Clinical Trial Regulation EU No. 536/2014 and safety requirements

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Public Declaration of transparency/interests*

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Interests in pharmaceutical industry	NO	Current	From 0 to 3 previous years	Over 3 preavious years
DIRECT INTERESTS:				
1.1 Employment with a company: pharmaceutical company in an executive role	X	☐	☐	☐ mandatory
1.2 Employment with a company: in a lead role in the development of a medicinal product	X	☐	☐	☐ mandatory
1.3 Employment with a company: other activities	X	☐	☐	☐ optional
2. Consultancy for a company	X	☐	☐	☐ optional
3. Strategic advisory role for a company	X	☐	☐	☐ optional
4. Financial interests	X	☐	☐	☐ optional
5. Ownership of a patent	X	☐	☐	☐ optional
INDIRECT INTERESTS:				
6. Principal investigator	X	☐	☐	☐ optional
7. Investigator	X	☐	☐	☐ optional
8. Grant or other funding	X	☐	☐	☐ optional
9. Family members interests	X	☐	☐	☐ optional

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N.B. I am not receiving any compensation

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Implementation

Published on 27 May 2014.

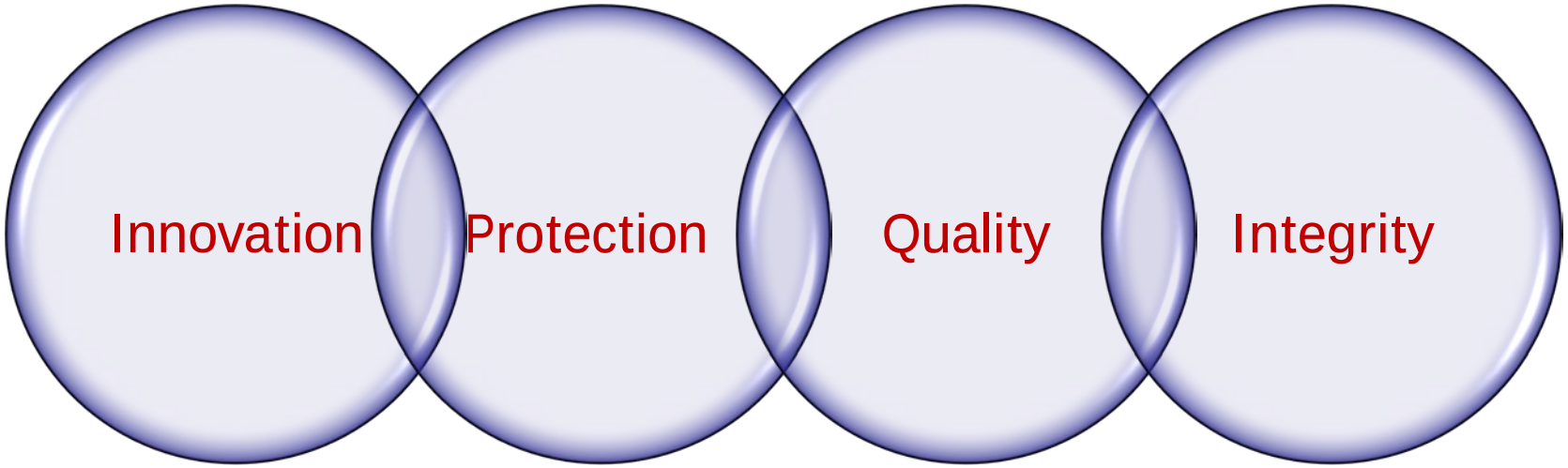
Application 6 months after confirmation published in the OJ of full functionality of EU portal and EU database, through an independent audit (August 2017).

If the systems pass the audit, the Regulation will come into effect by October 2018

Transitional arrangements

The goal

The goal of the Regulation is to foster innovation whilst ensuring the protection of the participants in clinical trials and the quality and integrity of the trial outcomes



Key benefits of the new Regulation

- Harmonised electronic submission and assessment process for clinical trials conducted in multiple Member States
- Improved collaboration, information-sharing and decision-making between and within Member States
- Increased transparency of information on clinical trials

- Highest standards of safety for all participants in EU clinical trials
- Introducing a risk adapted approach by applying less stringent rules to those trials conducted with medicines which are already authorised and which pose only minimal risk compared to normal clinical practice;
- Simplifying safety reporting requirements

Scope of Regulation (EU) No. 536/2014

- **Unchanged scope:**
  - **Interventional clinical trials with medicinal products for human use**
  - **NEW:** new category of low-intervention clinical trials with adapted requirements.
    - The investigational medicinal products (IMP) are authorised;
    - If the IMP is not used in accordance with the terms of the MA, that use is supported by published scientific evidence on S&E;
    - Minimal additional risk or burden to the safety of the subjects compared to normal clinical practice.

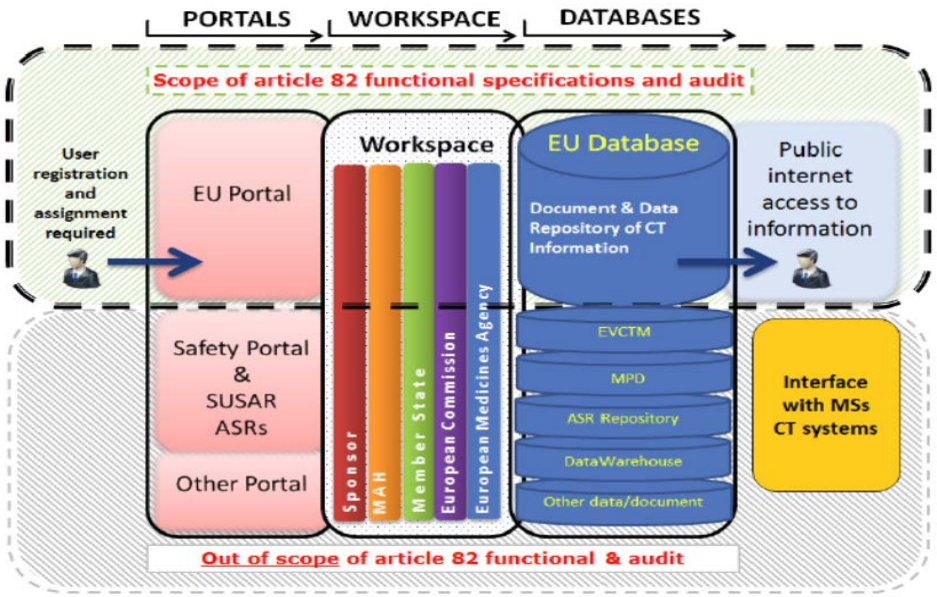
- **Not covered:**
  - Non-interventional trials;
  - Trials without medicinal products (e.g. devices, surgery, etc).

Low intervention clinical trials

- The determination of whether a clinical trial is low intervention or not, is largely based on the marketing authorisation status of the IMP and its intended use in the trial.

EU Portal & Database: Project Safety Reporting

- Creation of an e-web based form for the reporting of SUSARs
- Upgrade of the EudraVigilance CT Modules
- Development of an Annual Safety Report (ASR) Repository
- Add a functionality to allow the forwarding of SUSARs and ASRs to the MS



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Regulation 536/2014 – Safety

- Chapter VII: Safety Reporting in the Context of a Clinical Trial
- Chapter VIII: Conduct of a Clinical Trial, Supervision by the Sponsor, Training, and Experience, Auxiliary Medical Products
- Annex III: Safety Reporting (SUSARS) by the Sponsor to the Agency

Chapter VII: Safety Reporting in the Context of a Clinical Trial

Article 40 Electronic database for safety reporting

- *Agency to set up and maintain an electronic database (for safety reporting provided for in art 42 (SUSARS) and 43 (ASR)*

- *The Agency shall, in collaboration with Member States, develop a standard web-based structured form for the reporting by sponsors to the database for SUSARs.*

Chapter VII

Article 41. Reporting of adverse events and serious adverse events by the investigator to the sponsor

- *Investigator to report AEs and laboratory abnormalities to the Sponsor in accordance with the protocol*
- *Investigator required to report all AEs to the Sponsor; Investigator to report all SAEs to the Sponsor within 24 hours of coming to know of the SAE or in accordance with protocol*
- *The sponsor shall keep detailed records of all adverse events reported to it by the investigator*
- *Investigator to report serious adverse event with a suspected causal relationship to the IMP even after the end of the clinical trial without undue delay*

Risk proportionate approach

The Regulation includes provisions (art. 41) for applying a risk proportionate approach for safety reporting:

- selective recording and reporting of adverse events,
- adaptations to expedited reporting from the investigator to the sponsor, for certain serious adverse events.

Any such adaptation should be clearly stated and justified in the protocol, which will be submitted to the Member States for clinical trial authorisation.

This applies in particular, but not only, to marketed products, with a known safety profile, which are tested within the framework of low-intervention clinical trials

Risk proportionate approach

- Detailed collection and reporting of adverse events (serious and non-serious) is particularly important where data about the safety profile of an IMP from available pre-clinical and clinical trials is scarce.

- As the knowledge of a medicine and its use evolve and increasing amounts of data become available in order to determine the benefits and risks of an IMP, the level of detail and reporting requirements for adverse events may be adapted in the protocol, in line with the scope and type of a clinical trial and the level of knowledge on the safety profile of the IMP tested and the disease profile of the trial subjects.

Chapter VII

Article 42. Reporting of suspected unexpected serious adverse reactions by the sponsor to the Agency

The sponsor of a clinical trial must report the following SUSARs:

a) All SUSARs must be reported even if they occur at a site within or outside of the Union

b) all SUSARs of the same IMP, regardless of dosage form and strength or indication investigated, in the IMP, occurring in a clinical trial performed exclusively in a third country, if that clinical trial is sponsored by that sponsor or by another sponsor who is either part of the same parent company as the sponsor of the clinical trial, or who develops a medicinal product jointly, on the basis of a formal agreement, with the sponsor of the clinical trial.

c) Report SUSARs even when the clinical trial has completed

Chapter VII

The period for the reporting of SUSARs by the sponsor to the Agency shall take account of the seriousness of the reaction and shall be as follows:

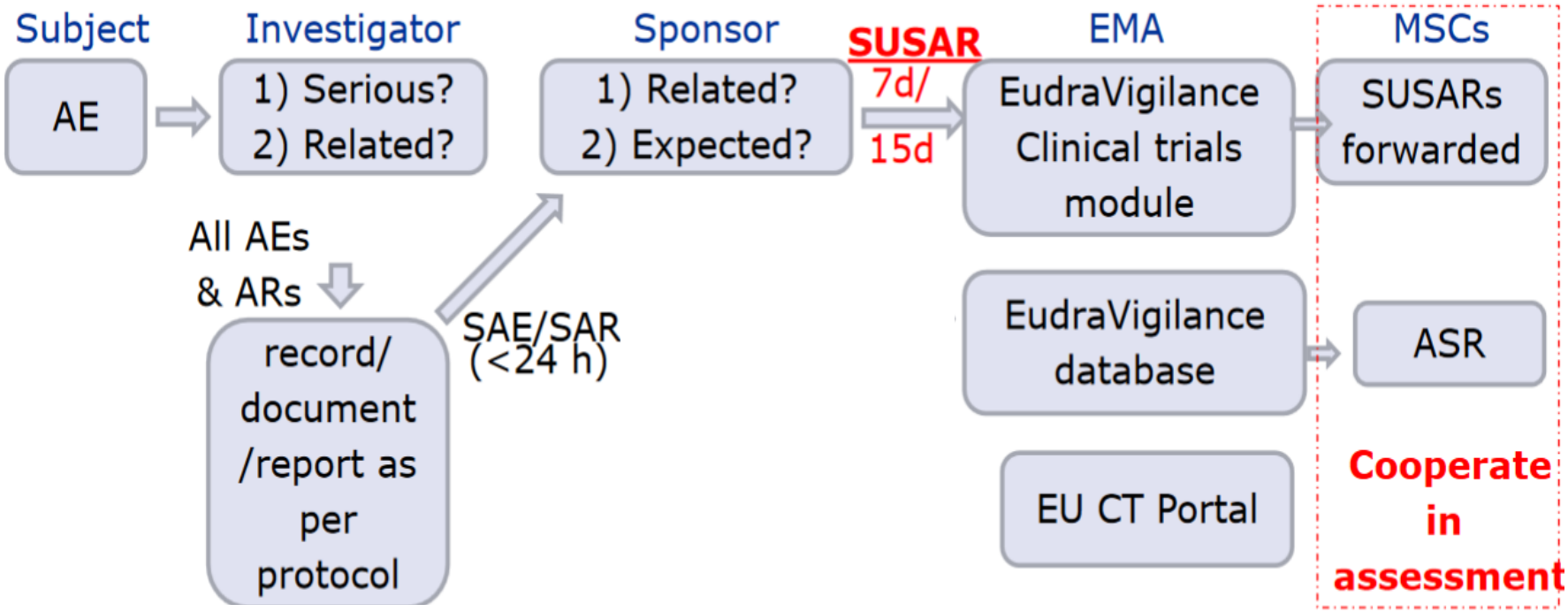
a) in the case of fatal or life-threatening SUSARs, no later than 7 days after the sponsor became aware of the reaction;

b) in the case of non-fatal or non-life-threatening SUSARs, not later than 15 days after the sponsor became aware of the reaction;

c) in the case of a SUSAR which was initially considered to be non-fatal or non-life threatening but which turns out to be fatal or life-threatening, no later than seven days after the sponsor became aware of the reaction being fatal or life-threatening.

b) Follow up report with additional information should be submitted

What changes with the new Regulation
Trial safety reporting requirements similar



Chapter VII

Article 43. Annual reporting by the sponsor to the Agency

- *Sponsor shall submit annually through the database referred to in art. 40 a safety report for each IMP used in the clinical trial*
- *For a clinical trial involving the use of more than one IMP, the sponsor may, submit a single safety report.*
- *The annual report shall only contain aggregate and anonymized data.*
- *Safety reporting required with the first authorization of a clinical trial and it ends with the end of the last clinical trial conducted by the sponsor with the IMP*

Chapter VII

Article 44. Assessment by Member States

The Agency shall, by electronic means, forward to the Member States safety information.

Member States shall cooperate in assessing the safety information reported for a clinical trial.

The responsible ethics committee shall be involved in the assessment of the safety information, if it has been provided for in the law of the Member State concerned

Chapter VIII

Article 53. Other reporting obligations relevant for subject safety

- *Sponsor must report through the portal any adverse events that impact the benefit/risk of the IMP (not SUSARs) no later than 15 days.*

- *The sponsor must submit, through the EU portal, all inspection reports of third country authorities concerning the clinical trial.*

Chapter VIII

Article 54. Urgent safety measures

- *Sponsor must implement urgent safety measures when benefit/risk is impacted*
- *Sponsor shall notify of the measures no later than 7 days*

Annex III: Safety Reporting (SUSARS) by the Sponsor to the Agency

Adverse Events and Causality

Medication errors, pregnancies and uses outside what is foreseen in the protocol, including misuse and abuse of the product, shall be subject to the same obligation to report as adverse reactions.

Clinical trial SUSAR reporting

- Until the clinical trials regulation is applicable there is no change to the current process for the submission of SUSARs for clinical trials.

- The clinical trials regulation will become applicable six months after the European Commission publishes a notice in the Official Journal that the clinical trials EU portal and the EU clinical trials database have achieved full functionality and the systems meet the functional specifications. The clinical trials regulation will start to apply from this “Application Date”.

- Clinical trials already approved through the clinical trials directive 2001/20/EC will continue to have the same SUSAR reporting requirements as specified in the directive for a transition period of 3 years after the clinical trials regulation is applicable.

What Changes for Safety Reporting per Regulation 536/2014 – 1/2

- Overall, modest changes regarding safety reporting
- All safety reporting for clinical trials must be done via a centralized portal, not by local affiliates/countries
- Web-based structured form for reporting SUSARs
- Medication errors, pregnancies, misuse or abuse of IMP should be subject to the same reporting obligations as adverse reactions
- More detailed timelines on safety reporting than previously (e.g. urgent safety measures to be reported within 7 days in the portal); expedited reporting of safety that impacts benefit/risk by 15 days

What Changes for Safety Reporting per Regulation 536/2014 - 2/2

- The Regulation establishes simplified safety reporting requirements and a streamlined review of safety information. Under the EU-CTR framework, the sponsor will submit all SUSAR's as well as the DSUR/ASR through the dedicated module of the Eudravigilance database maintained by the European Medicines Agency (EMA). The EMA will then forward the safety information electronically to all CMS, and CMS will cooperate in assessing the information reported.

- The Regulation also specifies that the responsible ethics committee shall be involved in the evaluation. This required collaboration is new in the framework of clinical trials legislation in the EU. Details in the form of Delegated Acts are expected from the Commission to formalise the modality rules concerning this cooperation

Grazie dell'attenzione

CONTATTI

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