Ensuring Flexibility when Approaching CTIS

When Catalyst Oncology implements the European Union Clinical Trial Regulation (EU CTR) across Sponsor studies the Site Activation Management (SAM) team is often asked what impact certain elements will have on the submission process. We frequently find ourselves responding with "it depends." There is no one-size-fits-all approach to clinical research, and the EU CTR is no exception. As clinical trials become more complex and regulations evolve, Sponsors' goals remain the same: a need for dynamic solutions requiring flexibility and creativity tailor–made to their specific scenarios.

Below are three case studies illustrating several challenges the SAM team has mitigated, the opportunities the team has explored with our Sponsors based on their strategies, and our approaches with EU CTR and the Clinical Trials Information System (CTIS) process. In these examples, we supported Sponsors throughout the process to ensure efficient regulatory approval timelines.

Close Collaboration for Overcoming Hurdles

Sponsors must understand that making changes to the protocol or other clinical trial documents after CTIS submission can create challenges. More important than the changes themselves, how the changes are responded to affects the activation timelines either positively or negatively; therefore, responses and experience are important in understanding the impact of critical decisions that need to be tailored to each project.

Case Study 1. During the part I assessment, the Sponsor received several queries related to the investigational medicinal product dossier (IMPD), investigator's brochure (IB), and protocol resulting in a protocol amendment, and in other requested changes to the documents. Our SAM team instructed the Sponsor on the steps to take to understand the impact of the document changes, including the deadlines to hit the required response timeline and the effects on their strategy. Three days after the timeline was set, the Sponsor released a protocol amendment, updated IB, IMPD, and synopsis to our team. Some of the protocol amendment updates impacted the main informed consent form (ICF) and the country ICFs in Spain, France, and their translations. At this time, the part II assessment for Spain was concluded and closed with an approved country ICF version for Spain linked to the original protocol version submitted in part I.

Following consultation with the Sponsor, the SAM team contacted the Spanish ethics committee and requested re-opening the part II assessment to raise an additional query for the part II assessment in the system for the country ICF for Spain. This allowed Catalyst Oncology to make changes within the CTIS system part II and resubmit a revised country ICF for Spain linked with the new revised protocol version as a result of the queries received in the part I assessment review.

This complex strategy and thinking outside of the box enabled Catalyst Oncology to provide a new main ICF version and country ICF updates (Spain and France) with completed translations within 24 hours along with a submission to the committee's RFI in part II. All other queries in the protocol, IB, and IMPD were addressed in parallel and on time with the new documents during the RFIs in part I.

As illustrated, it is vital to address queries and receive documents within the provided due dates to manage any hurdles. Otherwise, delays or amended documents can impact and derail timings. When such events occur, diligence, flexibility, creative thinking, and attention to the EU CTR guidance helps to mitigate challenges.

Flexibility in Addressing Delays

Case study 2. Formal selection of several sites in Spain occurred only two days ahead of a planned submission date due to a delay in site identification. In this scenario two standard valid options are advisable: first, delay the submission until all site-specific documents for the recent sites selected are collected; or second, submit the application without those sites in the initial application and add them as new sites at a later date. With the latter option, the Sponsor would need to accept a two-month delay in the site activation timeline for those sites.

Instead, the SAM team enabled a different successful approach. We proceeded with the application within the planned timeline and submitted it for all sites. While the application proceeded as planned, the part II package remained incomplete due to the missing site-specific documents for the recent sites selected. Anticipating receiving validation queries for the missing site documents 10 business days after the submission, we worked with the sites' principal investigators (PIs) and collected the required signed documents during the validation assessment timeline. We then answered the validation requests for information with the missing documents on time. Our strong relationship with these sites was critical to the success of this approach.

Our actions resulted in no impact on the submission or approval timelines. It also did not negatively impact the site activation projection plan for the sites in Spain as they were submitted and approved within the initial application.

Approaching Shortened Timelines

Case Study 3. In one of our studies, while collecting the required core regulatory documents for the CTIS submission part I deadline, we had not received all required core regulatory documents from the Sponsor. The SAM team remained flexible with a strategy in place that incorporated multiple supporting resources to review the last-minute documents when received from the Sponsor. We performed a final quality check, revised any necessary inconsistencies, and applied necessary document redactions within 24 hours.

While a new regulation and process can create difficulties for the Sponsor, they do not have to. Flexibility, creativity, risk mitigation, and dependability are all contributing factors for the continual success of the delivery of clinical trial submissions. In summary, here are the actions Catalyst Oncology took to ensure that there were no consequences on the submission timelines:

1. In the first case mentioned above, all queries were answered on time and within 12 days with a new protocol amendment, IB, and ICF in Spain and France with the synopsis translated.

2. In the second case, all sites in Spain were submitted in the initial application without impact on the approval timeline or the site activation plan.

3. In the third case, there were no negative effects on the approval timeline.

Each of these studies illustrate a high-level of expertise and close collaboration between the Sponsor and Catalyst Oncology. Throughout each study, Catalyst communicated with the Sponsor and kept in close contact to ensure any issues were anticipated and resolved quickly.

As previously mentioned, there is no "one-size-fits-all" approach to conducting clinical research. Maintaining thoughtful and simple processes that are built to allow customisation for study-specific needs are critical for the overall success of the EU CTR submission process. At Catalyst Oncology, we split the submission package preparation process into three main steps, and run them in parallel to allow an efficient and streamlined approach:

1. **Pre-preparation –** Catalyst Oncology supports the Sponsor throughout the critical steps with the European Medicines Agency (EMA) account, CTIS access, CTIS permissions assignments, creation of the new trial and getting the EU clinical trial number, and the investigational product (IP) registration in Eudravigilance.

2. **Preparation –** The SAM team prepares the part I and part II submission packages from the collection of the core regulatory submission documents from the Sponsor until the collection of signed site-specific documents from sites are available. The team prepares all country and site-specific documents, including any relevant translations and redactions, and the manual entry of the CTIS application form. During this step, in our experience, it is critical to set up a document delivery tracker to monitor the status of the required submission documents and deadlines per country and site. It is important to start filling out the CTIS application form on an ongoing basis, saving the form as information is added until its final completion, paying attention when uploading documents between the redacted versus non-redacted documents.

3. **Review –** SAM team completes an internal and external quality review process and Sponsor approval before the final application of part I and part II submissions packages. Catalyst Oncology uses quality checklists during the review process. The higher the quality of the documents being prepared, the faster the review process, which helps with meeting any submission target dates. To ensure the quality and the timeline of the submission, it is vital to conduct daily reviews of the submission inclusive of a completion status of the documents, and to closely communicate with the Sponsors on the status of the documents, translations, and redactions.

Catalyst Oncology knows that when it comes to the CTIS process, much rests on us and our expertise. The processes and actions above illustrate flexibility, creativity, and the dependable delivery for clinical trials; however, any solutions connected to CTIS will always depend on the specific needs of the clinical trial with a tailor–made response to achieve ultimate goals and objectives.

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Blaine Maloney, Associate Director, Catalyst Oncology, began his career in oncology, becoming passionate about helping to provide access to cutting-edge compounds in over 60 countries. In 2021, Blaine joined Catalyst Clinical Research to help create and develop global regulatory and site activations teams with the goal of inspiring people to design and deliver better clinical trials. Blaine earned a master's degree in regulatory affairs from Northeastern University.