White Paper

EU Clinical Trials

Regulation

GKM
Gesellschaft für
Therapieforschung mbH

GKM is a reliable partner of pharmaceutical, biotech and medical device companies for planning and conducting clinical trials phase II-IV as well as for non-interventional studies.

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Introduction

In 2001, the European Parliament introduced the Clinical Trials Directive 2001/20/EC (CTD) to harmonise the submission of clinical trials across the countries of the European Union (EU). This directive accepted many national peculiarities, which in the end led to a less harmonised submission procedure than expected. Therefore, in 2014 the Clinical Trials Regulation 536/2014 (CTR) was initiated to further harmonise the submission process and regulations to conduct clinical trials in the EU and European Economic Area (EEA) and pursues a faster and more thorough assessment by the European countries where a clinical trial submission takes place.
The entry into force of the EU CTR was conditional on a successful audit of a central database, called Clinical Trials Information System (CTIS), the heart of the new regulation.

Eventually, after nearly 8 years, the Clinical Trials Regulation 536/2014 (CTR) finally became fully applicable on 31 January 2022, together with CTIS, which

- mandates a centralized application procedure for all clinical trials conducted in the EU/EEA
- leads to a consolidated assessment of all involved Competent Authorities resulting in a single decision, and
- strengthens transparency for clinical trials data.

Relevant aspects in a nutshell

Low-intervention clinical trial and sponsor definition

The EU CTR introduces a new concept of a so-called 'low-interventional trial'. In general, low-interventional clinical trials undergo the same application process as other clinical trials within the EU CTR, except for less stringent rules with regard to monitoring, requirements for the content of the trial master file and traceability of Investigational Medicinal Product (IMPs). Furthermore, the EU CTR contains a slightly modified Sponsor definition.

Risk-based approach

The EU CTR sets by law the conduct of clinical trials according to Good Clinical Practice (GCP) and quality standards. According to ICH GCP E6 (R2) a risk proportionate approach in clinical trials should be followed. The sponsor oversight should be adequate for the specific trial based on the goals and kind of clinical trial, the methods used and degree of deviation from routine daily practice. The European Medicines Agency (EMA) published a recommendation paper, which outlines areas for risk adaptation with regard to trial management and monitoring activities. The revised ICH guideline E8 (R1) also provides information on risk-based approaches related to quality factors.

Transition process

The EU CTR foresees a transition period of three years. Sponsors can decide whether to submit a new clinical trial application under the Clinical Trial Directive 2001/20/EC or Regulation (EU CTR No 536/2014) until 30 January 2023. As of 31 January 2023, all submissions must occur through CTIS. This deadline also applies to the addition of new member states in ongoing clinical trials. New member states can only be added to a running clinical trial after a successful transfer to the EU CTR. Ongoing trials beyond January 2025 must be transferred to CTIS and approved by 31 January 2025.

Clinical Trial Oversight and EudraVigilance

To ensure appropriate oversight of clinical trials the EU CTR extends the reporting requirements (see section additional reporting requirements). In addition to the safety reporting requirements and regulatory submission activities sponsors are required to notify the member states via CTIS about

- start/end dates of clinical trial and recruitment in each member state (within 15 calendar days)
- serious breaches and urgent safety measures (within 7 calendar days)
- unexpected events, which affect the benefit-risk balance (within 15 calendar days), and
- trial oversight information in accordance with article 81 (Non-substantial modifications) that should be updated continuously.

All Suspected Unexpected Serious Adverse Reactions (SUSARs) occurred on EU CTR as well as CTD trials should be submitted via the EudraVigilance system from 31 January 2022 onwards. No separate submissions to national authorities and Ethics Committees (ECs) are needed for EU CTR trials.

Transparency and Lay summary

Sponsors must be aware that trial documents will be published as submitted and won't be amended before publication. Therefore, all submitted documents must be considered ready for publication.

EU CTR Article 37 introduces a new requirement. Sponsors must also provide a Lay Summary of the study results within one year after the end of the trial. Furthermore, the regulation imposes a minimum 25-year retention of Trial Master Files (TMF).

Low-intervention clinical trial

As defined in the EU CTR, a low-intervention clinical trial fulfils the following conditions:

a. Investigational Medicinal Products (IMPs), excluding placebos, are authorised;
b. according to the protocol of the clinical trial,
  i. IMPs are used in accordance with the terms of the marketing authorisation; or
  ii. the use of IMPs is evidence-based and supported by published scientific evidence on the safety and efficacy of those IMPs in any of the member states concerned; and
c. additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice in any Member State concerned;

In general, low-interventional clinical trials undergo the same application process as other clinical trials within the EU CTR. Only less stringent rules with regard to monitoring, requirements for the content of the trial master file and traceability of IMPs may apply. One advantage of a low-interventional clinical trial is that no additional insurance policy is required if a potential damage is already covered by another means (e.g. §84 German AMG). This applies under the premise that the damage results from the use of the IMP in accordance with the protocol of the clinical trial on the Member State territory.

Sponsor definition, co-sponsorship and legal representative

The EU CTR allows pharmaceutical companies or third parties to financially support a clinical trial without taking over the sponsor responsibility. The EU CTR permits co-sponsorship. In case of several sponsors, all sponsors have the same duties unless differently divided in a written agreement.

During submission all sponsors need to appoint one sponsor responsible for:

- addressing all questions from subjects, investigators or any Member State concerned regarding the clinical trial
- ensuring adherence to all obligations within the submission process, and
- implementing corrective measures in accordance with article 77.

'Sponsor'
means an individual, company, institution or organisation, which takes responsibility for the initiation, for the management and for setting up the financing of the clinical trial.
CTR 536/2014 Art. 2 Sentence 2 (14)

The sponsor for all three tasks can be the same but it is also possible to appoint different sponsors for each task in case of co-sponsorship.
In general, if a sponsor is not established in the EU a legal representative in the EU is required. In case only a single EU country is involved in the trial, the concerned member state can refrain from this requirement and agree on a contact person in the concerned member state. The contact person shall be the addressee for all communications between the authorities and the sponsor.

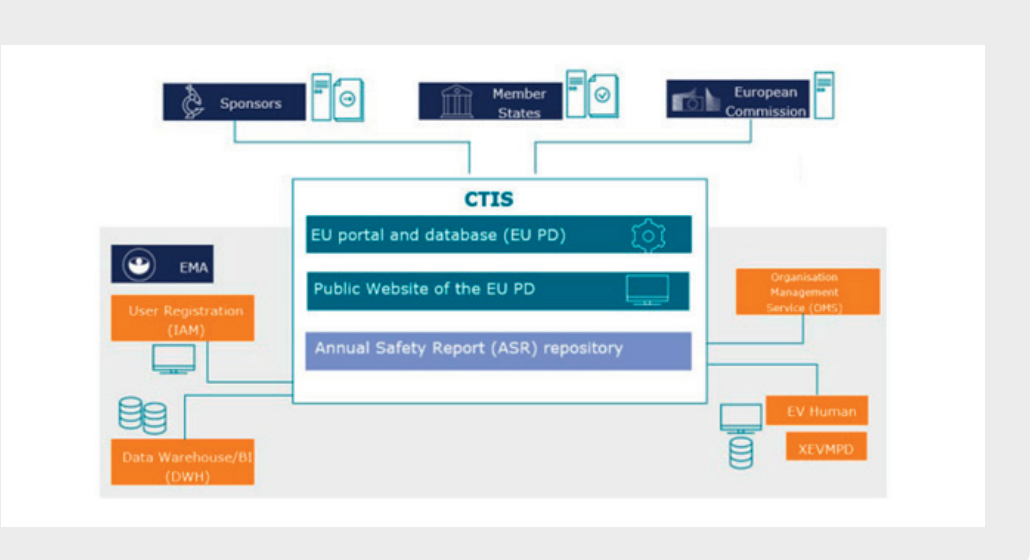
Risk-based quality management

The EU CTR sets by law the conduct of clinical trials according to Good Clinical Practice (GCP) and quality standards (article 47). According to ICH GCP E6 (R2) a risk proportionate approach in clinical trials should be followed. The sponsor should use methods to assure and control the quality of the trial that are proportionate to the risks of the trial and the importance of the information collected. Managing risks in clinical trials should be considered at all levels: at system level (e.g. standard operation procedures, computerized systems, personnel including vendors, etc) as well as at trial level (e.g. trial design, IMP, interventions, data collection and recording, etc).

Risk management includes the steps of risk identification, risk evaluation and risk control (e.g. by avoidance or mitigation) followed by continuous monitoring and readjustment. The process should cover the whole process from protocol development during conduct until analysing and reporting.
The EMA published a *recommendation paper*, which outlines areas for risk adaptation with regard to trial management. The guideline applies to all types of clinical trials. It also highlights the importance to individually plan and adapt the monitoring activities to each clinical trial. The revised ICH guideline E8 (R1) also provides information on risk-based approaches related to quality factors.

Clinical Trials Information System (CTIS), submission and transition process

The central EU portal and clinical trial database CTIS shall capture all information around clinical trials conducted in the EU. This central platform aims to facilitate the communication between member states and sponsors.
CTIS consists of two workspaces and a public portal. Access to the workspaces "sponsor" and "authority" is limited to registered users from sponsor organisations and respective national competent authorities. The EU portal interfaces with other EMA data sources such as Organisation Management Services (OMS), EMA account management portal (IAM), medication database and Eudravigilance database (EV).



Picture 2: [DRAFT] Guidance document on how to approach the protection of personal data and commercially confidential information in documents uploaded and published in CTIS published on 7 April 2022; EMA/212507/2021

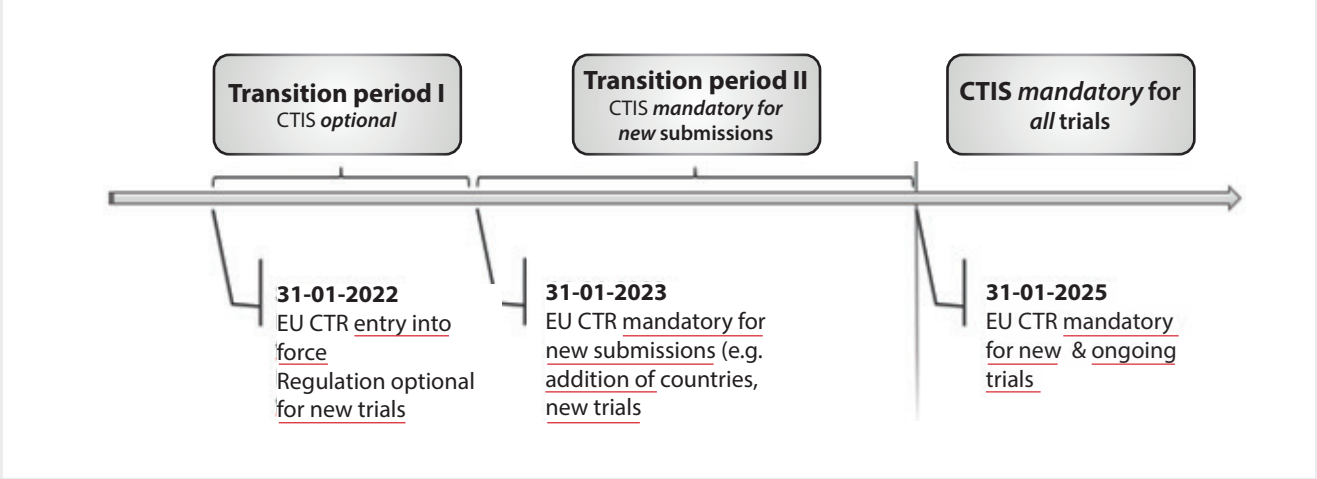
All clinical trial information must be submitted on CTIS. Sponsors should consider the following points regarding the submission of clinical trials via CTIS:

- **All participating parties must register** before submitting a clinical trial application.
- Submission to ECs will go through CTIS. **No additional submission to local ECs** is required.
- The EU CTR defines tight timelines for each submission step (12 calendar days maximum to address request for information (RFI) during initial submission/substantial modifications). **Failure to respond within deadlines results in withdrawal** of the trial and requires a new submission.
- Short timelines require **thorough preparation and submission coordination** on sponsor/CRO side including identification of back-up team members to cover the "response" periods.
- Notifications and alerts will only be communicated in CTIS. **No additional Email notifications will be sent.**
- In CTIS, **only sequential filing is possible.** Therefore, Substantial Modifications cannot be submitted in parallel to another ongoing assessment. An exception is the addition of a new member state during an ongoing assessment of a substantial modification for Part II in another member state. This requires diligent upfront planning.
- Due to the sequential filing rule, it is preferable to submit for all (or at least most) countries at once. Therefore, **submission planning will shift from first country ready for submission to last country ready for submission.**
- Sponsors should **consider options for deferred publication** (see section 'Transparency') already during initial submission.

In the current transition period, until 31 Jan 2025, the Clinical Trials Directive 2001/20/EC (CTD) and the Clinical Trial Regulation 536/2014 are effective in parallel. Ongoing trials can continue under the CTD until 31 January 2025.

Longer running clinical trials must follow the rules of the EU CTR at latest by 31 January 2025. The transition period intends to allow sponsors to progressively transfer long-running trials to the EU CTR.

During 2022 and until 31 January 2023 the sponsor can choose to submit a new clinical trial under the "old" CTD or the "new" EU CTR. After 31 January 2023, all new submissions must occur under the EU CTR.



Picture 1: Clinical Trials Information System (CTIS) submission during transition periods: CTIS submission optional for trials until 31 January 2023, from then until 31 January 2025 CTIS mandatory for new submissions; from 31 January 2025 CTIS mandatory for all clinical trials, both new and ongoing.

From 31 January 2025 all ongoing clinical trials must have been transferred to the EU CTR. In case the clinical trial does not comply with the EU CTR (e.g. harmonised study documents across members states such as the protocol, the IB and the IMPD), the sponsor must first request a substantial amendment under the CTD specifying the intention to align the trial to the EU CTR. Article 5 of the EU CTR outlines that the sponsor shall submit an initial application dossier through CTIS. In principle, this must rely on the dossier already assessed by the member states.

The application will consist of a new cover letter, the application form completed in CTIS, (harmonised/consolidated) protocol, and the latest approved versions of part I and II documents. Before a clinical trial can be transferred to the EU CTR, all substantial amendments under the CTD must have been approved.

Part I and Part II

Analogous to the former EudraCT Number each clinical trial is identified via a unique number, the so-called EU CT number. The EU CT number is generated when the trial is set-up in CTIS. The submission dossier is divided in two parts:

- Part I addresses the scientific aspects of the clinical trial
- Part II covers the ethical aspects.

Part I and Part II are submitted simultaneously or sequentially.

In Part I, harmonised application documents (study protocol, application form, Investigator's brochure, GMP documentation, IMPD and IMP labels) valid for all participating member states are provided for evaluation. All member states where the submitted clinical trial takes place evaluate these documents. One consolidated assessment on Part I is communicated to the sponsor which is valid for all concerned member states. For multinational studies, the main language should be English except for a some items where local language requirements apply (e.g. labels, trial objectives and study title translations).

Part II needs to be completed for each participating country separately. Each member state assesses for its own territory the ethical aspects of the trial. A national or appointed EC in each country prepares the assessment on Part II. The involvement of local ECs is not foreseen in the assessment process but national ECs might consult those.

Part II includes the following information:

- Subject information
- Informed consent
- Insurance
- Financials with the investigator and clinical trial sites
- Suitability of the investigator and clinical trial sites
- Recruitment arrangements.

If required details are not covered by the protocol, these may be outlined in a separate document. The EMA provides several helpful templates on its webpage.

Based on the assessment of Part I and Part II a single decision per member state will be communicated. If a national EC refuses the trial, the national authority is bound to the decision of the EC and the trial cannot take place in the respective member state. Regulators will issue only one fee notification per country covering the charges of the authority and the EC

Transparency

New transparency rules aim to increase information sharing and to achieve greater public awareness of clinical trials. The EU CTR requests that all clinical trial related information generated during the full life cycle must be published (see whereas 67, Art. 81). Generally, all data and documents in the system will be disclosed on the public portal of CTIS (e.g. protocol, assessment and decision on trial conduct, summary of trial results including a lay summary, study reports for those trials in the system subsequently included in a marketing authorisation submission in the EU, inspections, etc.). Exceptions include personal data, commercially confidential information (e.g. with regard to the marketing authorisation status of the medicinal product), confidential communication between member states concerning the preparation of the assessment report and information ensuring effective supervision of the conduct of a clinical trial by member states.

Regarding the timeline, Article 81 requires that trial-related content is published upon trial decision. A deferral mechanism in CTIS offers the sponsor the possibility to delay the publication of clinical trial information with the objective to protect commercially confidential information. The documents and duration of deferred publishing varies with the clinical trials category which is defined in "Appendix, on disclosure rules, to the "Functional specifications for the EU portal and EU database to be audited - EMA/42176/2014". The sponsor needs to apply for the deferral during initial submission. The application is subject of the member states assessment. Importantly, the specific timing of publication must be provided in the initial submission as it can't be amended at a later stage.

Sponsors have two options to protect sensitive information:

- They can make use of the deferral option in CTIS to delay publication of trial documents (depending on trial category and document type up to a maximum of 7 years after end of trial) and/or
- Redact trial documents to protect personal data and commercially confidential information beyond the period of deferral.

Recently, EMA published a draft guidance document on how to address the protection of personal data and commercially confidential information in documents uploaded and published in CTIS. While EMA expects redactions of trial documents with regard to personal data (e.g. signatures, names/contacts, etc) which are not mandated by EU CTR, it requires a critical assessment of redactions of commercially confidential information.

Therefore, with the EU CTR in place, sponsors will need to consider transparency from early on.

Lay summary

In order to increase transparency for trial participants and the public, Article 37 requires sponsors to provide a Lay Summary. Lay summaries explain clinical trial results in plain language and intend to enable lay persons to understand complex medical information. Annex V of the regulation defines 10 essential items that lay summaries must cover:

1. Clinical trial identification (including title of the trial, protocol number, EU CT number, and other identifiers);
2. Name and contact details of the sponsor;
3. General information about the clinical trial (including where and when the trial was conducted, the main objectives of the trial, and an explanation of the reasons for conducting the trial);
4. Population of subjects (including information on the number of subjects included in the trial in the Member State concerned, in the Union, and in third countries; age group breakdown and gender breakdown; inclusion and exclusion criteria);
5. Investigational medicinal products used;
6. Description of adverse reactions and their frequency;
7. Overall results of the clinical trial;
8. Comments on the outcome of the clinical trial;
9. Indication if follow-up clinical trials are foreseen;
10. Indication where additional information can be found.

The EU CTR guidance recommends the use of literacy proficiency level of 2–3 on the International Adult Literacy Survey Scale. The visualization of content, e.g. the use of infographics for better understanding is advised. For the paediatric audience sponsors can consider a graphical presentation in the form of an illustration or even a cartoon. If the trial has been conducted in several countries, a translation of the lay summary in all local languages is required. The content must be strictly non-promotional in all aspects, e.g. presentation of results must be objective and non-selective; use of substance names is preferred over tradenames.

Sponsors are highly encouraged to involve laypersons, in particular patients or patient organisations, early on in the development and the review process. Additional dissemination measures include sharing on a website, direct mailing to trial participants through third parties or through the investigative site.

More details can be found here

Safety

The following comparison outlines how the EU CTR adopts current best practices as well as streamlines safety reporting requirements and processes:

Directive 2001/20/EC, Art 16	EU CTR 536/2014
The investigator shall immediately report all Serious Adverse Events (SAEs) to the sponsor, except for events that do not require immediate reporting by the protocol or investigator information.	The investigator shall record and document all adverse events, unless the protocol provides differently. The investigator shall report serious adverse events to the sponsor **without undue delay but not later than within 24 hours of obtaining knowledge of the events**, unless, for certain SAEs, the protocol provides that no immediate reporting is required." (Art. 41)
The sponsor shall ensure that all relevant information about SUSARs are reported to the competent authorities in all the Member States concerned and to the ECs (Art. 17).	The sponsor shall report information about **SUSARs electronically only via EudraVigilance** (Art. 42). No direct reporting to National Competent Authorities and other regulatory bodies. National Competent Authorities will access SUSARs directly through EudraVigilance. No direct submission of SUSARs to the ECs (ECs shall be involved in the assessment if it has been provided for in the law of the Member state concerned).
Timelines for SUSAR reporting:	✓ fatal or life-threatening: within 7 days ✓ other: within 15 days
ASR: Once a year throughout the clinical trial, the sponsor shall provide the Member States in whose territory the clinical trial is being conducted and the EC with a listing of all suspected serious adverse reactions which have occurred over this period and a report of the subjects'safety (Art. 17)	ASR: The sponsor shall **submit annually to the Agency a report on the safety of each investigational medicinal product** used in a clinical trial for which it is the sponsor (Art. 43). (ECs shall be involved in the assessment if provided for in the law of the Member state concerned) ASR in CTIS is required with the first trial for a substance under the CTR. All member states concerned for ongoing clinical trials must be named.

Additional reporting requirements

New notifications inform the member state of relevant events during the clinical trial and aim to facilitate its oversight. General notifications on the start of a clinical trial and the end of the recruitment must occur within 15 days. For each member state the information must be submitted separately (Article 36).

With regard to patient safety, the EU CTR introduces additional reporting obligations. Sponsors must report serious breaches within seven days after becoming aware of the breach. Serious breaches are defined as either significantly affecting the

- safety and rights of a subject, or
- reliability and robustness of the data (Article 52).

More information can be found in 'The Guideline for the notification of serious breaches of Regulation (EU) No 536/2014 or the clinical trial protocol' (Dec 2021) that outlines practical aspects of serious breach notification.

Urgent safety measures to protect subjects may be taken (sponsor/investigator) if an unexpected event is likely to have a serious impact on the benefit-risk ratio. Sponsors must inform about such safety measures without undue delay but latest within seven days (Article 54). The occurrence of unexpected events that impact the benefit-risk ratio and do not qualify as SUSAR must be reported within 15 days after becoming aware (Article 53).

Inspection reports will be available in CTIS and sponsors are required to upload all inspection reports issued by third country authorities. Eventually translations will be required (Article 53).

The EU CTR shortens the timeline for End of trial notification from previously 90 days to 15 days. Also temporary halt notification must occur within 15 days. If the reason for the temporary halt is not affecting the benefit-risk balance, the restart of the clinical trial must be notified within 15 days. If the temporary halt is due to reasons affecting subject safety, a Substantial Modification must be submitted before the trial can be restarted. In case the trial remains discontinued within two years sponsors must provide an End of trial notification. Early termination of a trial must be reported as well and include reasons and follow-up measures for participants (Article 37).

Trial results summary (including Lay summary) should be published within one year after trial completion. For paediatric trials this is reduced to 6 months. In case the protocol defines intermediate data analyses before the End of trial, a summary of this analysis must be submitted via CTIS within one year. Sponsors are obliged to submit the Clinical Study Report within 30 days after completion of the marketing authorization approval process or withdrawal of application (Article 37).

Conclusion

The EU CTR promises harmonised and centralised submission procedures as well as reliable timelines for trials submitted in the EEA. Through CTIS, clinical trial sponsors can apply for a clinical trial in up to 30 EU/EEA countries with one single application. This application covers submissions to national competent authorities, ECs and public registration of the clinical trial. This is a great chance for sponsors to shorten the approval process and start clinical trials earlier.

Furthermore, the EU CTR extends the scope of clinical trials more towards risk-based measures (e.g. low-interventional trials) and transparency (e.g. publication of trial documents, lay summaries). Those aspects will pull through all activities of a clinical trial from planning until analysis and reporting. Consequently, patient safety and protection may be improved.

In order to accomplish positive effects through the EU CTR, all involved parties may need to overcome potential challenges. Next to initial operational bottlenecks when undergoing new processes, sponsors may struggle with ambitious deadlines set for the submission process within the EU CTR. So far, 14 out of in total 92 submissions through CTIS required a re-submission due to missed deadlines (status June 2022). In six studies, the validation deadlines were not met and in 8 studies the sponsor withdraw the submission due to missed deadlines in addressing outstanding questions. Therefore, thorough planning from early on will be essential to avoid trial withdrawals. It is recommended to consider the following aspects during trial set-up and in early trial phase:

- Start **risk evaluation and risk management process** during protocol development.
- **Reassess trial document templates for completeness.** Make sure that **only required personal data** (e.g. contact details) are included to avoid document redaction. Ensure that **site contracts** align with EU CTR (e.g. TMF archiving, serious breach reporting etc.).
- Be clear about **deferral documents**, define for which documentation a version **"for publication"** and **"not for publication"** will be provided. Carefully weight redactions to protect CCI against the principles of transparency.
- Thoroughly **set up processes** to **adhere to reporting obligations**.
- Request all trial sites to register in **OMS and keep track of them during feasibility or Pre-study visits**.
- **Appoint a submission coordinator** and agree on a **submission strategy** (e.g. Part I followed by Part II, submit all countries or in batches, which countries to submit together etc.).
- Plan **resources for lay summary creation**.
- **Train personnel to operate CTIS**.
- Clarify on **permissions of administrative and business roles in CTIS**.

Bibliography

Low-intervention clinical trial, Sponsor definition, co-sponsorship and legal representative	CTR 536/2014, Chapter I, XI and XII
Risk-based quality management	CTR 536/2014, Chapter VIII, Article 47, 48 ICH GCP E6 (R2), ICH E 8 (R1) on general considerations for clinical studies EMA recommendation paper: Risk proportionate approaches in clinical trials, Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use
Submission, CTIS	CTR 536/2014, Chapter II to IV and XIV, annex I and II EMA webpage
Transparency	CTR 536/2014, Chapter XIV (Article 81) Appendix, on disclosure rules, to the "Functional specifications for the EU portal and EU database to be audited - EMA/42176/2014" [DRAFT] Guidance document on how to approach the protection of personal data and commercially confidential information in documents uploaded and published in CTIS published on 7 April 2022; EMA/212507/2021
Lay Summary	CTR 536/2014, Chapter VI (Article 39), annex V
Safety	CTR 536/2014, Chapter VII
Additional reporting requirements	CTR 536/2014, Chapter VI (Article 36-39) and VIII (Article 52-54), Chapter XIII (Article 78) and annex IV

Abbreviations

ASR	Annual Safety Report
CCI	Commercial Confidential Information
CTD	Clinical Trials Directive
CTIS	Clinical Trials Information System
CTR	Clinical Trials Regulation
EEA	European Economic Area
EMA	European Medicines Agency
EC	Ethics Committee
EU	European Union
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigator's Brochure
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
OMS	Organisation Management Services
SAE	Serious Adverse Event
SDV	Source Data Verification
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master Files

About GKM

GKM Gesellschaft für Therapieforschung is a privately owned full-service Contract Research Organisation for planning and conducting clinical trials phase II-IV as well as for non-interventional studies. GKM also provides services for early benefit analyses (AMNOG), vigilance, and medical writing.

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