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The new Clinical Trial Regulation (CTR) explained

Serious Breaches– Session 4

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Legal requirement

Article 52 - Reporting of Serious Breaches

- The sponsor shall notify the Member States concerned about a serious breach of this Regulation or of the version of the protocol applicable at the time of the breach through the EU portal **without undue delay but not later than seven days** of becoming aware of that breach.

- A 'serious breach' means a breach likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated in the clinical trial.

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Guideline and Training

Guideline- expected to be finalised end of Q4 2021

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 31 January 2017
2 EMA/430909/2016

Clinical Trial Information System (CTIS) structured data form - Notifications (XLSX/1008.1 KB)

First published: 29/07/2021

3 Guideline for the notification of serious breaches of
4 Regulation (EU) No 536/2014 or the clinical trial protocol
5 Draft

EMA CTIS Training: https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trials-information-system-ctis-online-modular-training-programme (Module 05 – Manage a clinical trial through CTIS)

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Reporting a Serious Breach

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Who Should Report a Serious Breach

- The sponsor is responsible for the notification through CTIS
- The sponsor may delegate this task to a third party by means of a written agreement.

When to Report a Serious Breach

- Without **undue delay** and within **7** calendar days of the sponsor becoming aware of the breach
- If the sponsor receives information that provides reasonable grounds to believe that a serious breach has occurred, the sponsor reports the breach first within 7 calendar days, investigate and take action simultaneously or after notification.
- Should not wait to obtain all of the details of the breach prior to notification.
- In some cases, investigation and assessment may be required by the sponsor prior to notification, in order to confirm that a serious breach has actually occurred however this should not extend the reporting period of 7 calendar days.
- For any potential breaches that become evident at the trial site the principal investigator should have an appropriate contact point at the sponsor.
- Process should be in place to ensure that such information is promptly reported to the CT sponsor in order for the sponsor to meet the legal obligations.

How to Report a Serious Breach

Serious breaches of EU/EEA CT in the EU/EEA	• Reported as per article 52 – EU CT system CTIS • If it affects the benefit/risk balance of the trial in addition to article 52, consider reporting requirements under article 53 (unexpected event) or article 54 (urgent safety measure) • Consider other relevant notification – substantial modification
Occurred outside the EU/EEA while the CT application is under review in the EU/EEA	• If the breach has an impact on the accuracy or robustness of the data in the application • Sponsor should consider addressing the concerns during the evaluation of the CTA and may withdraw the application to make amendments as necessary
Serious breach of an EU/EEA authorized CT occurring outside the EU/EEA likely to affect the safety and rights of a subject/benefit risk of a CT in the EU/EEA	• Notified to the Member State under article 52 • consider reporting requirements under article 53 (unexpected event) or article 54 (urgent safety measure) as applicable

What needs to be reported

- Any serious breach of:
  - The Regulation (EU) No 536/2014.
  - The version of the protocol applicable at the time of the breach.

- A "serious breach" is a breach which is likely to affect to a significant degree
  - The safety and rights of a subject.
  - The reliability and robustness of the data generated in the clinical trial

- Judgement on whether a breach is likely to affect the reliability and robustness of the trial data depends on a variety of factors:
  - the design of the trial
  - the type and extent of the data affected by the breach
  - the overall contribution of the affected data to key analysis parameters
  - the impact of excluding the data from the analysis

Follow up

- MS performs assessment and may follow up with the sponsor for further information
- Actions to be taken by MS, where necessary
  - Inspections
  - corrective measures
    - revoke the authorisation of a clinical trial
    - suspend a clinical trial
    - require the sponsor to modify any aspect of the clinical trial
- Before the MS takes any of these corrective measures it will (except where immediate action is required) ask the sponsor and/or the investigator for their opinion. That opinion shall be delivered within seven days.

Sponsor Responsibilities

- Formal Process and contact information
- Receipt and assessment of extent and impact
- Report to EU CT system CTIS
- Investigation and root cause analysis
- Corrective and Preventative action
- Compliance with the 7 calendar day timeline

Delegated Party Responsibilities

Delegated tasks from sponsor

Information on the management of breaches relevant to the sponsor

Written process in place

Principal Investigator and Service Provider Responsibilities

- A process should be in place to ensure that:
  - staff are able to identify the occurrence of a potential serious breach
  - Any potential serious breach is promptly reported to the sponsor or delegated party, through the contact provided
- The process should be in a written procedure
  - could be a formal standard operating procedure or a process detailed in the protocol.

Examples

Details of the issue	Is this a serious breach?
Patient information leaflet and informed consent updated, but at one trial site this was not relayed to the patients until approximately 2-3 months after approval.	**Yes**, if there was a systematic or persistent problem and/or if it has a significant impact on the safety and rights of a trial subjects (e.g. there was key safety information not relayed to subjects in a timely manner).

Details of the issue	Is this a serious breach?
Patients incorrectly randomized/stratified according to the protocol.	**Yes,** as this will be likely to have a significant impact on rights of the subjects or the reliability and robustness of the generated data.
A cohort had invalid blood samples as they were processed incorrectly. As a result one of the secondary endpoints could not be met. Therefore, a substantial modification was required to recruit more subjects to meet the endpoint.	**Yes,** it is likely to affect to a significant degree the safety and rights of a trial subject as further additional subjects had to be dosed unnecessarily as a result of this error.

Details of the issue	Is this a serious breach?
The thrombosis risk of an IMP was monitored by some laboratory parameters. Investigator site failed to reduce or stop trial medication, in response to altered values of these laboratory parameters, as required by the protocol. This occurred with several subjects over a one year period, despite identification by the monitor of the first two occasions.	**Yes,** it is likely to affect to a significant degree the safety and rights of a trial subject as subjects were exposed to an increased risk of thrombosis.
Minor visit date deviation. A common deviation in clinical trials.	**No**, a minor protocol deviation, which does not meet the criteria for notification.
According to the protocol, a brain CT scan should be performed in the selection visit in order to exclude brain metastasis (exclusion criteria). The site used a previous version of the protocol where the CT scan wasn't required so 6 patients out of 10 were included without brain CT.	**Yes,** because it shows lack of safety data collection. This exclusion criteria could potentially affect patients safety and rights and would affect the reliability and robustness of the data if the majority of patients were ineligible.

Thank you!

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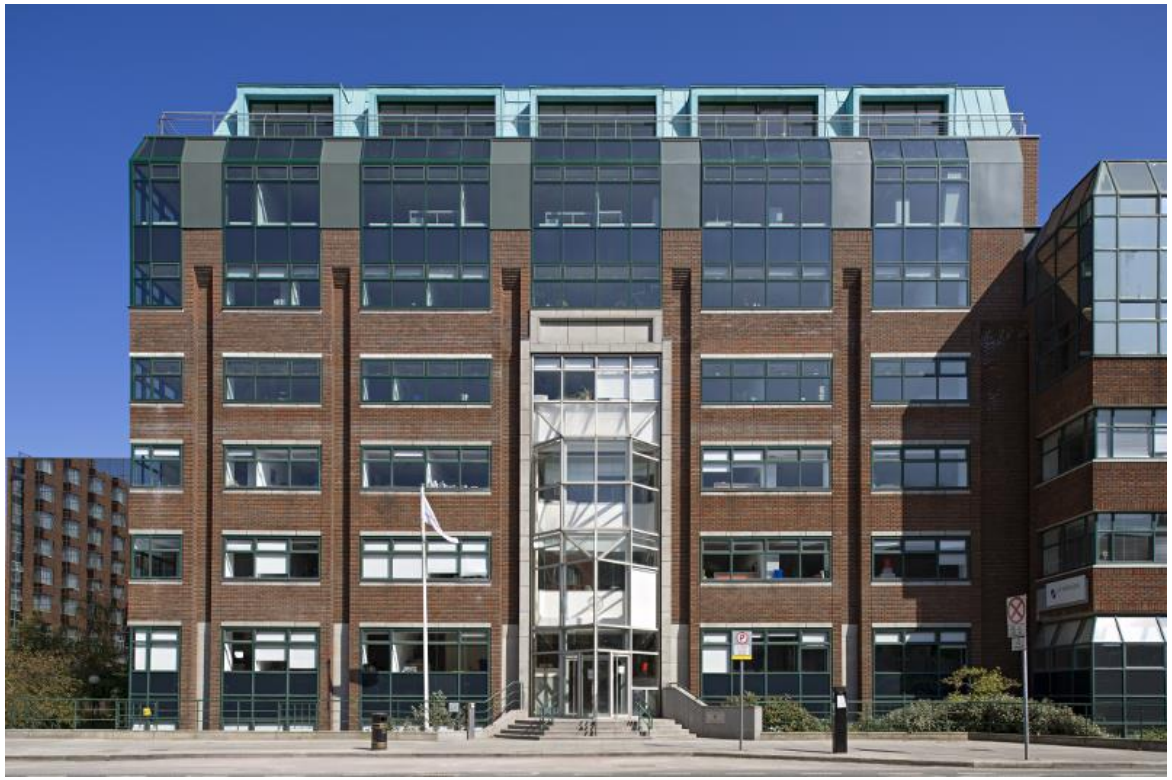

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