Early-phase development strategies for navigating regulatory complexity in the EU

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INTRODUCTION:

Managing challenges to expedite EU early-phase development

Insightful regulatory strategy is foundational to any clinical development program. And while we encounter complexities in every region, sponsors say the work of interpreting and addressing regulatory guidance is particularly challenging right now in the European Union (EU). Three recent regulations — Clinical Trial Regulation 536/2014 (EU-CTR), Medical Devices Regulation 2017/745 (EU-MDR), and In Vitro Diagnostics Regulation 2017/746 (EU-IVDR) — require sponsors to follow new processes and have resulted in delays in initiating clinical trials. This has prompted some companies, particularly non-European biotechs, to consider moving early-phase development out of the region.[1]

We're sensitive to the pressures that sponsors face. Conducting trials in North America, the U.K., or the Asia-Pacific region could make study launch simpler in the short term. But Europe is one of the world's largest pharmaceutical markets, so we urge sponsors to consider long-term impacts of shifting away from the EU.

The EU offers well established sites and experienced teams that can streamline patient recruitment and operations to help offset regulatory delays. And through its application process, the European Medicines Agency (EMA) offers access to 30 countries, which gives sponsors great freedom in site selection. We're encouraging sponsors to maximize these advantages as we also help them develop strategies for expediting early-phase development.

Most therapies on a path to market will eventually need EMA approval. Sponsors who learn now how to meet EU requirements will be positioned for future success. We wish you much of it.

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1 Health Advances Proprietary Early-Phase Clinical Unit Research Strategic Assessment, December 2023.

The current landscape

The recently implemented EU-CTR aims to harmonize studies by refining the submission process. Under its rules, stakeholders use the Clinical Trial Information System (CTIS) portal to submit, evaluate, and authorize clinical trial applications (CTAs) across all 30 countries in the European Economic Area, known as Member States Concerned (MSCs). The regulation also includes new documentation and transparency requirements, which were created in part to foster greater confidence among volunteers, patients, and the public. Compliance with EU-CTR, however, has proved challenging for phase I sponsors, with anecdotal reports of longer startup times due to delayed study approvals, and complex processes both for submissions, and rules for redacting proprietary data.[2] And because the approval path was designed to include multiple MSCs, it can be perceived as particularly burdensome for early-phase research, which often involves single-site studies within a single country.

Sponsors are also complying with the phased implementation of EU-MDR and EU-IVDR, under which medical devices and in vitro diagnostics must meet new safety and performance requirements. Compliant devices receive a CE mark from the EU. Any clinical trial that uses a non-CE-marked medical device for drug administration or other purposes or uses a non-CE-marked diagnostic test to enroll patients or make decisions about their treatment must conduct a performance study on the diagnostic test or a clinical investigation on the medical device. This research must be approved through a performance study application (PSA) or clinical investigation application (CIA). Sponsors report that the application process is complicated and commonly delayed.

2 Health Advances Proprietary Assessment.

Sponsor perspectives on new regulations

In interviews conducted by Parexel's consulting firm Health Advances,[3] sponsors reported three major concerns with EU-CTR as it relates to early-phase development.

- **Longer timelines.** Anecdotally, regulations have resulted in significantly longer approvals for new clinical trials. "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.

- **Increased complexity.** While CTAs in the EU have always been complex, administrative requirements under EU-CTR create additional burdens for sponsors. In Parexel's experience, for example, the initial application for a five-country, 50-site trial might require the creation and submission of more than 500 documents. "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.

- **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 (CCI) 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.

2 Health Advances Proprietary Assessment.

Health Advances predicts that EU-CTR will reduce short-term future sponsor interest in EU sites, particularly from U.S. biotech companies. Sponsors who spoke with Health Advances reported that the U.K. is the most appealing alternative to EU study locations. "The U.K. is one of the best locations to conduct phase I studies and with EU-CTR now, it's the clear choice when going to Europe," said one U.S. biotech professional. Sponsors also expressed interest in launching more studies in the U.S., Australia, and Canada.

To learn how EU-IVDR is impacting sponsors, Life Science Strategy Group (LSSG) surveyed 90 biopharma industry professionals.[4] Approximately 60 percent of respondents reported delays in the PSA process, with nearly half reporting delays of three to six months. Some respondents reported delays as long as 18 months. When the European Federation of Pharmaceutical Industries and Associations (EFPIA) surveyed its members about the new regulations, about 60 percent of respondents said EU-IVDR documentation requirements were burdensome, more than 80 percent said application documentation was not consistent across MSCs, and nearly 90 percent said it is not clear which diagnostics require performance study applications under the new rules.[5]

When asked by LSSG how they would respond to IVDR-related delays, nearly three-quarters of respondents said they were likely or very likely to shift clinical trials to North American sites or to sites in the U.K. or non-EU countries. Phase I and phase II studies were the most likely to be impacted. The EFPIA reports similar findings in its survey, with about two-thirds of respondents saying that with continued delays they would consider shifting their clinical trials away from the EU.

4 Impact of the Invitro Diagnostic Regulation (IVDR) on the Conduct of Clinical Trials in the EU and CRO Outsourcing, January 2024.
5 Critical impacts of IVDR implementation on patient access to clinical trials, March 2023.

Strategies for long-term success

While regulatory complexity and resulting delays are impacting many studies with sites in the EU, shifting studies into other regions is only a stop-gap measure. For a well-rounded approach, sponsors must develop strategies for long-term success in the region, working as effectively as possible within the current regulatory landscape.

To expedite the process, we recommend that sponsors:

- **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, 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 like to begin with a protocol framework that de-risks design by considering not only technical aspects of the study but regulatory precedent, our knowledge of regulatory guidelines (such as EU-CTR), and our experience interacting with regulators and payers. We find that such a framework helps establish endpoints that generate compelling evidence.

- **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 can offer strategies for compiling these documents in a way that best meets regulatory expectations.
- **Submit in parallel.** While sponsors have the option to create a combined protocol that includes both the primary study and the performance study for any in vitro diagnostics used, we recommend designing separate protocols that can be submitted in parallel so that issues specific to one protocol do not delay the other. For the same reason, we recommend that sponsors create and submit separate patient consent forms for studies of diagnostics and therapeutic products.
- **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 and speed approvals by revealing regulators' preferred approaches to trial design. An experienced partner can help sponsors prepare for and maximize the value of these pre-submission meetings.

- **Address redactions efficiently.** Sponsor concerns about CCI and the protection of proprietary data may be alleviated by revised CTIS transparency rules that will be fully implemented by the first half of 2024. Under the revised rules, 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. To help speed the process, we recommend as a component of an overall solution using an AI-based tool that can be 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.
- **Adjust site selection and startup plans.** For example, if a sponsor's initial plan called for sites in 10 EU countries, we might recommend choosing sites within only three countries as getting approval from fewer MSCs will likely make the process faster and less complex. Choosing sites with existing site documentation will also help speed the process. 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.

- **Bring assay manufacturers into the PSA process as early as possible.** Because sponsors do not usually manufacture their own in vitro diagnostics, they will need to collaborate with the manufacturing lab during the PSA process. The lab must provide highly technical documents that are critical to study approval, so manufacturers should be included in study planning as early as possible.
- **Enlist a partner for support.** Compliance with EU-CTR, EU-IVDR, and EU-MDR requires specialized knowledge of new processes, templates, and regulatory expectations. Compliance also requires vigilance, as new regulatory guidance can be issued as often as monthly. Sponsors — particularly biotech companies based outside of the EU — may not have the in-house expertise necessary for navigating the current landscape. Enlisting a partner like Parexel allows sponsor teams to remain focused on their core responsibilities while Parexel experts direct the creation and submission of CTAs, PSAs, and CIAs.

An encouraging outlook

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

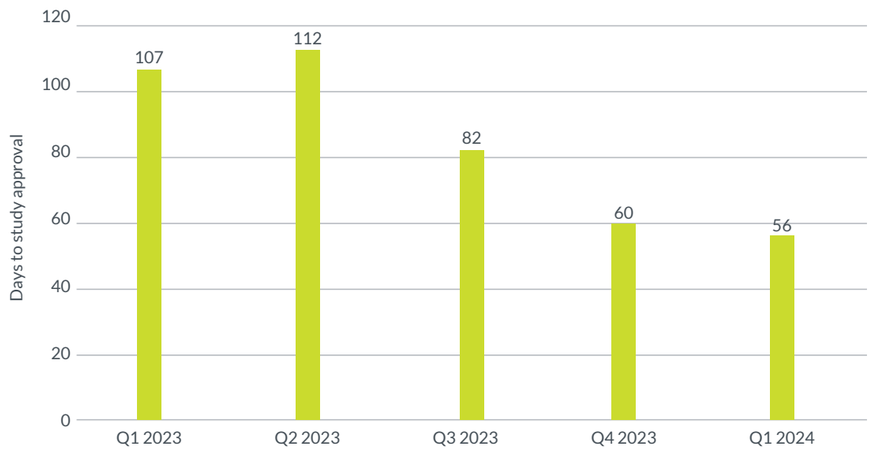
In December 2023, the German Federal Health Ministry presented a draft of the Medical Research Act (known as Medizinforschungsgesetz) that will make it easier for sponsors to launch studies within the country. When adopted, the act will create an interdisciplinary Federal Ethics Commission that will oversee urgent or complex trials. The act will also reorganize the BfArM and PEI — Germany's two regulatory agencies — to improve cooperation. Both changes will help streamline and expedite approvals for CTAs.

Additionally, Germany has pledged to shorten processing times for all single-country clinical trials. Validated CTAs for a mononational trial will be assessed within 26 days. If regulators find no deficiencies, the agency will grant final authorization within 31 days of CTA validation. And for single-site mononational studies, regulators say they may be able to shorten the validation phase, with exceptions considered on a per-study basis.

From our own experience, we see that Germany is delivering on this pledge. At our early-phase clinical unit in Berlin, days to study approval have dropped from over 100 days for studies conducted in the first half of 2023 to 60 days for a study approved in the last quarter of 2023. In the first quarter of 2024, a study was approved in 56 days — very close to the 50-day approvals we expect as the year progresses.[6]

6 Berlin EPCU, internal data on file.

Average approval times for clinical studies at Parexel's Berlin Early Phase Clinical Unit



We've also had success using a two-country strategy for phase I trials in Europe that need to recruit large participant populations. For such trials, we often recommend that sponsors launch in both Berlin and London. While separate CTAs must be submitted — one to the EMA, one to the U.K.'s MHRA — we have found that recruiting simultaneously in two metropolitan areas helps studies finish faster than if recruiting from a single region.

As of April 2024, Parexel has prepared nearly 300 EU-CTR submissions, with more than 125 clinical trials approved. As of March 2024, we have managed approximately 55 regulatory submissions and approvals of clinical studies under EU-IVDR and EU-MDR. We have also supported more than 100 regulatory assessments for clinical trials involving medical devices or IVDs under the new regulations. Our team includes more than 200 trained regulatory leads in all time zones, backed by more than 4,000 regulatory professionals, including CTIS submission specialists and experts in assays for clinical studies.

Our team can help yours navigate the EU regulatory landscape, giving your product its best chance for success — in Europe and beyond. Contact us to learn more.

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We're always available for a conversation.

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