Streamlining development in the EU:

Strategies for smoother CTA submissions

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Introduction

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With more than 448 million citizens,[1] the European Union (EU) offers immense opportunities to serve patients and conduct life-changing clinical research. For global pharmaceutical sponsors and medical device manufacturers, however, the EU isn't just a critical market — it's also a complex one. Each member state uses a regulatory process governed by country-specific legislation, which requires sponsors to engage with multiple regulatory bodies and ethics committees, submit documentation in different languages, and address differences in standards of care and reimbursement policies among countries.

Since its formation in 1995, the European Medicines Agency (EMA) has been harmonizing the work of national regulatory authorities for the ultimate purpose of making medical products more accessible to the people who need them. To support EMA efforts to streamline approval processes and reduce redundancies, the EU has introduced recent changes that have reshaped the regulatory landscape, including implementation of:

- The EU Clinical Trials Regulation (EU-CTR)
- The first phase of Joint Clinical Assessments
- The EU Medical Device Regulation (EU-MDR)
- The EU In Vitro Diagnostic Regulation (EU-IVDR)
- The upcoming reform of the EU pharmaceutical legislation

These changes are helping ensure the safety and efficacy of medicines and medical devices. We recognize, however, that they have also been a source of frustration for many sponsors, due in part to increased documentation requirements as well as the need to engage with multiple Member States Concerned (MSCs) that have not fully harmonized their processes.

Given the European market's significance, every biopharmaceutical organization needs a strategy to navigate the EU's evolving regulatory landscape.

Understanding Europe's clinical trial landscape: EU-CTR in focus

To illustrate how sponsors can successfully approach this, we look at the implementation of EU-CTR as an example. Perhaps the most widely known of the recent changes, this regulation which came into effect on January 31, 2022, aims to harmonize submission, assessment, and supervision processes for clinical trials across member states. New trial applications submitted after the regulation's effective date were required to comply with all EU-CTR processes. In-progress studies were allowed a transition period and were required to be in full compliance by January 2025.

1 Facts and figures on the European Union, **The European Union, 2025.**

At the center of the regulation is the Clinical Trials Information System (CTIS), the EU's central portal for clinical trial applications (CTAs) and authorizations. The portal provides a single-entry point for submitting clinical trial information and facilitates collaboration among sponsors and MSCs. The EU-CTR also introduced a unified submission process, allowing sponsors to submit one application dossier for all countries, followed by a coordinated assessment procedure. As a result, a country's regulatory authority and national ethics committee issue one joint decision on CTAs.

EU-CTR uses a risk-adapted approach, ensuring that regulatory requirements are proportionate to the potential risk of the trial. This is balanced with strengthened patient protection measures, including enhanced provisions for informed consent and special protections for vulnerable populations. The regulation also includes new documentation and transparency requirements — created in part to foster greater confidence among participants, patients, and the public. These requirements include mandatory registration and results reporting, with measures to protect sponsors' commercially confidential information (CCI). Additionally, the regulation streamlines safety reporting, with a harmonized process for reporting suspected unexpected serious adverse reactions (SUSARs).

Here, we examine strategies for long-term success in adapting to EU-CTR. We also derive principles, learnings, and recommendations that can be applied across all development programs to manage potential complexity within the evolving regulatory landscape in Europe.

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Perspectives on current regulations

In interviews conducted by Parexel's consulting firm Health Advances, sponsors reported three major concerns with EU-CTR.[2]

- **Longer timelines.** Anecdotally, new regulations have resulted in significantly longer CTA approvals. "Study startup times in the EU following EU-CTR nearly doubled from initially a three-to-four-month timeline to now a six-to-eight-month process," said a leader from one U.S. biotech company.

  Our view: In our experience, timelines have not doubled. EU-CTR implementation has accelerated CTA approvals in some countries when compared to timelines under the previous directive. Those countries include Romania, Poland, Bulgaria, and Greece. Timelines have not improved significantly, however, in Germany, France, Spain, or Italy.

- **Increased complexity.** While CTAs in the EU have always been complex, administrative requirements under EU-CTR create additional burdens for sponsors. "The new rules are more cumbersome and bureaucratic than before, which means that you need to put more effort into developing your dossier," reported a biotech leader based in Europe.

  Our view: The CTIS portal does require a significant initial investment of time for setup and training and users occasionally face technical issues and system downtimes. However, we see advantages in moving from paper or CD-ROM submissions to an electronic gateway, which will be faster in the long term. CTIS also provides immediate receipt confirmation, simplifies submission tracking and management, and allows for easier collaboration among stakeholders. Overall, administrative complexity can also can be managed through proactive, early planning for dossier development.

- **Burdensome transparency requirements.** Once a study application is approved, its submitted documentation becomes publicly available. EU-CTR allows for the redaction of commercially confidential information, but sponsors are still concerned about protecting intellectual property, particularly in early-phase research. "Overall, the companies are going to want to redact more than EU regulators want and this new level of required transparency creates a major competitive risk for phase I programs," one U.S. biotech leader told researchers.

- ***Our view:*** New transparency rules were implemented on June 18, 2024, greatly reducing the number of CTA documents that must be published. Transparency requirements vary by study phase.

2 Health Advances Proprietary Assessment, 2024.

Strategies for long-term success

Based on its research, Health Advances believes that EU-CTR may temporarily reduce sponsor interest in EU sites, particularly among U.S. biotech companies. Sponsors should keep in mind, however, that EU-CTR also offers advantages. Drug developers can pursue simultaneous approvals from regulatory and ethics bodies rather than waiting to make the sequential submissions required by other countries — saving fees and possibly time. Earning single-submission CTA approval in the EU also offers sponsors access to 30 countries, giving them great freedom in site selection.

While we understand the motivation to avoid regulatory complexity, the EU is a significant region that needs to be represented in any well-rounded clinical development strategy. We recommend that sponsors focus on planning and ways of working to create opportunities for alignment and mitigate obstacles on the path to CTA submission and approval:

Strategy and alignment

- **Assemble a cross-functional study design team:** A robust protocol is the basis for a strong CTA. Study design teams should include experts in every aspect of research: medical, regulatory, biostatistics, project leadership, data management, clinical operations, non-clinical, CMC management, logistics, medical communications, and real-world evidence. A well-planned study will likely experience fewer regulatory roadblocks because authorities will have fewer questions about its design. At Parexel, we recommend starting with a protocol framework that considers the objective of the study and the study's technical aspects through the lens of our experience with regulators and payers. Our deep understanding of market approval and access decision-making helps us de-risk a study and establish endpoints that generate compelling evidence. We can also offer insight into EU-CTR-specific circumstances. For example, we strongly recommend a flexible approach to dose escalation protocols to avoid future substantial modifications that could increase timelines and delays in the startup process.
- **Develop an integrated evidence plan (IEP):** An IEP details the evidence needed to demonstrate a product's value as well as the specific tactics to generate the necessary data points. By creating an IEP, sponsors can specify, prioritize, and refine evidence needs throughout a product's lifecycle. An IEP is developed by a cross-functional steering team that represents every internal stakeholder group, each of which is accountable to external stakeholders: regulators, heath technology assessment (HTA) bodies, clinicians, and patients. Creating this type of plan at the start of development helps teams be both nimble and focused, which is particularly important in a complex regulatory environment like that of the EU.

- **Take advantage of scientific advice and protocol assistance meetings:** Both allow sponsors to ask questions of regulators to ensure that study applications will meet evidentiary requirements and conform to regulatory expectations. These meetings can help eliminate risk by revealing regulators' preferred approaches to trial design. Joint scientific consultations (JSCs), which are conducted by the EMA and multiple HTA bodies, provide sponsors with multinational input that can also help address any differences in standards. An experienced partner like Parexel can help sponsors prepare for and maximize the value of these pre-submission meetings and improve the quality of their CTAs.
- **Create a strategy for country selection:** This strategy, which will vary based on the phase of the trial, will allow sponsors to work around recurrent CTIS portal functionality issues. Sponsors will likely want to prioritize countries that have more experience serving as the Reporting Member State (RMS) and, to avoid unnecessary delays, should include in the CTA every country in which the sponsor plans to launch trials. Whenever possible, we strongly recommend parallel submissions (Article 5) over sequential submissions (Article 11) , as parallel submissions reduce timelines for approval. In our experience, Article 5 submissions take from 60 - 106 days, and Article 11 timelines are 110 - 187 days (depending on different scenarios). Article 11 could be considered when you do not have submissions ready for all countries. In addition to considering countries based on evaluation speed, sponsors will also want to know that a country can offer adequate patient populations and reliable sites. Choosing sites with existing site documentation will help speed the process as well. Additionally, sponsors could use a staggered approach to study startup, launching first in the U.S., then opening EU sites later to accommodate possible regulatory delays.
- **Establish strong relationships with ethics committees:** Sponsors should engage early to understand local requirements and incorporate committee feedback into protocol design whenever feasible.

Training and quality

- **Invest in training:** Understanding the expectations and processes of regulatory and ethics bodies will help streamline CTA submissions, so sponsors should create or outsource ongoing EU-CTR training for staff, taking advantage of EMA webinars and workshops when possible. Sponsors can also recruit or develop talent with specific expertise in EU-CTR compliance.
- **Prioritize first-time quality:** We recommend developing robust internal quality-control processes for all submissions and trial conduct. We also encourage sponsors to conduct regular internal audits to identify and address potential compliance issues.
- **Implement risk-based monitoring:** The process of ensuring the quality of clinical trials by identifying, assessing, monitoring, and mitigating possible risks to patient safety and study quality. This aligns with the EU's risk-adapted approach and can include both data-driven and centralized monitoring. The former provides insights into how a site collects data and treats patients, allowing early intervention for emerging risks. The latter considers study-wide data to detect risks, trends, outliers, and additional atypicality. When used in conjunction, both kinds of monitoring can lead to increased efficiency and data quality.

Informed preparation and delivery

- **Know which documents are frequently flagged by regulators:** In addition to creating a robust protocol, sponsors should also give special attention to supporting documents about which regulators frequently raise concerns. In our experience, this includes the investigator brochure (IB) and the investigational medicinal product dossier (IMPD), the latter of which details the clinical risk-benefit analysis. A consulting partner like Parexel can offer strategies for compiling these documents in a way that best meets regulatory expectations.
- **Build flexibility into timelines and develop plans for addressing requests for additional information (RFIs):** Flexible timelines will help address potential delays in the assessment process, as will having a plan to respond to RFIs. Because RFIs must be answered within 12 calendar days, the sponsor should appoint specific staff to monitor CTIS for incoming communications and gather required responses from the larger product team.
- **Address redactions efficiently:** Sponsor concerns about CCI and the protection of proprietary data may be alleviated by revised transparency rules. Under this revision, fewer documents will need to be made publicly available. The transparency rules also address patient-identifiable personal data (PD), the redaction of which can be incredibly time consuming. As a component of an overall solution, sponsors can speed the process with an AI-based tool trained to accurately and reproducibly redact PD from submission documents. In our experience, this AI-aided work can reduce processing time by up 30 percent.[3]

3 Internal data, 2024.

An encouraging outlook

As sponsors work to accelerate studies conducted in the EU, some MSCs are also finding ways to speed the CTA process.

In Germany, the Medical Research Act — much of which was implemented in October 2024 — established a specialized, interdisciplinary ethics commission to oversee urgent or complex trials beginning in July 2025. Regulators anticipate that giving focused attention to particularly challenging cases will help accelerate approvals for all CTAs.[4]

Additionally, through the German Medicinal Products Act, regulators have reduced processing times for all clinical trials conducted exclusively in Germany. Validated CTAs for single-country trials will be assessed within 26 days —19 days shorter than the previous assessment period.[5] From our own experience, we see that Germany is delivering on its plans for acceleration. At our early-phase clinical unit in Berlin, single-country studies conducted in the first half of 2023 averaged 100 days to study approval. By the end of 2024, that average had dropped to 30 days.[6]

Other countries, including Denmark, Belgium, Romania, and Spain, have also implemented faster timelines for single-country studies under certain conditions. Spain, for example, has accelerated the review of applications for single-country, early-phase studies for advanced-therapy medicinal products (ATMPs) that treat debilitating conditions with no therapeutic alternatives. In such cases, CTAs are evaluated within 26 days, reduced from the standard 45-day assessment period.

4 Medical Research Act. Bundestag (German federal parliament), January 2024.
5 Medicinal Products Act. German Federal Ministry of Justice, 2024.
6 Internal data, 2024.

Enlisting the support of a trusted partner

Navigating the regulatory landscape in the EU calls for a pan-European strategy — one in which studies are designed with attention to the requirements of multiple MSCs. The most successful sponsors will adopt an approach that accounts for variations in national requirements without compromising the essential objectives of the trial.

Such an approach requires specialized knowledge of country-specific standards, processes, and preferences, so sponsors utilize opportunities for scientific advice from the EMA and other authorities as early and often as possible. Enlisting a partner to develop and execute strategies for creating European CTAs, allows your internal team to remain focused on their core responsibilities.

Parexel's EU-CTR readiness has enabled us to expertly navigate new regulatory processes on behalf of biopharma companies of all sizes. As of January 2025, we have submitted approximately 500 single-country and multinational CTAs via the CTIS platform, with more than 370 studies approved.

Nearly every product on a path to market will eventually need approval in the EU. Sponsors who learn now how to meet EMA requirements position themselves for future success. Through preparation, proactive engagement with regulatory bodies and stakeholders, and a patient-centered approach, sponsors can align themselves with EU regulations while also streamlining their development efforts worldwide. Our team can help yours navigate the EU regulatory landscape, giving your product an edge in Europe and beyond.

We're always available for a conversation. **Get in touch to learn more**.

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