2023 – When the CTR will be in force for all – Let's be prepared

Reporting Obligations under the Clinical Trial Regulation: SUSARS, Serious Breaches, Summary and Lay Summary of Trial Results via CTIS

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REPORTING REQUIREMENTS

Recital 25

In order to increase transparency in the area of clinical trials, data from a clinical trial should be submitted *in support of a clinical trial application* if that *clinical trial has been recorded* in a *publicly accessible* and *free of charge database* which is a primary or partner registry of, or a data provider to, the international clinical trials registry platform of the World Health Organization (WHO ICTRP). Data providers to the WHO ICTRP create and manage clinical trial records in a manner that is consistent with the WHO registry criteria.

Specific provision should be made for data from clinical trials started before the date of application of this Regulation.

REPORTING REQUIREMENTS

Recital 37

In order to allow *patients* to assess possibilities to participate in a clinical trial, and to allow for effective *supervision* of a clinical trial by the Member State concerned, the *start* of a clinical trial, the *end of the recruitment* of subjects for the clinical trial and the *end of the clinical trial* should be notified. In accordance with international standards, the *results* of the clinical trial should be reported within *one year* from the end of the clinical trial.

START OF THE CLINICAL TRIAL

Recital 38

The date of the *first act of recruitment* of a potential subject is the date on which the first act of the *recruitment strategy described in the protocol was performed*, e.g., the date of a contact with a potential subject or the date of the publication of an advertisement for a particular clinical trial.

Definition 25

„Start of a clinical trial“ means the first act of recruitment of a potential subject for a specific clinical trial, unless defined differently in the protocol“

START OF THE CLINICAL TRIAL

Art. 36

1. The sponsor shall notify each Member State concerned of the *start of a clinical trial in relation to that Member State* through the EU portal. That notification shall be made within *15 days* from the start of the clinical trial in relation to that Member State.

2. The sponsor shall notify each Member State concerned of the *first visit of the first subject in relation to that Member State* through the EU portal. That notification shall be made within *15 days* from the first visit of the first subject in relation to that Member State.

START OF THE CLINICAL TRIAL

Art. 36

3. The sponsor shall notify each Member State concerned of the *end of the recruitment of subjects for a clinical trial in that Member State* through the EU portal. That notification shall be made within *15 days* from the end of the recruitment of subjects. In case of a re-start of recruitment, paragraph 1 shall apply.

END OF THE CLINICAL TRIAL

Definition 26

„End of a clinical trial“ means the last visit of the last subject, or at a later point in time as defined in the protocol“

Art. 37

1. The sponsor shall notify each Member State concerned of the *end* of a clinical trial *in relation to that Member State* through the EU portal. That notification shall be made within *15 days* from the end of the clinical trial in relation to that Member State.

END OF THE CLINICAL TRIAL

Art. 37

2. The sponsor shall notify each Member State concerned of the *end* of a clinical trial *in **all** Member States* concerned through the EU portal. That notification shall be made within *15 days* from the end of the clinical trial in the last Member State concerned.

3. The sponsor shall notify each Member State concerned of the *end* of a clinical trial *in **all** Member States* concerned and *in **all third countries*** in which the clinical trial has been conducted through the EU portal. That notification shall be made within 15 days from the end of the clinical trial in the last of the Member States concerned and third countries in which the clinical trial has been conducted.

TEMPORARY HALT OF THE CLINICAL TRIAL

Art. 37

5. The sponsor shall notify each Member State concerned of a temporary halt of a clinical trial in all Member States concerned *for reasons not affecting the benefit-risk balance* through the EU portal. That notification shall be made within *15 days* from the temporary halt of the clinical trial in all Member State concerned and shall include the reason for such action.

6. When a *temporarily halted* clinical trial referred to in para.5 is *resumed* the sponsor shall notify each Member State concerned through the EU portal. That notification shall be made within *15 days* from the restart of the temporarily halted clinical trial in all Member States concerned.

TEMPORARY HALT OF THE CLINICAL TRIAL

Art. 38

1. ... the *temporary halt or early termination* of a clinical trial for reasons of a *change in the benefit-risk balance* shall be notified to the Member States concerned through the EU portal. That shall be made *without undue delay but not later than 15 days* of the date of the temporary halt or early termination. It shall include the reasons for such action and specify all follow-up measures.

2. The *restart* of the clinical trial following a temporary halt as referred to in para 1 shall be deemed to be a *substantial modification* subject to the authorisation procedure laid down in Chapter III.

SAFETY REPORTING

Art. 40-44

- Investigator‘s reporting obligation of SAEs remains unchanged
- Sponsor‘s reporting obligations of SUSARs
  - Timelines remain unchanged
  - Reporting of ALL SUSARs, wherever they occurred, and also after a subject has left the study, only into EudraVigilance
- Sponsor‘s reporting obligation concerning Annual Safety Report remains unchanged.
- Annual Safety Report (ASR) will be uploaded in CTIS. SUSARs and ASR will be jointly assessed by the Member States‘ authorities and, where requested by national legislation, also by the ethics committee

SAFETY REPORTING

Annex III

- Medication errors, pregnancies and use outside the protocol need to be reported like adverse reactions
- Expectedness needs to be assessed by the Sponsor in relation to the Reference Safety Information (RSI) presented in the IB or SmPC
- Cover Letter needs to reference to the location of the RSI
- Unblinding of Serious Adverse Reactions (SARs) before potential reporting as SUSAR should only be done by sponsor staff not involved in the trial and reported to the DSMB and EMA

SERIOUS BREACHES

Guideline

Guideline for the notification of serious breaches of Regulation (EU) 536/2014 or the clinical trial protocol (in EudraLex Vol.10): https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-notification-serious-breaches-regulation-eu-no-536/2014-clinical-trial-protocol_en.pdf

- Appendix I: Examples of serious breaches
- Appendix II: Points to consider for sponsors in relation to the assessment of a breach
- Appendix III a: Template form for reporting serious breaches
- Appendix III b: Information to be submitted with a notification of serious breaches

SERIOUS BREACHES

Definitions

- **Serious breach**: Any deviation of the approved protocol version or the clinical trial regulation that is likely to affect the safety, rights of trial participants and/or data reliability and robustness to a significant degree in a clinical trial.

- **Affected Member State (AMS)**: Is the Member State directly affected by the serious breach. For example the Member State where the sponsor is based (as they have the overall responsibility), the Member State where patients are affected by the breach, or it could be the Member State where the breach occurred (note this is not always a Member State concerned, as the breach could occur in an organization in a Member State, i.e. and IRT provider, for a trial that has no sites in that Member State.

SERIOUS BREACHES

Examples

Category	Details of breach reported	Is this a serious breach?
		assessed adequately.
	9.2 The sponsor was not clear on the reporting requirements for the trial and was incorrectly classifying events as expected, as they were common events seen with that particular disease.	**Yes**, under-reporting of large numbers of SUSARs due to incorrect understanding of expectedness.
	9.3 The investigator was not documenting all the AEs associated with the trial.	**Yes**, depending on the type of trial, for example inadequate safety reporting in dose escalation studies may impact on the decision to escalate to the next dose level.
10. Consent	10.1 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).
11. Access to data	11.1 The investigator would not allow sponsor/CRO access to the trial participants' notes.	**Yes**, it is likely to affect the safety and rights of a trial subject and the reliability and robustness of the data generated in the trial as the data could not be verified. The protocol should contain a clause to state that Sponsor representative and Regulatory authorities will have access to the data, and this is also reflected in the informed consent.
	11.2 Loss of data.	**Yes**, it is likely to affect the safety and rights of a trial subject and the reliability and robustness of the data generated in the trial. Clinical trial sponsors and vendors should have agreements in place addressing business continuity and ensuring that clinical trials data are retrievable at any point in time.
12. Randomisation/ stratification errors	12.1 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.
13. DSMB/DMC	13.1 The Data and Safety Monitoring Board (DSMB)/ Data Monitoring Committees (DMC), which should be implemented according to the protocol and the clinical trial authorisation in a	**Yes**, the missing implementation of the DSMB/DMC is likely to affect to a significant degree the safety and rights of trial subjects and the reliability and robustness of the data generated

SERIOUS BREACHES

Examples

Category	Details of breach reported	Is this a serious breach?
	blinded trial, has in fact not been implemented.	in the trial.
14. Privacy	14.1 The Sponsor contracted a CRO to build an e-CRF – the e-CRF contained patient identifiable information. Both the Sponsor and CRO had access to all this information.	**Yes**, it affects to a significant degree the rights of a trial subject as it affects their privacy. Trial participant's confidentiality is a fundamental right by national requirements, by ICH-GCP and by ethical principles, which needs to be respected.
	14.2 A coordinating investigator site was sending follow-up questionnaires to trials subjects of other investigator sites (to save the other sites the extra work). For this they had the names and addresses of trial subjects of other investigator sites. The trial subjects were not informed about this and had not given consent for this. This does not affect subject safety but it does affect the privacy of trial subject.	**Yes**, it is likely to affect to a significant degree the rights of a trial subject as it affects their privacy.
	14.3 During an inspection, it was observed that the informed consent forms from trial subjects of one investigator site were being kept at another investigator site (also being the sponsor of the trial because it was an investigator initiated trial). The trial subjects affected were not informed about this and had not given consent for it.	**Yes**, it is likely to affect to a significant degree the rights of a trial subject as it affects their privacy.

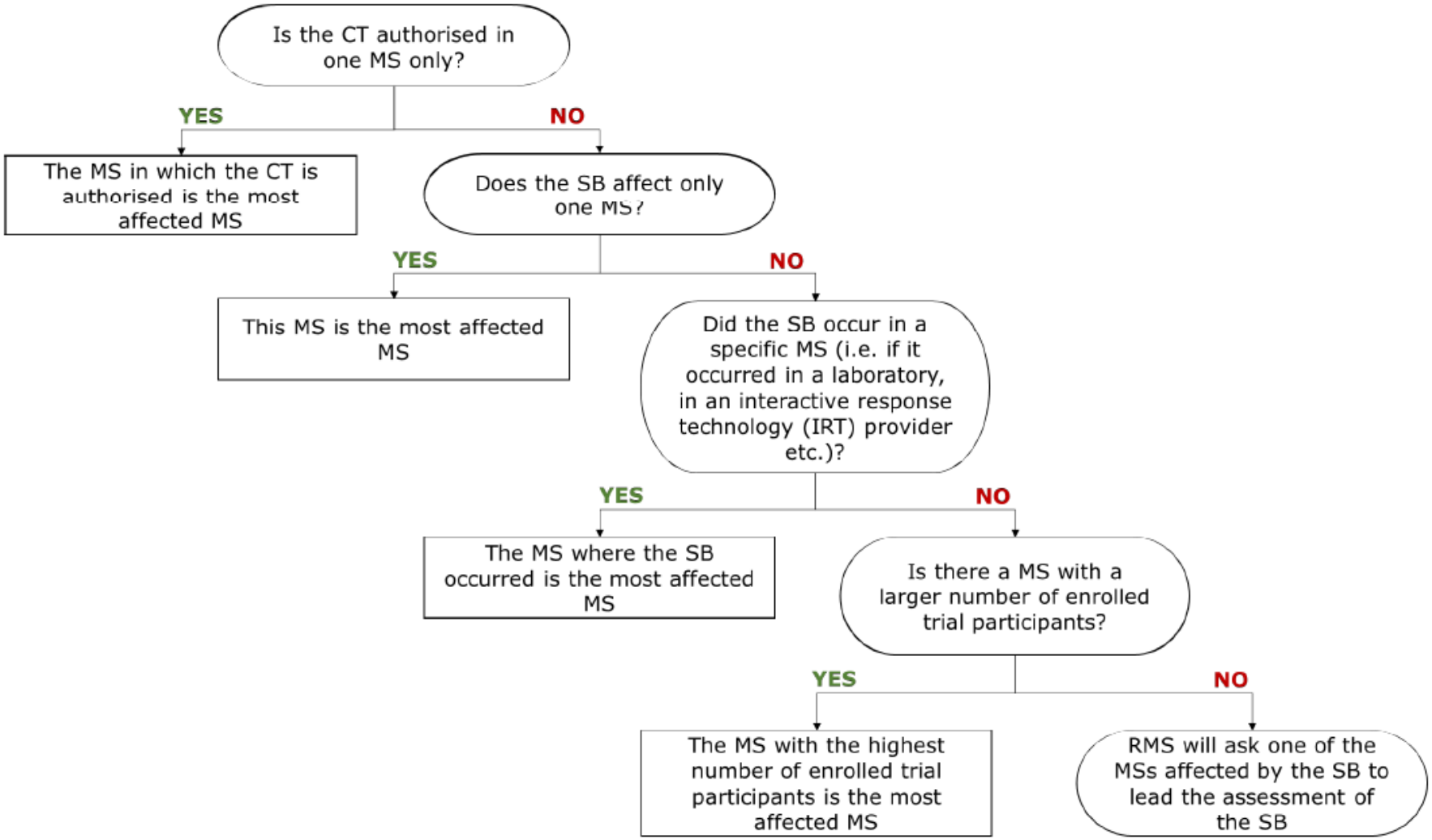
SERIOUS BREACHES

Reporting

- When a sponsor has reasonable grounds based on evidence to believe that a serious breach has occurred, it is expected to report the serious breach first, within 7 days, and investigate and take action simultaneously or after the notification
- Notification of serious breaches to the Regulation or the protocol has to occur by the sponsor through CTIS, the Clinical Trial Information System, to the Member States concerned within 7 days after the sponsor has become aware of the breach
- In other cases, some degree of investigation and assessment may be required by the sponsor prior to the notification, in order to confirm that a serious breach has actually occurred. It should be underlined that according to the Regulation, only serious breaches must be notified, not suspected serious breaches. On the other hand, however, the sponsor should notify a serious breach without undue delay

SERIOUS BREACHES

Reporting of most affected Member States in CTIS



SERIOUS BREACHES

Sponsor Obligations

- Root cause analysis to identify the cause of the serious breach and to assess the impact of the breach on the reliability and robustness of data as well as the impact on trial participants' safety and/or rights
- Documentation of the assessment and appropriateness of the decision and actions taken which might be examined during any process triggered by the notification, e.g. during a GCP inspection
- Where sponsor tasks were delegated to a party, and disagreement rises on classification/assessment of the breach between sponsor and the delegated party resulting in no notification of the serious breach, the related communication between the sponsor and delegated party should be documented.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謝謝
teşekkür ederim
спасибо
dank je
thank you
gracias
tapadh leat
mochchakkeram
bedankt
dziękuję
go raibh maith agat
obrigado
sukriya
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