

White Paper
The EU Clinical Trials Regulation –
Main Changes and Challenges



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1. Introduction

Currently all clinical trials performed in the European Union must be conducted in accordance with the EU Clinical Trials Directive (EU-CTD)¹. Issued in April 2001, the EU-CTD was implemented by May 2004 by transposition into the national laws of the EU Member States. By incorporating the principles of Good Clinical Practice within EU legislation, the EU-CTD imposed standards which have improved both the safety of participants in clinical trials and the quality of the generated data. However, the EU-CTD has also been criticised by all stakeholders because of its disharmonised interpretation and application between the Member States, increased costs and administrative burdens, and delays especially for launching multi-national trials. Indeed, under the EU-CTD framework, a sponsor wishing to conduct a clinical trial in several Member States must submit a clinical trial application to the Competent Authorities and Ethics Committees in each individual Member State and the authorisation procedures are performed separately in each Member State. As well as being time consuming and inefficient, this has led to the possibility of regulatory approval being granted in one EU country but not in another.

With the aim to remedy to the shortcomings and improve the attractiveness of EU for clinical research, the European Commission published on 17 July 2012 a proposal for an EU Clinical Trials Regulation. This proposal went to extensive consultation and debates by the European Parliament and Council of Ministers. The Clinical Trials Regulation (EU-CTR)² was finally adopted on 16 April 2014 and it was published on 27 May 2014 in the Official Journal. Nevertheless, the application of the Regulation will not occur before 28 May 2016 as it is conditional on the confirmed functionality of the required IT infrastructure (EU-portal and EU-database) that will be developed by the European Medicines Agency (EMA), in collaboration with the Member States. The EU-portal will be the single entry point for the submission of all data and information relating to clinical trials. The EU-database will constitute the single repository of all submitted information through the EU-portal, related to a clinical trial and, unless confidentiality is justified, it will be publicly accessible.

When applicable, the EU-CTR will repeal the EU-CTD. As any regulation, the EU-CTR will directly be binding for all Member States and will therefore ensure identical rules throughout the EU. Currently, it is expected that the new regulatory framework set up by the EU-CTR will apply by mid-2016.

The scope of the new Regulation is identical to the existing EU-CTD in that it concerns all clinical trials conducted in EU. Several key definitions have, however, been clarified (e.g. clinical study, clinical trial, non-interventional study, substantial modification) or introduced (e.g. start of a clinical trial).

On the other hand, the EU-CTR establishes new rules in particular for the authorisation procedures, for notifications on subject recruitment and clinical trial events, for safety

reporting requirements and for reporting of clinical trial results. This white paper will focus on these changes and highlight their associated challenges.

2. Main Changes and Associated Challenges

2.1 Procedure for Initial Authorisation

Submission

In order to obtain an authorisation the sponsor/applicant will submit at the same time, via the EU-portal, a single application dossier to all Concerned Member States (CMS) where it is intended to conduct the trial.

Using a harmonised format (see Annex I of EU-CTR for details), the application dossier will consist of two parts:

- **Part I** contains the common scientific documents : application form, protocol, investigator brochure, Good Manufacturing Practice documentation, Investigational Medicinal Product Dossier (IMPD), Auxiliary Medicinal Product Dossier, IMP/Auxiliary labels, scientific advice and Paediatric Investigation Plan (PIP) decision
- **Part II** contains the national documents : subject recruitment arrangements, patient information sheet and informed consent form, investigators and facilities suitability, subject damage compensation, financial compensation to subjects, investigators and sites, data protection requirements



In the application dossier, the sponsor will be required to propose one of the Concerned Member States (CMS) as the Reporting Member State (RMS) who will coordinate the validation and evaluation of the application. The proposed RMS may decline or another CMS may be willing to act as RMS. In this case, all CMS will need to find an agreement and within 6 days from submission, confirmation about

RMS shall be provided to the sponsor through the EU-Portal. The Regulation foresees that recommendations on criteria for the RMS selection will be prepared by a dedicated advisory group, the CTAG (Clinical Trials Coordination and Advisory Group). In view of RMS' responsibilities, this is particularly important to avoid that workload is concentrated on a small number of Member States.

Generally, Part I and Part II will be submitted together. However there is a possibility for a sponsor to request to first submit an application limited to Part I for review, followed by Part II application up to 2 years after Part I conclusion. In these circumstances, the sponsor

will have to certify that there is no new scientific information that could change the validity of Part I information and assessment.

Validation

Within 10 days from submission, the RMS will validate the application for completeness, taking into account comments expressed by the other CMS. Only the RMS may send a request for additional information to the sponsor. To resolve validation deficiencies, one clock-stop (10 days for sponsor's response and 5 days for RMS decision) is allowed. If the RMS does not provide feedback within the defined timeframe, this will be considered as a tacit validation of the application. On the other hand, sponsor's failure to reply within the fixed deadline will lead to the automatic withdrawal of the application in all CMS.

Assessment

The new evaluation procedure distinguishes between the aspects covered by Part I or Part II of the application dossier.

○ **Part I – Scientific Part**

The RMS will perform the review and within 45 days from validation date, it shall draw up a Part I assessment report.

In the case of a multinational trial, all CMS must collaborate in the evaluation.

The 45 days reporting period is then divided as follows:

- 1) initial assessment and preparation of a draft Part I assessment report by RMS within 26 days
- 2) coordinated review of the draft Part I report by all CMS within 12 days
- 3) finalisation of the Part I assessment report by RMS and submission to sponsor and all CMS, within 7 days.

Between the validation date and the reporting date (Day 45), considering issues raised by CMS, only RMS may request additional information to the sponsor. In this case, the reporting period may be extended up to 31 days by RMS (12 days for sponsor answers, 12 days for joint review of additional provided information by all CMS, 7 days for finalisation of assessment report by RMS). Just as for the validation of the application, the lack of sponsor's response by the fixed deadline will be considered as withdrawal of the application in all CMS.

In order to consult experts, for trials involving an advanced therapy or a biotechnology medicinal product, the RMS may extend the initial review period by 50 days.

At the end of the review, the RMS shall provide in the Part I assessment report a conclusion whether the conduct of the trial is acceptable, acceptable subject to specific conditions or not acceptable. A conclusion by the RMS that the trial is not acceptable shall be deemed to be the conclusion of all CMS.

○ Part II – National Part

The Part II assessment will be conducted separately by each individual CMS for its own country. When Part I and Part II are submitted together (i.e. the most common situation), Part II assessment will be performed in parallel with Part I review. The same timelines than for Part I evaluation apply. When additional information is needed, the CMS may extend the evaluation period by up to 31 days (12 days for sponsor answer, 19 days for final assessment by CMS). The sponsor must provide their answer to the CMS within the deadline, otherwise automatic rejection of the trial in that country will result.



It should be noted that despite a common format is defined for the clinical trial application, the precise information which must be provided to satisfy Part II requirements is not explicitly defined. Accordingly, amount and type of data for Part II will remain governed by national laws.

Part II covers aspects typically examined by Ethics Committees. However, as indicated in the Regulation, the review by the ethics committee may encompass aspects covered by Part I.

It is left to each Member State to determine which appropriate body(ies) will be involved in the assessment of the application and to organise the involvement of ethics committees.

Nevertheless, the Regulation stipulates that a Member State must provide a single decision within 5 days of the Part I assessment reporting date or by the last day of the Part II assessment. Moreover, it specifies that Member States shall ensure that the timelines and procedures for the review by the Ethics Committees are compatible with the timelines and procedures set out in the Regulation. Therefore, ensuring an effective coordination and collaboration between Competent Authorities and Ethics Committees for the application review will constitute a major challenge, for a successful implementation of the EU-CTR.

Decision

Each CMS will notify the sponsor through the EU-portal, of its single decision covering both Part I and Part II, within 5 days of the Part I assessment report date or from the last day of Part II assessment, whichever is later. If the CMS does not give its decision within this timeframe then the conclusion of the RMS Part I assessment report will automatically be considered as CMS decision on the application.

CMS will provide a decision whether the trial is authorised, authorised subject to specific conditions or refused.

A CMS may refuse to authorise a clinical trial when:

- a) an ethics committee has issued a negative opinion, which in accordance with the CMS' law is valid for the entire country;
- b) it finds, on duly justified grounds, that Part II requirements are not complied with;
- c) it disagrees with the conclusion of the RMS of Part I assessment report.

A CMS has only three grounds to disagree with RMS conclusion of Part I assessment report:

- 1) infringement of its national law as referred to in Article 90 (i.e. with regards to prohibited or restricted use of specific types of human or animal cells or medicinal products containing or deriving from these cells or on abortifacients or narcotics)
- 2) considerations as regards subject safety and data reliability and robustness
- 3) considerations that participation in the clinical trial would lead to a subject receiving an inferior treatment than in normal clinical practice in the CMS.

Although the CMS will need to provide a detailed justification in case of disagreement, the possibilities to opt out leave room for national interpretation.

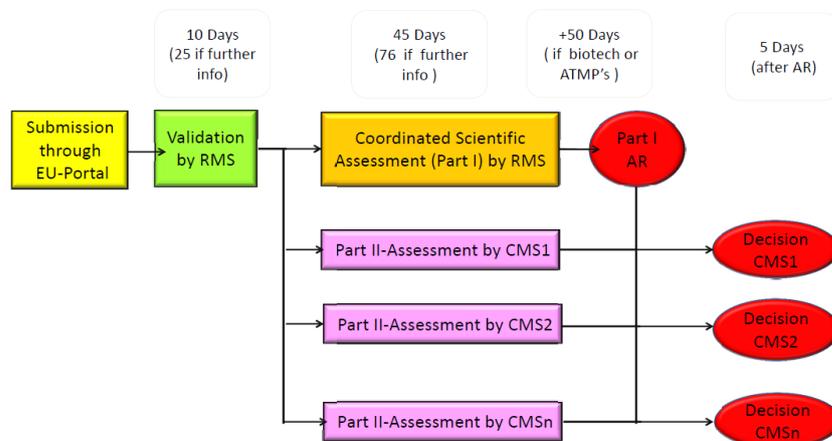


Figure 1: Summary of initial authorisation procedure under EU-CTR

2.2 Procedure for Addition of a Member State

The procedure to extend the trial to a new Member State follows the same approach as for the initial authorisation: the same provisions for application submission, CMS application evaluation and CMS disagreement apply. The RMS remains the same and the CMS shall notify its decision to sponsor within 52 days or 83 days in case of request for additional information.

2.3 Procedure for Substantial Modification

After a trial has started, changes may need to be made by a sponsor (e.g. protocol modifications, addition of a site...). As is the case now under the EU-CTD framework, approval prior to implementation will only be required for substantial modifications under the new framework. The definition of substantial modification in the Regulation is comparable to that of substantial amendment under EU-CTD. The definition covers any change to any aspect of the clinical trial which is made after notification of a decision and which is likely to have a substantial impact on the safety or rights of the subjects or on the reliability and robustness of the data generated in the clinical trial.

A substantial modification may concern a change to Part I, to Part II or to both parts. The procedure for introducing a substantial modification follows the same principles as for the initial authorisation. The same RMS as for initial application will be involved. If the modification only concerns Part I, the RMS shall validate the application within 6 days (+ 15 days in case of request for additional information) and complete its assessment report within 38 or 69 days, depending on whether comments have been raised and required answer from sponsor. Each CMS has then 5 days to communicate decision to sponsor on the substantial modification.

If the modification only concerns Part II, only the CMS is involved in the assessment, with same timeframe as for a Part I modification. When the change affects both Part I and Part II, each assessment as described above will be run in parallel.

2.4 Notifications on Patient Recruitment and Clinical Trial Events

Under EU-CTD framework, the only clinical trial events to be notified on an EU basis by the sponsor to Competent Authorities and Ethics of Committees are the global end of the trial, a temporary halt and early trial termination, within 90 or 15 days respectively. Some EU Member States (e.g. France or Netherlands) also ask to be informed on the start of the trial or on other clinical trial events (e.g. in France, the national end of the trial).

With the objective to increase transparency surrounding patient recruitment, the Regulation sets up a harmonised but more demanding notification scheme. Under the Regulation the sponsor must notify each CMS within 15 days of the following events: start of the trial (i.e. first act of recruitment of a potential subject, unless otherwise defined in approved protocol), first visit of first patient, end of recruitment, end of trial, end of trial in all EU Member States, end of trial in all third countries, temporary halt of trial, resuming the trial after a temporary halt and early termination of trial. The sponsor will be required to perform these notifications through the EU-portal. In order to comply with all these notification requirements in a timely and organised fashion, it is recommended that sponsors or their delegates implement an appropriate system.

2.5 Safety Reporting Requirements

The Regulation establishes simplified safety reporting requirements and a streamlined review of safety information. At present, suspected unexpected serious adverse reactions (SUSAR's) are submitted to and assessed separately by all Competent Authorities and Ethics Committees of the different concerned Member States. The same is true for the Development Safety Update Report (DSUR) for an investigational medicinal product, which must be provided on a yearly basis.

Under the EU-CTR framework, the sponsor will submit all SUSAR's as well as the DSUR through the dedicated module of the Eudragilance 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.

2.6 Clinical Trial Data Transparency

In recent years there has been growing support for increased transparency and disclosure of clinical trial information. The EU-CTR recognises this and establishes new rules for the reporting of clinical trial results and public disclosure. The EU-CTR requires that unless otherwise provided in the approved protocol, within one year from the end of the trial in all CMS, the sponsor must submit a summary of clinical trial results to the EU-database. This summary shall be accompanied by a layperson summary. The content for the clinical trial results summary and the layperson summary is defined in respectively Annex IV and V of the EU-CTR. However, it can be expected that the Commission will adopt delegated acts to further specify the requirements.

Furthermore, when the trial performed was intended to support a marketing authorisation for the medicinal product, the marketing authorisation applicant will be required to submit to the EU-database the clinical study report within 30 days following marketing authorisation decision.

These features introduced by the EU-CTR should meet general public demand for transparency on clinical trial data.

3. Conclusions

The Regulation certainly represents a significant step towards harmonisation for the conduct of clinical trials in EU. It sets up a common procedure for all types of clinical trial applications with a coordinated assessment by the Reporting Member State for the scientific documents (Part I), with one single decision issued by each Concerned Member State covering scientific and ethical review and within defined deadlines applicable for all



Member States. In addition, the Regulation also provides simplified and streamlined safety reporting requirements and establishes that Member States shall cooperate on safety information assessment. However several aspects remain to be determined or evaluated at national level and hence this leaves room for national requirements and interpretation. Furthermore, the provisions laid down in the Regulation also reflect societal demands for increased transparency on clinical trial information.

Before the implementation of the Regulation foreseen for mid-2016, a lot of work remains to be done.

This concerns, in particular:

- o the development of the required IT-infrastructure (EU-Portal and EU-Database) by the EMA. The EMA has started to work with Member States and a range of stakeholders, with the intent to confirm full functionality by December 2015
- o the adaptation of the national legislations to fit the new EU framework, specifically in setting an efficient collaboration model between competent authorities and ethics committees to ensure clinical application review. Consequently, it can be expected that updates of national legislations will occur in the course of 2015 to prepare the EU-CTR implementation
- o the recommendations concerning the criteria for RMS selection
- o the delegated acts from European Commission to provide procedural details for safety reporting and clinical trials results summary requirements.

In order to ensure a smooth transition to the new regulatory framework, sponsors should not only follow closely the development of the upcoming implementing measures (see above for some examples) but also start to put in place relevant measures to ensure compliance (e.g. adaptation of clinical trial application process, implementation of a suitable system for notifications).

CROMSOURCE is aware of the need to prepare for the upcoming changes and continuously monitor the changes in the regulatory framework. Regulatory update trainings are regularly

provided for employees and the CROMSOURCE Regulatory Compliance Unit publishes Regulatory Newsletters on a quarterly basis. If you are interested, you can view these newsletters via the CROMSOURCE website, <http://www.cromsource.com/category/news/>.

4. References

1. EU-CTD or Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.
2. EU-CTR or 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.

5. About The Author

Veronique Debaut holds a master in bioengineering from Université Catholique de Louvain (Belgium). She started her career in the pharmaceutical industry in the year 2000, where she led regulatory affairs projects related to the marketing authorisation and life cycle management of medicinal products. In 2011, she joined CROMSOURCE in Kraainem (Belgium) where she works as Regulatory Compliance Manager.

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6. About CROMSOURCE

CROMSOURCE is a highly qualified ISO-certified international provider of outsourced services to the pharmaceutical, biotechnology and medical device industries, specialized in clinical development and staffing solutions.

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