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Health Products Regulatory Authority

The new Clinical Trial Regulation (CTR) explained-

Post-authorisation – Session 2, November 23, 2021

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Classification of changes to ongoing CTs under the CTR

- Changes can be classified as:
  - Substantial modifications
    - The safety or rights of the subject
    - The reliability or robustness of the data generated
  - Change relevant to the supervision of a trial (Article 81.9 changes)
  - Non substantial modifications
- **Sponsors responsibility** to decide whether a proposed modification is 'substantial'
- Examples of appropriate classification are included in Annex III of the commissions Q and A document on the CTR.

Selected examples of classifications

- Sponsor
  - Change of Sponsor entity – Substantial modification
  - Change of Sponsor name or contact details – Article 81.9 Non-substantial modification
- Investigators Brochure
  - Addition of updated data or update to the RSI – Substantial modification
  - Annual update without any change to the document – Article 81.9 Non-substantial modification
- Further examples in Annex III of the commissions Q and A document

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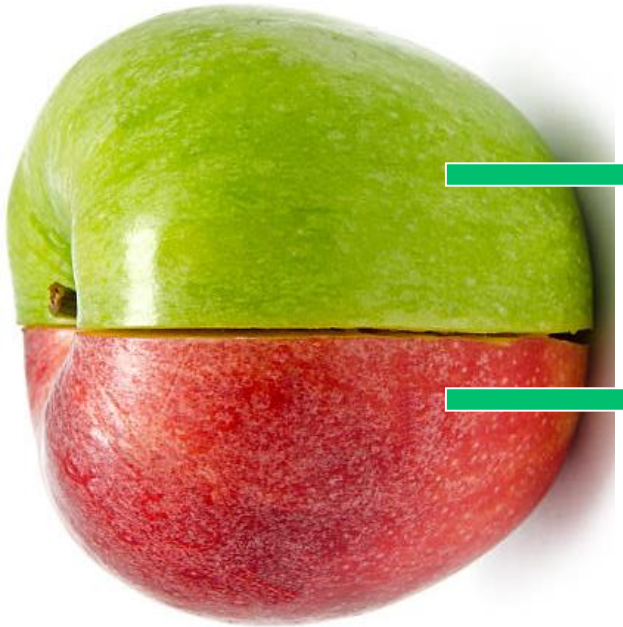
Substantial Modifications

Application – Part I and Part II



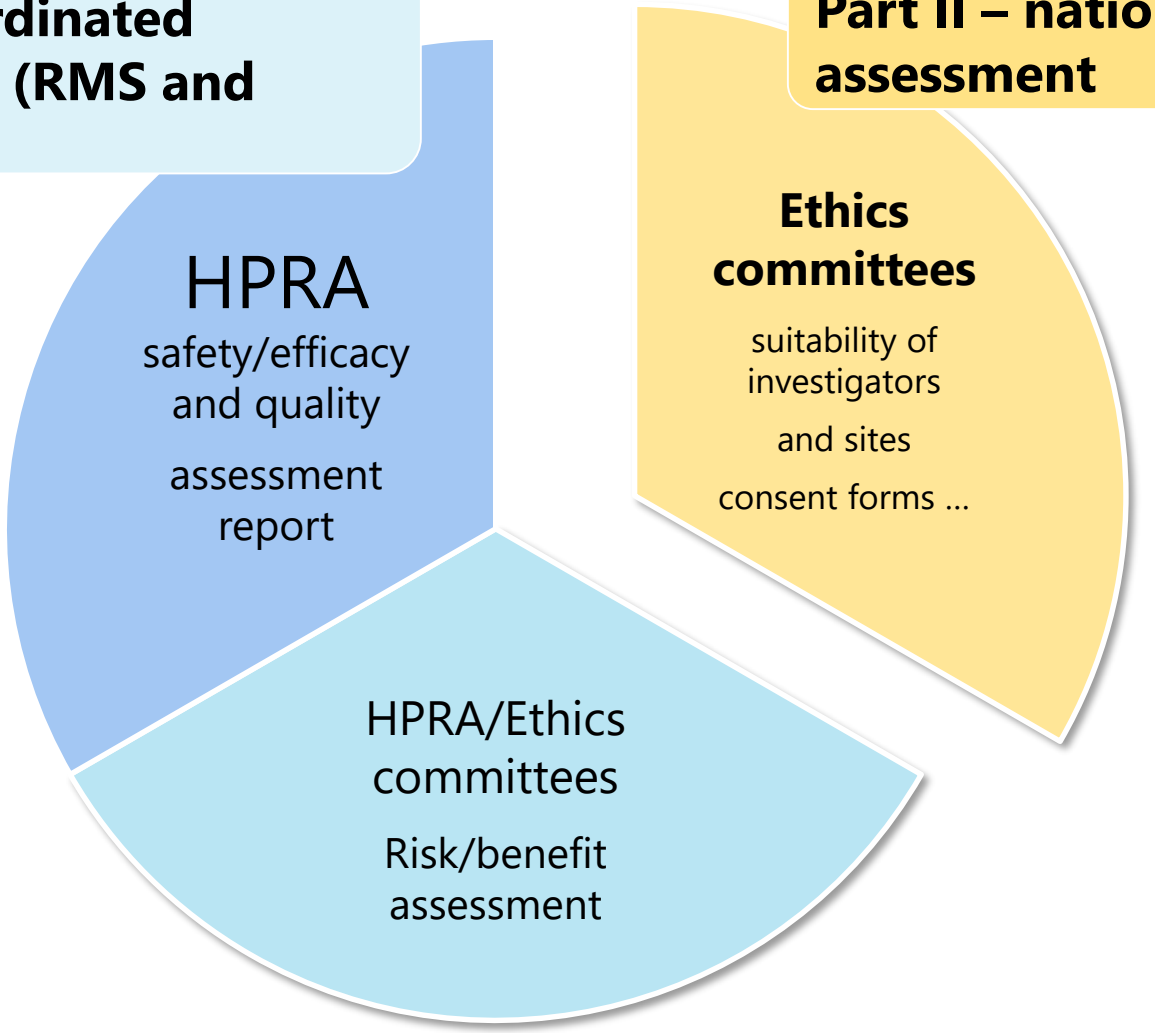
Part I - scientific part, common for all MSCs, coordinated review

Part II – national/local part – ethical review

Who will assess what ?

Part I – coordinated assessment (RMS and MSCs)

Part II – national assessment



Substantial Modifications

- Can be submitted to modify aspects related to:

» Part I aspects

» Part II aspects

» Part I + Part II aspects

Substantial Modifications

- SM to part I, or part I and part II can only be submitted:
  - All other part I, or part I and part II SM procedures must be complete.
  - Any Article 14 procedures to add an additional MSC must be complete.
  - In the case of Article 11 staggered submission, at go-live, submission of a SM to part I or part I and II will only be possible after **all MSC** to the original application have notified a decision.
  - In the future, for trials authorised under Article 11, it will be possible to submit a SM following receipt of decision from all MSC to which a **full** (i.e. Part I and Part II) initial application was submitted even in the case where not all MSC have received a part II.

Substantial Modifications

- SM to part II can be submitted:
  - Following full authorisation of the trial in the MSC.
  - When there is no ongoing assessment of a part I, part I+II or part II SM ongoing in that MSC
  - Part II SM in different MSC can overlap.

Substantial Modifications

- Key Takeway – **overlapping Part 1 substantial modification procedures are not permitted under the CTR.**

- In the case where SM are required to common documents for use in multiple clinical trials (e.g. IMPD, IB, RSI) it is recommended that the Sponsor submit SM to all trials which use these documents together. This information can be summarised in the cover letter.

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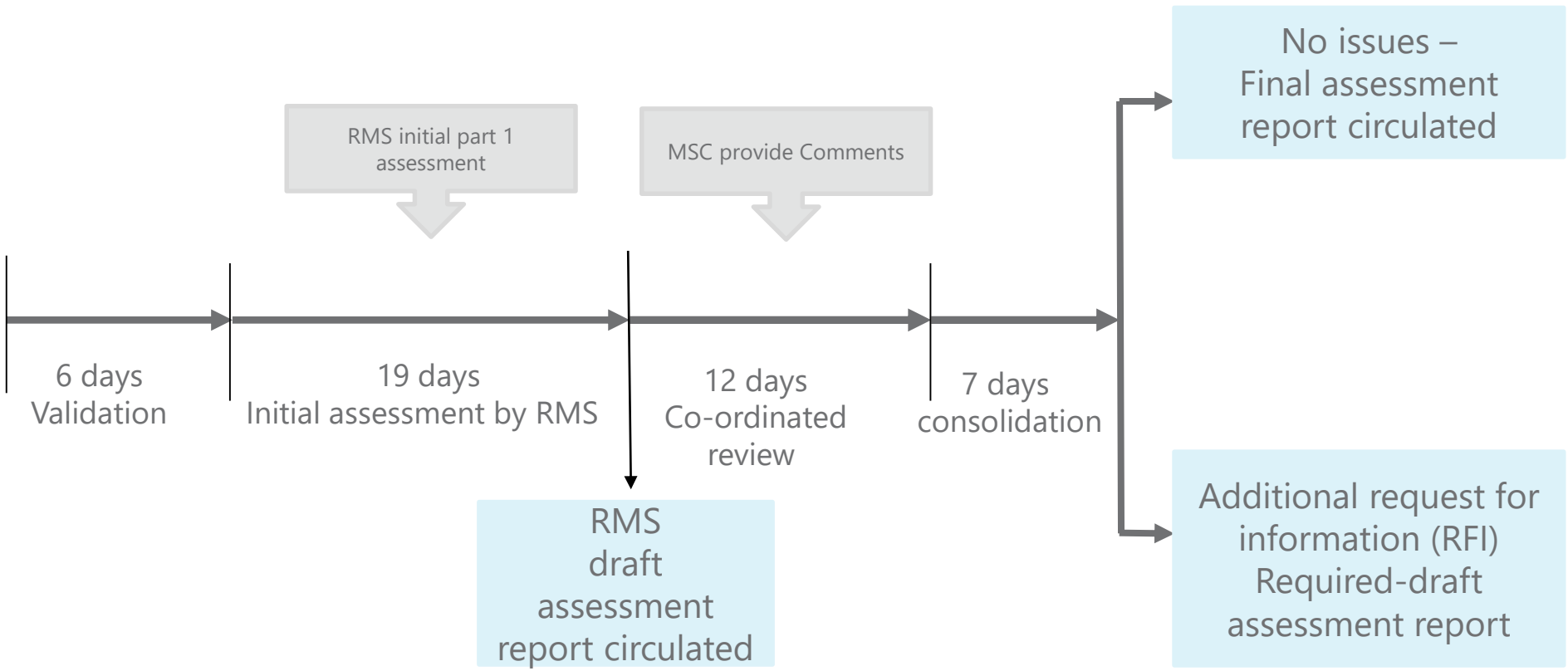
Timelines

Assessment timelines – Part 1

Validation	Assessment	Final Decision notified
6 days	38 days	5 days

Assessment timelines – Part I

Validation	Assessment	Final Decision notified
6 days	38 days	5 days



Assessment timelines – Part I

Validation	Assessment	Final Decision notified
6 days	38 days	5 days

In the case of requests for further information, timelines can be extended to a maximum outlined below:

Validation	Assessment	Final Decision notified
21 days 6+10+5	69 days 38+12+12+7	5 days

Article 20 – SM to aspects covered by Part II

- **Each Member State** shall assess a SM to aspects covered by **Part II** and prepare an assessment report within 38 days from the validation date.

Validation	Assessment + notification	Final decision
6 days	38 days	

In the case of requests for further information, timelines can be extended to a maximum outlined below:

Validation	Assessment + notification	Final decision
21 days 6+10+5	69 days 38+12+19	

Article 21-22 – SM to aspects covered by Part I+II

- Procedure follows timelines for part I assessment previously discussed.
- When a SM covering both part I and part II aspects is submitted, it is **not possible** to partially authorise it. Both part I and part II aspects must be authorised in this instance or the SM refused.

Article 19,20,23 – Decision on SM

- For SM related to aspects covered by part I, part II, and part I and II, each MSC shall notify the sponsor through the CTIS as to whether the substantial modification is
  - authorised,
  - authorised subject to conditions
  - refused.
- In the absence of communication from an MSC within 5 days of the reporting date, the RMS opinion is tacitly approved.
- **MSC can disagree** with conclusions of the RMS
  - on the assessment of the Part I SM on specified grounds in the CTR.
  - where an ethics committee gives a negative opinion.
- In these instances, **the SM can still be implemented in other MSC.**
- MSC shall refuse to authorise a substantial modification to aspects covered by part II on duly justified grounds, or where an ethics committee has issued a negative opinion.

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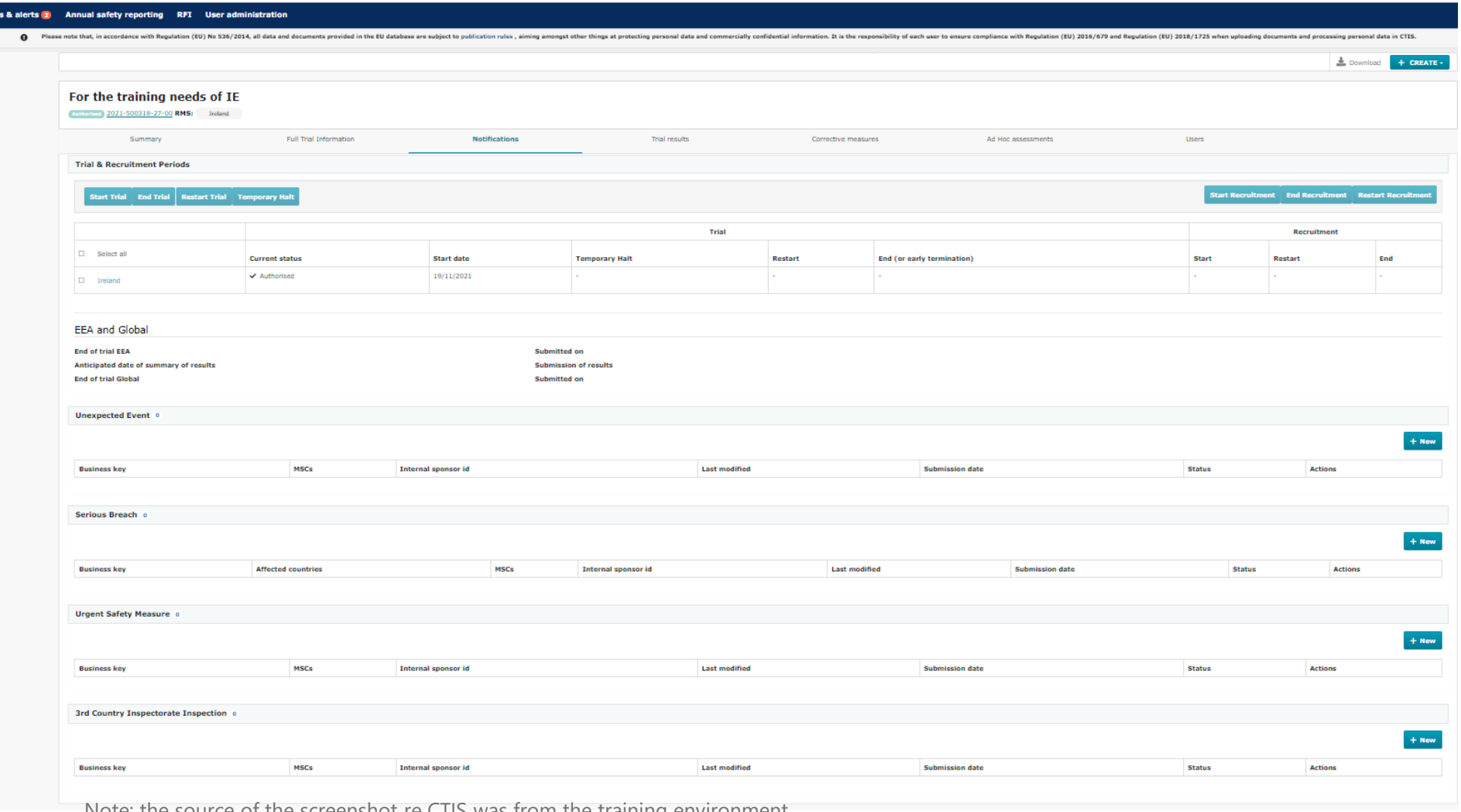
Sponsor notifications

Sponsor notifications under the CTR

- Article 36- Sponsor to notify each MSC through CTIS within 15 days of:
  - the start of the trial;
  - first visit of first patient;
  - end of recruitment in that MSC.
- Article 37- Sponsor to notify each MSC through CTIS within 15 days of:
  - the end of the CT in that MSC;
  - the end of the CT in all MSC;
  - end of the CT in all MSC and third countries;
  - halt to a trial for reasons not affecting B/R;
  - restart of a halted trial in all MSC.
- Article 37 also stipulates that within 1 year following EOT in all MSC the Sponsor should submit a summary of results to CTIS.
- Article 38 – Sponsor to notify a temporary halt or early termination for reasons of safety with undue delay but within 15 days

Sponsor notifications under the CTR



Note: the source of the screenshot re CTIS was from the training environment

Thank you!

Health Products Regulatory Authority

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