



The New Clinical Trials Regulation

I. Introduction

Requirements for the conduct of clinical trials in the EU are currently provided for in Directive 2001/20/EC (**CTD**), which was approved in 2001 and implemented in May 2004. Although the aim of the CTD was to simplify and approximate legislative and regulatory provisions governing the conduct of clinical trials in the EU, it received a considerable amount of criticism due to its disharmonised interpretation and application among Member States, increased costs, delays and administrative burdens – especially in case of trials involving different Member States – which resulted in a significant reduction in the number of clinical trial applications.

For these reasons, on 10 December 2008, the European Commission announced that an assessment would be made of the functioning of the CTD. Public consultations were launched both in 2009 and 2011 in order to consider various options for improving the CTD's functionality, including the making of legislative proposals. As a result of this process, on 17 July 2012, the Commission adopted a proposal for an EU Clinical Trials Regulation aimed at ensuring a uniform interpretation and application of the rules governing clinical trials in the EU.

Following extensive consultations and debates by the European Parliament and the Council of Ministers, Regulation (EU) No. 536/2014 on clinical trials on medicinal products for human use (**CTR**) was finally adopted on 16 April 2014 with the purpose of creating a favourable environment for conducting clinical trials and overcoming the shortcomings of the CTD.

The CTR introduced significant changes to the previous regulatory framework on clinical trials by envisaging, among other things, a streamlined application procedure via a single entry point, the EU portal, a single set of documents to be submitted for the application, a harmonised procedure – providing for strictly defined deadlines – for the

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assessment of clinical trial applications and increased transparency in relation to clinical trials and their outcomes.

Moreover, the CTR empowers the Commission to adopt implementing and delegated acts for the purposes of providing and updating details for safety reporting and clinical trial results summary requirements, application dossiers for the authorisation and/or substantial modification of clinical trials, as well as of specifying the principles and guidelines of good manufacturing practice and the arrangements for inspection for ensuring the quality of investigational medicinal products.

Although the provisions of the CTR entered into force on 16 June 2014, they shall not apply until confirmation of the full functionality of the EU portal and database through an independent audit. The EU portal and database are to be established by the European Medicines Agency (**EMA**). The CTR shall apply from 6 months after the Commission's publication of a notice of this confirmation. According to a delivery timeframe established by the EMA along with the Commission and the Member States, the EU portal and database should be available for the independent audit by August 2017. The subsequent audit is expected to be completed by November 2017 and endorsed by the EMA Management Board by December 2017. Provided that the systems pass the audit, its full functionality should be confirmed by the European Commission by the end of March 2018 with the CTR coming into effect by the beginning of October 2018.

Once applicable, the CTR will repeal the CTD. Until that moment, all clinical trials performed in the EU shall continue to be governed by the CTD. The CTR also provides for a transitory period of 3 years from the date it will become applicable. During this 3-year period, the CTD shall continue to apply to clinical trial applications submitted before the CTR enters into force and those submitted within 1 year after the same date provided that the sponsor opted for the old system.

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II. Authorisation procedure

Clinical trial's authorisation procedure

One of the most important changes under the CTR is the new streamlined authorisation procedure via a single point of entry:

The authorisation procedure, which includes a scientific and ethical review, starts with the sponsor's submission of a single application dossier through the portal referred to in Article 80 of the CTR (the "**EU Portal**"). The sponsor shall propose one of the concerned Member States, as the "**reporting Member State**", and the reporting Member State shall notify the sponsor and the other concerned Member States through the EU portal that it will act as the reporting Member State. It will do so within 6 days from the submission of the application dossier.

If the sponsor applies for a low-intervention clinical trial, where the investigational medicinal product use is evidence-based and supported by published scientific evidence on the safety and efficacy of that product, then the sponsor shall propose as the reporting Member State one of the concerned Member States where the use is evidence-based.



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Submission: The CTR establishes a harmonised format for the application dossier, which is divided into two parts: (i) Part I includes the common scientific documents, such as the application form, protocol, investigator brochure, Good Manufacturing Practices documentation, scientific advice, Investigational Medicinal Product Dossier, auxiliary Medicinal Product Dossier, labels and Paediatric Investigation Plan decision ("**Part I**"); and (ii) Part II includes the national documents, such as patient recruitment arrangements; patient information sheet and informed consent form, investigators and facilities suitability, patient damage compensation, financial compensation to patients, investigators and sites, and data protection requirements ("**Part II**").

Validation: Within 10 days from the submission of the application dossier, the reporting Member State shall validate the application taking into account the considerations expressed by the other concerned Member States, which should be submitted within 7 days. The reporting Member State shall notify the sponsor through the EU portal of whether the clinical trial applied for falls within the scope of the CTR and whether the application is complete pursuant to Annex 1 of the CTR. If the reporting Member State has not notified the sponsor within the 10 day-period, the application dossier shall be deemed to be complete.

Assessment: The assessment procedure and report follows the division of the application dossier on Part I and Part II.

- **Part I:** Within 45 days from the validation date, the reporting Member State shall submit the final Part I assessment report, including its conclusion, to the sponsor. For trials involving advanced therapy or biotechnology medicinal products, the reporting Member State may extend the 45-day period to 50 days.

For clinical trials involving more than one Member State, the assessment process shall include three phases: (i) an initial assessment phase performed by the reporting Member State within 26 days from the validation date; (ii) a coordinated review phase performed within 12 days from the end of the initial assessment phase involving all concerned Member States; and (iii) a consolidation phase performed by the reporting Member State within seven days from the end of the coordinated review phase. The reporting Member State shall submit the final Part I assessment report to all concerned Member States.

Between the validation date and the reporting date, only the reporting Member State may request additional information from the sponsor through the EU portal. In such case, the 45-day period may be extended by a maximum of 31 days. Where the sponsor does not provide the additional information within the period set by the reporting Member State, the application shall be deemed to have lapsed in all concerned Member States.

- **Part II:** Each concerned Member State shall assess, for its own territory, compliance with the aspects covered by Part II of the application dossier within 45 days from the validation date and submit Part II of the assessment report, including its conclusion, to the sponsor through the EU portal. Each concerned Member State may request, with justified reason, additional information from the sponsor through the EU portal only within the 45-day period (the sponsor has a maximum of 12 days to submit the requested information and the concerned Member State shall complete the



assessment report within a maximum of 19 days upon receipt of the requested information). Where the sponsor does not provide the additional information within the period set by the Member State concerned, the application shall be deemed to have lapsed in that Member State. A national-level body will review the documents as per the national applicable law but with one contact point and one fee per country.

- Part I and II can be reviewed in parallel or, alternatively, Part I can be reviewed first followed by Part II, depending on the sponsor's preference.

Decision on the clinical trial: Each concerned Member State shall notify the sponsor through the EU portal as to whether the clinical trial is authorised, whether it is authorised subject to conditions, or whether authorisation is refused. Notification shall be done by way of a single decision within 5 days of the Part I assessment report date or from the last day of the assessment of Part II by any concerned Member State (whichever is the latest). If the concerned Member States do not notify their decision within this timeframe, then the conclusion of the reporting Member State will be automatically considered as the concerned Member State's decision on the application. A concerned Member State may refuse to authorise a clinical trial if (i) it disagrees with the conclusion of the reporting Member State regarding Part 1 based on a number of limited grounds (i.e., the patient receiving inferior treatment compared with normal practice, infringement of national law as communicated to the Commission under Article 90, patient safety, data reliability and robustness issues); (ii) it concludes, on duly justified grounds, that Part II requirements are not complied with; or (iii) where an ethics committee has issued a negative opinion valid for the entire Member State.

Subsequent addition of a concerned Member State

This procedure applies where the sponsor wishes to extend an authorised clinical trial to another Member State ("**additional concerned Member State**"). In this event, the sponsor shall submit an application dossier to the additional Member State through the EU portal. The additional application dossier may be submitted only once the initial authorisation decision has been notified. The reporting Member State shall be the same as for the initial authorisation procedure.

The authorisation procedure is similar to the one applicable to the initial authorisation:

- The additional Member State concerned shall notify the sponsor through the EU portal within 52 days (or 83 days in case of request for additional information) from the date of submission of the application dossier by way of a single decision as to whether the clinical trial is authorised, authorised subject to conditions, or whether the authorisation is refused.
- Where the conclusion of the reporting Member State regarding Part I of the assessment report is that the conduct of the clinical trial is acceptable or acceptable subject to compliance with specific conditions, that conclusion shall be deemed to be the conclusion of the additional Member State concerned, which may only disagree based on specific listed grounds (the patient will receive inferior treatment compared with normal clinical practice in that Member

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State, infringement of national law as per Article 90 of the CTR, or patient safety and data reliability and robustness issues).

- The additional Member State concerned shall assess, for its territory, the aspects addressed in Part II of the application dossier.
- Any request for additional information and the additional information itself shall be submitted through the EU portal. Where the sponsor does not provide the additional information requested within the period set, the application shall be deemed to have lapsed in the additional Member State concerned.

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Authorisation procedure for a substantial modification of a clinical trial

A substantial modification, including the addition of a clinical trial site or the change of a principal investigator in the clinical trial site, shall be approved pursuant to a procedure established in the CTR. The reporting Member State shall be the reporting Member State for the initial authorisation procedure.

- Within 6 days from the submission of the application dossier the reporting Member State and the concerned Member States shall validate whether the substantial modification concerns aspects covered by Part I and/or Part II of the assessment report and whether the application dossier is complete.
- The reporting Member State shall assess the application with regard to aspects covered by Part I of the assessment report. Each concerned Member State shall assess the application with regard to aspects covered by Part II of the assessment report.

Notifications

The CTR has increased the notifications to be made by the sponsor in order to increase and ensure transparency: A sponsor will need to notify through the EU portal each concerned Member State within a 15 day period:

- Of the start of the clinical trial, the first visit of the first patient and the end of the recruitment of patients in relation to that Member State.
- Of the end of the clinical trial in relation to that Member State, of the end of the clinical trial in all Member States and of the end of the clinical trial in all third countries.
- Of the temporary halt or early termination of a clinical trial for any reason, as well as the resumption of the trial after a temporary halt.

Irrespective of the outcome of a clinical trial, within 1 year from the end of a clinical trial in all Member States concerned, the sponsor shall submit to the EU database a summary of the results of the clinical trial. It shall be accompanied by a summary written in a manner that is understandable to a layperson.

III. Good Clinical Practice

Under the CTD, details on good clinical practices are provided in Commission Directive 2005/28/EC ("**GCP Directive**"). Some of these



provisions have been incorporated in the CTR and will apply directly as soon as the CTR becomes applicable.

However, the CTR goes further than the CTD and GCP Directive and sets forth additional details:

In relation to informed consent, the CTR provides additional detail on the prior interview with the patient and/or his/her representative. Requirements are included regarding qualified staff, the type of information given to the patient, the format in which such information is given (taking into account the special needs of the patient), and the requirement to verify if the patient has understood the information. It also requires that a copy of the informed consent be delivered to the patient or his/her representative.

The CTR also provides for the possibility of a simplified informed consent for certain low intervention clinical trials which are conducted in 1 Member State only and it sets forth the conditions for obtaining informed consent when including the patient in a clinical trial in an emergency situation.

The good clinical practice provisions in the CTR will be further complemented with an implementing regulation with detailed arrangements for inspection procedures on good clinical practice, including qualification and training requirements for inspectors. A public consultation took place in 2015 on the Commission working document in view of preparing an implementing regulation, which is anticipated to be adopted before the end of 2016.

Increasingly, data submitted in marketing authorisation applications in the EU are generated from clinical trials conducted in third countries. Annex 1 of Directive 2001/83/EC provides that such clinical trials must comply with principles equivalent to those that apply in the EU. To ensure that such principles are supervised and enforced, the CTR gives the European Commission the power to set up a programme of controls in collaboration with the Member States.

In addition, if an application for a clinical trial is made in accordance with the requirements of the CTR and if such application makes reference to data from a clinical trial conducted outside the EU, the CTR requires that such third country clinical trial is conducted in accordance with principles equivalent to those of the CTR regarding the rights and safety of the patient and the reliability of the data generated in the clinical trial.

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IV. Safety Reporting

Under the CTD, sponsors are submitting suspected unexpected serious adverse reactions (**SUSARs**) and annual safety reports to the national competent authorities and ethics committees in the concerned Member States which are assessing these reports separately.

Going forward under the CTR, the EMA will set up a dedicated module in the Eudravigilance database and sponsors will be able to submit the SUSARs and annual safety reports to this database by way of one-stop shop. The EMA will forward the reports to the concerned Member States who will cooperate with each other for assessment. The European Commission, by way of implementing acts, may set the rules for such cooperation. Ethics committees will still be involved in the assessment of

the safety reports only if the law of the Member States concerned provides for it.

V. Co-sponsorship

In implementing the CTD, Member States gave different meanings to the concept of sponsor. As such, some Member States provided for the possibility of co-sponsorship while other Member States did not recognise multiple sponsors.

The CTR explicitly confirms the possibility of having several sponsors and introduces the concept of co-sponsorship. It provides that, where there is more than one sponsor, such sponsors are jointly responsible for all obligations of a sponsor unless they decide otherwise in a written contract setting out their respective responsibilities.

VI. Clinical Trial Data Transparency

Among the most debated provisions of the CTR are those providing for increased transparency and disclosure of clinical trials data and information. The CTR recognises and lays down the principle that all information in the EU database submitted as part of the clinical trial application and in the course of the assessment procedure are not confidential and must be publicly accessible.

Also, the CTR requires sponsors to submit to the EU database both a summary of the results of the clinical trial and a layperson summary within 1 year after the end of the trial in the EU. In addition, in case the trial performed is used for obtaining a marketing authorisation in the EU, the applicant shall also submit a clinical study report to the EU database within 30 days after the procedure for granting the marketing authorisation has been completed (with either a positive or negative outcome), or the applicant for the marketing authorization has withdrawn the application.

That being said, in order to meet the concerns of marketing authorisation holders regarding their confidential commercial information becoming public, thus allowing others to benefit from their investments, the CTR provides for some exceptions to the abovementioned rules where the confidentiality of the information is justified by the need to protect commercially confidential information, personal data, confidential communications with authorities in connection with the preparation of the assessment report or to ensure the effective supervision of the conduct of clinical trials by the Members States.

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