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National Clinical Trial Office – International CT Event Day HPRA

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Core topics

1. Implementation of CTR and transition to CTR for trials approved under CTD
2. Experience to date and common issues in applications

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Disclaimer

This presentation does not purport to be an interpretation of law and/or regulations and is for guidance purposes only. This advice does not override legislation and published guidelines. We would recommend referring to associated legislation and guidelines where applicable.

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HPAR – Implementation of the Clinical Trial Regulation (CTR) 536/2014

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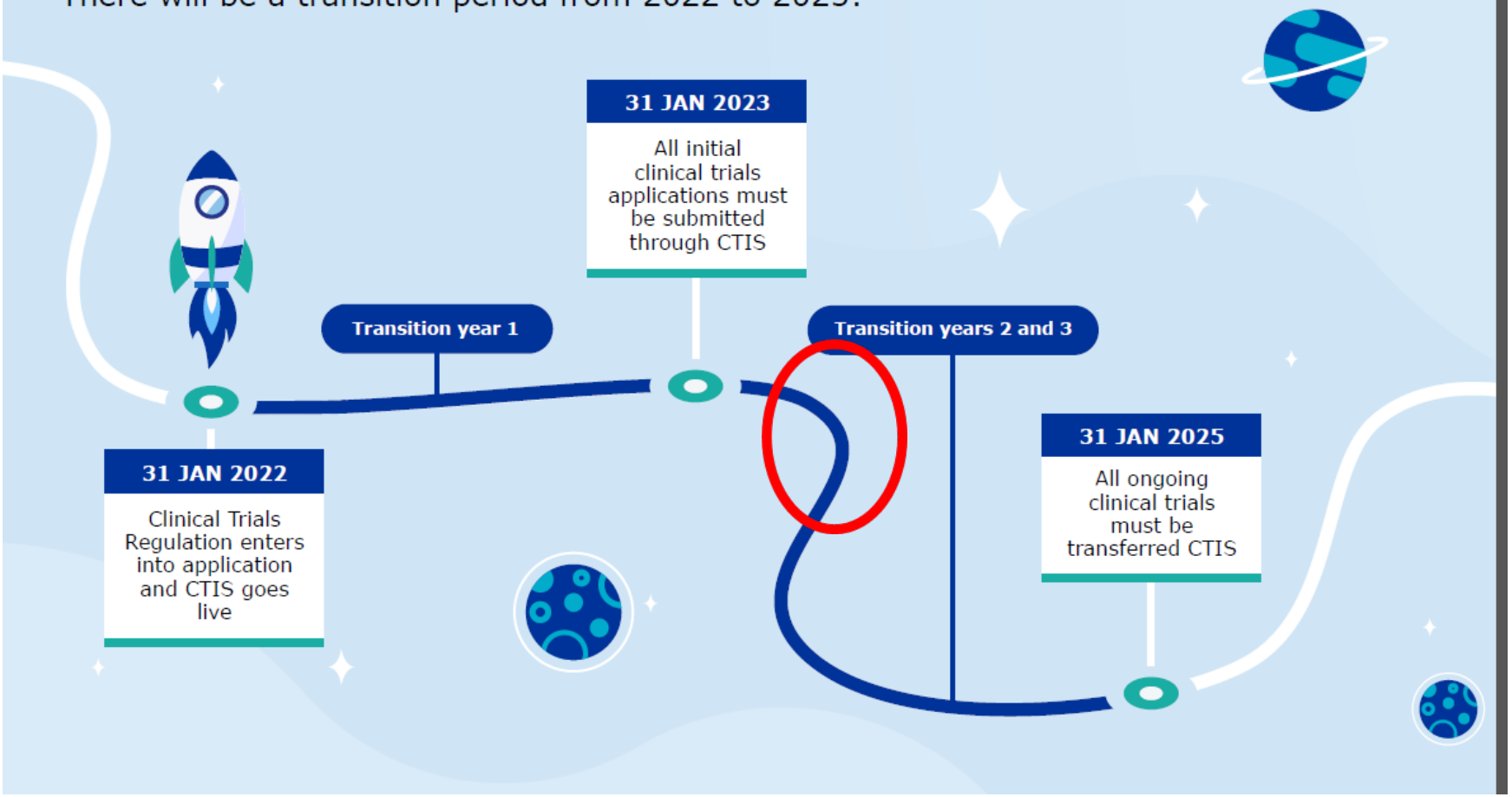
Transition period

There will be a transition period from 2022 to 2025:



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Transition Year 2 & 3

- Since 31 Jan 2023 all new CT applications must now be made via CTIS under the CTR
- Before 31 January 2025 – All ongoing clinical trials will be required to have transitioned to the Clinical Trial Regulation and will need to be migrated to CTIS
- During this transition period, substantial amendments of clinical trials approved under CTD can continue to be submitted under CTD.

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Transition procedure – from CTD to CTR

- CTD decision will be respected for transitioning CTs and there will be no "reassessment"
- The procedure for transition is described in Chapter 11 of Q&A – CTR
- Transition required for trials which will have at least one site active in the EU on 30/01/2025
- Only active trials **without any pending/ongoing assessment** in any EEA country are eligible to transition.
- A new cover letter and new application form (Part I and II) should be completed in CTIS, and in case of multinational clinical trials, a **harmonised** or at least a **consolidated protocol must be submitted see CTFG Best Practice for Sponsors**

Transition procedure – from CTD to CTR

** When the sponsor cannot provide certain documents listed in annex I of the Regulation, a blank document should be uploaded clarifying that this aspect was assessed by National Competent Authority (NCA) and/or Research Ethics Committee (REC) and therefore is covered by the conclusion of the assessment under the CTD.

- Documents with a placeholder blank document will need to be submitted as part of the first substantial modification application after the authorisation of the transition application.
- If the first substantial modification to the application is a part I change, the sponsor should complete all elements related to Part I of the dossier.
- If the first substantial modification would be a part II change, the sponsor should complete all elements related to part II of the dossier

Harmonised/Consolidated Protocol

Substantial differences across MSs in terms of protocol should be addressed via substantial amendments under Directive 2001/20/EC in order to be able to transition them as one trial under the Clinical Trials Regulation

- Harmonised protocol – identical protocol and trial procedures in all MSC;
- Consolidated protocol – identical protocol, but MSC specific considerations on specific trial procedures are included.
  - Core protocol information (to be identical) in any consolidated version
    - EudraCT number
    - CT Title
    - Primary objective
    - Primary end point
    - End of CT definition
    - Main inclusion and exclusion criteria

Transition procedure – from CTD to CTR

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Part I application (latest approved versions of documents under CTD)

- new cover letter
  - include a statement that protocol does substantially differ from version authorised in all MSC include a declaration that all other part I documents are identical
  - the name of the ethics committee who has given a favorable opinion on the clinical trial under CTD and the EudraCT number shall be included.
- new application form (Part I and Part II) → direct data input CTIS
- Protocol (harmonised or consolidated)
- Investigator's Brochure
- GMP relevant documents
- IMPD (latest harmonised version);
- The latest approved version of documents related to non-investigational medicinal products (i.e. auxiliary medicinal products under the CTR, if applicable)

Part II application

- The latest approved versions of the subjects' information sheet and the informed consent form.

• ***Signatures** on various part I and II documents (e.g. investigator CV, DoI, cover letter), are **not part of the clinical trial application in CTIS** (exceptions are **site suitability** and **QP declaration**)

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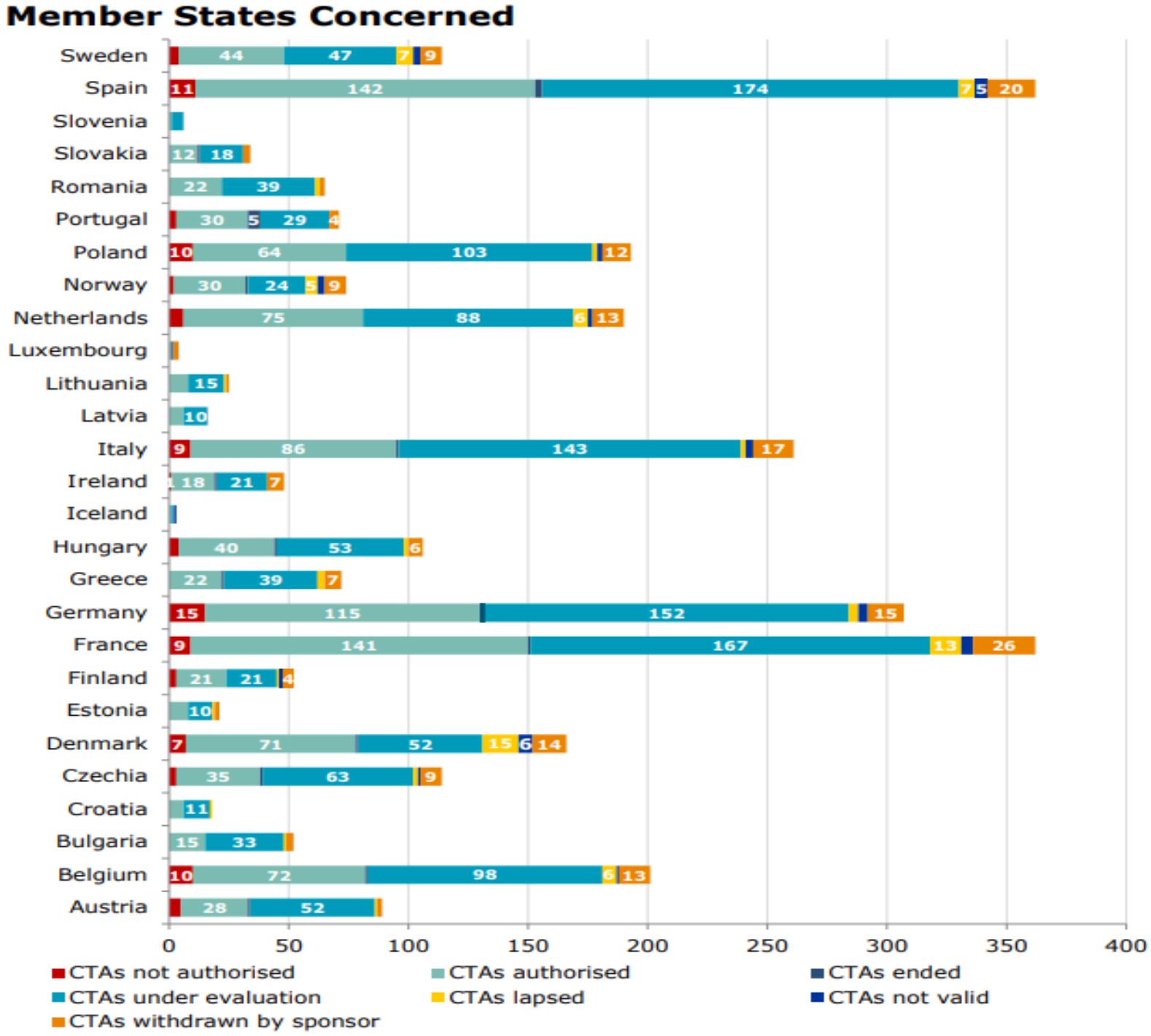
Transition –additional resources

- How to Create and Submit a Transition trial
- Questions and Answers Document - Regulation (EU) 536/2014 – Chapter

EMA KPI metrics 1st-31st March – Article 5 (full dossier applications) at MS level. Published monthly here

Article 11 (part 1 only applications), Article 14 (additional MSC) not captured here



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Common issues in applications to date

New initial dossier not in line with CTR

- Applicants should review the Annex 1 of the CTR and ensure the submitted documents are in line with CTR requirements
  - Requirements for Cover letter, Protocol, IB, IMPD, Actions in relation to Scientific Advice and Paediatric Investigational Plan, Labelling, Recruitment etc etc all clearly set out here

A	B	C	D	E
Is a medicinal product being investigated ? *(1)* If you answer no to I the question in column A below, the investigation does not fall within the scope of Regulation EU No 536/2014 If you answer yes to f the question below go to column B.	**What effects of the medicinal product are you looking for?** If you answer no to all the questions in column B below, the investigation does not fall within the scope of Regulation EU No 536/2014 If you answer yes to any of the questions below go to column C	**Why are you looking for those effects?** If you answer no to all the questions in column C below, the investigation does not fall within the scope of Regulation EU No 536/2014 If you answer yes to any of the questions below go to column D - the investigation is a clinical study as described in article 2(2)(1) of Regulation EU No 536/2014.	**How are you looking for those effects?** If you answer NO to all the questions in column D below, the clinical study is a non-interventional study that does not fall within the scope of Regulation EU No 536/2014 If you answer yes to any of the questions below go to column E – the study is a clinical trial according to Regulation EU No 536/2014	**Is your clinical trial a low-intervention clinical trial?** If your answer NO to any of the questions below in column E, the trial is a clinical trial within the scope of Regulation EU No 536/2014 but is NOT a low-intervention clinical trial as defined in Regulation EU No 536/2014. If you answer YES to ALL of the questions below, the trial is a low-intervention clinical trial. A specific set of risk-adaptations can be applied.
A. Is the investigated substance or product either presented as a medicinal product or does it function as such, in accordance with point 2 of article 1 of Directive 2001/83/EC ? *(2)*	B. Is the aim of the investigation on the medicinal product : B.1. To discover or verify/compare its clinical effects? B.2. To discover or verify/compare its pharmacological effects, e.g. pharmacodynamics? B.3. To identify or verify/compare its adverse reactions? B.4. To study or verify/compare its pharmacokinetics, e.g., absorption, distribution, metabolism or excretion?	C. Is the objective of the investigation on a medicinal product : C.1. To ascertain or verify/compare the efficacy of the medicine? *(3)(4)* C.2. To ascertain or verify/compare the safety of the medicine?	D.1. Is the assignment of any patient involved in the study to a particular therapeutic strategy decided in advance by a clinical trial protocol *(5)*, and does the assignment not fall within normal clinical practice in the Member State(s) Concerned ? *(6)* D.2. Is the decision to prescribe a particular medicinal product clearly taken together with the decision to include the patient in the study? D.3. Are diagnostic or monitoring procedures applied to the patients included in the study, other than those which are applied in normal clinical practice in any of the Member State(s) concerned? *(6)*	E.1. Is this a study of one or more medicinal products, which all have a marketing authorisation in the Member State(s) concerned? E.2. Does the protocol of the clinical trial specify that (i) the investigational medicinal products are used in accordance with the terms of the marketing authorisation; or (ii) the use of the investigational medicinal products is evidence-based and supported by published scientific evidence on the safety and efficacy of those investigational medicinal products in any of the Member States concerned; E.3.Do the additional diagnostic or monitoring procedures not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice

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Low-intervention clinical trials ≠Non-interventional studies

A "Low-intervention Clinical Trial" is an interventional clinical trial which also meets **all** of the following conditions as defined in Article 2(2)(3) of the CTR:

- the IMPs are authorised
- IMPs are used in accordance with the terms of the MA; or the use of the IMP is evidence-based and supported by published scientific evidence on the safety and efficacy
- the additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice in any Member State concerned

Partial/incomplete responses to RFI

- Once an application is submitted there is limited scope for advice or discussion outside of CTIS
- CTR has very limited scope for additional rounds of RFI
- Similarly, the scope for approval with conditions is greatly reduced
- So there is a greater risk that incomplete or partial responses will lead to a rejection
- Therefore it is important that dossiers submitted are CTR compliant from the start and provide fulsome responses to RFI
- Non-commercial sponsors are welcome to come for **pre-submission** advice, especially if you intend on nominating IE as RMS for multinational CT
  - Advice is available free of charge for non-commercial/non-academic sponsors.

Approach to CCI and personal data

- Sponsors are directed towards the recently published Interim guidance document on how to approach the protection of personal data and commercially confidential information while using the Clinical Trials Information System (CTIS) version 1.0 as well as the Annex 1 of this document which lists data/document types which data and documents that might contain personal data
- Academic sponsors are also recommended to review Section 3 in training module 02 for advice on how to avoid inclusion of personal data of the author of a document, included as part of the metadata of a file: clinical-trials-information-system-ctis-common-features-ctis-training-programmemodule-02_en.pdf (europa.eu)

Other tips

- Initial application should have HPRA fee form and proof of payment to avoid RFI on this

CTIS list of know issues (and work arounds) are published here

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Planned system interruptions

Users are advised to avoid using CTIS or this website during the regular maintenance windows:

- Tuesdays and Thursdays, from 18:00 to 21:00 Amsterdam time
- Every first Saturday of the month, from 10:00 to 14:00 Amsterdam time

The time zone used in CTIS is Central European Time (CET). All due dates and deadlines are displayed in CET despite the daylight-saving time change taking place in Europe on 26 March 2023.

About release notes

These documents outline the latest updates to the CTIS system, including the secure Sponsor and Authority workspaces, and to the Clinical Trials website. Updates may include improvements to existing features and functionality, the addition of new features and functionality and technical improvements.

Release notes March 2023

Release notes v1.0.16.0 (PDF, in English)

Release notes v1.0.18.0 (PDF, in English)

Release notes v1.0.19.0 (PDF, in English)

Release notes v1.0.20.0 (PDF, in English)

Upcoming events

CTIS bitesize talk CTIS Bitesize talk 10 May 2023 – IMPD-Q only

- On 10 May 2023 EMA is hosting a CTIS Bitesize talk at 15:30-17:00 CEST. The talk will focus on part I-only submission of the investigational medicinal product dossier on quality (IMPD-Q), and related scenarios.
- Participants will be able to submit their questions in advance until 4 May or during the event via Slido with the event code #bt10may.
- For more information on previous training sessions, including supporting materials, see: CTIS training and support materials and question and answer 2.15 from Clinical Trials Regulation (EU) no 536/2014 - Questions and answers - volume 10 - Guidance documents applying to clinical trials

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Key links for Clinical Trial Sponsors

- CTIS training and support
- Quick guide for sponsors - Regulation 536/2014 in practice
- HPRA Guide to Conducting Clinical Trials under CTR
- Clinical Trials Information System (CTIS): online modular training programme
- Guide to CTIS Training Catalogue
- CTIS Sponsor Handbook
- CTIS Newsletter
- EudraLex Vol 10

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Thank you