Commissions role on implementation of the CTR

Edit Szepessy
EC DG SANTE B4
Medicinal products: quality, safety, innovation

1

Clinical trials in EU and CTR

Clinical trials → Medical innovation → Promotion and protection of public health

Clinical Trials Regulation (EU No 536/2014)
- Make Europe more attractive to conduct trials
- Ensure patients' safety, rights and dignity and reliability of the collected data

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Clinical Trials Regulation

- *The Clinical Trials Regulation (No 536/2014) was published in May 2014 and will become applicable as soon as the **Clinical Trial Portal and Database achieves full functionality**.*
- *The Commission works closely with EMA, Member States and stakeholders to ensure the efficient implementation of the Regulation. Key priority is the (1) **development of the single European Clinical Trials Portal and Database** (condition for the Regulation to enter into application);*
- *Additional priorities: practical (2) **implementation of CTR**, (3) combination trials with **companion diagnostics**, (4) **trial data transparency**, (5) **academic research** especially on fields where economic interest is weaker.*

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1. CTIS development

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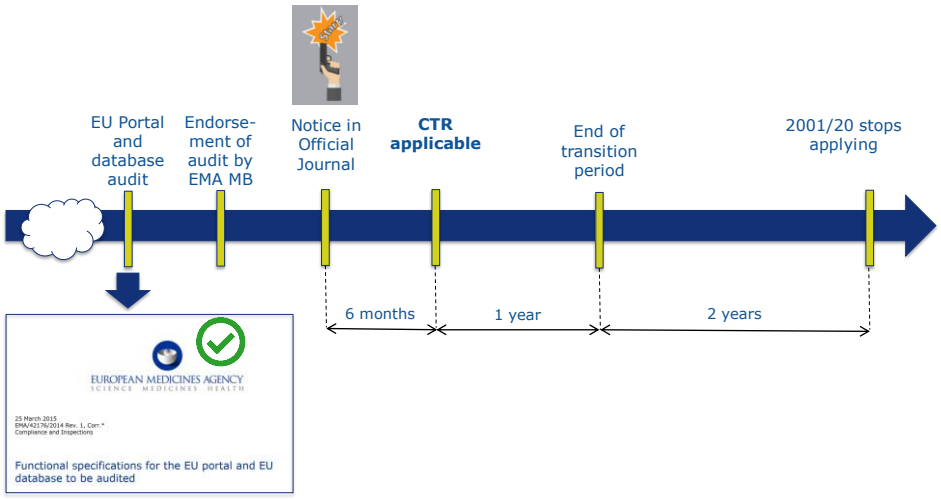

- **Endorsement of the full functionality** is a condition for the publication of the notice in the official journal which is the start of the transition period of 6 months that precedes the applicability of the CTR

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Link CTIS - CTR

- CTIS: (1) **streamlines and facilitates the flow of information** for the autorisation and supervision of clinical trials in the EU and (2) **support publication of information.**
- The **functional specifications**[1] describe the elements of the database for the audit.

- 1 https://www.ema.europa.eu/documents/other/functional-specifications-european-union-eu-portal-eu-database-be-audited_en.pdf

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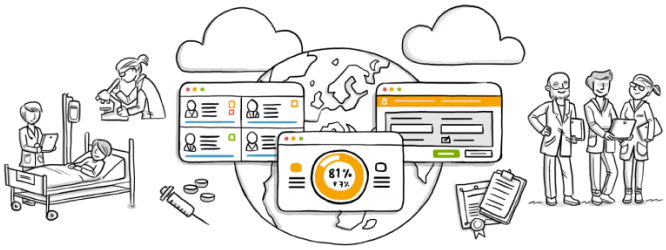
Link CTIS - CTR

- **High-level functionalities**:
  - Sponsors: application submission, supervision and update of information
  - Member States: authorisation of applications and supervision
  - EU Commission: supervision of regulatory systems in EU and in 3rd countries (union controls)
  - General public: access clinical trials information for transparency
  - EMA: database control

- **Additional key functionalities are not part of the audit**. (e.g. annual safety reports, reporting tools, link to the EudraVigilance database)



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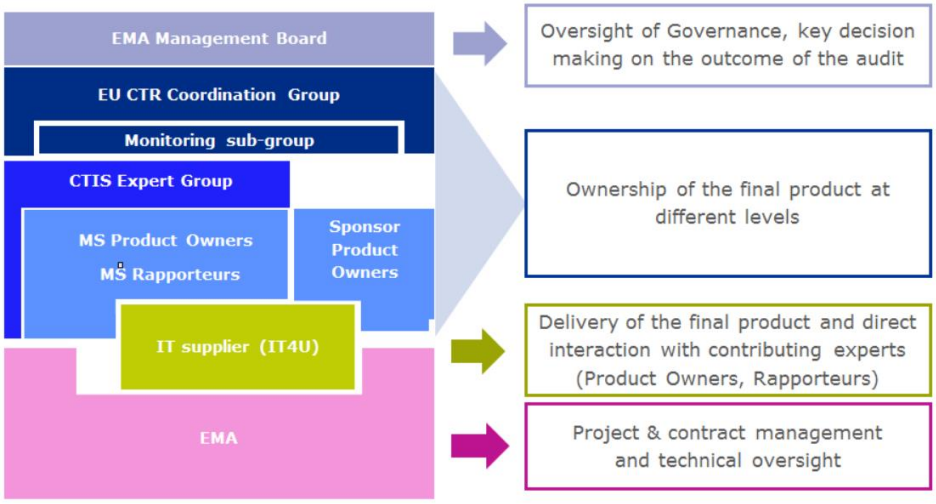
CTIS governance structures



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CTR – Timeframe (1)

- EMA management board endorsed a **timeframe** in 2015, foreseeing an audit in August 2017. In June 2017, this date was postponed to 2019 due to technical difficulties with the development of the IT systems.
- In December 2018, the Management Board decided to revise the delivery approach and to set up a close **monitoring** of the project.
- **Iterative development** driven by product owners from Member State and Sponsors side has started on the 11th of June 2019

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CTR – Timeframe (2)

- EMA MB decided in October 2019 to prolong the monitoring period for at least 3 releases (i.e. 9 months) and to **develop two actions** further:
  1) **Improvement of the quality** of the supplier
  2) **Reprioritisation** of the critical items needed for audit
- Reprioritisation is based on (selected) **end-to-end testing** in a "sandbox" (i.e. a functional version of CTIS)
- EMA MB will consider the timing of the audit on the basis of the results of the two actions – the exact timeframe for the audit remains **to be announced**.

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2. Guidance documents for the implementation of the CTR

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The Commission involvement for supporting guidance documents

- DG SANTE/MS (CTEG) guidance documents: EudraLex-Volume 10
- Collaboration with EMA and CTFG
- Separately for the Directive 2001/20/EC and the Regulation (EU) No 536/2014
- Stakeholders are encouraged to follow the documents for CTR as much as possible and in compliance with the Directive.

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Clinical Trials Expert Group

1 NCA and 1 Ethics Committee member from each MS, EMA as observer

http://ec.europa.eu/transparency/regexpert/index.cfm?do=groupDetail.groupDetail&groupID=1464&NewSearch=1&NewSearch=1

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Guidance/support documents

Harmonised templates for part II applications (Annex I, CTR):

- CV for investigators, Declaration of Interest, Site suitability forms (Annex I, M64-66, N67): published on EudraLex10
- Procedure for IC: under development
- Guidance for sponsors about a text to be included in the ICF about data processing under GDPR (Art 28): under development
- Guidance document for part II application submissions (Art 28-35), reimbursement agreement: under consideration

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Guidance/support documents

***Q&A document for Clinical Trials Regulation* (v2 on EudraLex10)**

- information on the technical aspects of CTR to facilitate its implementation
- developed by DG SANTE-CTEG, HMA-CTFG, EMA – endorsed for publication by CTEG
- addressed mainly to sponsors and CROs
- currently 130 Q&As in 12 chapters – live document for continuous improvement
  - Chapter 7: Q&A on safety reporting with cc. 50 questions (co-developed with CTFG, HMA) – endorsed in June 2019
- Separate Q&A on GDPR: based on the report by EDPB (published in February) – EudraLex-10 April 2019

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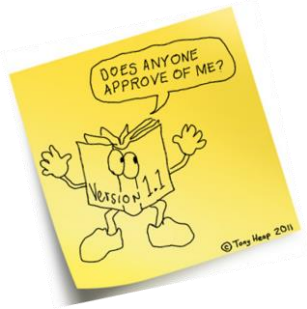
Q&A



***Q&A document for Clinical Trials Regulation* ("hot topics")**

- substantial modifications
- the use of conditions (initial applications, substantial modifications, addition of a MSC under Art 14)
- normal clinical practice (including physiological studies, intervention) ->non-interventional studies vs. low-intervention trials
- classification of in vitro diagnostic assays as IVDs in the scope of clinical trials (CTFG in the lead with DG SANTE, CTEG, DG GROW, IVDEG, MDCG) – CTFG stakeholder discussion end of October by CTFG

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Q&A

***Q&A document for Clinical Trials Regulation*: additional recent endorsements**

- co-sponsorship
- legal representative
- trials where IMP exposure took place before the start of the trial
- non-substantial changes (Art 81.9 and other)
- early end of the trial
- layperson summary

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Q&A

***Q&A document for Clinical Trials Regulation*: under consideration**

- Timelines involving stand-alone part II applications (Art 11, Art 14)
- Post-trial treatment access
- Union controls

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CTR/IVDR interface

Aim: Clarification of intersection between new regulations to ensure **patient safety** and **treatment efficacy** by appropriate **oversight** while supporting **innovation**:

- Clinical Trials Regulation (REG/2014/536) published in 2014 and apply with CTIS system reaching full functionality
- In vitro diagnostic (IVD) Regulation (REG/2017/746), apply May 2022

Current focus: qualification of diagnostic assays in clinical trials and clarification of requirements applicable to them.

Output: Q&As regarding the qualification is expected in the coming months for joint endorsement by CTEG, MDCG and CTFG. Additional guidance for the assessment of diagnostic assays used in clinical trials will be developed afterwards.

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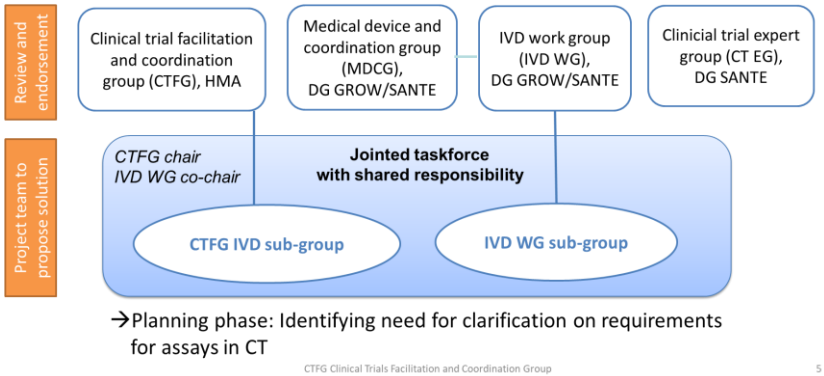
EU CT IVD Project Governance



→Planning phase: Identifying need for clarification on requirements for assays in CT

CTFG Clinical Trials Facilitation and Coordination Group 5

Ditte Zerlang Christensen, CTEG plenary, October 9, 2019

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CTR/GDPR

GDPR/CTR Q&A:

- final opinion of the EDPB on the Q&A about CTR/GDPR interplay: February, 2019
- DG SANTE published the final version of the Q&A in April, 2019

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CTR/GDPR

GDPR/CTR Q&A:

- Legal basis for personal data processing in clinical trials
- Data controller
- Informed consent (Art. 28.2, CTR) vs. explicit consent (GDPR)
- Withdrawal of consent for data processing
- Data processing in emergency trials
- Data protection rules in trials with 3rd country sponsor
- Data transfers to outside of the EU
- Trials authorised under CTD

** A guidance will be drafted by the CT EG about the text to be included in the Informed Consent forms about data protection*

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CTR/GDPR Q&A

Legal obligations under CTR for data processing:

- Trial **result** reporting (Article 37(4) and (8) of CTR);
- **Safety** reporting (Articles 41-43 of CTR);
- **Archival** of the clinical trials master file for 25 years and the medical files of subjects for the time period as prescribed by national law (Article 58 of the CTR
- Member States **inspections** (Article 78 of CTR) with access to clinical trial data and individual patient records to GCP inspectors.

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CTR/GDPR Q&A: legal basis for data processing

Primary use (processing **related to a specific clinical trial protocol** during its whole lifecycle): Art 6(1) and 9(2) of GDPR

- Legal obligations: **safety** (Art 41-43 CTR), **archiving** (Art 58 CTR), **inspection** (Art 78CTR): Art.6(1)c GDPR
- For scientific or research purposes:
  - public interest: Article 6(1) (e) and Article 9(2)(i) or (j) of the GDPR;
  - legitimate interests of the controller: Article 6(1) (f) and Article 9(2) (j) of the GDPR;
  - exceptionally, under specific conditions, subject's explicit consent: Article 6(1) (a) and 9(2) (a) of the GDPR.

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CTR/GDPR Q&A: legal basis for data processing in a clinical trial

Use			Legal basis	
Primary	Legal obligation under CTR	Safety	Art.6(1)c	Art. 9(2)(i)
		Archiving		
		Inspection		
	Research purposes	Public interest	Art. 6(1)(e)	Art. 9(2)(i) or (j)
		Legitimate interest	Art. 6(1)(f)	Art 9(2)(i) or (j)
		Explicit consent (exceptionally)	Art. 6(1)(a)	Art. 9(2)(a)

The **data controller** ensures **compliance** with the data protection rules (Article 24 of GDPR) and determine the **legal basis** for processing of personal data.

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https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/regulation5362014_qa_en.pdf

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Additional guidance/support documents

Trial results reporting compliance:

- On EudraCT within 12 months (6 months for paediatric trials) after the end-date -> scrutiny and transparency
- Joint letter to sponsors with supporting links (DG SANTE, EMA, HMA, RTD; July 3)
- Updated EC forms for results and end of trial dates
- Updated EC technical guidances for fields that become public on EudraCT (paediatric, non-paediatric trials)
- EMA monitoring activities
- Annex I application form to be updated for better monitoring of EU grant beneficiaries
- Development of additional support material (technical tutorial on EudraCT)

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HMA

Joint Letter by the European Commission, EMA and HMA

June 2019

LETTER TO STAKEHOLDERS REGARDING THE REQUIREMENTS TO PROVIDE RESULTS FOR AUTHORISED CLINICAL TRIALS IN EUDRACT

Clinical trials are the key drivers of medical innovation and progress in patient-care and disease prevention. A sufficient level of scrutiny and transparency in clinical trials is essential to protect public health and to foster innovation in the medical research field. In order to achieve this, all relevant protocol and results related information regarding clinical trials that are authorised in the EU needs to be kept in the EU Clinical Trials Database (EudraCT) and publicly available through the EU Clinical Trials Register. This is particularly true for the timely publication of clinical trial result summaries, including information on the objectives, design and main conclusions and results of a given study. Comprehensive access to summary results has been regarded an essential feature for clinical trials in order to allow patients, practitioners, policy makers and other economic operators to make well-informed decisions about health-care and medical research.

The requirements for publishing clinical trial summary results in the EU Clinical Trials Database are included in the European Commission Guideline 2012/302 03/EC[1]. Accordingly, as of July 2014, result-related information should be posted within one year (6 months for paediatric trials) after the end of a clinical trial[2]. The submission of the results to EudraCT is the direct responsibility of the sponsors. Once the sponsor submits the result in EudraCT, the information, with about 2-week delay, is automatically fed into the European Union Clinical Trials Register and become available for public scrutiny.

These provisions will remain applicable with a clear legal basis under the European Clinical Trials Regulation (No 536/2014[3]). The EU Portal and Database foreseen in this Regulation, as a single entry point for the submission and maintenance of clinical trials by the sponsors, will be a key instrument to realise this aim.

As of April 2019, there are 27,093 clinical trials completed out of 57,687 trials included in the EudraCT database, of which 18,432 should have results posted. This means that 68.2% (12,577) are in compliance with the publication rules whereas 31.8% (5,855) of the trials have missing results. This is an encouraging trend, though there is still significant progress to be made. In particular, the reporting compliance for non-commercial sponsors is much lower than for commercial sponsors (77.2% for commercial sponsors vs 23.6 % for non-commercial sponsors)[4].

Underreporting in general and selective reporting of trials with positive outcome may lead to potentially avoidable redundancies in the conduct of clinical trials and compromise the economic and scientific efficiency of clinical research. In addition, unreported clinical trials with unfavourable outcome can have negative public health implications. Academic and other non-commercial sponsors are particularly encouraged to post the results of their trials in EudraCT in order to maximise their valuable contribution to meet public health needs and to advance clinical research especially where commercial interest is weaker.

In order to improve compliance on the posting of results, the primary aim of this communication is to remind all sponsors about their obligation for the reporting of clinical trial summaries in the EU Clinical Trials Database. In the spirit of the EU legislation, it is important that all stakeholders act together to ensure compliance as soon as possible for the promotion of public health.

The following materials and tools are available for stakeholders in order to provide them with information and guidance on reporting trial results to EudraCT:

- Results information documentation: https://eudract.ema.europa.eu/result.html
- EudraCT & EU-CTR Question and Answer table "Results" section (Q&A 34-62): https://eudract.ema.europa.eu/docs/guidance/EudraCT%20FAQ_for%20publication.pdf
- Technical guideline on the format of the data fields of results-related information on clinical trials: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/2013_01_22_tg_en.pdf

Additional resources:

- Multi-media tutorials: https://eudract.ema.europa.eu/multimedia_tutorials.html
- Training material (Q&As from previous training): https://eudract.ema.europa.eu/training.html
- List of fields contained in EudraCT to be made public for paediatric and non-paediatric trials: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/eudract_nonpaediatric_listofffields_en.pdf (non-paediatric trials)

[1] Guidance on posting and publication of result-related information on clinical trials in relation to the implementation of Article 57(2) of Regulation (EC) No 726/2004 and Article 41(2) of Regulation (EC) No 1901/2006

[2] Please note that although EudraCT contains results for phase I-IV trials, results for those Phase 1 trials, which are conducted solely in adults and are not part of an agreed PIP, will not become public in the EU Clinical Trials Register.

[3] Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC (EU00000000)

[4] Please note that the data available in the EU Clinical Trials Register is a subset of the data from EudraCT.

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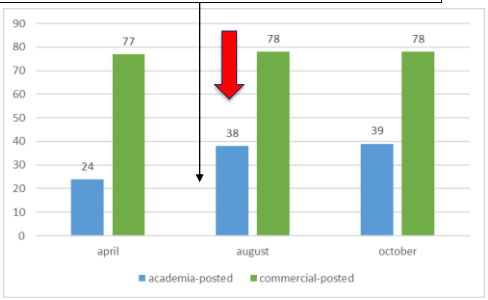
Trial result posting compliance

Publication of joint letter: July 3, 2019



APRIL	Commercial (% compliance)	Non-Commercial (% compliance)
Results posted	11851 (77,2%)	726 (23.6%)
Non-results posted	3509 (22.8%)	2346 (76.4%)
Total	15360 (100%)	3072 (100%)

AUGUST	Commercial (% compliance)	Non-Commercial (% compliance)
Results posted	12431 (78%)	1387 (38%)
Non-results posted	3592 (22%)	2293 (62%)
Total	16023 (100%)	3680 (100%)

OCTOBER	Commercial (% compliance)	Non-Commercial (% compliance)
Results posted	12696 (77,7%)	1476 (39%)
Non-results posted	3641 (22.3%)	2304 (61%)
Total	16337 (100%)	3780 (100%)

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Academic sponsors

- **CTEG:**

- information exchange about national initiatives;
- normal clinical practice -> low-interventional trials

- **RTD:** initiatives to improve the regulatory compliance of projects with EU funding
- **CTEG+RTD:** CTA form for closer follow-up of trials with funding from EU and/or national grant schemes (in progress)
- **Result publication:** development of supporting material
- **CTIS development:** PO status

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Union Controls

Art 79.1:

(a) Member States correctly supervise **compliance** with the Regulation;

(b) CT regulatory framework in 3rd countries **equivalent** protection of rights and safety of patients' and reliability of the generated data

Art 79.2: public Commission reports with findings and recommendations

Union Control teams:

- EC inspectors (DG SANTE F5) and national experts;
- Co-ordinated by the DG SANTE.

Preparatory (fact-finding) **mission**s in EU and 3rd countries start in 2020. Technical **trainings** to Commission inspectors on CTIS and regulatory aspects and development of draft **audit documents**, **guidance** have started. Trainings for national experts will start in 2020.

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THANK YOU FOR YOUR ATTENTION

DG SANTE B4 Clinical Trial Team

SANTE-PHARMACEUTICALS-B4@ec.europa.eu

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