EU CTR/CTIS: Adoption and Early Experience
Questions and Answers from the Ask the Experts session

The EU Clinical Trials Regulation no. 536/2014 became effective on 31 January 2022 and the first approved trials are now showing up in CTIS. Nevertheless, planning for a successful submission and knowing what to expect from the new system can be a challenge.

Our Experts

- **Ruxandra Popescu, PharmD.** is a Certified EMA CTIS Sponsor Master Trainer, qualified to disseminate the knowledge on the submission of clinical trials in EEA under the Reg. (EU&) no. 536/2014. She ensures clients' readiness for EU-CTR implementation and provides regulatory oversight of the clinical trial process particularly the submission strategy for multinational studies.
- **Lucy Palatin, MA** has 10+ years of experience in setting up and managing clinical safety and pharmacovigilance systems. This includes the preparation of Safety Management Plans (SMPs), the management of Individual Case Safety Reports (ICSRs), EudraVigilance registration (company and product).

Question: When should you transition your ongoing trial to the EU CTR?

VCLS Answer: If your clinical trial started under the Clinical Trial Directive (CTD) and is expected to be ongoing after 31 Jan 2025, it is mandatory to transition it to the CTR before this date. There is a common misconception that you can perform such a transition only from 31 Jan 2023, but this is possible since the entry into application of the CTR.

Even if your trial may not be ongoing after 31 Jan 2025, you will still have to transition it in case you wish to conduct it in additional EU/EEA countries after 31 Jan 2023, because initial CTAs under the Directive will not be possible anymore after this date.

Furthermore, if none of these obligations apply to your trial, you may still transition your trial to benefit from a single submission and coordinated assessment of substantial modifications or ASRs.

However, there are many aspects to consider before you decide if you should transition or not and what is the right moment to do so, and this strategy should be tailored to your trial and specific needs.

Question: **Can one switch from the trial-centric approach to the organization-centric approach?**

VCLS Answer: The choice of the user management approach is not explicit but is dictated by the Sponsor High-Level Administrator being registered or not.

If your company has not yet registered a Sponsor High-Level Administrator, any user can create a clinical trial on your behalf in CTIS. If this happens, the trial-centric approach will be in place for your company, and you will not be able to re-group and control all the users working on your trials under the same umbrella. That is, you will not be able to switch to the organization-centric approach.

If you wish to have full oversight on your trials and users, the organization-centric approach is recommended, especially if you expect a higher number of clinical trials conducted in the EU as a clinical trials sponsor.

Question: How and to whom should sponsors submit safety reports under the EU CTR?

VCLS Answer: One of the aims of the EU CTR as far as safety reporting is concerned, is to simplify and streamline safety reporting via a single submission and a harmonized assessment. In practice, this means that for clinical trials approved under the EU CTR, SUSARs are submitted via EudraVigilance to EVCTM only, and annual safety reports (ASR) are submitted via CTIS, with no additional submissions to competent authorities or ethics committees required.

During the transition phase, safety reports should be submitted according to the legal framework under which the trial is approved. So, if your trial is approved under the Directive, the reporting rules under the Directive apply (for example, submissions to ethics committees still apply). For trials approved under the EU CTR, sponsors shall apply the single submission rule. If you have several trials, some under the Directive and some under the Regulation, you need to apply the reporting rules applicable to each trial concerned. However, duplicate reporting should be avoided. For example, if an ASR is submitted via CTIS because there is a trial ongoing under the EU CTR, the sponsor would not need to submit the same ASR again to a competent authority who has another trial approved under the Directive for the same product.

Question: Who can submit the ASR (Annual Safety Report)?

Answer: In CTIS there is a specific role for the ASR submission in the CTIS. There is a specific ASR submitter role and any user or any person who wants to submit an ASR will have to have this role in the CTIS.

We know that the Clinical Trial Administrator role is a super user and can do many things in the CTIS, but this super-user does not have the right permissions to be able to submit the ASR. The CT Administrator would need to be able to assign the ASR Submitter role to themselves to be able to submit ASRs.

Questions: How can we check if our organization is already registered?

Answer: There are two possibilities here. In case this question refers to the Sponsor High Level Administrator for this Sponsor High Level Administrator to be registered in IAM, an active request needs to be submitted with an assignment letter. So, you as sponsor would need to know if any of your users have submitted such a request supported by a relevant appointment letter.

The second option is referring to the registration of the sponsor in the organization management system (OMS). For this you would need to go to the OMS website and search in the organizations database to see if your organization is registered. If not, you would need to submit a request to register it.

Question: Do we need to adjust our Investigator Brochure now because it will be posted and made available to the public?

VCLS Answer: If the Investigator's Brochure for a new clinical trial has been prepared already, sponsors have the option to redact the Commercially Confidential Information (CCI) and Protected Personal Data (PPD) before submitting this document via CTIS. Also, depending on the trial category, there are some options to request a deferral on the publication of this document. The PPD should in any case be redacted, but if the CCI will not be considered commercially confidential anymore at the time of the publication (e.g., in 5 years' time), the deferral may be sufficient to satisfy this need of confidentiality.

If the IB is still to be prepared, sponsors can reconsider their procedures so that the amount of PPD and CCI included in the IB is minimized, to avoid the need for redaction/deferral.

Question: If you are in the process of transitioning one of the studies to the CTR, but at the same time you have a DSUR that needs to be submitted, how should this be approached? Submit the DSUR (Development Safety Update Report) by the Directive in the old way? Will there be any implication on your ongoing transition application?

Answer: The DSUR will only be able to be submitted in the CTIS once the trial is approved. If the trial is not yet approved the DSUR submission would need to be done under the rules of the Directive. This DSUR submission would not have any implication on the application that is ongoing as it is reviewed separately to the CTA so this should not have any impact on that.

The possibility to notify ASR is open for a specific trial only after a decision in CTIS, so this cannot be done before for clinical trial applications still under evaluation.

Question: What is the current experience with timelines of evaluation? Are those specified in the regulation fulfilled?

Answer: In terms of current experience, if we go to the CTIS we can see some CTAs that have been approved, so we can see the timelines are shorter than those stipulated by the Clinical Trials Regulation. The approval was quite quick in these cases.

There is a key point to mention regarding the timelines in the regulation, namely these are maximum timelines, so we cannot have delays. For an initial CTA for a product that is not an Advanced Therapy Medicinal Product (ATMP) we cannot have more than approximately 106 days. We are saying “approximately” because if a deadline falls on a weekend, it will be deferred to the next working day, so there might be an additional 2-3 days on each application.

Question: As a Swiss based company, which requirements should we expect from the legal representative for trials conducted in Europe (access to our QMS systems? submission in CTIS via our company account or through legal representative? Who will have the responsibility for sponsor oversight?)

VCLS Answer: While the CTD (Clinical Trial Directive) only indicated that for non-EU sponsors a Legal Representative must be established in the EU and the Member States had the possibility to complement this via implementation of the Directive in their national legal framework. The CTR further specifies the responsibilities of the EU Legal Representative: ensuring compliance with the sponsor's obligations as per the CTR, and should be the addressee for all communications with the sponsor under the CTR. The latter provision is interpreted in a way that the EU Legal Representative should be able to address questions on the trial received from Member States.

The means through which the legal representative may choose to ensure compliance with these requirements are however not stipulated in the CTR, and these should be covered in a contract between the sponsor and the EU Legal Representative. The choice of these

means will depend on each provider of EU legal representation services, and they may include review of sponsor's QMS or full visibility on submissions in CTIS.

Of note, Member States may agree to have just a contact point established on their territory, and not necessarily an EU Legal Representative, but they must actively agree to this.

Question: Another question relating to the co-sponsorship: how does this work? Can we split sponsorship between different participating countries, do we need to determine one overall sponsor?

VCLS Answer: As per our interpretation of the CTR, there are two types of sponsor responsibilities: those that can be split with co-sponsors and those that cannot be split. By joint contractual agreement by all the co-sponsors, only one of these sponsors may take each of the following roles:

- Compliance with the sponsor's obligations in the authorisation procedure (including SM or Add MSC) - interactions in CTIS. Just one of the co-sponsors should be responsible for this.
- Contact point for questions
- Implementing corrective measures imposed by MSCs.

For the other sponsor responsibilities, all the co-sponsors will be jointly responsible unless the contract between them stipulates otherwise.

In conclusion, it is not necessary to determine one overall sponsor, and the splitting of responsibilities per country must be carefully considered, considering the restrictions mentioned before. In CTIS we cannot have one sponsor responsible for one country and another sponsor responsible for another country because there is a coordinated assessment, and it would be difficult to separate.

Question: When submitting a new trial, can we cross-refer to core documents IB, IMPD, already submitted in other trials and in a way link them, similar question for subsequent amendment of such documents concerning several trials, do they need to be submitted separately to all trials?

Answer: To be able to associate clinical trials (mother-daughter trials), there are some restrictions, for example to have the same list of Member States Concerned and mainly the same core documents.

However, we can indeed cross-refer to core documents. For example, for the IMPD there is such a possibility in case we have a third party providing the IMP and IMPD and the main

sponsor should not have access to the IMPD. In this case, the recommendation would be to submit a letter cross-referring the IMPD if it has already been submitted for a different trial.

Also, to submit a single substantial modification on the same core document for several trials, we would need to choose the option “Multi-Trial Substantial Modification” and specify the concerned trials in the cover letter.

More implications of this are described in the Q&A on the Clinical Trials Regulation available in Eudralex Volume 10.

Question: How does the coordinated safety assessment work in practice?

Answer: The EU CTR provides for a single submission of safety reports and a coordinated safety assessment between member states. Sponsors will submit SUSARs and Annual Safety Reports to the EMA, and the EMA will forward the safety information to the member states concerned and they will cooperate in the assessment. Ethics committees can be involved in the assessment, and this is something that is decided on a national level, depending on the country. Each active substance will be designated a Safety assessing Member State (SaMS). The SaMS is responsible for coordinating the safety assessment for that active substance. In practice this is done via screening of EudraVigilance for SUSARs. The SaMS should screen EudraVigilance on a regular basis and if necessary, can request any additional information from sponsors. In addition, following the ASR (Annual Safety Report) submission, the SaMS will compile the feedback from the different member states concerned. If there any requests for information to the sponsor, they will review and coordinate the responses once received, then issue a final assessment on the ASR. During their review of SUSARs in EudraVigilance, or ASRs, if any safety concerns arise, the SaMS can make recommendations to the Reporting Member State and the concerned member states for the trials concerned, which will enable them to take any action as needed. For example, if a safety issue was identified, they may request Reporting Member States to put a trial on hold or request action from the sponsor.