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The new Clinical Trial Regulation (CTR) explained-

Preparation for Transition– Session 2, November 23, 2021

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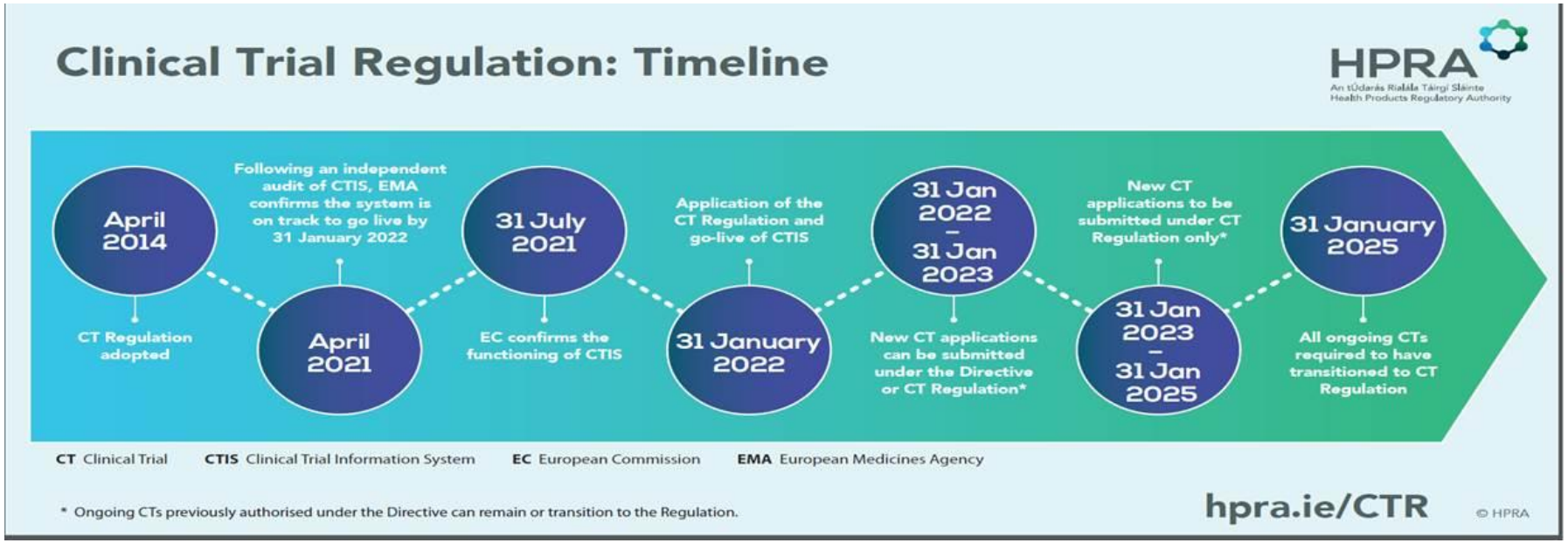
Timeline for transition



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When to transition?

- Possible to transition at any time post January 31st 2022.
- All trials must transition by 31st January 2025
  - Sponsors should take into consideration the authorisation procedure time (60 days) when considering this deadline.
- Only **active** trials without any **pending/ongoing assessment** in any EEA country are eligible to transition.

How to transition trials authorised under the CTD to the CTR

- Transition is via submission of an application in line with Article 5 of the CTR through CTIS.
- Specific requirements may differ depending on the nature of the currently authorised trial
  - Mononational;
  - Multinational;
  - Voluntary Harmonisation Procedure (VHP).
- In all instances, it is the **Sponsors responsibility** to ensure compliance with the CTR prior to submission.

Mononational Clinical Trials

- For trials only authorised in one member state Sponsor should submit a new CT application through CTIS including:
  - Cover letter –
    - include a statement that protocol does not differ from authorised version
    - Include a declaration that all other part I documents are identical
  - New application form (part I and part II)
  - Part I documents:
    - Latest approved protocol
    - IB
    - GMP related documents
    - IMPD
    - Any existing documents related to auxiliary medicinal products

Mononational Clinical Trials

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- Part II documents:
  - Informed consent form and information on procedure
  - Subjects information sheet

- In the case the sponsor cannot provide any Annex I dossier requirements specific to the CTR, they should include a blank document explaining these have been assessed by NCA or REC
- Any additional Annex I dossier requirements should be completed at the time of the first SM.

Multinational Clinical Trials

- Sponsor must ensure that the clinical trial has a harmonised or consolidated protocol approved in all MSC prior to transitioning.
  - Harmonised protocol – identical protocol and trial procedures in all MSC;
  - Consolidated protocol – identical protocol, but MSC specific considerations on specific trial procedures are included.

Multinational Clinical Trials

- Following aspects of the protocol must be identical in all MSC
  - EudraCT number
  - Trial Title
  - Protocol version number
  - Primary objective
  - Primary endpoint
  - Definition of end of trial
  - Main inclusion and exclusion criteria

Multinational Clinical Trials – Protocol differences across MSC scenarios

- Harmonised (i.e. identical) protocol in all MSC – no need to submit a substantial amendment under the directive prior to transitioning.
- Non-substantial (i.e. administrative) differences in protocols in MSC – a consolidated or harmonised version can be submitted.
  - Sponsor must declare there are **no substantial differences** in the protocol relative to that approved in all MSCs under the directive.
- Substantial differences – a substantial amendment should be submitted to the NCA of each MSC to harmonise the protocols prior to transition.

Multinational Clinical Trials

- For trials authorised in more than one member state with the same EudraCT, Sponsor should submit a new CT application through CTIS including:
  - 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
  - New application form (part I and part II)
  - Part I documents:
    - **Consolidated/harmonised** protocol
    - IB
    - GMP related documents
    - IMPD
    - Any existing documents related to auxiliary medicinal products

Multinational Clinical Trials

- Part II documents:
  - Informed consent form and information on procedure
  - Subjects information sheet

- In the case the sponsor cannot provide any Annex I dossier requirements specific to the CTR, they should include a blank document explaining these have been assessed by NCA or REC.

Multinational Clinical Trials - VHP

- VHP will discontinue as of entry into force of the regulation.
- For VHP trials transitioning, the ref-NCA for the VHP should be nominated as the RMS with all concerned MS identified in the application in CTIS.
- Sponsor must ensure that harmonised documentation exists in all MSC to the VHP as per the multinational procedure already discussed.
- If a harmonised protocol does not exist, substantial amendments under the directive should be submitted to harmonise documents prior to submission of the application for authorisation under the CTR.

Transition process

- Validation of the submitted documents to take place, but no assessment is foreseen.
- **Sponsors responsibility** to ensure document requirements are in line with the CTR.
- Tacit approval within 60 days of submission.
- MSC can take **corrective measures** as per Article 77 if they subsequently find out the Trial is not in compliance with the CTR.
  - Revoke;
  - Suspend;
  - Modify.
- Documents submitted through CTIS will be subject to transparency and publication rules post-authorisation.

Resources

- Regulation 536/2014: https://ec.Europa.eu/health/sites/default/files/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf
- Current and future Commission guidelines: https://ec.europa.eu/health/documents/eudralex/vol-10
- General Q+A: https://ec.europa.eu/health/sites/default/files/files/eudralex/vol-10/regulation5362014_qa_en.pdf
- Transition period:2018_05_CTFG_Best_Practice_Guide_for_sponsors_of_transition_multinational_clinical_trials.pdf (hma.eu)
- Transparency: https://www.ema.europa.eu/en/documents/other/appendix-disclosure-rules-functional-specifications-eu-portal-eu-database-be-audited_en.pdf
- Risk proportionate approaches: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/2017_04_25_risk_proportionate_approaches_in_ct.pdf
- Auxiliary meds: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/2017_06_28_recommendation_on_axmps.pdf
- Serious breaches: https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-notification-serious-breaches-regulation-eu-no-536/2014-clinical-trial-protocol_en.pdf
- Commission training course March 2021: https://ec.europa.eu/health/human-use/events/ev_20210309_en

Thank you!

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