of summary results. Access to this information is fundamental to enable trust in the clinical research conducted in the European Union.

The EUPD and associated workspaces provide MSs, the European Commission, the Agency, sponsors and applicants[3] of a marketing authorisation with an effective network to streamline and facilitate the preparation of the flow of information for the authorisation and supervision of clinical trials in the EU/EEA.

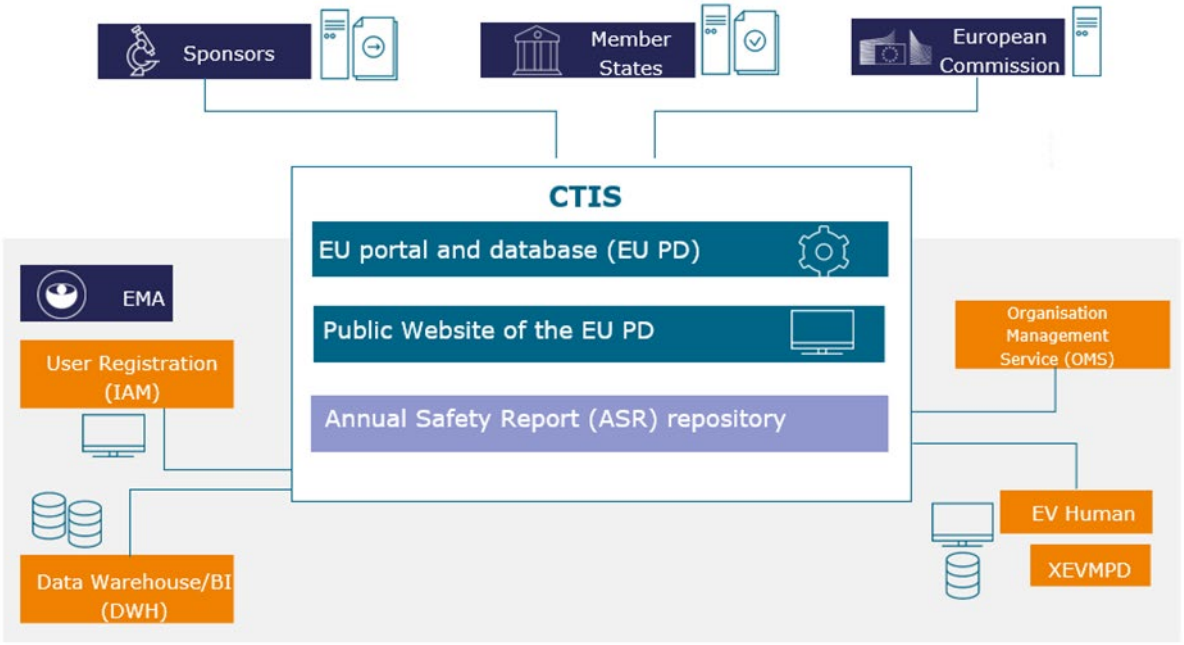
The EUPD enables the submission and storing of clinical trial information and is one of the two components of the Clinical Trials Information System (CTIS), also including the module for submission of the Annual Safety Reports (ASRs). Throughout the document overall reference is made to the use of CTIS.

[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.
[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.
[3] Note that where this document refers to 'sponsor users' or 'sponsor domain', this may refer to, respectively as applicable, users acting on behalf of marketing authorisation applicants/holders and related user domain areas in the system.

To streamline the use of the already available information stored in other databases managed by the Agency and to promote consistency and standardisation, CTIS consumes data from the following data sources:

- Extended EudraVigilance Medicinal Product Dictionary (XEVMPD).
- Organisation Management Service (OMS).
- Identity Access Management (IAM).

The interface of CTIS with other EMA data sources is shown in the figure below:



1.2. Scope

The CTR brings an unprecedented level of transparency in terms of publication of clinical trials information for trials conducted in the EU/EEA. Access to this information, including trial results, is important to allow prompt recruitment of patients at the site, avoid duplication of efforts and ultimately foster innovation and promote clinical research in the European Union and the European Economic Area.

This guidance document aims to help CTIS users to navigate through the system functionalities and understand the main principles to be followed to enable protection of personal data and commercially confidential information while using CTIS and publishing clinical trials data and documents.

The following chapters provide information on:

- Description of CTIS structure and components, including a description of the functionalities and publication rules for clinical trials information submitted to CTIS (chapter 2).
- Principles to be followed enabling protection of personal data as part of the clinical trial information submitted to CTIS (chapter 3).
- Principles to be followed enabling protection of commercially confidential information (CCI) as part of the clinical trial information submitted to CTIS (chapter 4).
- The protection of personal data and CCI in inspection reports (chapter 5).

1.3. Legal framework

The CTR sets out requirements for the protection of personal data, CCI and increased transparency of clinical trials in the EU/EEA. These requirements apply to information contained in the EU Database.

Data and documents defined in the CTR are submitted via the EU Portal, stored in the EU Database and subject to the disclosure rules.

Article 81(4) of the CTR states that the EU Database shall be publicly accessible unless, for all or parts of the data and information contained therein, confidentiality is justified on any of the following grounds:

a) protecting personal data in accordance with Regulation (EU) 2018/1725[4];

b) protecting commercially confidential information, in particular through taking into account the status of the marketing authorisation for the medicinal product, unless there is an overriding public interest in disclosure.

c) protecting confidential communication between Member States in relation to the preparation of the assessment report.

d) ensuring effective supervision of the conduct of a clinical trial by Member States.

Recital 68 of the CTR states that: in general, the data included in a clinical study report should not be considered commercially confidential once a marketing authorisation has been granted, the procedure for granting the marketing authorisation has been completed, the application for marketing authorisation has been withdrawn. In addition, the main characteristics of a clinical trial, the conclusion on Part I of the assessment report for the authorisation of a clinical trial, the decision on the authorisation of a clinical trial, the substantial modification of a clinical trial, and the clinical trial results including reasons for temporary halt and early termination, in general, should not be considered confidential.

Structured data fields and documents from the clinical trial application dossier can be made public after the decision on the clinical trial has been taken (Article 81(5) of the CTR), unless there is an overriding public interest for a particular clinical trial to do so earlier. This applies only in exceptional circumstances where the general public interest in having information made publicly available may outweigh considerations for the information to remain confidential. Thus, only applications on which a decision has been issued by a Member State concerned (MSC) will be made public. This applies to any decision outcome, i.e., authorisation, authorisation with condition(s) or whether the authorisation is refused.

Information on initial applications which are only for assessment of Part I of the dossier (Article 11 applications) will not be made public until a Part II has been submitted to the MSC and a decision has been issued by at least one of the MSC(s).

Applications which are not validated or those withdrawn by the sponsors before a decision is issued will not be made public.

In addition, the following provisions related to the protection of personal data and CCI should be also taken into account as part of the guidance provided in this document.

[4] Article 81(4) of Regulation EU (No) 536/2014 refers to Regulation (EU) No 45/2001 replaced by Regulation 2018/1725, the EUDPR

Data protection related provisions:

Article 93 of the CTR expressly makes reference to EU data protection legislation i.e., to the now applicable GDPR with reference to the processing of personal data carried out in MSs (including processing by regulatory authorities and ethics committees) as well as sponsors, marketing authorisation applicants or holders and the EUDPR, which applies to the processing of personal data by the European Commission and the Agency.

CTR details the need for the protection of personal data as follows:

- Recital 67: *No personal data of data subjects participating in a clinical trial should be recorded in the EU database. The information in the EU database should be public, unless specific reasons require that a piece of information should not be published, in order to protect the right of the individual to private life and the right to the protection of personal data, recognised by Articles 7 and 8 of the Charter (…).*
- Article 56(1): *All clinical trial information shall be recorded, processed, handled, and stored by the sponsor or investigator, as applicable, in such a way that it can be accurately reported, interpreted and verified while the confidentiality of records and the personal data of the subjects remain protected in accordance with the applicable law on personal data protection.*
- Article 56(2): *Appropriate technical and organisational measures shall be implemented to protect information and personal data processed against unauthorised or unlawful access, disclosure, dissemination, alteration, or destruction or accidental loss, in particular where the processing involves the transmission over a network.*
- Article 81(2): *The EU database shall be established to enable cooperation between the competent authorities of the Member States concerned to the extent that it is necessary for the application of this Regulation and to search for specific clinical trials. It shall also facilitate the communication between sponsors and Member States concerned and enable sponsors to refer to previous submissions of an application for authorisation of a clinical trial or a substantial modification (…).*
- Article 81(4): *The EU database shall be publicly accessible unless, for all or part of the data and information contained therein, confidentiality is justified on any of the following grounds:*
  (a) protecting personal data in accordance with Regulation (EC) No 45/2001.
- Article 81(6): *The EU database shall contain personal data only insofar as this is necessary for the purposes of paragraph 2.*
- Article 81(7): *No personal data of subjects shall be publicly accessible.*
- Article 93(1): *Member States shall apply Directive 95/46/EC[5] to the processing of personal data carried out in the Member States pursuant to this Regulation.*
- Article 93(2): *Regulation (EC) No 45/2001[6] shall apply to the processing of personal data carried out by the Commission and the Agency pursuant to this Regulation.*

[5] Replaced by Regulation (EU) 2016/679 (GDPR).
[6] Replaced by Regulation (EU) 2018/1725 (EUDPR).

Commercially Confidential Information (CCI) related provisions:

- Recital 68 clarifies that, for the purposes of the CTR, in general the data included in a clinical study report should not be considered commercially confidential once the procedure is finalised.
- For clinical trials intended to be used in a marketing authorisation application in the EU/EEA, Article 37(4) of the CTR requires that the applicant for a marketing authorisation submits the clinical study report to the EU database within 30 days after the day the marketing authorisation has been granted, the procedure for granting marketing authorisation has been completed, or the applicant has withdrawn the application.
- Article 81(4) of the CTR states that: *The EU database shall be publicly accessible unless, for all or part of the data and information contained therein, confidentiality is justified on any of the following grounds: ……. (b) protecting commercially confidential information, in particular through taking into account the status of the marketing authorisation for the medicinal product, unless there is an overriding public interest in disclosure.*

Overriding public interest anticipating the publication of clinical trials information means that the general public interest in having information made publicly available may outweigh considerations that the same information should remain confidential. It applies in exceptional circumstances only.

In the context of inspection reports, the CTR sets out the following:

- Article 53(2): *The sponsor shall submit to the Member States concerned, through the EU portal, all inspection reports of third country authorities concerning the clinical trial.*
  When requested by a Member State concerned, the sponsor shall submit a translation of the report or of its summary in an official language of the Union indicated in the request.
- Article 78(6): *Following an inspection, the Member State under whose responsibility the inspection has been conducted shall draw up an inspection report. That Member State shall make the inspection report available to the inspected entity and the sponsor of the relevant clinical trial and shall submit the inspection report through the EU portal.*
- Furthermore, Article 13 of the Commission Implementing Regulation (EU) 2017/556 of 24 March 2017[7] states (…) *The inspection reports submitted through the EU portal shall not contain personal data of clinical trials' subjects.*

The implementation of the disclosure rules of the Clinical Trials Regulation is without prejudice to the application of Regulation (EC) No 1049/2001[8] and citizens' right to request documents under that Regulation.

[7] COMMISSION IMPLEMENTING REGULATION (EU) 2017/ 556 - of 24 March 2017 - on the detailed arrangements for the good clinical practice inspection procedures pursuant to Regulation (EU) No 536 / 2014 of the European Parliament and of the Council (europa.eu).
[8] 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

2. Rules of clinical trial information in CTIS pertaining to submission and publication

2.1. Introduction

This chapter describes CTIS functionalities implemented to enable protection of personal data and commercially confidential information. Content of this chapter might be impacted by the results of the public consultation on CTIS transparency rules launched in May 2023.

Please note that clinical trials with a decision issued after mid-August 2022, for which sponsors have requested any type of deferrals in the application form, are currently not published in CTIS public domain. This is a temporary measure until EMA completes the review of the functionalities of the CTIS public portal following the public consultation held in May and June 2023.

This chapter describes the type of clinical trial information, including data and documents, submitted to CTIS and how this information should be managed to protect personal data and commercially confidential information (CCI), while ensuring publication principles are met.

Principles of protection of personal data and CCI should be followed while using CTIS, as required in the CTR. The clinical trial information flow starts in the CTIS secure domain with a clinical trial application submitted by the sponsor, or delegated entities, to carry out a clinical trial in the EU/EEA and the corresponding evaluation performed by the MSC.

Following the evaluation of the application, a decision is issued by each MSC for the application, on whether the trial is authorised, authorised with conditions or not authorised. After a decision has been issued by the Member States concerned, the data and documents submitted to the CTIS for the trial will be made available to the public, unless the sponsor has applied for a deferral.

Where requested, a deferral will delay the publication of a set of data and documents (e.g. protocol, investigator brochure, informed consent information sheet) for a certain number of months or years after the end of the trial in the EU/EEA or until the publication of the final summary of results, as specified in the Appendix, on disclosure rules, to the "Functional specifications for the EU portal and EU database to be audited - EMA/42176/2014."[9]

In case of a 'Not Authorised' initial clinical trial application (CTA) with deferrals, the last MSC decision date will be considered as equal to the date of the end of the trial in the EU/EEA for publication purposes.

Data and documents of an application that are not subject to publication (e.g., IMPD-Q, draft assessment reports, financial arrangements) will not be published after a decision on the application has been issued, regardless if deferrals were applied or not for the trial.

After the authorisation is obtained, the trial may start, and the MSC will supervise the trial running in their territory. After the initial application, other application types may be submitted by the sponsor for the same trial such as, substantial modifications to the initial application or the addition of new MSC which are also subject to the assessment and decision by each MSC.

In addition to the above, non-substantial modifications to the content of the application dossier can be applied by the sponsor during the trial life cycle up to its completion, as well as notifications to the MSC by the trial, of events of relevance, such as the occurrence of a serious breach or an urgent safety measure. The MSC supervise the conduct of the trial in their territory with different means, including

[9] https://www.ema.europa.eu/en/documents/other/appendix-disclosure-rules-functional-specifications-eu-portal-eu-database-be-audited_en.pdf

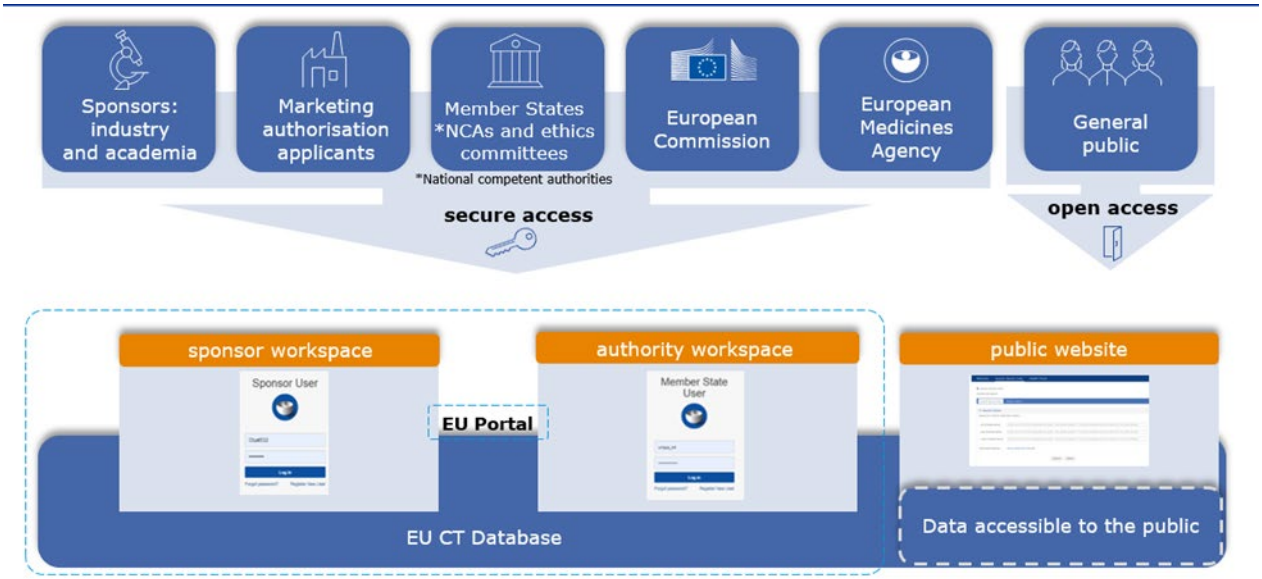
monitoring and assessing safety reports such as Annual Safety Reporting (ASRs), performing *ad hoc* assessment including for safety related matters, performing Good Clinical Practice (GCP) inspections and having the possibility to apply corrective measures to request modifications, suspend the trial or revoke the trial authorisation, for example.

The sequence of events occurring during the trial life cycle might require the collection and processing of personal data for the purposes set out in Article 81(2) of the Clinical Trials Regulation. Data and documents provided by the users in CTIS may also contain information that is considered commercially confidential. As defined in Article 81(4) of the CTR, personal data of trial participants, as well as other types of personal data, and commercial confidential information are exempted from publication.

Within CTIS secure domains for sponsors and Member States, users can have access to clinical trial data and documents for the trials of their concern. These users are clinical trial sponsors or delegated parties, marketing authorisation applicants/holders, EU/EEA Member States (encompassing responsible national competent authorities and Ethics Committees), the European Commission and the Agency.

Access to data and documents in CTIS secure domain is managed through the user's profile.

The image below represents the different domains in CTIS, including sponsors' and authorities' domains with secure access and a public domain.



2.2. Clinical trial information in CTIS and document submissions 'for publication' and 'not for publication'

Table I and table II in the Annex to this document provide an overview of the types of data and documents submitted to CTIS by sponsors and Member states users, respectively, during the trial life cycle, from CTA submission to summary of results and clinical study reports, as applicable.

In CTIS, documents can be provided in version 'for publication' and 'not for publication'. The requirements to have both versions will depend on the document type and content and may not be necessarily the same in every instance.

When both versions are required, for example for GMP documentation with signature of the qualified person, as applicable, these documents should be provided at the same time.

The following general principles apply:

- The CTIS functionality allows for the submission of required information in the secure domain and provides users access depending on their user profile, thus protecting personal data and the legitimate economic interest of sponsors for what concerns CCI.
- Sponsors should submit high quality documentation to CTIS to enable an assessment by the MSC. The need to have both versions of documents will depend on the document type and whether protection of personal data and/or CCI would be applicable based on document content.
- Except for those document types exempt from publication, for any clinical trial document submitted to CTIS in an initial application or during the trial life cycle, the document version 'for publication' is to be provided, regardless whether a deferral for publication is requested.
- The document version 'for publication' is the one that will be published with timing depending on the deferral rules, as applicable.
- In principle no alteration of the documents content should occur in the document versions 'for publication' and 'not for publication', where the difference should be only personal data and commercially confidential information being redacted.

  Protection of personal data of trial participants should be done with the available anonymisation techniques that might require modification of the text, as redaction might not be the preferred options to use in that case.

Considerations on protection of personal data:

- Personal data, if needed during the scientific and regulatory review carried out by the MSC, should be provided in the document version 'not for publication'. This will enable the MSC to have all the necessary information for evaluation. Principles of minimisation should however be followed when providing personal data, only as needed in light of Articles 81(6) referring to 81(2) of the CTR.
- Personal data in the document version 'for publication' should be anonymised, for the purpose of public disclosure except the name and surname of the principal investigator at the clinical site(s), of the head of the clinic/institution or other responsible person issuing the statement of suitability of the facility, of the sponsor legal representative[10] and of the persons signing the clinical study reports, in line with the requirements of the Appendix, on disclosure rules, to the "Functional specifications for the EU portal and EU database to be audited - EMA/42176/2014".
- Signatures, if available in documents uploaded in CTIS, should not be disclosed in the document version 'for publication'.
- There is no equivalent of having a version 'for publication' and 'not for publication' in the structured data fields populated by the CTIS users, as these fields cannot be redacted. Therefore, sponsors and Member States users should be mindful of this aspect when populating structured data fields, for example in RFI and RFI responses, using the data minimisation principles to protect personal data, as applicable.

[10] The role of the sponsor legal representative is clearly defined in Article 74(1) of the CTR: ''Where the sponsor of a clinical trial is not established in the Union, that sponsor shall ensure that a natural or legal person is established in the Union as its legal representative.''

Considerations on protection of CCI:

- In general, the data included in a clinical study report should not be considered commercially confidential once a marketing authorisation has been granted, the procedure for granting the marketing authorisation has been completed or the application for a marketing authorisation has been withdrawn. In addition, the main characteristics of a clinical trial, the conclusion on Part I of the assessment report for the authorisation of a clinical trial, the decision on the authorisation of a clinical trial, the substantial modification of a clinical trial, and the clinical trial results including reasons for temporary halt and early termination, in general, should not be considered confidential[11].

  It should be noted that for category 1 trials, the sponsor may opt to have main characteristic (structured data fields and documents) deferred for publication to the time when the final summary of results is made public.

- Deferral mechanism can be used to protect CCI. Alternatively, CCI can be redacted, where applicable, in the document version 'for publication'.

- Nonetheless CCI should be available in the document version 'not for publication' as needed for Member State evaluation, and therefore it should not be redacted. Sponsors may mark/highlight the text that they consider CCI in documents 'not for publication' for awareness of the Regulatory Authorities. The version of a document 'not for publication' should be considered as the original, integral version of the document containing all information required for the assessment by the MSC.

- There is no equivalent of having a version 'for publication' and 'not for publication' in the structured data fields populated by the CTIS users, as these fields cannot be redacted. Therefore, sponsors and Member States users should be mindful of this aspect when populating structured data fields, for example in RFI and RFI responses, to protect commercially confidential information, if applicable.

More details on what should be protected in the version of the documents 'for publication' in relation to personal data and CCI, can be found in chapter 3 and 4 of this document, respectively.

2.3. Use of the deferral mechanism and publication rules

The deferral mechanism in CTIS provides sponsors and Member States with the possibility to delay the publication of clinical trial information, with the objective to protect CCI. Publication rules in CTIS are set out in the Appendix, on disclosure rules, to the "Functional specifications for the EU portal and EU database to be audited - EMA/42176/2014", describing three categories for clinical trials depending on the trial phase and clinical development of the medicinal product(s) being tested.

More details on trial categories and applicable deferrals depending on the category can also be found in tables III and IV in the Annex to this document.

Deferrals requested by sponsor users

Considerations on deferrals acceptability:

- When submitting the initial application, the sponsor has the possibility to apply for a deferral. The extent of the deferral, for the data and documents deferred, and consequent timing for publication

[11] Recital 68 of the Clinical Trials Regulation.

of the clinical trial data and documents depends on the selected trial category[12]. Any justification provided by the sponsors when requesting deferrals should be on the selection of the trial category. Deferrals can only be set with an initial application and cannot be modified with subsequent applications for the remainder of the trial life cycle.

- The assessment performed by the RMS/MSC on an initial application takes into account whether the trial category chosen is correct depending on the trial phase and the clinical development status of the medicinal product(s) being tested. It is expected that RMS/MSC will comment mainly on the trial category rather than on the sponsor proposed timelines for deferrals. However, the possibility to receive more detailed comments on the proposed timelines for deferrals should not be excluded.
- In case of integrated trial phases or adaptive study design, i.e., phase I / II trials, phase II/III trial category should be treated in line with the higher designation, for example sponsors should consider that when a protocol sets out a multiphase or adaptive design that falls in both category 1 and 2, the trial should be treated according to category 2.[13]
- Sponsors will know that a deferral is granted if no RFIs are raised in that respect during the initial application evaluation or if the issues raised with RFI are addressed in a satisfactory fashion by the sponsor (e.g., no further RFI raised on the matter). There is no specific mechanism to flag in the system that deferrals are accepted, they are part of the application evaluation overall. Therefore, by authorising the initial application the Member State also agrees on the deferral timelines as deferrals are part of the CTA and apply to the remainder of the trial life cycle.
- If there is disagreement with the sponsor proposed deferrals the RMS may ask the sponsor to apply changes to the deferral settings via a request for information (RFI) on Part I. RFI on deferrals may be raised both at validation and assessment of Part I, however, it is expected to be raised by the RMS primarily at the time of Part I assessment. Via the RFI mechanism sponsors and MSC can communicate on the selected deferral settings. As an ultimate measure the sponsors can withdraw their application in case of any reported issues with the proposed deferrals settings.
- If a sponsor does not apply for a deferral, the document version 'for publication' will be published at the earliest opportunity, namely: time of the decision. For example, in case of a multinational initial clinical trial application, the publication will occur as soon as the first MSC issues its decision[14], i.e., authorise, authorise with conditions, not authorise the application.

Considerations on trials where deferrals are not accepted:

- For category 1 trials that are conducted in paediatric population or are included as part of a paediatric investigational plan (PIP) it is not possible to defer the publication of: main characteristics of the trial, notifications, summary of results, including for an intermediate data analysis, and layperson summary.
- For clinical trials in public health emergency settings[15], the protocol should be made public at the time of the start of trial and the summary of results later on during the trial life cycle. The publication of these documents cannot be deferred.

[12] Category 1 trials include: phase 1 trials, FIH, BE/BA and bio similarity trials. Category 2 includes: phase II and phase III. Category 3 includes: phase IV trials. More details on the Appendix of disclosure rules and tables III and IV of this document.
[13] Section 4.3.3. paragraph 3 of Appendix, on disclosure rules, to the "Functional specifications for the EU portal and EU database to be audited - EMA/42176/2014''.
[14] CTA are published after a decision, withdrawn and lapsed applications are not published.
[15] Article 17 of Regulation (EU) 2022/123

- In principle, clinical trials in emergency situations[16] fall either under category 2 or 3 (therapeutic intent), since for these trials Article 35 (1)(b) of the Clinical Trials Regulation requires scientific grounds for individual clinically relevant benefit for subjects.[17]

Considerations on deferrals and publication aspects:

- Regardless if deferrals are selected by the sponsor, the sponsor has the obligation to submit in CTIS a document version 'for publication'. A document version 'not for publication' may also be submitted based on the document type and document content, as long as the protection of CCI and personal data is necessary.
- This rule is also applicable to the documents provided by the MSC.
- Note that two versions will not always be needed, it will depend on documents type and content, i.e., if no CCI/PPD protection required, only a 'for publication' version will be necessary.
- The structured data fields and the document version 'for publication' are published at the designated time, meaning at the time of decision of an application, or months/years after the end of the trial in the EU/EEA or at the time of publication of the final summary of results, depending on if a deferral is applicable. The document version 'for publication' should not contain personal data and should not contain information that would still be considered 'commercially confidential' at the time of publication.
- The document version 'not for publication' is the original, integral version containing all the information required by MSC to perform the assessment, and it is not published. It may contain personal data, if necessary, in accordance with Article 81(6) referring to the purposes listed in Article 81(2) of the CTR, and it may contain CCI in order to allow for the evaluation of the application carried out by a MSC.
- In case both document versions 'for publication' and 'not for publication' are to be submitted, these documents should be submitted at the same time in CTIS secure domain as part of a clinical trial application, and during the clinical trial life cycle. The document version 'for publication' is the first one to be uploaded then optionally followed by the version not for publication by clicking on (+) icon next to the document. More information on this can also be found in CTIS training module 10.
- CTIS functionality to have document version 'for publication' and 'not for publication' is depicted below.

[16] Emergency situation: first trial specific intervention before signing the informed consent
[17] Article 35 of Regulation (EU) No 536/2014

Certain documents in CTIS are never published, for example: quality related documentation and quality assessment reports, financial arrangements, supporting documentation to a sponsor opinion on a corrective measure or a sponsor's response to an *ad hoc* request for information raised by the RMS/MSC, are categorised in CTIS as document 'not for publication'. ASRs are also exempted from publication rules and submitted in line with the requirements of chapter VII of the CTR.

Considerations on modification of a clinical trial dossier and deferrals:

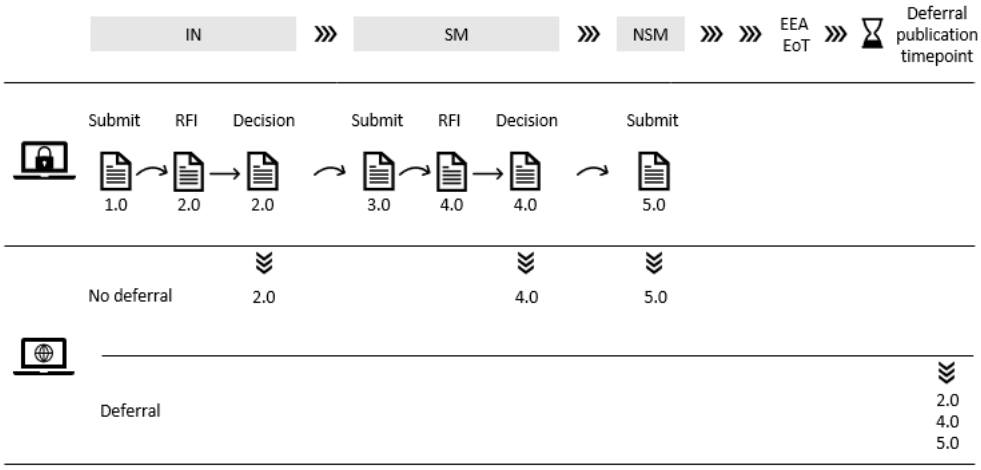
- Sponsors can modify structure data fields and document content to an application Part I and Part II while the application (of any type: initial, substantial modification, addition of a MSC) is under evaluation and if an RFI has been raised in that respect. If needed, via the RFI responses sponsors can update or permanently delete documents (of any type) in a CTA, that are within the scope of the RFI raised. Document versions submitted in a particular application type but superseded while responding to an RFI will not be published, leading to the publication only of the latest submitted version.

  Once a decision is issued on the application, it will no longer be possible for the sponsor to modify the structured data and documents content in that application, even if publication has not yet occurred because of the deferrals authorised.

- Substantial modifications can be submitted during the trial life cycle when changes are likely to substantially impact on the safety or rights of the subjects or on the reliability and robustness of the data generated in the clinical trial. These substantial modifications are subject to MSC assessment and decision.

  All applications are subject to the same publication rules and applicable deferral of publication set during the initial clinical trial application, as described in the Appendix on disclosure rules for CTIS[18]. For application types requiring a decision (initial application, subsequent substantial modifications or additions of a new MSC) once the decision has been issued the latest data and document versions are subject to publication, while data or document versions superseded during the application evaluation via one or multiple RFI responses are not published. For non-substantial modifications data and document versions are subject to publication once the submission has been made.

  Please note the graph below for illustration purposes only:



[18] https://www.ema.europa.eu/en/documents/other/appendix-disclosure-rules-functional-specifications-eu-portal-eu-database-be-audited_en.pdf

- Sponsors can also submit notifications (e.g., serious breaches, unexpected events, etc.) and summary of results. Also for these documents, in case an update is done, a new version can be submitted. It should be noted that in case there are several document versions 'for publication' due to the updates done, then all the submitted versions of the documents 'for publication' will be available in the public domain.
- After a decision has been issued on a clinical trial application the Agency will be the only party able to amend publication of published information and modify documents content on the CTIS secure domain, on justified grounds and on the basis of protection of personal data and CCI.

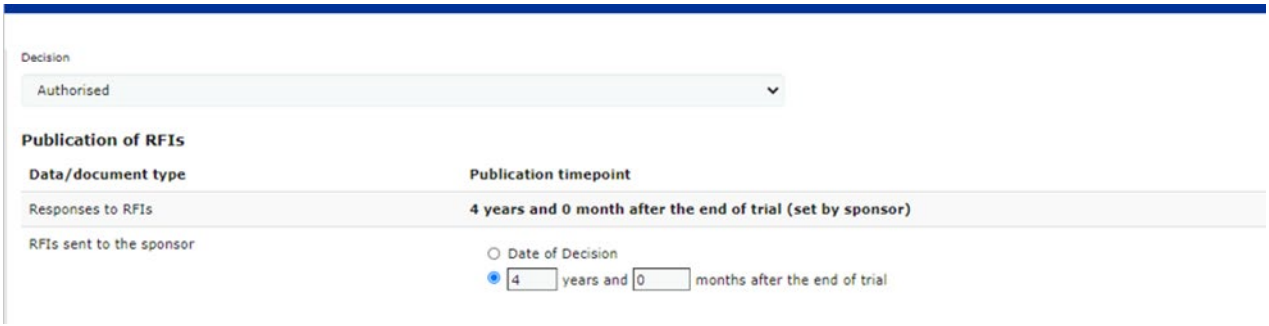
Deferrals applied by Member States users

If a sponsor applies for a deferral which is granted by the MSC during the evaluation, then the RMS and MSC can defer the publication of the RFI raised and certain documents for the same time period as selected by the sponsor. It is expected that, in principle, the RMS/MSCs will apply the same timelines as the sponsors to delay the publication for the elements of their concern.

More specifically:

- The RMS can defer the publication of information for Part I, in relation to request for information (RFI), the final assessment reports and conclusions.
- The MSC can defer the publication of information for Part II, in relation to request for information (RFI), the final assessment reports and conclusions.

This is defined in the CTIS by each MSC at the time of issuing a decision where Member States are presented with the deferrals values selected by the sponsors as default setting, please see the screenshot below for illustration purpose, also showing that not necessarily the maximum timelines for deferrals have to be selected by the sponsors and consequently by the Member States (4 years in this case).



The following principles apply:

- The publication of the considerations of RFIs sent to the sponsors, and any documents provided with an RFI, can be deferred by the MSC/RMS in line with the deferral timelines requested by the sponsor for their responses to such RFI.
- The publication of MSCs/RMS assessment reports and conditions can be deferred in line with the deferral timelines requested by the sponsors for the protocol and summary of scientific advice, investigator's brochure and investigational medicinal product dossier for safety and efficacy (IMPD S&E).
- Exceptionally, if MSC/RMS wish to deviate from the timelines proposed by the sponsors for the deferrals, they will inform the sponsor in advance via an RFI including a rationale for the necessary

changes for deviation. As an ultimate measure the sponsors can withdraw their application in case of any reported issues with deferrals settings.

- The deferral of publication of structured data fields and documents for a clinical trial will conclude:
  - When the agreed timelines for publication are reached for the respective trial category (e.g., 7 years after the end of the trial in the EU/EEA, or the publication of final summary of results)

    or

  - The trial results are used in any marketing authorisation application in the EU/EEA and a clinical study report (CSR) has been submitted to CTIS for this trial. In that instance, the submission of the CSR for the trial in CTIS, and its subsequent publication, will trigger the publication of the deferred structured data field and documents, as applicable, even if the deferral timelines have not yet been met.

Further details on the use of the deferral functionality to protect commercial confidential information is provided in chapter 4 of this guidance document.

3. Management of personal data in structured data fields and in documents submitted to CTIS

3.1. Introduction

The protection of personal data processed in CTIS is a joint responsibility of the EMA, the European Commission, the Member States (including National Competent Authorities and Ethics Committees) and commercial, non-commercial organisations including academia acting as sponsors of clinical trials and marketing authorisation applicants/holders. This joint responsibility is documented in the Joint Controllership Arrangement (JCA) for CTIS[19], which includes in Annex II the EMA Data Protection Notice, addressed to data subjects namely CTIS users, sponsors, principal investigators, trial participants and that explains the purpose of the processing of personal data, the way CTIS collects, handles and protects personal data, how the information is evaluated and the rights of data subjects in relation to their personal data.

The processing of personal data in CTIS, entailing the collection, publication and archiving of clinical trial information in documents and structured data fields is necessary for the management and functioning of the Agency and the performance of its tasks carried out in the public interest mandated by Union law, as joint controller of the CTIS, which includes the EU Portal and Database, for the effective materialisation of the objectives of the Clinical Trials Regulation. Therefore, this data processing by the Agency is lawful under Article 5(1)(a) of the EUDPR and justified on the grounds of public interest.

In addition, the Member States, the European Commission, the commercial, non-commercial organisation including academia acting as sponsors of clinical trials and marketing authorisation applicants/holders, are also joint controllers in the CTIS. They are legally obliged to collect and upload relevant documents in the CTIS. Therefore, the data processing by the Member States and the European Commission also relies on the lawful ground of public interest under Article 6(1)(e) of the GDPR and Article 5(1)(a) of the EUDPR, respectively.

In the case of sponsors and marketing authorisation applicants/holders their activities in CTIS and the related personal data processing is necessary for compliance with their legal obligations under the Clinical Trials Regulation in accordance with Article 6(1)(c) of the GDPR.

In the context of transparency of clinical trials in CTIS, to protect the rights of trial participants to private life and the right to the protection of personal data, Article 81(7) of the CTR sets out that no personal data of trial participants shall be publicly accessible, which is further reinforced by Article 81(4) of the CTR that states that the CTIS shall be publicly accessible except where justified to protect the confidentiality of personal data.

Personal data, including special categories of personal data of trial participants, should only be provided in CTIS as strictly necessary to allow for the scientific and regulatory assessment of the documents submitted to Member States.

Chapter 2.1 of the EMA Privacy Statement (Annex II of the CTIS JCA), referring to the personal data in documents provided by the joint controllers in CTIS, states the following: 'Should any of these documents contain personal data, as applicable and as required in light of Article 81(2) of Regulation (EU) No 536/2014, this can be provided in the version of the documents 'not for publication'. The version of the documents 'for publication' should not contain personal data.'

[19] https://www.ema.europa.eu/en/documents/other/joint-controllership-arrangement-regard-clinical-trials-information-system-ctis_en.pdf

To ensure that no personal data are made public these data should be anonymised, in the versions of documents 'for publication' with the following exceptions:

- In documents that are submitted in a clinical trial application dossier this principle does not apply to the following personal data as this information is required to be in the public domain as defined in the Appendix on disclosure rules[20]:
  - the name and surname of the principal investigator and address of the clinical trial site.
  - the name and surname of the head of the clinic/institution, or by some other responsible person, declaring the status of compliance of the clinical trial site.
  - the name and surname of the sponsor legal representative, as defined in Article 74 of the CTR for sponsors that are not based in the European Union.
- Contact details provided in CTIS for the principal investigator and the sponsor legal representative should be professional contact details or functional contact details and they will be published via the applicable structured data fields. These contact details should, therefore, not be redacted, or otherwise anonymised, in the documents uploaded in CTIS.
- In the clinical study report (CSR) submitted in CTIS by the marketing authorisation applicant/holder the principle of protection of personal data does not apply to the individual signing the CSR, whose names and surnames, but not the signatures, should be available in the document version 'for publication'[21].

In addition to the EMA data protection notice, Tables I and II in the Annex to this document should be consulted for a more detailed description of the documents submitted via CTIS and the type of personal data that they might typically contain.

3.2. The principles of anonymisation

Anonymisation refers to information which does not relate to an identified or identifiable natural person or to personal data rendered anonymous in such a manner that the data subject is not or no longer identifiable (Recital 26 of GDPR and Recital 16 of EUDPR). The processing of such anonymous information is not subject to the provisions of the GDPR/EUDPR.

To determine whether a natural person is identifiable, account should be taken of all the means reasonably likely to be used, such as singling out, either by the controller or by another person to identify the natural person directly or indirectly. To ascertain whether means are reasonably likely to be used to identify the natural person, account should be taken of all objective factors, such as the costs of and the amount of time required for identification, taking into consideration the available technology at the time of the processing and technological developments (Recital 26 of GDPR and Recital 16 of EUDPR).

The Article 29 Working Party has issued an Opinion on Anonymisation Techniques[22]. The Opinion discusses that the effectiveness of anonymisation techniques should be checked against three criteria:

i. is it still possible to single out an individual,

ii. is it still possible to link records relating to an individual, and

[20] https://www.ema.europa.eu/en/documents/other/appendix-disclosure-rules-functional-specifications-eu-portal-eu-database-be-audited_en.pdf
[21] See section 4.2.5 of the Appendix on disclosure rules
[22] Opinion 05/2014 on Anonymisation Techniques, 0829/14/EN WP216, available : https://ec.europa.eu/justice/article-29/documentation/opinion-recommendation/files/2014/wp216_en.pdf

iii. can information be inferred concerning an individual?[23]

The Opinion also recognises that the use of one individual anonymisation technique alone may not meet with certainty, in every instance, the criteria of effective anonymisation. However, some of the criteria may be met in whole or in part by a given anonymisation technique, therefore a combination of techniques should be carefully applied together to enhance the robustness of the outcome.[24]

Combination of anonymisation techniques could be used, for example, in clinical study reports. For documents part of the CTA, which are expected to contain mainly direct identifiers, redaction would be most likely the anonymisation technique of choice.

An anonymisation report describing the anonymisation techniques used is not expected to be provided in CTIS, unless specifically requested.

When establishing a process for ensuring an adequate level of anonymisation, the following factors may be considered:

- the likelihood of re-identification being attempted.
- the likelihood the reidentification would be successful.
- the anonymisation techniques which are available to use; and
- the quality of the data after anonymisation has taken place and whether this will meet the needs of the organisation (and the public) using the anonymised information. For example, once the anonymisation has been completed, an analysis of the interpretability of the anonymised data and information could be carried out to ensure they still remain meaningful and having utility for the public.

3.3. General principles on anonymisation of personal data in the documents version 'for publication'

In the context of CTIS, it is paramount to differentiate between:

a) Personal data, other than those of trial participants, such as of staff of the sponsor and of the marketing authorisation applicant/holder, qualified person for GMP documentation, principal investigators, etc.

and

b) **Personal data of clinical trial participants**.

Regarding anonymisation of personal data in CTIS, the following principles should be taken into account:

- Anonymisation of personal data in the documents submitted to CTIS 'for publication' should occur outside of CTIS and be applied consistently across all documents.
- The publication of documents in CTIS can occur at the time of decision on an application, or later on in case deferrals are applied (see chapter 2).
- Where only one version of a document is provided in CTIS secure domain, namely the version 'for publication' this version will be subject to publication and used for review by the MSC(s), in the absence of a version 'not for publication'.

[23] Ibid, Executive Summary.
[24] Ibid, Section 5.2.

- It is the sole responsibility of CTIS users to ensure the quality, accuracy and adequacy of anonymisation applied and that the document versions 'for publication' are anonymised in accordance with the applicable process agreed within their organisation.
- CTIS does not automatically verify if anonymisation has been applied in the version of documents intended for publication.
- When progressing with the submission of the documents via CTIS, the authorised user confirms that the recording, storage and publication of the documents in question are in accordance with Union data protection legislation. A dedicated template is available for use[25].
- The Agency, as the system administrator, is entitled to delete corrupted, incorrect, or unlawfully processed data, including removing information from CTIS public domain. This refers to requests for removal raised by the parties[26] that uploaded the document in CTIS. Such requests can be raised by contacting the dedicated EMA service desk[27].
- In addition, EMA can delete incorrect information identified in the public domain, in which case EMA will inform the party that has provided the document, that an amendment to the published document is needed. The Agency, or other joint controllers in accordance with the joint controllership arrangement, can also edit the inaccurate or outdated information contained in the CTIS secure domain to comply with Union data protection legislation.
- The Agency, the European Commission, the Member States, commercial and non-commercial organisations, including academia acting as sponsors and/or marketing authorisation applicants/holders, have joint responsibilities in submitting clinical trial data and documents in accordance with the Clinical Trials Regulation and Union data protection legislation. They also have joint responsibilities towards the data subjects and should have clear, defined processes in place to deal with any personal data breaches.
- Other shared aspects of CTIS falling under the joint controllership scheme, such as the handling of data subjects' rights, is addressed in a published joint controllership arrangement (JCA) for CTIS.[28]

3.3.1. Anonymisation of personal data other than those of trial participants in the documents version 'for publication'

Personal data of individuals including names and surnames are captured, as applicable, in CTIS structured data fields and related documents in the version 'not for publication' and should be anonymised in the document version 'for publication'.

The identifiers which are expected to be provided in CTIS documents are further described in the ACT EU Q&A[29] on CTIS transparency aspects. More specifically the name and surname of applicable persons are required in the following documents:

- Principal investigator on the CV
- Qualified Person (QP) on the GMP declaration

[25] https://health.ec.europa.eu/system/files/2022-09/compliance_reg2016_679_template_en.pdf
[26] Deletion of incorrect/corrupted documentation should not occur on routine basis but rather on justified grounds to remove corrupted/unlawful information. This should not be seen as an instrument for modification / protection of personal data or commercial confidential information provided by CTIS users that retain the ultimate responsibility
[27] https://servicedesk.ema.europa.eu/
[28] https://www.ema.europa.eu/en/documents/other/joint-controllership-arrangement-regard-clinical-trials-information-system-ctis_en.pdf
[29] ACT EU Q&A on the protection of Commercially Confidential Information and Personal data while using CTIS, version 1.1, 27 March 2023, https://www.ema.europa.eu/en/documents/other/questions-answers-protection-commercially-confidential-information-personal-data-while-using-ctis_en.pdf

- The person issuing the clinical trial site suitability document
- Data Safety Monitoring Board (DSMB) composition on the charter or applicable document
- Minimum amount of sponsor staff in the protocol
- GDPR compliance statement provided under the CTIS 'form' section, in line with available template

Specifically, for signatures the ACT EU Q&A clarifies that the only CTA documents to be signed are the suitability of the site and the QP declaration per GMP, in addition to few MSs specific requirements for Part II. Signatures should always be anonymised in the document version for publication.

The anonymisation of personal data can be achieved by applying redaction as the sole anonymisation technique. Redactions can be performed by using any available tool which ensures that the redacted information is irreversibly blacked out by applying a permanent and unremovable overlay and, at the same time, making the redacted text unreadable in the document.

Redaction of pre-specified identifiers, e.g., names, surnames, telephone numbers, can be done manually and/or automatically with software functionalities which enable the user to identify the pre-specified identifiers intended for redaction. Redaction would be the anonymisation technique of choice for personal data of individuals other than those of trial participants.

As previously described the following exceptions apply to names and surnames that should be disclosed in the document version 'for publication':

- Names and surnames of principal investigators, legal representative of the sponsors, head of the clinic/institution or other responsible person issuing the statement of suitability of the facility, which are subject to publication as explained in sections 4.2.2 and 4.2.4 of the Appendix on disclosure rules[30].
- The full name (not signatures) of the sponsor and coordinating investigator signatories of the clinical study report and the identities of the principal investigator(s) who conducted the trial, which are subject to publication as explained in sections 4.2.5 of the Appendix on disclosure rules[31].

All contact details, e-mail addresses and telephone numbers of the above-mentioned individuals should be their professional contact details or provided in CTIS as functional contact details. Private contact details should not be provided in structured data fields in CTIS and if included in the documents should be redacted in the published documents.

Personal data of the author of a document, included as part of the metadata of a file, should equally be removed prior to uploading the document in CTIS secure domain and subsequent publication of the document. Instructions are available in dedicated CTIS training material, Module 02 – Guide on CTIS common features[32].

3.3.2. Anonymisation of personal data of trial participants in the document version 'for publication'

Personal data of trial participants may only appear, as applicable, in CTIS document versions 'not for publication' and encompass personal data in a pseudonymised format (e.g., clinical trial subject ID

[30] Appendix, on disclosure rules, to the "Functional specifications for the EU portal and EU database to be audited - EMA/42176/2014", https://www.ema.europa.eu/en/documents/other/appendix-disclosure-rules-functional-specifications-eu-portal-eu-database-be-audited_en.pdf
[31] Idem.
[32] Section 3 in training module 02: clinical-trials-information-system-ctis-common-features-ctis-training-programme-module-02_en.pdf (europa.eu)

number) as well as indirect identifiers such as weight, height, age, gender, etc. These personal data are to be anonymised in the document version 'for publication'.

The following elements should be considered when applying anonymisation in the documents to be published:

- **The choice of anonymisation techniques**[33]

In the context of CTIS, no specific anonymisation methodology to protect personal data of clinical trial participants is prescribed, acknowledging that each anonymisation technique has its own strengths and weaknesses. The robustness of each anonymisation technique is based upon the anonymisation criteria and will help in identifying the most suitable technique (or combination of different techniques) to establish an adequate anonymisation process for a given document.

- **Data utility**

Personal data of trial participants could be present in document version 'not for publication' (e.g., notification of serious breaches, unexpected events or urgent safety measures, clinical study reports). It should be noted that it is equally important to preserve data utility in the public version of the documents, as much as possible, whilst ensuring adequate anonymisation. Besides, a quantitative approach to the measurement of the risk of re-identification could be favoured.

- **The sensitivity of the data**

The specificities of the relevant data should be taken into consideration when selecting the most appropriate anonymisation technique(s). For example, clinical trials conducted on rare diseases and/or on small populations may carry a high risk of re-identification of trial participants. A thorough risk assessment should be performed for such scenarios and the anonymisation of personal data should be adapted to the identified risk. Moreover, such an approach is also applicable to genetic information and low frequency events (e.g., rare events, extreme values, unusual treatments, pregnancy outcomes).

For a more detailed description of the available anonymisation techniques and their strengths and weaknesses please refer to Article 29 Working Party Opinion on Anonymisation Techniques. The same principles will apply to the protection of personal data of trial participants in the documents submitted to CTIS.

3.4. The principle of pseudonymisation applicable in the version of documents 'not for publication'

The documents uploaded in CTIS may contain personal data in a pseudonymised format. Mostly frequently included one is the clinical trial subject ID number. For the reasons presented above the clinical trial subject ID number should not be disclosed in the document version 'for publication'. It should be adequatly anonymised by employing appropriate anonymisation techniques.

The pseudonymisation of personal data can reduce the risks to the data subjects concerned (e.g., trial participants). Pseudonymisation refers to processing of personal data in such a manner that the personal data can no longer be attributed to a specific data subject without the use of additional information, provided that such additional information is kept separately and is subject to technical and organisational measures to ensure that the personal data are not attributed to an identified or identifiable natural person (Article 4(5) of GDPR and Article 3(6) of the EUDPR).

[33] The EMA Guidance on the implementation of Policy 0070 https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/external-guidance-implementation-european-medicines-agency-policy-publication-clinical-data_en-3.pdf

Practically, pseudonymisation consists of replacing one attribute (typically a unique attribute) in a record by another. When pseudonymisation is used alone, the natural person could still be identified indirectly. Therefore, pseudonymisation reduces the linkability of a dataset with the original identity of a data subject, but when used alone will not result in an anonymised dataset. Thereby, pseudonymisation is not an anonymisation technique but a useful security measure.

Personal data which have undergone pseudonymisation and which could be attributed to a natural person by the use of additional information, should be considered to be information on an identifiable natural person, therefore data protection rules still apply.

3.4.1. Personal data of trial participants, including pseudonymised personal data, in the document version 'not for publication'

Personal data of trial participants which could appear, as applicable, in CTIS document versions 'not for publication' encompass personal data in pseudonymised format (e.g., clinical trial subject ID number) and indirect identifiers such as weight, height, age, gender, etc. Such personal data may be contained in CTIS secure domain and if provided should only be included in the document version 'not for publication'.

A non-exhaustive list of documents that may contain personal data of trial participants is provided below:

- Investigator Brochure
- Paediatric Investigational Plan
- IMPD sections on Safety and Efficacy
- Unexpected event reports and supporting information
- Urgent safety measure reports and supporting information
- Serious Breach Reports and supporting information
- Clinical study reports
- Assessment reports
- Inspection reports

It should be noted that the principle of data minimisation should be followed when providing pseudonymised personal data of trial participants in the documents 'not for publication' in CTIS secure domain. The use of personal data of trial participants should be proportionate. The clinical trial documents should include sufficient level of details to permit for the scientific evaluation and include sufficient data to evaluate the benefit/risk profile of the investigational medicinal product(s) used.

4. Management of commercially confidential information (CCI) in clinical trial information submitted to CTIS

4.1. Introduction

This chapter aims at the identification and protection of CCI in the clinical trials information submitted to CTIS.

The goals of this chapter are:

- To ensure a common understanding of what may be, or may not be, considered CCI within clinical trial structured data fields and documents provided in a clinical trial application and during the trial life cycle

  and

- To present the system functionalities that enable protection of CCI in CTIS.

CCI could be contained in a clinical trial application dossier or provided during the trial life cycle including in the CSR. Its disclosure may undermine the legitimate economic interest or competitive position of the concerned entities, e.g., clinical trial sponsors, marketing authorisation applicants/holders or service providers.[34]

The Appendix, on disclosure rules, to the "Functional specifications for the EU portal and EU database to be audited - EMA/42176/2014"[35] states that clinical trial structured data fields and documents submitted to CTIS may contain information which may be considered CCI. According to the disclosure rules, a number of documents uploaded in the database are not made public, such as the quality-IMPD, assessment reports related to quality aspects, request for information (RFI) and corresponding responses on quality aspects of the application, financial arrangements and more. For a comprehensive list please consult Annex I to this document.

The identification of the commercially confidential information available in the structured data fields and in the documents submitted to CTIS is time dependent and should be approached as such by the CTIS users.

4.2. Mechanisms available in CTIS to protect CCI

The users can employ one of the following two mechanisms to protect CCI in CTIS: redactions applied in document versions 'for publication' or use of deferrals.

Redaction of documents: The application of redactions to protect CCI should be limited to information that meets the definition above and should carefully be weighed against the principles of transparency and ease of access to clinical trial information. Certain pieces of information which are present in documents, other than those exempted from publication, may be considered as constituting CCI and therefore may be redacted from the documents to be made publicly available at the time of the decision of the initial application, and in subsequent other application types submitted during the trial life cycle.

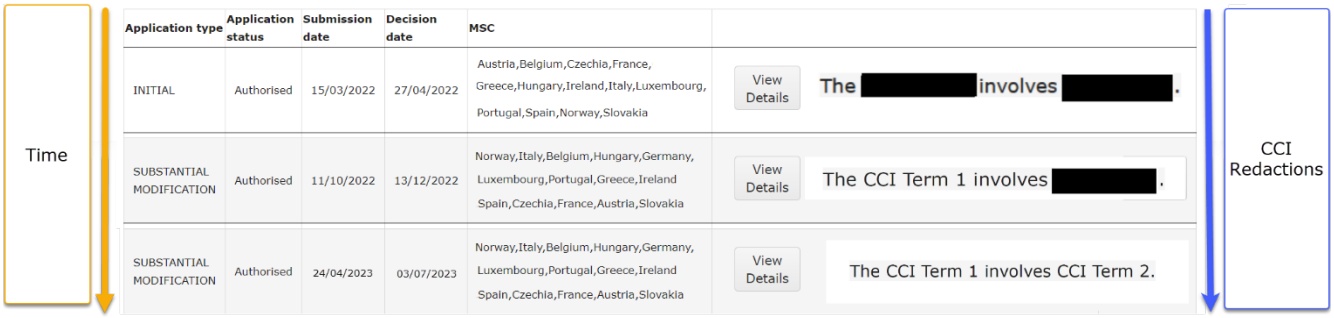
When identifying potential CCI, CTIS users are strongly encouraged to consider whether the information is already published, for example via the structured data fields in CTIS, or via different

[34] EMA's definition of CCI in Policy 0043 has been endorsed by the Court of Justice in its case-law on access to documents. The definition of CCI in this document is an extrapolation and adaptation of the definition appearing in Policy 0043.
[35] Available at: https://www.ema.europa.eu/en/documents/other/appendix-disclosure-rules-functional-specifications-eu-portal-eu-database-be-audited_en.pdf

publication sources. In addition, sponsors should consider whether the documents submitted as part of a clinical trial application, for example investigator brochure or IMPD safety and efficacy, are already in the public domain in connection to other trials registered in CTIS public website, or via other public sources, and if any redactions had been applied in these published documents. Consistency should be maintained and the extent of the redactions should be similar across published documents.

It is expected that as the development plans advance, information on clinical trials which initially was considered CCI may no longer be considered CCI due to technical and scientific advancements in that research field. This should, therefore, translate into a decreased level of CCI redactions applied over time in the new and modified documents submitted to CTIS during the trial life cycle, while the development plan for the medicinal product progresses. Retrospective removal of redactions from the documents already published is not expected. The latest version of each document type should, with time, be less and less redacted, as applicable, during the trial life cycle.

Please see an example below for illustration purposes only:



Redacted documents submitted to CTIS for publication have to remain meaningful to the public, including potential trial participants and health care professionals[36]. Sponsors are responsible for the redactions applied and for maintaining the clinical utility of the relevant redacted documents. In addition to the scientific and regulatory review of the documentation provided during the lifecycle of a clinical trial, RMS/MSC might reserve the right to comment, via an RFI, on the extent of the redactions applied by the sponsor to ensure that the principles of transparency are followed.[37] When requested by the RMS/MSC, sponsors should be able to demonstrate why the redaction in the documents is needed, as an early disclosure might, otherwise, impact their legitimate economic interest or competitive position.

Deferrals: As an alternative option to applying extensive redactions, the deferral mechanism described in the Appendix on disclosure rules mentioned above, and in chapter 2 of this guidance document, can be used by the clinical trial sponsors to protect CCI in the trial information submitted in CTIS. With the use of deferrals all the applicable versions of documents submitted during the trial life cycle will be published together at the designated timepoints defined by the deferral rules.

The deferral rules apply to a subset of the CTA documents such as protocol, investigator brochure, IMPD safety and efficacy, responses to RFI, as well as, for category I/ phase I trials only,[38] summary of results and certain main characteristics. Please refer to Tables III and IV in the Annex I to this guidance document for additional details on the deferrals' categorisation.

[36] Clinical Trials Regulation (EU) No 536/2014, Questions & Answers, Version 6.4, point 260. https://health.ec.europa.eu/system/files/2023-04/regulation5362014_qa_en.pdf
[37] ACT EU Questions and answers on the protection of Commercially Confidential Information and Personal Data while using CTIS, Version 1.2, point 1.7. Article 94 (2)(a) of the Regulation (EU) No 536/2014 refers to application of penalties including non-compliance with the provisions laid down in the Regulation on submission of information intended to be made publicly available to the EU database.
[38] This would not be applicable to clinical trials including paediatric population (i.e., subjects ≤18 years of age) or if the trial is part of paediatric investigation plan.

Most of the elements considered CCI at the time of the CTA submission, based on the progress of the clinical development, will no longer be considered CCI when the deferral period elapses and, therefore, should not be redacted from the documents uploaded and submitted via CTIS.

It is acknowledged, however, that, in limited circumstances, specific pieces of information (e.g., of quality data in the trial protocol) could still be considered CCI even after the deferral period elapses, and consequently their redaction would be acceptable even in documents subject to deferral requests.

This approach should not translate, however, in an extensive redaction of CCI applied in documents subject to deferrals as they will be made available in the public domain either months/years after the end of the trial in the EU/EEA, or at the time of publication of trial summary of results, or at the time of finalisation of the marketing authorisation procedure (whichever is the earlier).

Deferral requests are broadly expected to be accepted by the Member States Concerned and therefore extensive redaction of documents should be avoided. In case of disagreement with the proposed deferral timelines the sponsors will be notified as explained in chapter 2 of this guidance.

Submission of a CSR for a trial, in case the results are included in a marketing authorisation application, overrides the agreed deferral timelines. In such cases, the publication of all the structured data fields and documents still subject to deferral requests, that were not yet published, will occur when the CSR is submitted in CTIS and published.

In the CSR only minimum amount of redaction to protect CCI is expected: in line with recital 68 of the CTR[39], CSR content should in principle not be considered CCI at the end of the marketing authorisation process.

The same principles for CCI redaction of CSRs published via Policy 0070 will prospectively apply in respect of the CSRs submitted and published via CTIS at the end of the deferral period. Therefore, marketing authorisation applicants/holders are advised that only those elements that, at the time of publication, would still be considered CCI should be redacted.

4.3. Relevant expertise and consistent decision-making process on the identification and redaction of CCI

The following elements should be considered when identifying CCI in the clinical trial information submitted to CTIS:

(a) involve in the CCI identification process experts with relevant scientific and technical skills, and

(b) to follow a consistent decision-making process.

It is envisaged that incorporating these two elements into the CCI identification strategy would not only significantly reduce the need for applying redactions in the CTIS documents, but also increase the efficiency during the process of reviewing the documents in order to identify those pieces of information which may be considered CCI.

CTIS users, especially clinical trial sponsors and marketing authorisation applicants/holders, should follow a consistent decision-making process when evaluating whether a certain piece of information indeed constitutes commercially confidential information or not.

According to the definition provided in section 4.1 above a piece of information can be considered CCI if it meets simultaneously two criteria: (1) not being available in the public domain or publicly available

[39] For the purposes of this Regulation, in general the data included in a clinical study report should not be considered commercially confidential once a marketing authorisation has been granted, the procedure for granting the marketing authorisation has been completed, the application for marketing authorisation has been withdrawn.

and (2) it undermines the legitimate economic interests or competitive position of the concerned entities, e.g, sponsor, marketing authorisation applicants/holders or service providers.

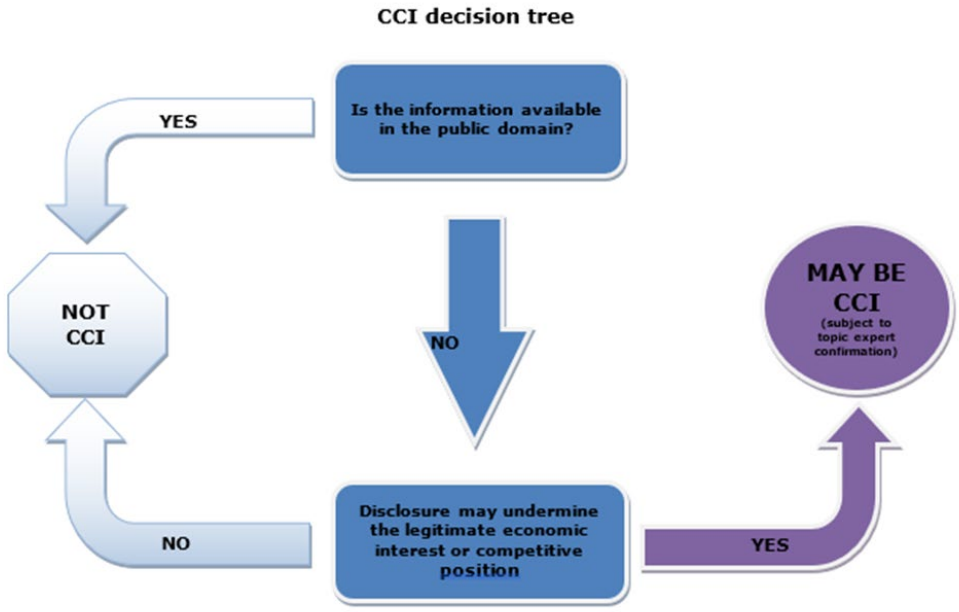
Based on this, in order to facilitate the identification of CCI a 2-step approach is suggested below:

First step: rule out the possibility that the particular piece of information is available in the public domain (for further guidance please see section 4.5.1), or otherwise made publicly available. In case the information is already available in the public domain, it cannot constitute CCI, therefore no redaction should be implemented and the second step below is no longer applicable.

and

Second Step: in case the information is not available in the public domain, it can be determined, in collaboration with experienced professionals having a relevant expertise in the clinical research area, whether the disclosure of the piece of information may undermine the legitimate economic interest or competitive position of the sponsor, marketing authorisation applicant/holder or service providers.

If step 2 is also confirmed, the relevant portion of information can be considered CCI and be redacted from the documents.



Medical writing can also play an important role in reducing the need for redactions. It is expected that embedding a CCI identification and tracing strategy during the writing of the CTIS related documentation would limit the unnecessary dissemination of commercially confidential information in documents where these pieces of information are not essential, required or relevant.

This strategy can be further complemented by using document templates which specifically indicate which information is required to be included in the documents according to the legislation, scientific guidelines and regulatory guidance for clinical trials. As a complementary approach, tagging those pieces of information which are considered CCI at the time the clinical trial documents are written would facilitate the preparation of the redacted document versions meant to be published.

4.4 Information that may be considered CCI

It is recommended that where CTIS users, including clinical trial sponsors or marketing authorisation applicants/holders, identify a portion of information such as a word or figure, part of a sentence, part

of a paragraph that they wish to include amongst the redactions to protect CCI, they should consider whether that portion of information meets the definition of CCI. If the information is CCI, the extent of the redactions should be limited to the word(s), figure(s), and specific sentences/elements in the text that, in the CTIS user's view, can be considered CCI. In case only some sentences within the text or some specific figures within the tables are claimed to be CCI, the users should not redact entire pages, sub-sections of a document or full tables, which for instance is accepted instead in respect of quality-related information.

In order to facilitate the identification of CCI, a short list of specific types of pieces of information that may carry commercially confidential value is presented below. CTIS users should not redact these types of information automatically in the documentation submitted for publication in CTIS, yet they should assess whether the information is CCI on a case-by-case basis.

The list of elements that may be considered CCI at the time of submission of a CTA and during the trial life cycle including submission of results/CSRs, includes as indicative examples:

- The names, address and contact details of manufacturers or suppliers of the active substance or the excipients and finished product as well as of investigational medical devices, unless disclosure is required as per current pharmaceutical legislation (e.g., for some biological products).
- The excipients quantitative composition of the investigational/authorised product.
- Detailed information on the synthesis or manufacture of the active substance.
- Detailed descriptions of the manufacturing and control processes for the investigational/authorised final product.
- Information related to future development plans for indications other than the one under investigation and not yet disclosed in the public domain.
- New biomarkers or novel methodologies not yet qualified (to the extent that the information is not yet disclosed in the public domain), including new methodologies to support future developments as regards secondary or exploratory endpoints.
- Detailed information concerning innovative analytical methods.
- Detailed information on the facilities and equipment available at the sponsors and clinical sites.
- Only in clinical trial application dossiers: the details of the daily dose allowed and maximum dose allowed for the medicinal product under investigation on justified grounds, i.e. when the sponsor proves that the specific information on the posology is not in the public domain and constitutes patentable matter, the disclosure of which before a patent application is filed (typically, after the completion of the trial and during the trial readout) would jeopardise its protection.

  This might be applicable, for example, to integrated phase I/phase II trials that are to be marked in CTIS as category 2 trials. The grounds for considering dose details as CCI should be clearly documented in the cover letter of the application[40].

[40] ACT EU questions and answers pm protection of personal data and commercially confidential information while using CTIS, Version 1.2, Q&A 3.3. https://www.ema.europa.eu/en/documents/other/questions-answers-protection-commercially-confidential-information-personal-data-while-using-ctis_en.pdf

4.5 Information that may not be considered CCI

In order to achieve a high level of consistency in the identification of CCI across the clinical trial documents, the sections presented below list some additional examples of types of information which may not be considered CCI[41]..

4.5.1 Information that is already in the public domain or publicly available

It is recommended that the clinical trial sponsor and marketing authorisation applicants/holders compile a list of the most common websites/locations where information regarding their own medicinal product is usually made available. They may consider creating and maintaining their own specific lists detailing the level of public information concerning their product(s). The following sources of information be included in the list (as a minimum):

- Sponsors, Applicants'/MAHs' own website(s).
- EMA web-site (e.g. scientific guidelines, and for, centrally authorised products, the product EPAR,);
- Clinical trials registries (such as CTIS, EU Clinical Trials Register, ClinicalTrials.gov);
- Web-sites of other regulatory authorities within the EU and outside the EU (such as FDA, PMDA, TGA, Health Canada) especially when the product (or another product containing the same active substance) is approved in those specific jurisdictions;
- Scientific literature and articles (such as Textbooks, PubMed, Medline).

The information sources suggested above are not intended to constitute an exhaustive list, but rather to serve as a starting point for the creation of their own (more exhaustive, customized) lists. In this case, the above-mentioned examples should be considered as the minimum number of information sources to be scrutinised in order to reach a basic level of awareness on publicly available information related to the product concerned.

4.5.2 Information that does not bear any innovative elements

Information which has already been revealed to certain extent, that can be inferred from information available in the public domain or has the content of textbooks or scientific guidelines as basis, should not be withheld from the public versions of the clinical trial documents.

The fact that certain pieces of information are not in the public domain as such does not necessarily mean that they should be considered by default to constitute CCI.

In many instances, particular pieces of text contained in clinical trial documents describe how the sponsors and marketing authorisation applicants/holders complied with regulatory and scientific guidelines and how they applied the scientific knowledge available at that time to their own development programme. In essence, these pieces of text do not reveal any innovative elements (of any regulatory or scientific nature) as the approaches described in the text are built upon logic and common sense in line with the content of publicly available documents such as:

- Scientific literature and articles (Textbooks, PubMed, Medline).
- Scientific and regulatory guidelines and guidance documents (ICH).
- Treatment/clinical practice/disease management guidelines (Learn societies, HTAs).

[41] These examples reflect the most common redactions proposed by applicants/MAHs which are usually rejected by EMA in the framework of Access to Documents in accordance with Regulation (EC) No 1049/2001.

4.5.3 Information that would not qualify as commercially confidential

When considering commercially confidential information while using CTIS it is important to stress once again that the concept of CCI is time dependent, with a particular focus on the development phase of the medicinal product used in a clinical trial. It is important, therefore, to differentiate between CCI applicable in an earlier development phase at the time of submission of a clinical trial application and during the trial life cycle, and CCI at the end of the development cycle when trial results are provided in the clinical study report as part of a marketing authorisation procedure.

As mentioned in the introductory section 4.1 of this chapter it is expected that the redaction of CCI in the documents uploaded and submitted in CTIS will decrease overtime in line with the evolution of the development plan.

It is also acknowledged that, in addition to CCI for the medicinal product used in the trial, there might be other CCI component in the documents, for example of third parties and service providers provided in CTIS, that may be equally protected if the disclosure would undermine the legitimate economic interest or competitive position of the concerned parties.

Some data elements should not be redacted from CTIS documentation since they are unlikely to constitute commercially confidential information at any point in time, in a CTA or in a CSR. Some of these data elements are presented below. The list is not intended to be exhaustive, rather as indicative examples about details of the data elements generally not considered to be CCI:

General or administrative information

- Unit measurements, in such cases only the actual value may be considered CCI. [e.g.] 2.5mL/kg → xx mL/kg.
- Study identification number(s) (e.g., EudraCT, ClinicalTrials.gov Identifier (NCT…), sponsor's internal study number).
- Names and addresses of investigator sites and the names of the principal investigators at each study site.
- Names of the countries where the clinical study is/was conducted.
- Number (how many) of study sites/research facilities were involved in the research.
- Name of the applicant's/sponsor's own research facility(ies) where clinical studies were conducted (e.g., phase I studies).
- Name of the trial sponsor or the legal entity (CRO) that acted on behalf of the sponsor for clinical trial application submission.
- Names of all CROs, vendors and service providers involved in trial-related duties and functions (e.g., central laboratories, IVRS provider, image reading centres).
- Standard Operating Procedure (SOP) numbers and titles.
- Information on worldwide approval status, Marketing Authorisation dates and launch status.

In the clinical trial application(s), and during the whole trial life cycle, sponsors should only redact in the document version 'for publication' the CCI identified based on the principles described in section

4.3 above. In case the sponsors wish to flag what they consider CCI in the document version 'not for publication' uploaded in CTIS, they can mark the text with red border boxes.[42]

For clinical study reports to be submitted to CTIS, marketing authorisation applicants/holders should follow the same principles for the protection of CCI that are described in chapter 4 of the document on Policy 0070 on the publication of clinical study reports submitted to EMA as part of the centralised procedure for marketing authorisation.[43]

Where applicable, duplication of efforts should be avoided when preparing for publication those CSRs supporting centralised applications for marketing authorisation or variations thereof. As the submission and corresponding publication of CSRs via CTIS and publication via Policy 0070 initiative are triggered by the same regulatory milestone (i.e., the completion of the marketing authorisation procedure), the same level of CCI redaction applied in the CSR published on Clinical Data Publication portal (under Policy 0070 initiative) should be applied in the CSR provided in CTIS.

[42] https://www.ema.europa.eu/en/documents/other/questions-answers-protection-commercially-confidential-information-personal-data-while-using-ctis_en.pdf
[43] https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/external-guidance-implementation-european-medicines-agency-policy-publication-clinical-data_en-1.pdf

5. GCP inspection reports

5.1. Inspection reports provided by EU/EEA regulatory Authorities

CTIS contains a dedicated module to be used and populated by EU/EEA GCP inspectors for the provision of information related to GCP inspections conducted for clinical trials authorised under the regime of the CTR. Provision of such inspection reports to CTIS is in line with the requirements of Article 78 of the CTR.

In the inspection module of CTIS, the inspectors complete a list of structured data fields and upload an inspection report for the trials inspected at each single site. GCP inspections can take place in a multitude of different sites including, clinical investigator sites, sponsor offices, various laboratories, and any facility that has been part of the conduct of the trial[44]. Publication rules of the inspection reports in CTIS are based on the following principles:

- Publication of the inspection report(s) will occur when the inspection procedure at all the inspected sites has been completed and the inspection reports finalised and submitted to CTIS.
- In case of inspections performed in the context of a marketing authorisation procedure, inspection report(s) will be published when the Clinical Study Report (CSR) for the inspected trials is uploaded in CTIS by the marketing authorisation applicant[45] and published.
- Publication of inspection reports take place via CTIS automated means and based on the implemented system rules. No manual intervention from the inspectors is needed to trigger the publication of the inspection reports. It will occur automatically based on the publication rules described above.
- Of note, publication of the inspection reports cannot be deferred. In case of a legal proceeding, the upload of the inspection reports in CTIS (both versions 'for publication' and 'not for publication', which are to be uploaded at the same time) should be postponed until the completion of the legal case.

As mentioned above, and similarly to other documents in CTIS, two versions of GCP inspection reports can be uploaded in the CTIS secure authority domain: a version 'for publication' and one 'not for publication'. The inspection report version 'not for publication' may contain CCI and personal data of the inspectees and inspection team, as well as pseudonymised personal data of trial participants.

The inspection report version 'for publication' should not contain CCI and personal data with the exception of the name and surname of the principal investigator(s) at the clinical site(s), of the head of the clinic/institution or other responsible person issuing the statement of suitability of the facility and of the sponsor legal representative, as applicable, as this personal data can be published.

The inspection report of the inspected trials/facilities should be provided in CTIS, after the consultation steps with the inspectees are completed outside of CTIS system.

Redaction of the inspection reports is a responsibility of the Member States that will endeavour to follow a harmonised approach towards the redaction process for the version of the inspection report

[44] The type of sites where the inspection can take place include, but are not limited to, the following: Analytical and/or clinical facility, clinical investigator sites, sponsor sites (commercial/non-commercial), clinical research organisation (CRO), clinical facility for phase I trials, technical facility, other.
[45] This refers to inspections that are conducted as part of existing marketing authorisation procedures whose number can be provided in the system, for other inspections no further details on future possible inclusion of a trial in a marketing authorisation procedure should be provided in CTIS.

'for publication' taking into account the common principles of redaction described in this guidance document.

The inspection reports containing the final grading of the findings and final GCP inspectors' evaluation should be submitted to the CTIS secure domain, with any supporting documentation to substantiate the final grading of the findings, as applicable. These inspection reports should reflect the final outcome of the inspection.

When preparing an inspection report version 'for publication' for submission in CTIS protection of personal data and commercially confidential information as detailed below should be considered by the GCP inspectors:

5.1.1 Protection of personal data

No personal data of sponsor and clinical site staff (except names and surnames of principal investigators and the person issuing the site suitability), interviewed (study) personnel, inspectors writing the report, or attending the inspections and other inspection team members (e.g., experts and/or observers), should be available in the version of the inspection report 'for publication'.

This entails the name and surname of the persons, as well as any direct contact details such as e-mail addresses or phone numbers. The study roles and responsibilities within the trial or company can be disclosed as long as they don't lead to the identification of the individual, or otherwise should not be provided. Of note, if any personal data of study or sponsor personnel would be needed to facilitate collaboration between the parties in light of article 81(2) of the CTR, such personal data can be included in the version of the documents 'not for publication' which are available only in the CTIS secure domains.

Pseudonymised personal data of trial participants, if needed to facilitate collaboration between the parties, may equally be contained in the 'not for publication' version of the inspection reports and, in line with the requirements of Article 13 of the Commission Implementing Regulation (EU) 2017/556, such personal data of trial participants are to be anonymised in the inspection reports 'for publication' submitted to CTIS.

It is paramount that such information on trial participant details is not publicly disclosed as such and instead anonymised in line with requirements of Article 81(7) of the CTR.

It follows from the above that due diligence should be applied when inspection reports are drafted and provided to CTIS to ensure that adequate level of protection of personal data is applied.

5.1.2 Commercially confidential information

Inspection reports 'for publication' should not contain CCI, in line with the general requirement of Article 81(4) of the CTR on the protection of CCI. Statements on the outcome of inspections related to the (non-)compliance with CTR requirements, including (non-)compliance with GCP, will not be regarded as CCI.

Information already available in the public domain related to the trial(s) subject to inspection, the requested and granted deferrals, as well as the redactions applied by the sponsors in the uploaded clinical trial documentation, should be considered by the inspectors at the time of the preparation of the inspection reports. Therefore, inspectors can consult the clinical trial information (i.e., structured data fields and documents) available in the secure domain of CTIS and verify the content of the documents provided by the sponsors, in both versions 'for publication' and 'not for publication' or already published, as applicable.

Following receipt of the inspection report, inspectees or sponsors, as applicable, are recommended to indicate their proposal for redaction of the inspection report when providing a response and/or a corrective and preventive action plan. The proposal should be in accordance with the general expectations set out in this guidance document, and for inspectors' consideration.

It should be noted that in case the publication of clinical trial information is **deferred**, this would imply that, potentially, limited information related to the trial is available in the public domain at the time the inspection report is to be published. The applicability of the deferral to a clinical trial is clearly visible in the sections 'Form' and 'Evaluation' of a CTA in CTIS.

In this instance, inspectors should only disclose non-CCI information on the trial and identified findings at the site.

Inspectors should be mindful of the fact that especially for category 1 trials, including phase 1 trials, First in Human (FIH) and BE/BA trials, deferral might apply not only to the trial documents, RFI and responses but also to structured data field in CTIS (including the trial title, inclusion and exclusion criteria, study endpoints, details on trial design and product related information, strength and pharmaceutical form, amongst others, as main characteristics of the trial), notifications and summary of results, as applicable.

In case the inspected clinical trial is covered by deferrals applicable to category 1 trials, the template presented in Annex II to this guidance document should be used.

For category 2 and 3 trials, the deferrals apply only to RFI and RFI responses and certain documents, although to a limited extend.

Further details on the deferral functionalities in CTIS can be found in chapter 2 of this guidance document and its Annex I.

5.2. Inspection reports for inspections carried out by third countries inspectorates provided by the clinical trials sponsors

Sponsors are responsible to provide in CTIS also inspection reports for inspections carried out by third countries authorities of a trial authorised and conducted under the regime of the CTR. This is in line with the sponsors' obligations defined in Article 53 of the CTR. Inspection reports issued by third countries authorities can be deferred if the trial falls in the category 1 and a deferral has been requested for the notifications[46].

In case of a deferral of an inspection report of third countries authorities for a category 1 trial, the publication would occur at the time of publication of summary of results. Inspection reports of trials falling under categories 2 and 3 are published as soon as they are submitted and their publication cannot be deferred.

The same principles on protection of personal data described in chapter 3 of this document and principles of protection of CCI described chapter 4 of this document, respectively, also apply to the redaction of third countries inspection reports.

[46] This includes serious breaches, unexpected events, urgent safety measures, third countries inspectorate inspection reports