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White Paper

CLINICAL TRIALS REGULATION

The EU Clinical Trials Regulation – Preparing for the changes ahead

January 2019

CROMSOURCE is an international provider of outsourced services to the pharmaceutical, biotechnology and medical device industries, specialized in clinical development and staffing solutions.

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Introduction

The way clinical trials are conducted in the European Union (EU) will undergo a major change when the Clinical Trials Regulation (CTR) EU No 536/2014 becomes applicable towards the end of 2020. The Regulation will replace the existing Clinical Trial Directive (CTD) No. 2001/20/EC and national legislation that was put in place to implement it.

According to the CTD framework, a sponsor wishing to perform a clinical trial in several Member States has to submit a Clinical Trial Application (CTA) to each individual National Competent Authority (NCA) and Ethics Committee (EC). Clinical trials are conducted according to each individual Member State's rules and there has been a lack of standardisation in applying Good Clinical Practices (GCPs) and Good Manufacturing Practices (GMPs). On 17 July 2012, after an extended period of consultation involving the Heads of Medicines Agencies (HMAs) and patients groups, the European Commission adopted "Proposal for a Regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC". The objective was to reduce the obstacles stemming from the Clinical Trials Directive's implementation, harmonise requirements, timelines, and approvals in the EU and centralise the clinical trials process authorisation for multi-national trials.

On 16 April 2014 the CTR entered into force with an implementation deadline "no earlier than 28 May 2016 or once EU database and EU portal become fully functional". The Regulation is to be made applicable six months after the publication of full functionality of the EU portal and database in the Official Journal of the European Union. The EU portal will be the single point of entry for the submission all of the information relating to clinical trials and will serve as a communication tool between sponsors, Member States, European Commission and Marketing Authorization Holders. Data submitted through the EU portal will be collected in the EU database.

In October 2018, the European Medicinal Agency's (EMA) Management Board announced that release 0.7 (auditable version) is complete and the audit field work will take place once the EMA has settled in Amsterdam, after 29 March 2019. It is expected that the CTR will enter into application in 2020; precise timelines will be provided by the EMA after the audit.

Although the CTD will be repealed on the day of entry into application of the CTR, it will still apply three years from that day to clinical trials applications submitted to NCAs and ECs before entry into application of the CTR and within one year after the entry into application of the CTR, if the sponsor chooses to follow the old system.

This white paper will highlight significant changes under CTR in clinical trial initial authorisation and substantial modification procedures, requirements for streamlined reporting and public disclosure of data, as well as initiatives rolled out by several Member States to allow sponsors to familiarise themselves with CTR requirements.

SIGNIFICANT CHANGES UNDER REGULATION

Definitions

The Clinical Trials Regulation has retained some definitions and refined others. For example the definition of "clinical study": "Any investigation in relation to humans intended: (a) to discover or verify the clinical, pharmacological or other pharmacodynamic effects of one or more medicinal products; (b) to identify any adverse reactions to one or more medicinal products; or (c) to study the absorption, distribution, metabolism and excretion of one or more medicinal products" is similar to the definition in the CTD, but a "clinical trial" is defined more narrowly as a subset of a clinical study. The CTR defines a non-interventional clinical trial as "a clinical study other than clinical trial".

The CTR introduces new elements like Low-intervention Trial and Auxiliary Medicinal Product. A Low-intervention Trial is defined as a new category of trial which must fulfil the main conditions mentioned in the Regulation, but requires less stringent rules, for example regarding insurance, monitoring and Investigational Medicinal Product (IMP) traceability. The precise interpretation of this definition is left to each Member State where an application for authorisation of a clinical trial or of a substantial modification will be submitted (Concerned Member State; CMS). Auxiliary Medicinal Product (AuxMP) is defined as a medicinal product used in a clinical trial, for example for background treatment or rescue medication, but not as an investigational medicinal product.

The CTR uses the term "substantial modification" instead of "substantial amendment" used by CAs and ECs in accordance with the CTD. The two definitions are comparable and cover any changes 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.

Initial Authorisation Procedure

Submission

One of the main aims of the CTR for the authorisation procedure is for the sponsor/applicant to submit one application dossier including a single set of documents in harmonised format via the EU portal regardless of how many Member States are participating in the trial. Each Member State will issue one decision per study. According to the EMA guideline "Functional specifications for the EU portal and EU database to be audited" the sponsor will be a "super user" of the EU portal and EU database and will:

- manage other users (e.g. CRO);
- prepare and submit applications, notifications and responses to requests for additional information or delegate those tasks to users; and
- monitor the work flow of the clinical trial.

The super user will be able to designate other super users, if required. The users will need to register by themselves in the EU portal with login and password and will be assigned automatically to sponsor/super user with all rights.

The sponsor/super user or delegated user will submit the harmonised format of the application dossier for the clinical trial simultaneously to all Member States where a clinical trial is going to be conducted. The application dossier will consist of:

- Part I scientific review – to be assessed jointly by all CMSs; and
- Part II ethical review – to be assessed by each CMS separately.

Part I Refers to Annex I (sections B to J, Q)	Part II Refers to Annex I (Sections K to R)
Cover letter	**Recruitment arrangements** (information per Concerned Member State);
EU Application Form	**Subject Information, Informed Consent Form and Informed Concerned Procedure** (information per Concerned Member State)
Protocol	**Suitability of the Investigator** (information per Concerned Member State)
Investigator's Brochure/ Simplified medicinal Product Characteristic (SmPC)	**Suitability of the facilities** (information per Concerned Member State)
Documentation relating to compliance with GMP for the investigational medicinal product	**Proof of Insurance cover or indemnification** (information per Concerned Member State)
Investigational Medicinal Product Dossier (IMPD)	**Financial and other arrangements** (information per CMS)
Auxiliary medicinal product dossier, if applicable	**Proof that data will be processed in compliance with Union Law on Data protection**
Scientific advice and Paediatric Investigational Plan (PIP), if applicable	
Content of the labelling of the investigational medicinal products	
Proof of payment of fee (information per CMS)	

Table 1. List of required documents for the initial application under CTR.
Annex I, Application Dossier for the Initial Application:

https://ec.europa.eu/health//sites/health/files/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf

The language used for the application dossier should be common in the medical field (i.e. English) but documents addressed to the subjects should be in their national and understood language(s). The sponsor/ super user/user can submit Part I and Part II together, but there is also possibility for them to submit only Part I for review and agreement; Part II may be submitted up to two years after Part I assessment has been completed.

In the application dossier, the sponsor shall propose one of the CMSs as the Reporting Member State (RMS) which will coordinate the validation and evaluation of the assessment process of the application. There should be one RMS for each study/protocol. If no CMS is willing to be the RMS or more than one CMS is willing to be the RMS then the RMS should be selected by agreement among the CMSs. In case of only one CMS participating in the clinical trials that CMS will automatically be the RMS. The RMS shall notify the sponsor and, if applicable, other CMSs, within six days from the submission of the application dossier through the EU portal.

Validation and Assessment

The overall process, when Part I (scientific review) and Part II (ethical review) are submitted together, consists of two steps: validation and assessment.

The dossier is validated by the RMS within ten days from submission taking into account comments expressed by the other CMSs. If there is no feedback from CMSs the application dossier shall be considered complete. If there is a request for information or any inquiries, the RMS sends a request for additional information to the sponsor and one clock stop is allowed. The sponsor has maximum ten days to respond. The sponsor's failure to reply will lead to the automatic withdrawal of the application in all CMSs. The RMS has five days following receipt of the response to confirm validation to the applicant. If the RMS has not notified the sponsor within five days the application dossier shall be considered complete.

Once the validation process is completed, Parts I and II are assessed in parallel within 45 days and up to 76 days if there are any questions requiring an extension.

Assessment of Part I and Part II submissions is carried out as follows:

- Part I Assessment: Scientific part

In case of a multinational trial all CMSs must collaborate in the evaluation and the 45 days reporting period is then divided as follows:

- Initial assessment: within 26 days the RMS submits an initial Part I draft assessment report to CMSs (in case of trials involving an advanced therapy or a biotechnology medicinal product, the RMS extends the period by 50 days);
- Coordinated review: within 12 days CMSs review and provide comments to the RMS;
- Consolidation: within seven days the RMS consolidates the input from CMSs.

The RMS, considering issues raised by CMSs, may extend the reporting period up to 31 additional days. Only the RMS can request additional information from the sponsor. The sponsor has maximum 12 days to respond. Lack of response will be considered as withdrawal of the application in all CMSs.

The sponsor's responses are sent to all CMSs for joint coordinated review and the CMSs provide feedback to the RMS within 12 days. The RMS consolidates the input from CMSs within seven days and prepares the final assessment report.

- Part II Assessment: Ethical Part

Part II covers aspects typically examined by Ethics Committees and will be conducted separately by each CMS individually for its own territory. Each CMS shall complete its assessment of Part II within 45 days from the validation date.

To obtain and review additional information from the sponsor the Ethics Committee (EC) or the National Competent Authority on behalf of the EC, may request an extension of the initial assessment up to 31 days. All CMSs and ECs have the same deadlines but, independently and separately, can request an extension. The sponsor gets maximum 12 days to reply. In case of lack of responses the clinical trials submission will be withdrawn in all CMSs. Within the 31 days' extension and after receiving sponsor's responses, each CMS has 19 days for final assessment of ethical review.

Decision

The Regulation says that within five days of the final Part I assessment report or Part II assessment by each CMS, whichever is later, a single decision must be communicated to the sponsor. The Ethics Committee review may encompass aspects addressed in Part I (scientific) and Part II (ethical) of the assessment report. The final decision is made after Part I and Part II assessments are completed. The clinical trial may be found acceptable or acceptable subject to conditions, or it may be refused for all CMSs. The overall process of initial authorisation under the CTR is illustrated in Figure 1.

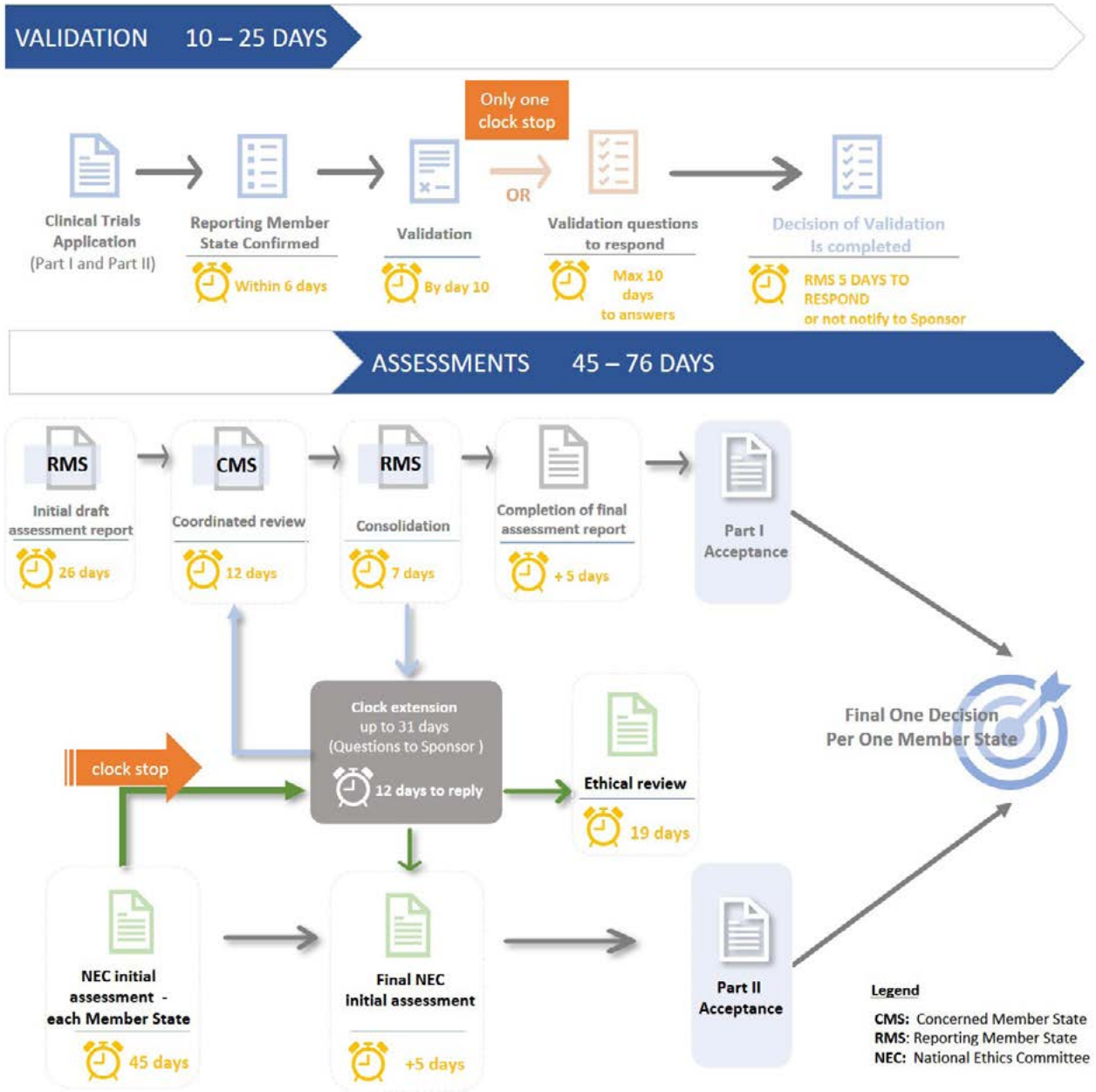

Figure 1. An overall process of Initial Authorisation Procedure under CTR.
Chapter II, Authorisation Procedure for a Clinical Trial:
https://ec.europa.eu/health//sites/health/files/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf

If a CMS does not give its decision within the regulated timeframe then the conclusion of the RMS Part I assessment report will automatically be considered as CMS decision. Where the conclusion of the RMS as regards Part I of the assessment report is that the clinical trial is not acceptable, that conclusion shall be deemed to be the conclusion of all CMSs.

A CMS can refuse to authorise a clinical trial if it disagrees with the conclusion of the RMS as regards Part I or an Ethics Committee can issue a negative opinion in a CMS. The CMS shall provide for an appeal procedure in respect of such refusal. Individual Member States may decline to participate in a trial even when others have already accepted it. The application can be withdrawn at any time by the sponsor, up to the reporting date, but only if withdrawn in all CMSs.

Resubmission of the clinical trial is possible in the CMS in which the study has been refused, but it will be considered as a separate new Clinical Trial Application with a new EudraCT number.

Substantial Modification Procedure

According to the CTR only substantial modification needs approval prior to implementation. A substantial modification may concern a change to Part I, Part II or to both parts of the submitted application dossier. The RMS for the authorisation of a substantial modification shall be the same RMS as for the initial authorisation procedure. If the substantial modification concerns only Part I (e. g. Protocol, Investigator's Brochure or IMP Dossier), the RMS in cooperation with CMSs shall validate the application within six days. If there are any questions the sponsor will get maximum ten days to provide a response and the RMS five days to confirm the validation. The assessment report shall be completed within 38 days or 69 days in case of request for additional information to the sponsor. Within five days each CMS shall communicate to the sponsor their decision on substantial modification.

In cases where the substantial modification concerns only Part II (e.g. recruitment arrangement, additional site in a CMS) only the CMS is involved in the assessment. The same timeframes apply for Part II as for Part I, including 19 days for ethical review.

When the changes affect both Parts I and II (e.g. change of main objective of the clinical trial or addition of a trial arm, or placebo group), both will be run in parallel with the same timeframe. As is the case with initial authorisation, the RMS will take the responsibility for coordinating the validation and evaluation of the assessment process of the application.

Addition of a Member State

After a clinical trial has received the initial authorisation decision, the sponsor may apply to the same RMS for adding another Member State. The procedures are the same as for initial submission. The sponsor/super user/user has to submit Part I and Part II through the EU portal for CMS evaluation, comments or disagreement to the clinical trial. The submission shall be done also through the EU portal and the CMS shall notify its decision to sponsor within 52 days or 83 days depending on whether comments have been raised and required answer from the sponsor.

Streamlined Reporting

Under the CTR, the sponsor will submit all Suspected Unexpected Serious Adverse Reactions (SUSARs) and Development Safety Update Reports (DSURs) through the dedicated new module of the EudraVigilance database. The EudraVigilance database will be maintained by the EMA. The EMA will forward the safety information electronically to all CMSs. The Ethics Committees and Investigators will not have access to the EudraVigilance and their safety analysis will be regulated under national laws unless the European Commission adopts Delegated Acts which regulate rules concerning MS cooperation in assessing information reported to the relevant Ethics Committee. The EMA will also be a controller of the EU database and responsible for avoiding unnecessary duplication between the EU database and the EudraCT and EudraVigilance databases.

The new reporting system for SUSARs and DSURs will start applying six months after the publication of the European Commission notice about the full functionality of the EU portal and EU database. It will streamline safety reporting and help sponsors to avoid separate submissions of SUSARs and DSURs to Competent Authorities and Ethics Committees of each CMS. The CTR has kept the same timeframes for reporting SUSARs and DSURs as specified under the CTD: fatal and life-threatening SUSARs - as soon as possible and in any event not later than seven days with follow up within eight days; other SUSARs - within 15 days; DSURs - yearly.

The CTD had no provisions to notify the CA/EC of the start of a clinical trial (first patient first visit; FPFV). The only requirement was to inform the CA/EC about: the end of the trial (within 90 days); a temporary halt and early termination (within 15 days). The CTR will require harmonised reporting of all clinical trial lifecycle events by obligating the sponsor or his delegated user (e.g. CRO) to notify each CMS within 15 days of all events listed in Table 2. The notification of events will be managed through the EU portal.

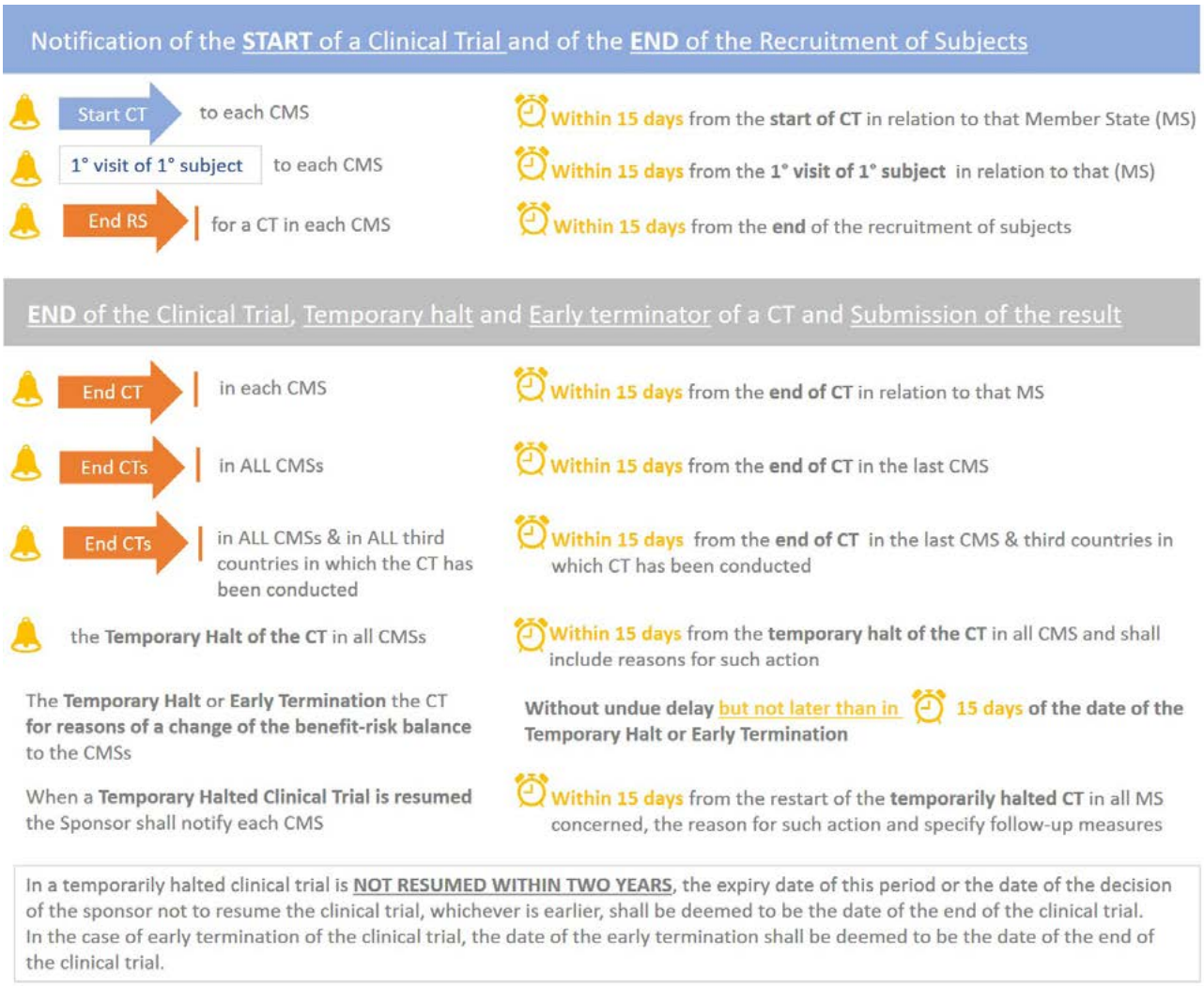

Table 2. Clinical trial lifecycle: notification of events within 15 days
(CHAPTER VI, START, END, TEMPORARY HALT, and EARLY TERMINATION OF A CLINICAL TRIAL):
https://ec.europa.eu/health//sites/health/files/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf

If a CMS does not give its decision within the regulated timeframe then the conclusion of the RMS Part I assessment report will automatically be considered as CMS decision. Where the conclusion of the RMS as regards Part I of the assessment report is that the clinical trial is not acceptable, that conclusion shall be deemed to be the conclusion of all CMSs.

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Resubmission of the clinical trial is possible in the CMS in which the study has been refused, but it will be considered as a separate new Clinical Trial Application with a new EudraCT number.

Public Disclosure of Data

Prior to 1 May 2004 when EudraCT database was established, clinical trial information was confidential and available only to Member States' Competent Authorities, the EMA and the European Commission. After 21 July 2014 it became mandatory for sponsors to post clinical trials results in the EudraCT database.

According to the CTR, once established, the EU database will contain all relevant clinical trial information submitted through the EU portal. The information will be available publicly and will include: inclusion and exclusion criteria; main objectives and endpoints; the dates of the start and end of patient recruitment; and the trial end date. However, no subject personal data will be entered into the EU database. To protect an individual's right to privacy and rights to personal data protection some information regarding clinical trials will continue to need to be anonymised.

The outcome of a clinical trial will also be published in the EU database. The sponsor shall submit a summary of the results of the clinical trial to the EU database within one year from the end of a clinical trial in all CMSs (as set out in Annex IV of the CTR). It shall be also accompanied by a summary written in a manner that is understandable to laypersons and translated into the Member State's national language (as set out in Annex V).

In addition, when clinical trials are intended to be used for obtaining a marketing authorisation for the medicinal product, the marketing authorisation applicant shall submit to the EU database the Clinical Study Report (CSR) within 30 days after "the day the marketing authorisation has been granted, the procedure for granting the marketing authorisation has been completed, or the applicant for marketing authorisation has withdrawn the application."

FIRST STEPS TOWARDS IMPLEMENTATION OF THE REGULATION

The entry into force of the CTR was originally scheduled for May 2016, but will be effective only when EU portal and EU database become available and fully functional. Most of the EU Member States decided not to wait for EU portal and database availability and have implemented certain new provisions to their laws (e.g. France, Spain, Greece, Denmark and Italy) or have launched Pilot Phase programmes for clinical trials involving medicinal products to ensure that they are ready when the Regulation comes into force.

At the beginning of 2018 six EU countries were offering sponsors Pilot Phase: Austria, Belgium, France, Germany, Ireland and Sweden. Brexit notwithstanding, United Kingdom started offering applicants a Pilot Phase programme in April 2018.

Participating in Pilot Phase is not mandatory but gives sponsors an idea of the new organisational structure enforced by the Regulation whilst complying with current legislation. The sponsor can choose whether to submit a Clinical Trials Application in accordance with the Clinical Trials Directive or Pilot Phase.

In addition, participating in Pilot Phase helps Member States to prepare for the upcoming CTR process, for example by better organising cooperation between the Competent Authority and Ethics Committees in Part II (ethical review). One of the first countries which started the experimental Pilot Phase procedure was France. In October 2017 the French CA - National Agency for the Safety of Medicine and Health Products (ANSM) - published results of the first two years of Pilot Phase. They recorded 260 submitted applications, of which 210 were managed in the context of the process under the CTR. One hundred and ninety three applications were approved and the observed average time of processing was 68.9 days.

Besides the Pilot Phase, in October 2018, the French CA has implemented new clinical trials authorisation programme, named Fast Track. The program offers patients fast access to innovative treatments. One of the aims of procedure is to prepare the ANSM to be more responsive in provision of the future European regulations on clinical trials.

CONCLUSION

Without doubt, the Clinical Trials Regulation will change the rules for authorization of all phases (I-IV) of clinical trials on medicinal products for human use. It will harmonise and centralise the processes from the start to the end of clinical trials. In addition, the information relating to clinical trials will become publicly available as it is in the USA (www.clinicaltrials.gov). To finalise the application process of the CTR, the European Commission and the EMA will need to focus on telematics tools: EU portal and EU database. Brexit and relocation of EMA's headquarters to Amsterdam may again postpone the timelines for testing and auditing the telematics tools.

Some EU guidelines have already been implemented by the European Commission and will be applicable as from the date of entry into application of the Regulation. Examples are: "Detailed Commission guideline of 8 December 2017 on the good manufacturing practice for investigational medicinal products pursuant to the second paragraph of the Article 63(1) of Regulation (EU) No 536/2014"; and "Template for IMP batch release".

A number of clinical trials guidance documents in Volume 10 of the EudraLex 10-volume collection of rules governing medicinal products in the EU are being revised and updated by the European Commission to bring them in line with the changes required by the CTR. Additionally, new documents have been prepared to cover new aspects introduced by the CTR. In order to make a distinction between documents applicable to clinical trials authorised under CTD and documents relevant to clinical trials authorised under CTR, these documents will be listed in two separate pages on the Eudralex Volume 10 website.

Once the Clinical Trials Regulation becomes applicable it will automatically apply to all EU Member States. It will be a challenge for some Member States to set up communications between the National CA and the Ethics Committee, and to execute ethical review of the trial for the entire territory. For all Member States it would be prudent to practice the new process, especially the need to adhere to strict timelines, comply with the required content of submitted documents and collaborate in issuing a joint decision with other CMSs in order to be ready when the Regulation becomes applicable. Some Member States have already began this process.

While it is important to begin preparations, as stated earlier transition period will be applicable and during this period the sponsor will get a choice: CTD or CTR. The sponsors should also be aware that under the CTR many of the requirements will be the same as under the CTD - for example timelines for safety reporting (SUSARs, DSURs), documents related to patients in national language, requirements for labelling, and any others.

The EU CTR will usher in a new era in the way clinical trials are conducted for sponsors, Member States, CROs and especially for patients whose rights, safety, dignity and well-being will be better protected. Sponsors and their delegated users should become familiar with CTR requirements explained in this white paper for initial authorization, substantial modification, reporting safety information and notification of clinical trial events.

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David joined CROMSOURCE in 2018 as Regulatory Services Department Director. He has more than 28 years' of leadership experience in the pharmaceutical and medical device industry within the regulatory affairs and compliance space.

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He is providing the global regulatory capabilities and regulatory intelligence support for clients and collaborating with our internal stakeholders. In addition, to being a professional member with industry associations, advisory boards, prolific speaker at industry events, he navigates the regulatory landscape throughout the product life cycle and regulatory crisis management. In addition, David is responsible for the development and launch of new services in the Regulatory and Strategic Consulting space.

About CROMSOURCE

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