2024

Whitepaper

Navigating the Landscape of Clinical Trial Applications under the EU Clinical Trials Regulation: Insights and Challenges

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Introduction

With less than 1 year remaining until all clinical trials conducted in the EU are required be compliant with the Clinical Trials Regulation, our DLRC EU CTR Whitepaper explores what we consider are the 6 topics to flag as ‘important’ or ‘potential challenges’ when submitting a clinical trial under the CTR regulatory framework.

DLRC consultants have supported clients with their readiness for the regulation and have partnered with clients for the execution of successful CTA authorisations.

Summary and Challenges of the Overall CTA Assessment Process under CTR

One of the key goals of the European Union Clinical Trials Regulation 536/2014 (EU CTR) is to harmonise the way clinical trials are assessed and conducted across all EU Member States (MS) to increase the efficiency of conducting a multi-national trial within Europe. It is hoped this will also improve the communication and collaboration between Member States which would enhance the status of the EU as an attractive prospect for conducting clinical trials. Harmonisation is therefore a recurring theme throughout the clinical trial application (CTA) process in terms of dossier content and the assessment process.

One of the most significant changes since the EU CTR came into effect in January 2022 is the use of a single electronic portal, the Clinical Trials Information System (CTIS), for the submission, evaluation, and authorisation of a clinical trial, and communication between the Sponsor and Member States Concerned (MSC).

The Sponsor inputs all the information and documentation required for a CTA into CTIS, and when the application is submitted all of this information is transferred to the MSC.

However, while much of this is applicable to, and standardised across, all MSCs, there are by necessity some components that are still country specific and together these comprise Part I and Part II of the application respectively.

Part I is the core scientific data dossier. This is standardised across all MSCs, including the use of CTR compliant templates and language for some items such as the protocol and Q-IMPD. The Part I assessment is coordinated assessed by the designated reporting member state (RMS) before the contribution of the other MSCs.

Part II components are local documents that would have traditionally been submitted for approval to Ethics Committees under the Clinical Trial Directive (CTD). Each local Part II dossier is, quite appropriately, assessed by each respective MSC. In addition, a CTA will not pass validation unless all MSCs are satisfied with the content of Part I and their respective Part II dossier, requiring a high standard across both Part I and all "local" Part II dossiers to proceed to the assessment stage.

One of the most ambitious aims of CTR is to standardise the assessment of CTAs and therefore harmonise the timelines involved from submission (day 0), through validation, assessment, requests for further information (RFIs), and eventually a decision by day 106 at the latest for non-ATMP products where Part I and Part II are submitted in parallel. After submission of the CTA via CTIS with a suggested RMS, the RMS will either be confirmed or re-allocated from amongst the MSCs by day 6, followed by validation to assess application completeness, with validation queries possible at this point.

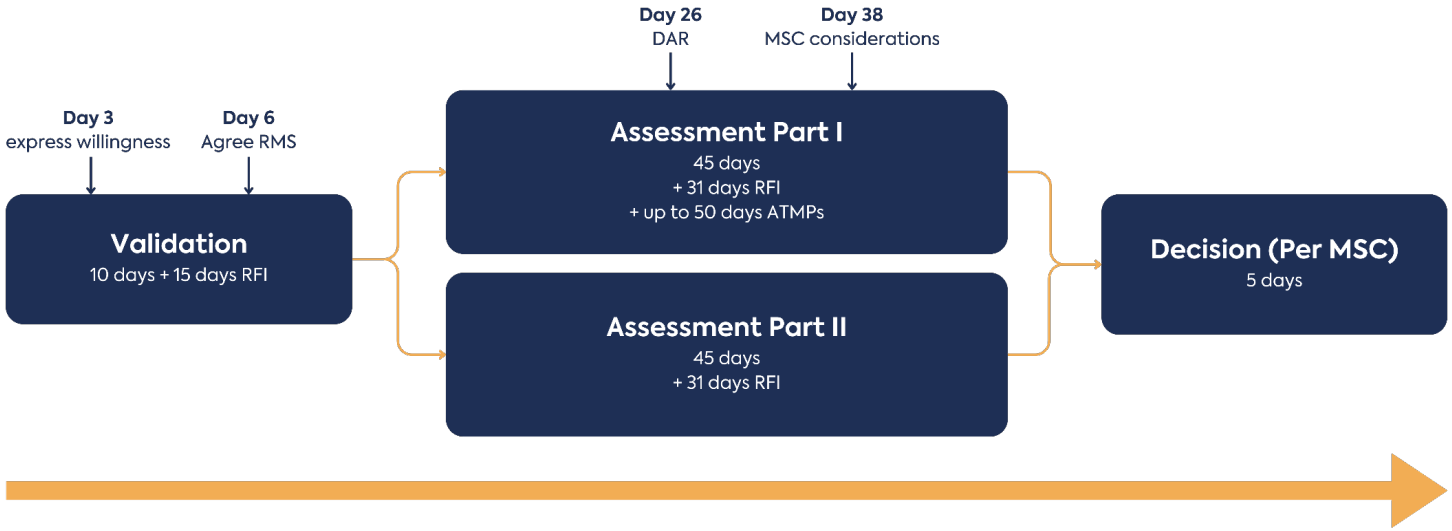
	Part I	Part II
Content:	Core scientific data dossier	Country specific documents
Assessment Report:	RMS issues a single conclusion	Each MSC issues a decision separately
Components:	Application form (CTIS)	Informed Consent and Recruitment Arrangements including copies of recruitment materials
	Cover Letter	Subject information and informed consent forms
	Protocol	Suitability of investigators
	IB	Suitability of sites
	GMP documentation	Proof of insurance or indemnification
	IMPD for Safety and Efficacy (S&E IMPD)	Financial and other arrangements
	Quality IMPD (Q-IMPD)	Compliance with national requirements on data protection
	Placebo IMPD	Compliance with use of Biological Samples
	Auxiliary Medicinal Product Dossier	
	Scientific advice	
	EU Paediatric Investigation Plan (PIP) decision	
	Labelling for each IMP	
	Patient-facing materials which are linked to the endpoints of the trial	
	Proof of fee payment	

Table 1: Part I and Part II dossier comparisons

Validation should be completed, or validation RFI queries sent, within 10 days of submission. Validation queries will add 15 days to this process, with a relatively short 10 calendar days to respond to questions. Assessment of Part I and Part II takes place in parallel, starting one day after the submission dossier is deemed valid.

For Part I, the RMS will circulate to the MSCs their draft assessment report which the MSCs then review. Within this time, there is the option for the RMS to issue consolidated RFIs to the clinical trial Sponsor which take into account comments from all MSCs, and this can add 31 days to the assessment phase with 12 of those days for the Sponsor to provide their responses. While it is possible to submit responses earlier than the deadline, reducing the time delay for that round of RFIs, it is not permitted for Sponsors to exceed the deadline for responses as the application will be considered lapsed if this occurs. At this point, the Sponsor would have to re-submit which would start the process again from the beginning, including re-payment of fees.

Initial Application Approval Timelines



The final conclusion on Part I is sent to the Sponsor by the RMS, which will be within 45 days of validation unless RFIs are issued.

Part II assessment is carried out by each MSC independently. As with Part I, an assessment report will be provided within 45 days of validation, with RFIs adding 31 days to the process. It is possible to defer the submission of the Part II dossier, but this must be submitted within 2 years of the prior Part I conclusion or the application for that MSC will lapse, and the Sponsor will need to start from the beginning. In the case of a Part I-only CTA under CTR (as per Article 11), despite Part II not being submitted and assessed in parallel, the Part I assessment follows the same timelines as previously described.

The complexities within this process for the Sponsor lie in the relatively short windows of time to turn around RFI responses. With only 10 calendar days for response to validation RFIs and 12 calendar days for assessment RFIs for Part I and/or Part II, and with this time also including weekends and public holidays, the deadlines are tight, especially when also considering the likely need for Part II document translations. This also does not allow the Sponsor much time to contact the RMS for Part I, or the MSCs for Part II, for RFIs where clarifications are needed, or where responding to the RFI may be particularly challenging. This has the potential to lead to a negative conclusion for Part I or Part II and may require a CTA resubmission to rectify the issue and gain approval, delaying the overall start of the clinical trial.

Another challenge faced by Sponsors is that while Part I RFIs from all MSCs are coordinated and sent to the Sponsor at the same time, RFIs from each individual MSC for Part II can be sent to the Sponsor at any time during the assessment period in line with the timelines set out by the CTR. It can therefore be challenging for Sponsors to be able to predict when these questions may come from each MSC and to manage workload.

Sponsors also need to carefully consider how to deal with RFIs which impact other parts of the dossier (e.g. Part I RFIs impacting Part II documents, or Part II RFI from one MSC impacting a document which should be harmonised across all MSCs), where the separate RFIs are issued with no overlap of response timeframe. In other words, for example, there could be a scenario where responses to Part II RFIs have been submitted, then Part I RFIs are received which impact Part II documents and technically, as per the regulation, there is no option to further revise the Part II documents.

Other points to note are that DLRC has also encountered Part II RFIs being raised in the national language, requiring further translation, and multiple questions being grouped together in one official RFI number in CTIS, meaning that the actual number of questions and issues being raised within CTIS is challenging to determine at first.

Data Transparency and Publication

Increased data transparency was one of the main perceived benefits to the CTR, allowing clinical trial information to be readily available on the CTIS public workspace for patients, researchers, and the general public.

To allow confidential and personal information to remain undisclosed, EMA suggested both the redaction of personal data and commercially confidential information from documentation, and deferral of publication of select clinical trial information and documentation. The extent of information made public about a trial was initially listed in the "CTR Appendix on Disclosure Rules", published in October 2015.

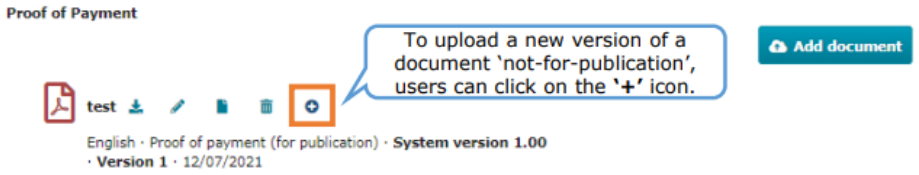
Details about what should be redacted from clinical trial documentation were included in a draft guidance, published April 2022. This was then updated and finalised in July 2023. The guidance underwent public consultation between May and June 2023, and in October 2023 the EMA consequently released the "Revised CTIS Transparency Rules" the implementation of which is planned to be finalised in Q2 2024.

As a whole, the transparency initiative was a significant change compared to the publication of clinical trial information in other registries such as the Clinical Trial Registry (under the CTD), clinicaltrial.gov, and ISRCTN. Far more patient-facing documentation is made publicly available, along with more information about the investigational product. With this change, there are inevitably more complexities for the clinical trial Sponsors to navigate.

The implementation of deferrals for when certain documents would be made public was a seemingly small yet crucial addition to the clinical trial application within CTIS. This was made slightly more complex as different types of information can be deferred for different amounts of time. If this is missed from an application, all clinical trial information will be made publicly available at the time of decision on the application. In addition, clinical trials are grouped into categories, largely based on trial phase, which determine the maximum deferral that can be set for each type of information, with category 1 trials having the longest deferrals, and category 3 the shortest.

There were also challenges in interpretation of the guidance for our clients to understand what could be considered as commercially confidential, as there is the added pressure of threat of additional requests to amend redacted documents within a tight deadline if not completed correctly. Moreover, because RFI responses are being made publicly available, any responses or updates to documents must be redacted or reworded to not include confidential information within the short response deadline for RFIs.

CTIS has many technical intricacies which are, at first glance, not very intuitive. An example includes uploading redacted and unredacted documents for the Health Authority assessment. There are "for publication" and "not for publication" document placeholders. However, these placeholders can be quite difficult to find as you need to upload the "For publication" documents first, then click a very small "add" button, which will allow for an additional "Not for publication" placeholder to be created.



(https:/www.ema.europa.eu/system/files/documents/other/cttm10_sbs_guide_en.pdf)

As previously mentioned, the technical implementation of the revised CTIS Transparency Rules is expected to be finalised in Q2 2024, and this will bring a large shift in the availability of trial information within the CTIS public workspace which Sponsors will now need to digest. The revision aims to make the publication of clinical trial information less complicated for both Sponsors and EMA CTIS administrators by taking out the optional elements of deferrals and instead having standardised publication dates for different clinical trial data, depending on the category of the trial.

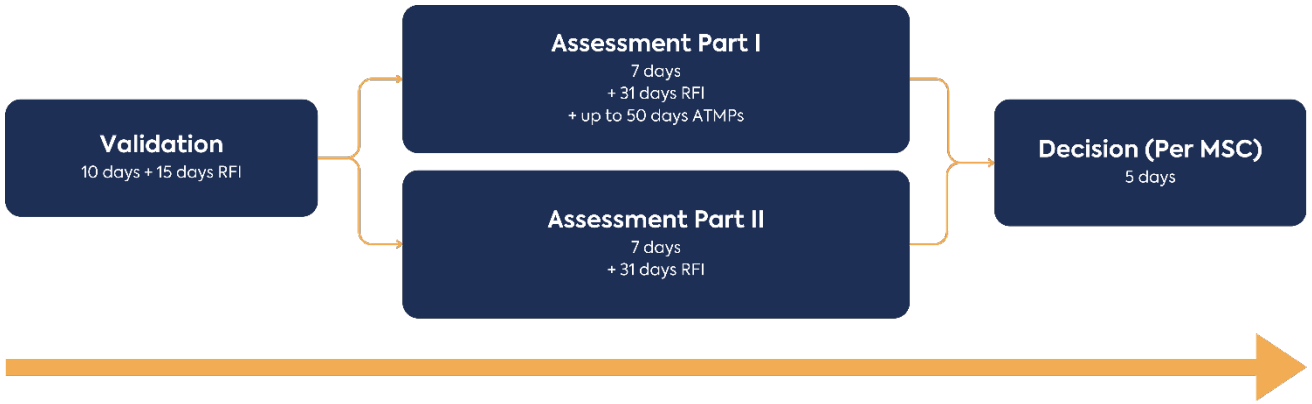
In addition, there is a significant decrease in the amount of information made publicly available, including both documentation and metadata. Despite full implementation of the rules in Q2 2024, Sponsors are able to already follow the revised transparency rule for initial applications. This involves providing a filler template in the "for publication" placeholder within CTIS, and the trial documentation within the "not for publication" placeholder for the applicable documentation. See our latest blog covering these new transparency rules in more detail.

Transition of a Clinical Trial from the CTD to the CTR

In the first year of the CTR going live in January 2022 to January 2023, Sponsors had a choice of whether to submit new clinical trial applications under the CTR or CTD. It was recommended to submit under the CTR if trials were expected to finish later than January 2025, to avoid the need for a transition procedure later. In addition, if Sponsors already had on-going clinical trials conducted under the CTD that would be running later than January 2025, it was encouraged to transition those trials from the Clinical Trial Directive to the regulation as soon as possible.

From January 2023, all new clinical trial applications had to be submitted under the CTR. This meant that any ongoing study under the CTD that wished to include a new country in the EU needed to transition to the CTR before being able to submit an application to add this country as an additional member state, which added some complexity for Sponsors.

Expedited Initial Application Approval Timelines



By January 31st 2025, all ongoing clinical trials in the EU will have to have completed transition from the CTD to the CTR. Now, transitioning trials can go through an expedited procedure where an 'initial' clinical trial application can take only 22 days to be approved. This is divided into 10 days for the validation phase, 7 days for the assessment phase, and 5 days for a decision. This is, however, as long as no RFIs are needed, which could add up to another 15 days for validation RFIs, and 31 days for Part I/II assessment RFIs.

Additionally, the expedited assessment of Part II is a soft deadline per member state, so each member state can add additional days for decision if required. The expedited assessment of transition trials has been announced to be open until 16th October 2024, which we have interpreted as the last day to submit transition trials to avoid the risk of missing the 31st January deadline.

To be eligible for the expedited review, transitioning trials documentation should be identical to the most recently authorised information by a national competent authority and an ethics committee under the CTD. The only exception to this rule is for the consolidated documents mentioned below.

For mono-national clinical trials, the approved information to be submitted includes:

- Protocol
- Investigator's brochure (IB)
- Good manufacturing practice documents
- Investigational medicinal product dossier (IMPD), and documents relating to any non-investigational medicinal products
- The subjects' informed consent form
- Subject information sheet

New information to be submitted includes:

- A new cover letter
- GDPR statement
- CTIS structured data

For multi-national trials, the same documents should be submitted, but Part I documents (apart from the protocol, IB and IMPD) need to be harmonised throughout the member states. The protocol, IB, and IMPD can either be consolidated or harmonised across member states, with the consolidated documents having separate annexes for specific member state requirements.

All other compulsory trial documentation in CTIS can have a placeholder document saying that the application was assessed with a positive opinion under the CTD until the first substantial modification under the CTR. All Sponsors submitting transitioning trials will need to redact any personal data or commercially confidential information from the documents that are being made public.

The first substantial modification of a transition trial should replace any placeholder documentation with the respective trial information, and this will be assessed at the same time as the substantial modification. The first substantial modification will also need to be submitted before any additional MSCs can be added to the trial, as the new national competent authority will need the full Part I dossier, and their MS's Part II information to assess the application fully.

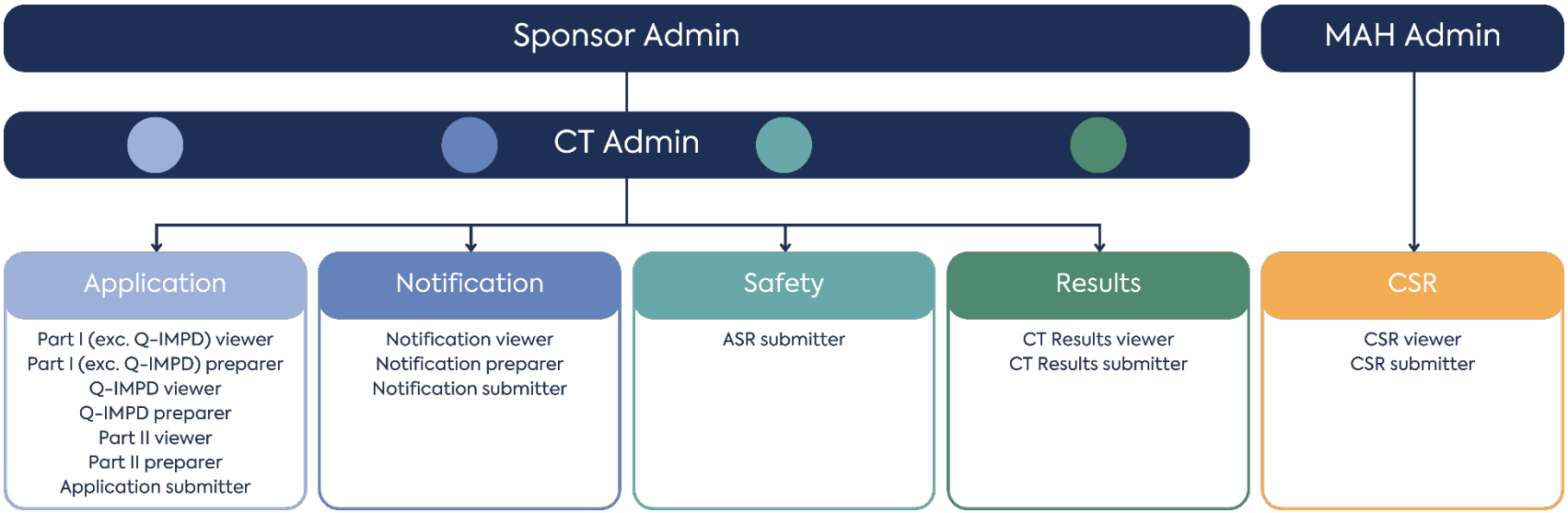
The expedited assessment for the transition to CTR can make the process a lot quicker for Sponsors, but it means that Sponsors may face additional work to prepare for the first substantial modification and could delay the addition of any new MSC.

As of the end of December 2023, 625 transitioning trials have been submitted within CTIS of an estimated 5,000 that should be transitioned. With under a year left to transition, it will be a big effort for both Member States and Sponsors to get all ongoing trials compliant.

EU CTR Systems Environment

The CTR introduced the new Clinical Trials Information System (CTIS), providing a single, centralised system for EU CTA submission and maintenance for both Sponsors and EU Member States. The system is role-based, therefore individuals working on an application need to be allocated a role in order to perform a function in the system (e.g. the Application Submitter role allows a user to submit an application). A user can have multiple roles acting on behalf of multiple organisations. Sponsors should therefore consider which roles should be assigned when outsourcing clinical trial procedure activities.

Expedited Initial Application Approval Timelines



As the EMA systems environment has evolved over the years, other EMA systems interface with CTIS; EudraVigilance, xEVMPD, and SPOR. Data held in these systems (IMP/other product information, Sponsor organisations, and trial sites) are used directly in CTIS when the clinical trial application is created and submitted. Without these data available, the Sponsor is unable to submit the application in CTIS, as the data from the other systems are mandatory. Sponsors, especially first-time EU CTA Sponsors, should consider the following questions while planning the application:

1. Are the trial Sponsor, planned EU trial sites, and third parties involved in the trial registered in the Organisation Management Service (OMS)?
2. Are you as the Sponsor registered in EudraVigilance?
3. Is your IMP registered in xEVMPD, and do you have the SUB and PRD codes?

EudraVigilance registration requires completion of various declaration forms, proof of OMS registration, EMA knowledge check certification for xEVMPD and ICSR safety reporting, and an agreed EU Legal Representative (See section below).

If all pre-requisites are in place, registration within these systems should not take longer than a few weeks, but it's important for this not to fall on the critical path of the EU CTA submission so understanding these requirements and planning early is imperative and is an area of strategic planning with which DLRC has significant experience.

EU Legal Representative

If a Sponsor wishes to conduct a clinical trial in the EU without an EU presence, they are required to have an EU Legal Representative (Legal Rep). The details of the EU Legal Rep are provided as part of the initial CTA and are required as part of other EMA system registration (e.g. EudraVigilance). EU Legal Rep as a concept is not new under the CTR as it was required under the Directive, however, the responsibilities of the EU Legal Rep have significantly increased under the Regulation in comparison to the Directive. If transitioning trials need to include the Legal Rep details, these should be included in the first substantial modification.

Rather than just acting as a 'Contact point' in the EU for the Sponsor, the EU Legal Rep under the CTR is additionally responsible for ensuring compliance with the Sponsor's obligations per both the Regulation and Good Clinical Practice (GCP). As such, Legal Reps will necessarily conduct an assessment of the Sponsor prior to agreeing to take on this role because of the increased responsibility/accountability. The Legal Rep should be involved as early as possible in the planning stages of the clinical trial to do their assessments to not hold-up any client timelines for submission.

DLRC Group currently acts as the EU Legal Representative for a number of our non-EU clients to allow them to submit a clinical trial under the CTR. In our experience, the initial risk assessment typically takes 4-6 weeks depending on availability and timeliness of information provided. Areas of particular focus for the assessment are overall organisational set up and procedures to cover CTR requirements. Common shortcomings that we have experienced that may delay these assessments include:

- Lack of clarity about the end-to-end responsibilities of various business partners involved in the planned trial, covering all Sponsor's trial related duties under GCP and CTR.
- Insufficient evidence that Sponsor's or its CRO's standard operating procedures cover all the necessary Sponsor's trial related duties under the GCP and the CTR (data protection, redactions, study milestone notifications, third country inspection result posting, result preparation and posting etc.).
- Not having a finalised list of countries that are planned to be included in the CTA. Legal representatives must be informed of the list of countries planned to be included in the trial, as some EU member states might have additional obligations for the Sponsors and Legal Representatives, which needs to be clarified on a case-by-case basis.

Article 32 Paediatric Requirements

Article 32 of the CTR discusses the clinical trial requirements for minors, which includes standalone paediatric studies as well as adult studies that also include paediatric participants.

Sponsors should note that DLRC has experience of working with clinical trials involving minors that have faced issues with obtaining approval under the CTR, despite the study being part of an approved Paediatric Investigational Plan (PIP) and having had Scientific Advice given nationally or via the Committee for Human Medicinal Products (CHMP) recommending the proposed study. Therefore, it's important that Article 32 is considered carefully before the submission of the study under CTR.

Sponsors should also consider that a minor cannot give full consent to be included in a study and require consent from a legally designated representative. Notwithstanding this, minors should be provided with information on the trial that is adapted to their age and mental maturity. The age at which a person is considered to be a minor may differ between MS and can be taken into consideration for the application of Article 32. Article 32(1) lists all the conditions that have to be met in order to conduct a study which includes minors. While a lot of these conditions are standard, some need further consideration such as the balance between the burden placed on the minor and the expected direct benefit for the minor, or the population represented by the minor. This is an important consideration for placebo-controlled studies which include minors.

Article 32(1) (e) states that the clinical trial should be intended to investigate treatments for a medical condition that only occurs in minors, or that the clinical trial is essential with respect to minors to validate data obtained in clinical trials on persons able to give informed consent or by other research methods. This also has the potential to create a challenging situation for indications where minors are primarily, but not exclusively, diagnosed, or where the expected efficacy of a treatment may be greater in minors than it is in adults due to disease progression.

DLRC has been able to discuss some of these challenges directly with members of the EMA and the Clinical Trial Coordination Group. This, in addition to participation in the EU ACT initiative, means we are able to support our clients with any challenges posed by Article 32. Please contact us if we are able to support your company with paediatric submissions under the CTR.

Conclusion

In conclusion, the CTR has introduced some major changes to how clinical trials in Europe are submitted and assessed. While the new procedures introduce changes which are complex for Sponsors to navigate, DLRC has experienced some additional challenges and has provided points that a Sponsor should consider if they wish to conduct a clinical trial in Europe. This whitepaper has summarised the main topics that we have experience with when submitting clinical trial applications under EU CTR on behalf of our clients and has given some hints and tips for optimal use of CTIS.

In addition, we have included information about the recently updated guidance and Q&As for both data transparency and publication, and transitioning trial requirements. Furthermore, we have included an overview of the different systems that Sponsors need to register with prior to submitting their clinical trial. Also, our insights into the role of a Legal Representative have been outlined. Finally, we explained about the conflicting guidance when including paediatrics within clinical trials, and how this can lead to issues with authorisation.

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