CTIS Bitesize Talk: End of transition period and notifications including serious breaches

16 October 2024

A few housekeeping rules

Questions were collected in advance on **www.sli.do**
With event code **#bt16oct**

Tips for optimal screen viewing

- Make use of the instructions under the **Live broadcast** section on the event page and connect directly to the **EMA's Vimeo channel 1** *for the full-screen experience*
- Have a stable internet connection

Agenda

1. End of transition period
2. Safety relevant Notifications
3. Reporting Serious Breaches
4. Publication of safety-relevant notifications and Serious Breaches
5. Q&A

The experts for this event are:

Moderator: Teresa Calandri

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Ornela Ademi
Change Manager

Federal Institute
for Drugs
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Elke Stahl
Senior Expert

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Camelia Mihaescu
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Giovanni Varricchio
Scientific Specialist

The experts for this event are:

Anne Lenaers

Regulatory Expert at the Belgian National Competent Authority

Cátia Gonçalves

Scientific Officer

Elena Marín Rodríguez

GCP and PhV Inspector

Lotte Skoulund Laursen

GCP-inspector at the Danish Medicines Agency

Sabrina Giacomelli

Senior GCP Inspector

End of transition period

Presented by Ornela Ademi on 16 October 2024
CTIS programme, Data Analytics and Methods Task Force (TDA)
European Medicines Agency

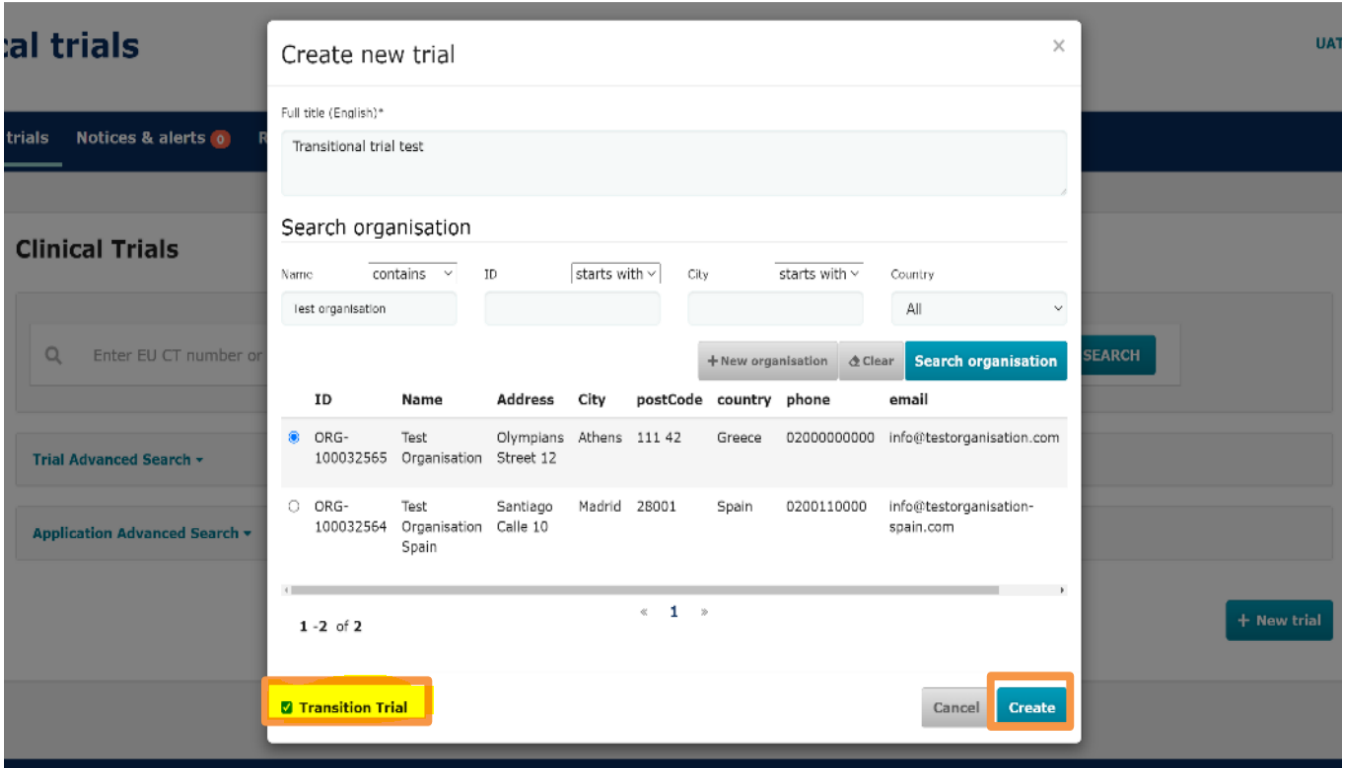
Transition of clinical trials

All trials expected to continue **after 30 January 2025** need to transition in CTR (CTIS). As of **31 January 2025**, all clinical trials need to be in CTR (CTIS).

Start transition **no later than 16 October 2024 (the last date for expedite transition procedure)**.

Consider the time necessary for completion of the MS(s) procedure - can take up to 3 months.

Transitional trials reminder



Remember to tick the box on the application to indicate that the trial is a transitional trial!

If technical issues during the submission of a transitional trial, raise a ticket with ServiceNow.

Information to help you transit a trial

- Resources to support on transitioning trials are available on the CTIS website
- Event on Training for non-commercial sponsors on transitioning trials to CTR and CTIS – 9 February 2024
- Latest bitesize talk - 29 February 2024 on Transitioning of trials
- CTIS webinar: last year of transition - 25 March 2024
- CTIS walk in clinic dedicated to transition - 18 September 2024
- CTCG updated best practice guide and annex I: cover letter template for sponsors transitioning trials to the CTR
- Annex II: Fees for transitional trials in EU/EEA Member States
- Chapter 5 of the CTIS Sponsor Handbook
- Module 23 of the CTIS online training programme (Step-by-step instructions: quick guide for sponsors)

Additional support and CTIS Training Environment

EMA webpage CTIS Training and Support

Regular updates on the CTIS Programme (subscribe): Clinical Trials Highlights

The training environment is a simulation of CTIS used in production and allows users to get familiar with system functionalities.

Sponsors can express interest in gaining access to the CTIS Training Environment by filling in the ongoing survey.

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Any questions?

Further information

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Safety relevant Notifications

Presented by Elke Stahl, BfArM
16 October 2024

Type of notification

- Start of trial
- Start of recruitment

- **Temporary halt,** due to potential safety issue (TH)
  → **restart only after approved** substantial amendment aligned to the TH
- **Premature end,** due to safety

- Re-start of trial → **link with approved** substantial amendment after the TH
- Re-start of recruitment

- End of recruitment
- End of trial in MS (EoT)
- End of trial global

- **Unexpected event** , not a SUSAR , changing benefit risk (UE)
- **Urgent safety measures** (USM)

- **Serious Breaches,** safety relevant (SB)
- 3rd country inspection

Orange = Safety relevant notifications

CTCG

Safety relevant notification

Submission of notification

- Sponsor please **complete all structured fields** with information on the notification, tick safety related if applicable
- Upload of **document in addition for further details** is possible (but not instead!)
- Sponsor **inform** with notification **of other CTs (**list EUCT numbers) affected by same issue, location : best in structured field, or in an attached document (see public portal)

Safety related notifications will be **assessed by MSs**

- CTCG BP on Pharmacovigilance, part 5:
  "Coordinated assessment of notifications submitted by sponsor via CTIS "

Assessment of UE, USM and SB will be linked to notification which will push publication **in public portal**

➢ Public portal will display all structured fields completed by sponsor only and 'assessed my MSs'; no documents or information which trials are affected too if not in structured fields

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Safety relevant notification - Assessment

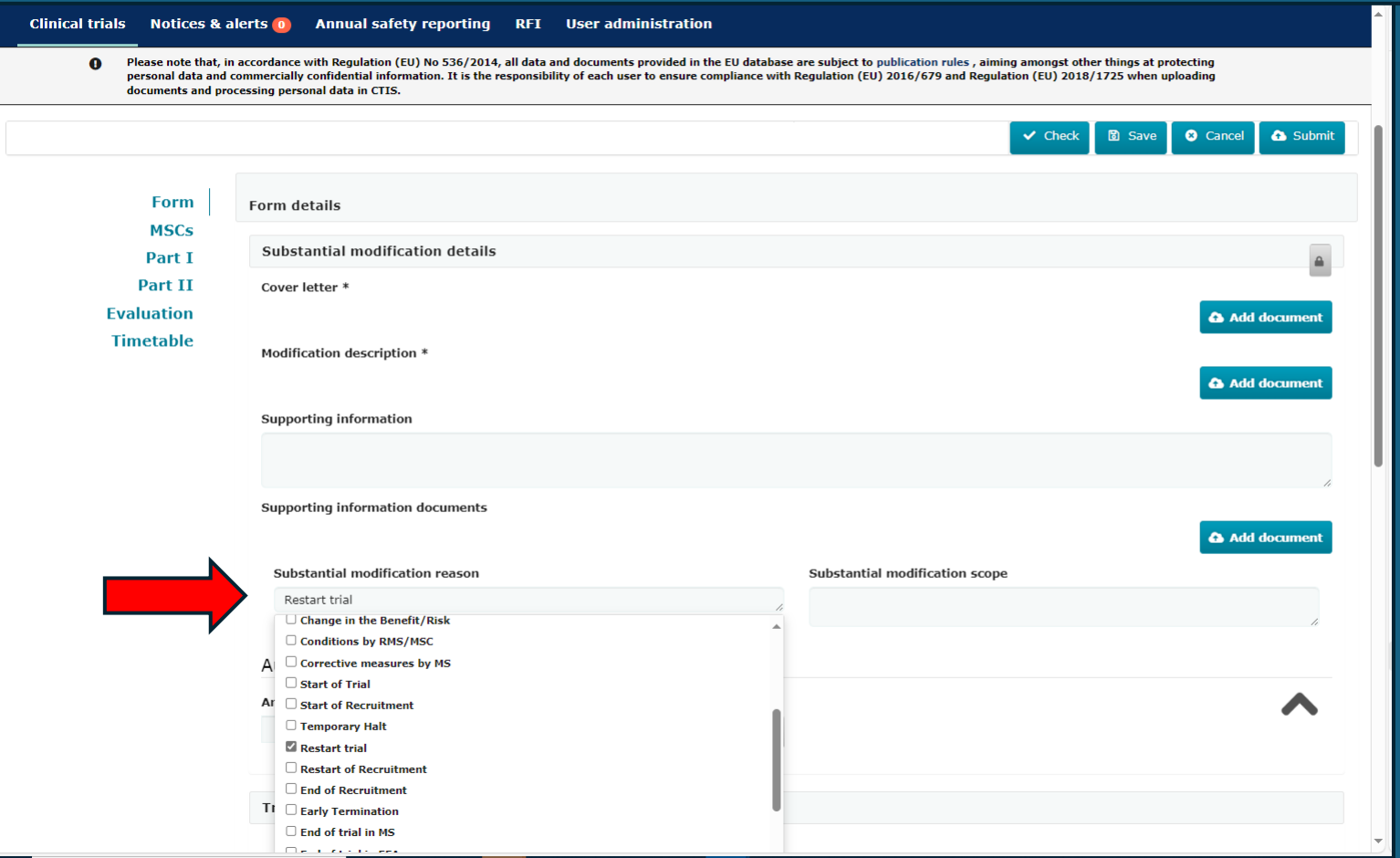
Safety related notifications will be **assessed by MSs**

- CTCG BP "Coordinated assessment of notifications submitted by sponsor via CTIS "

- Risk based approach
  - responsible *RMS (in testing phase)*, including safety assessing MS if appropriate
  - Review and **inform *in 'CTIS text field'*** - public
    - Notification is reviewed and noted
    - No further review, RFI, discussion w/MSs or actions is needed
  - Assessment and use of ***adhoc workflow***
    - Request of further information via 'adhoc' workflow – please **watch these RFI folder**!
    - Discussion with MSCs and /or saMSs (even you don't expect RFI)
    - Outcome of assessment – internal
      - ➢ Requirements need to **be sent as RFI** of the adhoc workflow, or Corrective measure if applicable
    - Possible to select a coordinating MS e.g. if multiple RMS, saMS concerned with the issue of the notification
  - Assessment can **be linked to notification** and will push publication

CTCG

Substantial amendment after temporary halt in order to apply for restart - Please select the right issue in the drop down:



Questions ?

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Reporting Serious Breaches according to the Regulation (EU) No. 536/2014

Presented by Camelia Mihaescu on 16 October 2024
Senior GCP Scientific Specialist
European Medicines Agency

Presentation overview

- Reporting requirements for serious breaches
- Terminology used
- Algorithm for the identification of the most affected Member State
- Key points to consider when reporting serious breaches
- Responsibilities of parties involved in the notification of serious breaches
- Possible actions taken by Member States Concerned in relation to serious breaches
- Reporting serious breaches in CTIS
- Examples of incidents: for discussion
- Take home messages

Reporting requirements for serious breaches

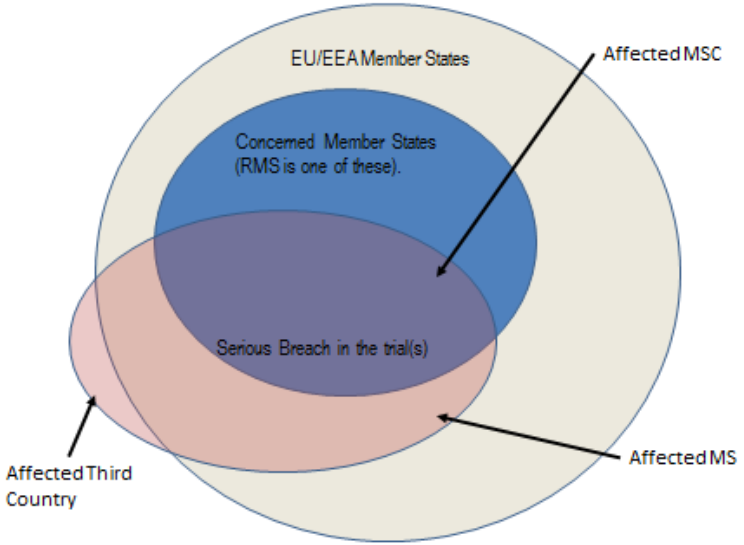
- According to Art. 52 of the CTR:
  - A serious breach (SB) is a breach likely to affect **to a significant degree** the safety and rights of trial participants or the data reliability and robustness.
- The sponsor (or delegated party) should report serious breaches (SBs) through CTIS without undue delay, but **no later than 7 (calendar) days** of becoming aware of the breach.
- If there are reasonable grounds based on evidence to believe that a SB has occurred, the sponsor should report it and investigate further, not wait until all details of the breach are obtained. Updates to the SB report can be made when further information becomes available.
- Only SBs should be notified, **not suspected SBs**.

Reporting requirements for serious breaches (cont.)

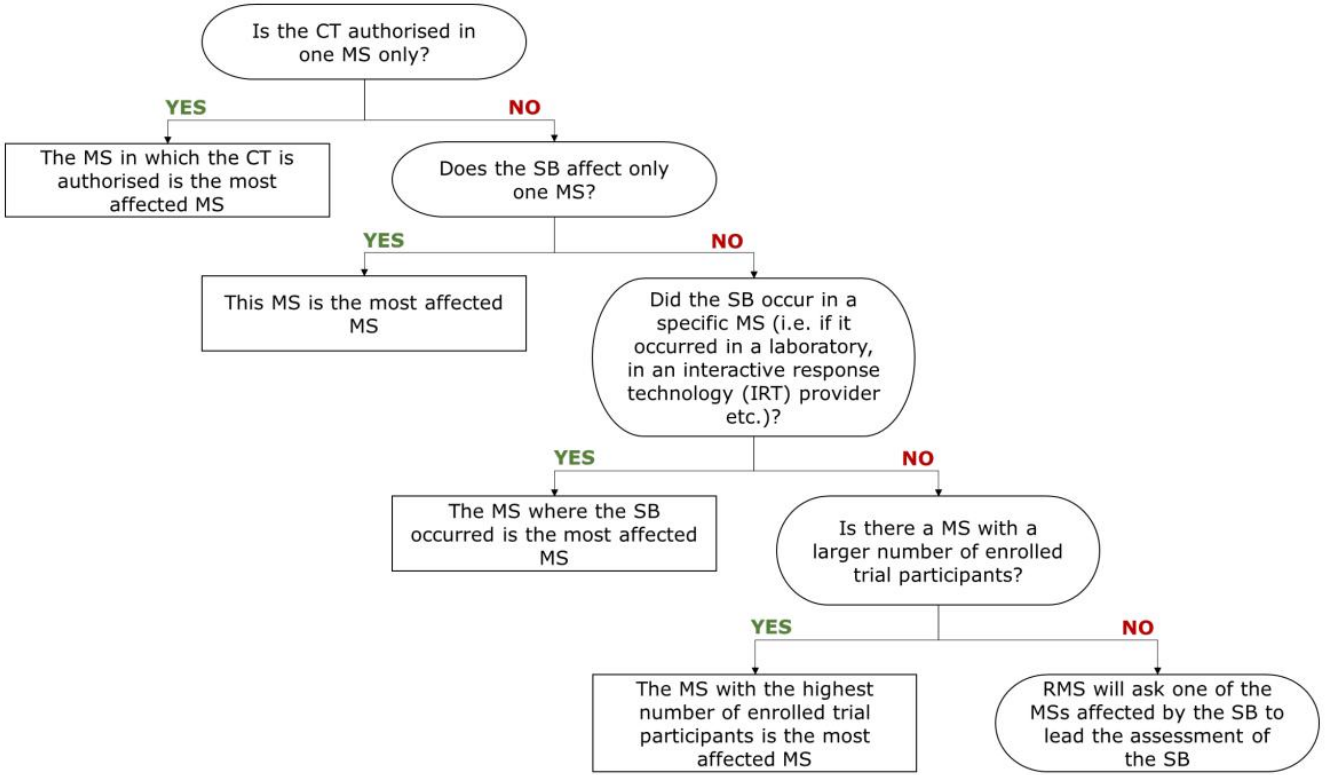
- For SBs occurring **exclusively outside the EU/EEA** and having an impact on trial participants safety and/or rights or on data reliability:
  - For on-going CTA assessments: sponsor should address the concerns during the evaluation of the CTA (no submission of the SB through CTIS) ;
  - For clinical trials already authorised/ conducted in EU/EEA: the SB should be reported via CTIS to all MSC (=no distinction between SBs occurring in or outside the EU/EEA, if the trial is authorised in the EU/EEA).
- All relevant fields in CTIS (see Appendix IIIa) should be filled in; the sponsor is encouraged to upload a report (see Appendix IIIb) containing additional documents which help MSs assessing the SB.
- All SBs should be included in the CSR.

Terminology used

- **RMS, MSC** (as per the CTA assessment)
- **AMS – Affected Member State**: is the Member State directly affected by the serious breach (e.g. the MS where the sponsor is based, the MS where trial participants are affected by the SB, the MS where the breach occurred (this may not be a MSC).
- **MAMS – Most Affected Member State**: Member State most affected by the serious breach (see algorithm presented in the guideline).



Algorithm for the identification of the most affected Member State



Key points to consider when reporting serious breaches

- Factors to be consider when determining whether an incident qualifies as a SB:
  - Trial design;
  - Type and extent of data affected by the incident;
  - Contribution of the affected data to the statistical analysis;
  - Whether a systematic and/or significant error occurred in the treatment of the trial participants.

- The sponsor should perform a root cause analysis and assess the impact of the SB on the safety and/or rights of trial participants and/or on data reliability and robustness.

Responsibilities of parties involved in the notification of a serious breach

- **Sponsor**:
  - Performs an investigation of potential SBs reported to them by an investigator or a third party (e.g. CRO) and decides whether the case qualifies as a SB and thus should be reported through CTIS;
  - Ensures that the management of SBs is included in their quality system;
  - Performs a root cause analysis for incidents meeting the criteria of a SB and implements appropriate CAPAs;
  - Reports the SB through CTIS within 7 calendar days of becoming aware of the SB.
- **Delegated party**:
  - Performs the above listed tasks on behalf of the sponsor, as per a written agreement with the sponsor.

Responsibilities of parties involved in the notification of a serious breach (cont.)

- **Service providers**:
  - Should have a system in place to identify suspected SBs;
  - Inform, in a timely manner the sponsor or the delegated party about a suspected SB.

- **Principal Investigator**:
  - Ensures that the site staff (or delegated service provider) is able to identify a suspected SB;
  - Informs, in a timely manner the sponsor or the delegated party about a suspected SB.

Responsibilities of parties involved in the notification of a serious breach (cont.)

Please note that

- CTIS does not provide a functionality for the indication of the Most Affected Member State (MAMS), so this information can either be included in the structured fields or in the uploaded document/report/Appendix IIIb (if any).
  - If in doubt, the diagram in the *Guideline for the notification of serious breaches* should be used.
  - If not provided, the RMS will contact the sponsor via a RFI (or in rare circumstances identify the MAMS itself).

- The provided CAPA should be thorough and with dual emphasis on corrective and preventive action points.
  - The more sufficient the CAPA is, the more efficient the regulator assessment will be.
  - It is accepted to supplement the submission with a more thorough CAPA, as soon as the SB is fully investigated.

Possible actions taken by Member States Concerned in relation to serious breaches

- **GCP inspection**:
  - Its outcome may lead to further regulatory or legal actions.

- **Regulatory actions**:
  - Corrective measures described in Art.77 of the CTR (e.g. revocation, suspension of the authorisation or modifications to a clinical trial);
  - Except where immediate action is required, the MSC will provide the sponsor with the possibility to comment/add any further clarifications. This input is expected to be provided within 7 calendar days;
  - Actions with reference to national legislation might be also applicable.

Reporting serious breaches in CTIS

- Mandatory fields in CTIS are to be filled in and additional information can be added either as free text or as a separate document uploaded in CTIS;

- **Appendix III b** – Information to be submitted with a notification of a SB:
  - can be used by sponsors to submit, in a structured way, additional information related to the SB (highly recommended to be used! It facilitates the assessment process for a SB!)

- **RFI – Request For Information:**
  - information to be submitted after the notification of a SB with a deadline proposed by the MAMS or the MS coordinating the assessment of a SB.
  - It's necessary to further assess the SB.

Responsibilities of parties involved in the notification of a SB

Please note that

- Although the regulatory authorities envisage to assess SBs in a timely and harmonized manner, the legislation does not stipulate exact timelines for this assessment.

- Communication with the sponsors regarding the SBs is mainly done through RFIs (please note that CTIS does not support notifications outside the system).

Examples of incidents: for discussion

1. One trial participant was administered unmasked IMP and therefore he was unintentionally unblinded. The sponsor considered that this event could impact the reliability and robustness of the data.

(Background information: The trial participants and the team at the clinical site are blinded to the treatment, except for a trial nurse and part of the pharmacy team, who are responsible for masking and dispensing the medication to the trial participants; the medication is administered at the trial site)

This incident **does not meet** the definition of a serious breach because it is not likely to affect, to a significant degree, the safety and rights of trial participants, nor the reliability and robustness of the data generated in the clinical trial.

Acknowledgements to: Alicia Sanchez-Caro Estruch,GCP Inspector, AEMPS, Spain

Examples of incidents: for discussion (cont.)

2. *Three lab samples for pharmacogenomic testing (a sub-study of the mail clinical trial) were obtained at three consecutive visits from a trial participant. The samples were sent to the central lab. The central lab personnel detected that this trial participant has not consented to participate in the sub-study, while cross-checking selected data from the samples received with the data in the eCRF, before performing the analysis. They immediately put the sample analysis on hold and queried the site and the CRA to check this inconsistency.*

(Background information: the sub-study (collection of pharmacogenomic data) is an optional one, that require separate consenting from the trial participants.)

This incident **does not meet** the definition of a serious breach because it is not likely to affect, to a significant degree, the safety and rights of trial participants, nor the reliability and robustness of the data generated in the clinical trial.

Acknowledgements to: Alicia Sanchez-Caro Estruch,GCP Inspector, AEMPS, Spain

Examples of incidents: for discussion (cont.)

3. *In a clinical trial the IMP was an authorised drug. The pharmacist dispensed to a trial participant a kit intended for the routine clinical care, instead of the kit provided by the sponsor for the clinical trial. The formulation and drug concentration were the same. Lack of training of the pharmacist (who was new to the team) was identified as root cause; the CAPAs were: retraining and double checking at the dispensing step.*

This incident **does not meet** the definition of a serious breach because it is not likely to affect, to a significant degree, the safety and rights of trial participants, nor the reliability and robustness of the data generated in the clinical trial.

Acknowledgements to: Sabrina Giacomelli, GCP Inspector, AIFA, Italy

Take home messages

- Importance of observing the reporting timeline stipulated in the CTR;

- The decision whether an incident qualifies as a serious breach depends on various factors related to the clinical trial and the details of the incident- always to be judged on a case by case basis;

- Reporting incidents that are not real serious breaches puts burden on assessors and deviates their focus from confirmed cases of serious breaches; Over-reporting to be avoided!

Take home messages (cont.)

- Most affected Member State should be always indicated, if determined;
- Appendix III b of the guideline: a helpful tool for both sponsors and assessors;
- Importance of performing a root cause analysis in order to identify the most appropriate CAPAs.

Thank you!

Further information

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Publication of safety-relevant notifications and Serious Breaches

Presented by Giovanni Varricchio on 16 October 2024
Scientific Specialist
European Medicines Agency

Launch of new CTIS Public Portal on 18 June 2024

- Revised CTIS transparency rules became applicable on 18 June 2024 with the launch of a new version of CTIS public portal
- Reference training: Quick user guide + CTIS Bitesize Talk on revised transparency rules
- **Over 6,300 trials are public**, of which over **2,300 with documents.** Overall, more than 51,500 documents are now publicly available

CTIS publication rules are summarised in the Annex 1 to the Guidance document on how to approach the protection of personal data and CCI while using the CTIS

More info is in the Q&A on the protection of CCI and Personal Data, and detailed list of fields subject to publication is the List of CTIS application fields and documents + notifications fields

Structured data of Notifications: what is published & when

Structured data	Category 1		Category 2 integrated p h1&2	Category 2 & 3 *(excl. integr. ph1&2)*
	Paediatrics and/or PIP	**Adults**		
CTIS application fields	First MSC decision	First MSC decision	First MSC decision	First MSC decision
		30 months after EU/EEA End of Trial		
CTIS application fields on dose and treatment duration[1]	30 months after EU/EEA End of Trial			
MSC(s) conclusions and decision outcomes	That MSC decision			
Notifications on trial status and recruitment	As soon as submitted by sponsor			
Notific. on serious breaches, urgent safety measures, unexpected events	After MSC assessment	30 months after EU/EEA EoT & MSC assessment	After MSC assessment	
Corrective measures (suspension, revocation, modification request)	When applied by MSC(s)			

[1]*As a temporary measure, the publication of fields 'strength of product' and 'strength of active substance' has been suspended: further information will follow*

The notification is published only once the Member State assessment is finalized in CTIS

All structured data filled in by the sponsor are subject to publication; no structured data filled in by the Authority is published:

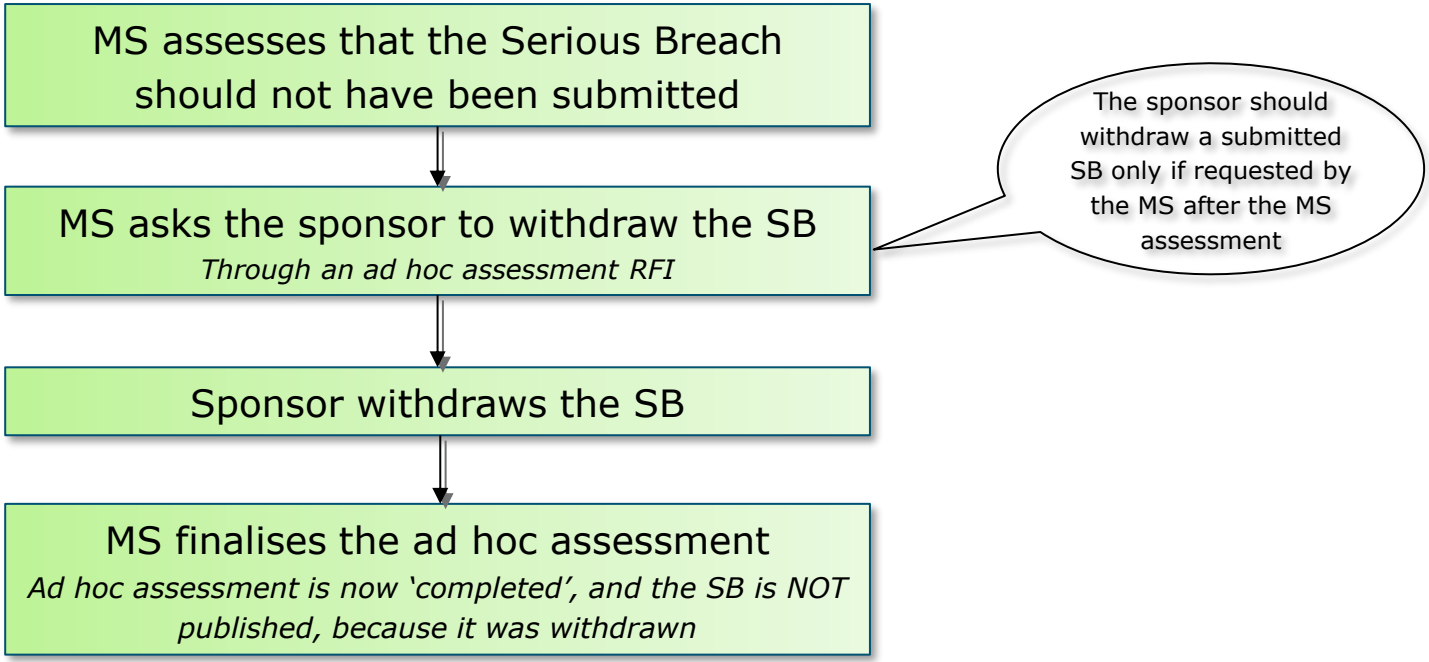
MS finalises the assessment in CTIS

Notification is published

Note

Since NO document on notifications is published, sponsors should avoid referring to 'attached documents':

Case scenario: if a Member State assesses that the Serious Breach should not have been submitted as such



Thank you!

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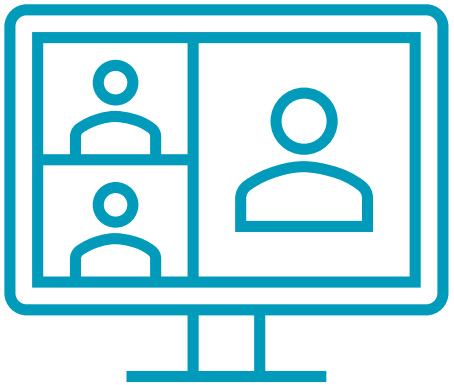
Upcoming CTIS events



- **20 November 2024**, 16:00 – 17:00 CET – CTIS Walk-in Clinic
- For 2024 CTIS events, please consult Clinical Trials Information System: training and support | European Medicines Agency (europa.eu) and EMA events pages

CTIS Bitesize Talk: End of transition period and notifications including serious breaches

Thank you for attending today's event

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