EU-Clinical Trial Regulation 536/2014:

What do you need to consider now when planning clinical trials to avoid delays in their initiation?

The EU Regulation 536/2014 (hereinafter referred to as CTR) for clinical trials of medicinal products is in effect throughout Europe since 31 January 2022. From 01 February 2023, clinical trials must be submitted for approval via the electronic EU portal in accordance with the CTR. This means that the transition period (since 01 February 2022), during which clinical trials could be submitted according to the previous or new standard, will terminate at the end of January 2023. With the start of the transition period since February 2022, authorities and sponsors have the opportunity to make preparations, identify system errors and work out solutions. All parties involved wish for a smooth implementation. The pharmaceutical industry and Clinical Research Organisations (CROs) in particular the Charité Research Organisation GmbH are well prepared, small companies and start-ups may seek the support of experienced CROs.

This white paper provides an insight into the main changes introduced by the regulation and an insight into the ongoing preparations of all stakeholders, the associated new challenges and planning strategies with the following focus areas:

- ❖ **Legal changes involved with the implementation of CTR**
- ❖ **Transparency and data protection**
- ❖ **Transition period and transitional provisions**
- ❖ **New requirements and deadlines**
- ❖ **EU-Portal: Clinical Trial Information System (CTIS)**
- ❖ **CTR-preparedness in the pharmaceutical industry**
- ❖ **CTR-compliance of the Charité Research Organisation GmbH**

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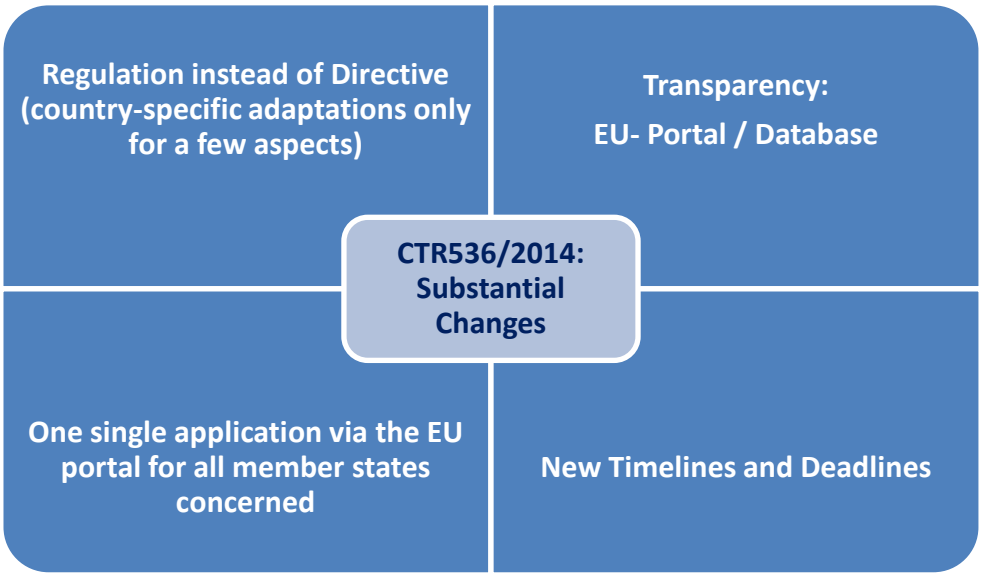
Legal changes involved with the implementation of CTR:

The CTR directly replaces the previous EU Clinical Trials Directive (EC) No. 2001/20/EC. With the validity of the CTR, the legal provisions for conducting clinical trials in Europe are being harmonised. The new streamlined authorisation procedure is valid not only for the EU, but for the entire European Economic Area, which also includes Norway, Iceland and Liechtenstein.

Main changes involved with CTR-implementation:



With the legal form of a regulation, the CTR will replace national law.

In Germany, the German Medicines Act (AMG) and other legal regulations are however still in force, as they contain other regulations beyond the area of clinical trials. The GCP Regulation (GCP-V) was repealed on 28 January 2022. However, it is still applicable during the transition period when sponsors opt for Directive 2001/20/EC as legal basis. The discontinuation of the GCP-V is associated with some relief. For example, substances for provocation tests (e.g. methacholine) will no longer be considered medical products in the future, i.e. they no longer have to be submitted as IMPs. With the CTR, the minimum archiving period of the trial documents (Trial Master File) is at least 25 years. The determination of archiving periods in the protocol is therefore unnecessary.

Transparency and Data protection: The EMA will make the stored clinical trial information publicly available via the EU portal and the associated database. However, sensitive data in the trial documents may be redacted (blackened). For trial documents of patent relevance of high complexity, there is the possibility to request a deferral for their publication. In addition, non-blackened versions with all relevant information must be submitted for the official evaluation.

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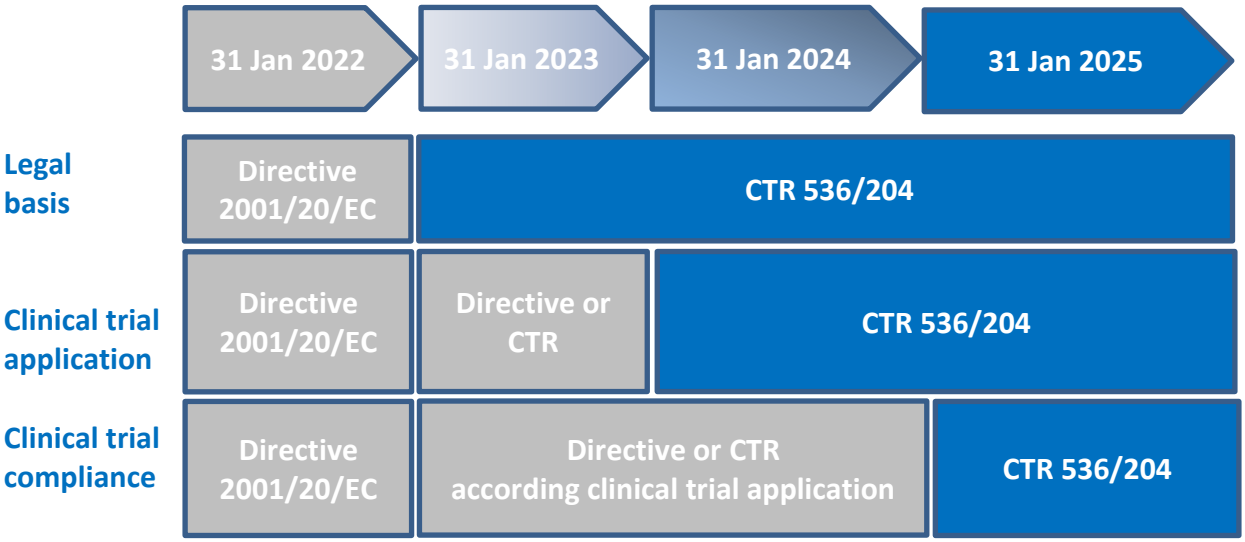
Transition period and transitional provisions: Transitional rules for the application and conduct of clinical trials with medicinal products apply for a period of 3 years: Clinical trials that are currently already in progress can continue until 31 January 2025 in accordance with Directive 2001/20 EC. All clinical trials that will not be completed and deregistered by this date must be adapted to the CTR in good time and an application for transfer (transition) must be submitted. If the duration of a clinical trial is fixed beyond 31 January 2025, the transfer procedure including the assessment process must be completed with an authorisation before 31 January 2025.

The evaluation process by the Competent Authority (CA) and the Ethics Committee (EC) can take up to 91 days, including subsequent requests (even longer deadlines apply for "Advanced Therapy Medicinal Products" and Genetically Modified Organisms). It is therefore strongly recommended to complete and submit the documents for transfer to the CTR in a timely manner, preferably before the end of August 2024. Only in this way can it be avoided that the clinical trial no longer has approval when the deadline expires on 31 January 2025, which would result in immediate termination. As of transfer, the trial must then be conducted under the CTR.

All initial submissions for approval of a clinical trial after 31 January 2023 must be made via the CTIS portal and the trials must be conducted under the CTR from the beginning.

Transition period of 3 years for CTR536/2014 implementation:



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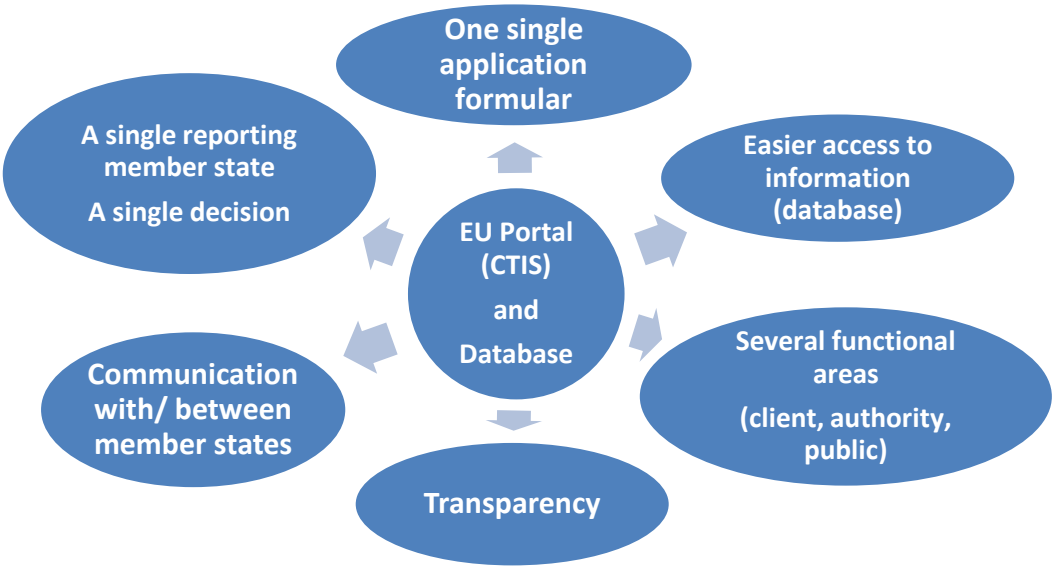
New requirements and deadlines: The CTR provides for harmonized (tighter) deadlines for the evaluation of initial applications for clinical trials as well as for the evaluation of applications for substantial amendments and the subsequent inclusion of a Member State concerned. In future, the applicant will have a deadline of only 12 days (previously 90) to respond to substantive deficiency letters. In the case of more complex substantive deficiencies, the only option is to withdraw the application in time, otherwise the application will be rejected. Within 19 days after replying, the rapporteur Member State will give its approval via CTIS.

EU-Portal: Clinical Trial Information System (CTIS): All clinical trials with medicinal products, i.e. also monocentric "Investigator Initiated Trials", are now only to be submitted electronically via the EMA's Europe-wide portal CTIS.
A single application must be submitted electronically via CTIS and a single (reporting) Member State coordinates the evaluation processes and communicates the decision on the authorisation or any conditions in a single response letter via CTIS within 45 days. The approval is based on the evaluation reports of the Member States concerned on Part I (General Aspects) and Part II (National Aspects). The selection of the reporting Member State is the responsibility of the sponsor and is agreed with the Member States. At national level, this means that there is now only one nationally competent EC per trial in Germany, which is assigned by the business allocation plan of the registered ECs in Germany. Under the CTR, the effort and costs of submitting to several German ECs are thus eliminated for multicentre studies.

Submission via CTIS: One application – One approval



LINK for CTIS online Training Moduls (last accessed on 23-Nov-2022): https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trials-information-system-ctis-online-modular-training-programme

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CTR-preparedness of the industry: From the industry's point of view, clinical trials will receive increased public attention through the introduction of CTR. This allows patients and sponsors to be informed about the latest state of clinical development in an indication at an early stage. For sponsors, it facilitates access to information and thus the positioning of their developments.
Innovative spirit for the benefit of patients is a costly endeavour in a highly regulated environment such as drug development. Positive surprises and failures will also be part of everyday life under the CTR. For example, disclosure of development programme content in the public domain of CTIS is subject to necessary restrictions for patent and competitive reasons. All documents of the clinical trial including IMPD, Investigator's Brochure, clinical trial protocol with appendices must be edited in such a way that development can proceed in the appropriate competitive environment. This step must be carried out under the responsibility of the patent-holding company, as only there can the sensitivity of the material be assessed. The internal company decision-making process on content worthy of protection should also not be underestimated in terms of time.

Editorial revision also requires compliance with data protection regulations. While the principal investigator (responsible head of an investigator team) is publicly disclosed, other staff of the clinical trial must be either pseudonymised or blackened in the documents. This also applies to subject/patient identification numbers in clinical trial reports. A supplementary document with more extensive information can be submitted to the authority upon request. If a deferral is approved by the authority, the documents should nevertheless have already been edited for passages worthy of protection in such a way that, in the event of a revocation, the documents can be released in the form submitted.

Whether the period from submission to "first subject first visit" will be shortened or lengthened remains to be seen. Dealing with only one nationally responsible EC reduces the complexity of previous interactions in multicentre trials. The sponsor has a window of 12 days to respond. The responsibility for meeting the deadline lies with the sponsor.

CTR-compliance of the Charité Research Organisation GmbH:

Compliance with new deadlines: The CRO's internal processes and standard operations have been adapted to the new requirements in all functional areas. Our CRO has participated in the joint pilot programme of the national competent authorities and ethics committees since 2015 and has already successfully trained to comply with a "simulated" deadline of 12 days for regulatory deficiency letters. By 2020, our CRO has submitted a total of 15 clinical trials as a so-called "pilot project" and if required the 12-day deadline has always been met.

GMP area: Under the CTR [1], there will be some new requirements that are likely to involve additional work and higher costs. For example, new labelling requirements for the inner packaging of investigational medicinal products have also been introduced. In future, the inner packaging of supplied investigational medicinal products must contain the expiry date.

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Previous EU GMP guidelines [2] allowed the expiry date to be omitted from the primary packaging. Our CRO can guarantee the printing, checking and application of new labels (relabeling) in a controlled GMP environment. In addition, the CRO processes for releasing the product are CTR-compliant.

Transparency and Data protection: The advertising and recruitment of clinical trials under CTR requires a higher level of transparency and data protection. This also applies to the creation of recruitment texts and to recruiting telephone calls for clinical trials. The CRO standard processes for reporting of recruitment strategies have been adapted accordingly.

GCP-Compliance according CTR: According to the curriculum of the German Medical Association and the Working Group of the German Ethics Committees, a GCP update course on EU Regulation 536/2014 is required. The qualifications of all investigators of our CRO comply with the current GCP requirements.

References:

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

(2) The Rules Governing Medicinal Products in the European Union Volume 4 EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use - Annex 13 Investigational Medicinal Products LINK: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-4/2009_06_annex13.pdf

Summary:

- ✓ **The CTR536/2014 leads to a simplification and harmonisation of the procedure for submitting and assessing clinical trial applications across Europe.**

- ✓ **The large companies and CROs are well prepared for the CTR. Smaller companies and start-ups may need support through competent cooperation by means of CROs. The concept of the "preferred provider" with a proven collaboration record should prove useful here.**

- ✓ **The Charité Research Organisation GmbH has adapted their processes to the new requirements in all functional areas, including the GMP area, and guarantees CTR conformity. We can support our worldwide customers with competence and experience in the implementation of CTR536/2014.**

- ✓ **The Charité Research Organisation GmbH guarantees the implementation of the CTR while maintaining the highest safety standards for the subjects and patients and safeguarding their rights, dignity and well-being.**

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