Update on the Clinical Trials Regulation (EU) No 536/2014 - Key developments

6TH CONFERENCE ON CLINICAL TRIALS IN THE NORDIC COUNTRIES

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Clinical Trials Regulation No 536/2014

Objectives

- *to create an environment that is favourable for conducting CT in Europe through a simplified regulatory framework, with the highest standards of patient safety*
- *to increase transparency and availability of information on CT and their results.*

Overall:

To make the EU attractive for R&D while ensuring high protection of CT subjects

Clinical Trials Regulation No 536/2014

- ***Identical rules*** *for conducting CT throughout the EU.*
- ***Increase in the efficiency of all trials*** *in Europe with the greatest benefit for* ***multinational*** *clinical trials by means of an EU CT portal and database.*
  - *A single set of documents via a single entry point.*
  - *Facilitates communication between sponsor and MS.*
  - *Harmonised procedure for assessment by MS.*
- *Foster innovation and research, while helping to* ***avoid unnecessary duplication*** *of clinical trials or repetition of unsuccessful trials.*
- *Source of public information.*

Transparency

- *The Clinical Trial Regulation requires all information stored in the database to be publicly available, unless exempted under the Regulation to protect:*
  - *personal data;*
  - *commercially confidential information, in particular the marketing-authorisation status of the medicine, unless there is an overriding public interest;*
  - *confidential communication between Member States in the preparation of their assessment;*
  - *supervision of clinical trials by Member States.*

Transparency & the EU CT Portal and Database

- *The key instrument to ensure transparency of clinical trials is the EU clinical trial portal and database, which EMA is currently developing in collaboration with MS and the Commission (Art 80 & 81)*
- *The EU CT Portal and Database will be the backbone of the new regime for clinical trials in Europe.*
  - *It will be used for submission and maintenance of clinical trial applications and authorisations within the European Union.*
  - *It will serve as the source of public information on clinical trial applications assessed, and clinical trials conducted in the EU, from the time of decision to authorise a trial up to the finalisation of those trials and inclusion of their results in the database.*

EU Clinical Trials Portal and Database

- *The entry into application of the Regulation is dependent on the full functionality of the system, which will be confirmed by an independent audit.*
- *The Regulation becomes applicable six months after the European Commission publishes notice of this confirmation.*

Implementation aspects at EU level

Legal obligations:

- *Commission Implementing Regulation (EU) 2017/556 on the detailed arrangements for the good clinical practice inspection procedures pursuant to Regulation (EU) No 536/2014 of the European Parliament and of the Council (CTR Art 78.7)*
  - Adopted on 24 March 2017
  - Published in the OJ of 25.03.2017, L 80/7

Implementation aspects at EU level

Commission Implementing Regulation (EU) 2017/556

- *Maintains the status quo:*
  - takes up Chapters 5 and 6 of the current Directive 2005/28/EC.
  - EU guidelines (general commonly recognized EU standards developed by the MS, COM and EMA mentioned in Article 9) and relevant national implementing legislation;
- *Some adaptations to the new legal framework: e.g. inspection reports;*
- *Few new provisions: situations of divergence in the GCP inspection conclusions*

Implementation aspects at EU level

Commission Implementing Regulation (EU) 2017/556

- *Entry into application = the day of entry into application of the Clinical Trials Regulation;*
- *It will apply to all GCP inspections conducted after that date (that is, also to inspections of clinical trials conducted under the Directive during the transitory period).*

- *Note: the GCP Directive 2005/28/EC will apply to clinical trials submitted under the Clinical Trials Directive until the end of transition period, except for the provisions in chapters 5 and 6 of this Directive which are related to inspectors and inspection procedures.*

Implementation aspects at EU level

- *The Commission Delegated Regulation (EU) 2017/1569 of 23 May 2017 supplementing Regulation (EU) No 536/2014 of the European Parliament and of the Council by specifying principles of and guidelines for GMP for IMP for human use and arrangements for inspections (CTR Art 63.1)*
  - Adopted on 23 May 2017
  - Published on 16 September
- *Entry into application = the day of entry into application of the Clinical Trials Regulation;*

Implementation aspects at EU level

- *Commission Directive (EU) 2017/1572 of 15 September 2017 supplementing Directive 2001/83/EC of the European Parliament and of the Council as regards the principles and guidelines of GMP for medicinal products for human use*
  - *Published on 16 September*
- *Detailed Guidelines on GMP for IMP (CTR art 63.1)*
  - *Maintains status quo of current Annex 13*
  - *Commission adoption procedure is ongoing*

Implementation aspects at EU level

- *If sponsors decide to share raw data on a voluntary basis, the Commission shall produce guidelines for the formatting and sharing of those data (CTR Art 37).*
- *If deemed necessary, the Commission may prepare an Implementing act on rules of cooperation among MS in relation to the assessment of safety reporting information (CTR Art 44(2)).*

Implementation aspects at EU level

Union Controls

- *The CT Regulation foresees the Commission conducting Union controls in Member States and non-EU countries to make sure the relevant rules are being properly supervised and enforced (CTR Art 79)*

Application of the CT Regulation

- *When the Regulation becomes applicable, it will replace the existing EU Clinical Trial Directive No. 2001/20/EC and national legislation that was put in place to implement the Directive.*
- *It will also apply to those trials authorised under the Directive if they are still ongoing three years after the Regulation has become applicable.*

Transitional period - CT Regulation

Article 98 of Clinical Trials Regulation

- *During the 3-year transitional period, which starts on the day of entry into application of the Clinical Trials Regulation, Directive 2001/20/EC will continue to apply to:*
  - *CT authorised before entry into application of CTR;*
  - *CT for which requests of authorisation are submitted within the first year of the transitional period, if a sponsor opts to follow the regime of the Directive.*

Transitional period - CT Regulation

- *The transitional period applies only to clinical trials authorised on the basis of Directive 2001/20/EC.*
- *The Commission is currently preparing technical information to allow the switch of these CT to the regime of the CT Regulation.*
- *Clinical trials authorised before Directive 2001/20/EC entered into force cannot continue during the transitional period. There is no transitional provision for these trials. These clinical trials should end at the moment of the entry into application of the CT Regulation.*
- *At the end of the transitional period all clinical trials which do not comply with the requirements of the Regulation cannot continue.*

Solutions contemplated for clinical trials authorised on the basis of Directive 2001/20/EC which will last beyond the transitional period

1. ***Sponsors should be allowed to switch the regime of the clinical trial to that of the Regulation during the transitional period.*** *A sponsor chooses which trials should be switched at what time.*
2. ***The systematic reassessment of all ongoing clinical trials (re-authorisation following the procedural rules of the Regulation) is to be avoided.***
   - *A presumption of authorisation under the Regulation for the trials authorised under the Directive.*

Solutions contemplated for clinical trials authorised on a basis of Directive 2001/20/EC which will last beyond the transitional period

3. The exact rules and procedures are being discussed

i. On a basis of the workflows existing in the Portal;

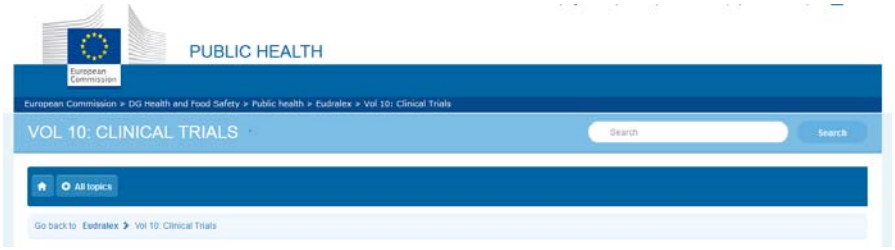
ii. Only essential documents will be uploaded and limited number of steps to be followed

iii. Multinational CT transition as multinational CT into the system (Harmonised/consolidated protocol)

Eudralex Volume 10

- *Update of current documents in Eudralex vol 10 and preparation of new guidelines:*
  - ***Recommendations of the expert group on CT***
  - ***GCP Inspection procedures***
  - ***Guidelines regarding quality documentation for IMP, including the biological IMP***
  - ***Guidelines on GCP specific to ATMPs***
  - ***Q&A document***

Eudralex Volume 10



- *2 sets of guidelines until end of transition period*
  1. ***Applicable to CT authorised under the Directive***
  2. ***Applicable to CT authorised under the Regulation.***

Recommendations of the Commission expert group on clinical trials

1. *Risk proportionate approaches in clinical trials* NEW
2. *Summary of Clinical Trial Results for Laypersons* NEW
3. *Auxiliary Medicinal Products in Clinical Trials*
4. *Ethical Considerations for Clinical Trials on Medicinal products conducted with Minors*

These have been published in Eudralex Volume 10.

GCP Inspection procedures - EMA

Chapter IV - Inspections

- Guidance for the preparation of GCP inspections (June 2008)
- Recommendation on inspection procedures for the verification of good clinical practice compliance (July 2006)
- Guidance for the conduct of GCP inspections (June 2008)
- Annex I to Guidance for the conduct of GCP inspections - Investigator site (June 2008)
- Annex II to Guidance for the conduct of GCP inspection - Clinical laboratories (June 2008)
- Annex III to Guidance for the conduct of GCP inspections - Computer systems (June 2008)
- Annex IV to Guidance for the conduct of GCP inspections - Sponsor and CRO (June 2008)
- Annex V to Guidance for the conduct of GCP inspections - Phase I Units (November 2008)
- Annex VI to Guidance for the conduct of GCP inspections - Record keeping and archiving of documents (March 2010)
- Annex VII to Guidance for the conduct of GCP inspections - Bioanalytical part, Pharmacokinetic and Statistical Analyses of Bioequivalence Trials (November 2008)
- Guidance for coordination of GCP inspections and co-operation between GCP inspectors, the reference and concerned Member States and CMD(h), in the context of the evaluation of the GCP compliance of marketing authorization applications for mutual recognition and decentralized procedures (June 2009)
- Guidance for exchange of GCP Inspection Reports according to Article 15(2) of Directive 2001/20/EC (revision 1 - May 2009)
- Guidance for the communication on GCP inspections and findings (June 2008)
- Procedure for standardisation of GCP inspection entries in EudraCT (November 2008)
- Guidance for the preparation of Good Clinical Practice inspection reports (June 2008)
- Recommendations on the qualifications of inspectors verifying compliance in clinical trials with the provisions of Good Clinical Practice (July 2006)

New guidance documents – EMA

- *New documents being prepared by the EMA/GCP IWG:*
  - ***Recommendations on the content of the trial master file and archiving***
  - ***Guidance for CT sponsors on serious breaches reporting;***
  - ***Guidance for managing serious breaches by MS including their assessment and the appointment of a lead MS;***

New guidance documents under development - EMA

- *Guidance to address interfaces between the manufacturer and the sponsor of the CT mainly with respect to:*
  - ***aspects of shipping (distribution) of IMPs and***
  - ***the second step of the two-step release procedure.***
- *Procedure for EMA coordination of the cooperation between MSs concerned on inspections conducted in MSs, in third countries and inspections conducted in the framework of an application for a marketing authorisation under regulation (EC) no 726/2004 (CTR Art 78.5)*
- *Guidance for EU MSs on the redaction of documents to be loaded in the EU portal and database.*

Other guidelines

- *Guidelines regarding chemical and pharmaceutical quality documentation for IMP (QWP)*
- *Guidelines regarding quality documentation for Biological IMP (BWP)*
  - *Both are being updated.*
- *Guidelines on GCP specific to ATMPs (COM)*
  - *Update ongoing.*

Q&A document

- *Update of the current Q&As*
- *Inclusion of new Q&As to clarify requirements of the CTR (inc. transition rules)*
- *Inclusion of relevant parts of CT1 and CT3*
- *Inclusion of Q&As from CTFG's Q&A document on DSUR of December 2011*
- *Inclusion of Q&As from CTFG's Q&A document on RSI of December 2013*

Useful links

- *Commission website on Clinical trials*

https://ec.europa.eu/health/human-use/clinical-trials_en

- The rules governing medicinal products in the European Union" – Vol 10 on clinical trials

https://ec.europa.eu/health/documents/eudralex/vol-10_en

- *EMA website on CT portal and database*

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000629.jsp

THANK YOU