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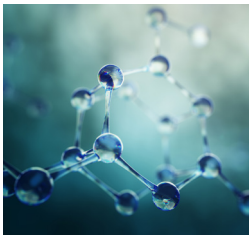
European Federation of Pharmaceutical Industries and Associations

EFPIA Communication to the European Commission Regarding the Article 97 Review of Regulation 2014/536

EU Clinical Trials Regulation



25 June 2024

Introduction

Clinical trials offer patients access to potentially ground-breaking treatments or therapies that are not yet available to the general public. They play a vital role in advancing medical knowledge, improving patient care, and ultimately, saving lives.

Europe has rich scientific traditions and a strong academic infrastructure, earning it a reputation as a pharmaceutical innovation powerhouse. In the past, many breakthrough treatments for cancer, cardiovascular diseases, infectious diseases, and neurological conditions among others were researched, developed and introduced in Europe. However, this proud legacy is fading. Just 25 years ago, every second new treatment originated in Europe. Today, that number has dwindled to less than one in every five[1].

While the number of European clinical trials might not be declining, they are not experiencing the same level of growth as seen in some other regions[2], where there is increased investment in clinical research ecosystems. Furthermore, in Enrico Letta's April 2024 report[3], 'Much More Than a Market', it is mentioned that "New global players are further reducing Europe's R&D and production capacities". Letta emphasises that implementation of "freedom of investigating, exploring and creating for the benefit of humankind without disciplinary or artificial borders and limitations" is vital to revitalise European healthcare.

As announced in the recent Commission Communication on Boosting Biotechnology and Biomanufacturing in the EU, the upcoming Commission report on the application of the EU Clinical Trials Regulation 536/2014 (EU CTR), as provided for in Article 97 of the Regulation, presents an opportunity to address this trend from a regulatory perspective. EFPIA is committed to advancing faster, smarter and more patient-centric trials, and increasing the global share of clinical trials in Europe. We would therefore like to pro-actively provide the Commission with some considerations on our member's experience with the EU CTR.

EFPIA held workshops with member companies on 5th and 12th June 2024 to gather issues faced by sponsors working under the EU CTR, the impacts of these, and any possible solutions that may make the EU environment more attractive. The scope of the workshops excluded issues with the transition of trials from the Clinical Trial Directive 2001/20/EC to the EU CTR, and technical issues with the Clinical Trials Information System (CTIS). A summary of the outcomes of these workshops is provided below.

EFPIA views on EU Clinical Trial Regulation and Clinical Research Ecosystem

Since the inception of the EU CTR in 2014, EFPIA has supported the original objectives of the regulation to enhance efficiency in the clinical trial processes and, consequently, to bolster the EU's competitiveness. EFPIA therefore agrees with the overarching goals of the EU CTR:

- To ensure that the European Union offers an attractive and favourable environment for carrying out clinical research on a large scale, with high standards of public transparency and safety for clinical trial participants.
- To harmonise the processes for assessment and supervision of clinical trials throughout the EU, facilitating the conduct of larger clinical trials in multiple EU Member States/EEA countries.
- To foster innovation and research in the EU.

However, after almost 18 months since the mandatory submission of all trial applications under the EU CTR, it is clear that both commercial and non-commercial sponsors are experiencing issues that significantly impact the attractiveness of the EU/EEA as a destination for clinical research. These are fundamental issues related to the differences in interpretation and implementation of the EU CTR by Member States (MSs), at both National Competent Authority (NCA) and Ethics Committee (EC) level, as well as inflexibilities with the regulation, the Clinical Trial Application (CTA) process, and CTIS itself.

1 - https://www.efpia.eu/media/676753/cra-efpia-investment-location-final-report.pdf

2 - https://pharmaboardroom.com/interviews/peter-arlett-head-of-data-analytics-and-methods-european-medicines-agency-ema/

3 - https://www.consilium.europa.eu/media/ny3j24sm/much-more-than-a-market-report-by-enrico-letta.pdf

The issues faced by sponsors can be broadly categorised into 3 main areas

1. LACK OF ALIGNMENT AND HARMONISATION AMONG NATIONAL COMPETENT AUTHORITIES AND ETHICS COMMITTEES IN INTERPRETING AND IMPLEMENTING THE EU CLINICAL TRIAL REGULATION

Based on our experience to date, we regularly observe that Member States interpret the EU CTR and associated guidance differently, leading to an **increase in administrative burden** and **lack of predictability** due to **inconsistencies** in the way the review is conducted. This inconsistency includes requests not aligned with the EU CTR (see below), and variability in terms of the pragmatism and flexibilities applied across MSs. This results in **delays in the submission and approval process** for Clinical Trial Applications (CTAs), inconsistent approaches to issuing approvals with conditions, and avoidable rejections of CTAs.

One of the main issues is the **diverse use of requests for additional information** (RFIs). Often sponsors are faced with a large number of questions, some of which may be duplicate or even contradictory. This indicates that the Reporting Member States (RMS) do not have the resource or potentially the empowerment to consolidate input from Concerned Member States and remove 'minor' questions not critical for patient safety, regulatory compliance or trial integrity or avoid redundant questions. Learnings from the best practices of experienced MSs could be applicable in this context. Questions categorised as "major" would render the study non-approvable if they are not resolved. The RMS should ensure that "other" questions are not issued (or at least will not impact the CTA approval, with the issuance of a conditional approval with a commitment to update at the time of the next substantial modification).

Further, some MSs allow for a second RFI for clarification purposes to avoid approvals with conditions or rejections, which is welcome, while other MSs (particularly ECs) issue a second round of RFI to ask completely unrelated queries following review of sponsor's responses to the initial RFI, unnecessarily complicating and delaying the start of a trial.

EFPIA notes the change of language regarding assessment from *"grounds for non-acceptance"* under Directive 2001/20/EC to *"request for additional information"* under the EU CTR and **urges a re-focussing of assessment outcomes** on those issues of a serious nature that would prevent the trial from going ahead via a **risk-proportionate approach**.

These challenges are further exacerbated by what appears to be **limited coordination of the CTA procedure within some MSs**. Often a Part II assessment is concluded before Part I, with an RFI for Part I questions are raised with RFIs for Part I which might result in a necessary change to Part II documentation. Some MSs have introduced "workarounds" to update the Part II information (such as allowing a non-substantial modification) while in many other cases a substantial modification is required, significantly delaying the trial start in some or all participating countries. This **misalignment between Part I and Part II assessments** with subsequent substantial modifications has repeatedly raised concerns regarding meeting the ambition for clinical trials in the EU to be faster and smarter with harmonised procedures for their assessment and supervision.

EFPIA has observed that **MSs do not seem to be taking advantage of the opportunity for enhanced work-sharing and efficiencies** offered by the EU CTR and the CTIS. Often RFIs are issued for Part I of a 'sister' trial when the documentation has already been approved for an earlier trial in another set of concerned MSs. This can have serious implications for the trial start-up, conduct and maintenance of the trial documentation. EFPIA's position is that trial documentation that is considered scientifically robust and safe in one set of concerned MSs should also be considered so in a second set of concerned MSs (accepting that there may be extenuating circumstances such as significantly different patient populations).

There is a need to streamline processes, improve harmonisation, and reduce the current lack of predictability by reinforcing the role of the Reporting Member State, allowing consistent use of existing and new efficiencies/ flexibilities. This could be achieved by aligning with and centrally implementing learnings from national best practices or implementing enhanced coordination similar to that in the centralised procedure for marketing authorisation applications.

2. SPECIFIC NATIONAL COMPETENT AUTHORITY AND ETHICS COMMITTEE REQUIREMENTS BEYOND SCOPE OF THE EU CLINICAL TRIAL REGULATION

Many EFPIA members reported receiving validation and assessment RFIs that fall out of the scope of the EU CTR. It appears that this has been facilitated by a regulatory/legal discrepancy between the 2020 Harmonisation Guidance on EudraLex Vol. 10 and recent versions of the CTR (EU) 536/2014 Q&A, as well as information provided in the EMA CTIS Walk-In Clinic. These provide conflicting advice on the ability of MSs to issue specific national requirements.

For example, some local legislation requires sponsors to wait 15 days before implementing a substantial modification, prolonging the time before the modification can be implemented. In other MSs, patient cards are expected to be submitted, or details (including names) of the investigator's teams are also expected. In addition, some MSs require regular reports on the progress of the trial to be submitted, referring to ICH E6 (R2) and national decrees. Protocol acceptance pages signed by the Principal Investigators have also been requested, justifying that the Part II Document "Harmonisation Guidance" makes it clear that information can be requested beyond the documents mentioned in the EU CTR.

Other examples include MSs using validation RFIs to confirm Proof of Payment and/or asking for multiple payments in contravention of Article 87 of the EU CTR.

These national requirements, particularly for Ethics Committees expectations, appear to be the result of an **absence of coordination for harmonised documentation expectations and leads to an almost 'bespoke' application for each country**, negating the objective of the EU CTR to harmonise the processes for assessment of clinical trials throughout the EU. The number and diversity of national requirements act as a **disincentive to the conduct of larger clinical trials** in multiple EU Member States/EEA countries, an important objective of the ACT EU programme.

There is a need to agree on common requirements and to limit or eliminate the current national flexibility for requirements beyond EU Clinical Trial Regulation.

3. INFLEXIBILITY IN PROCESSES UNDER THE EU CLINICAL TRIAL REGULATION AND LEGISLATIVE BLOCKERS TO INNOVATION

The EU CTR and CTIS processes result in a **lack of opportunities for flexible interactions** between the applicant and reviewers, especially towards the end of the clinical trials review process. Open dialogue with assessors from regulatory bodies and Ethics Committees is important to ensure that issues can be solved within the challenging EU CTR timelines and to avoid unnecessary delays or rejections. In some cases, to avoid a rejection, MS will issue an **approval with a condition** (sometimes only in certain countries) that requires a substantial modification to be submitted and approved prior to study start. As there is no accelerated path for approval of the changes related to the condition, this can prolong the start-up time by over 3 months, i.e. cause unnecessary delays and hamper predictability of timelines (also impacting the trust from clinical sites prepared to initiate the trial).

The system inflexibility is partly a result of CTIS being 'baked into' the EU CTR meaning that the IT **system often drives the regulatory process and not the other way round**. This extends to innovative trial designs such as master protocols with multiple arms and multiple read-outs being difficult to manage in CTIS. A blocker experienced by many companies is the **inability to submit a substantial modification** to an ongoing trial if another modification has been submitted but not yet authorised. This has a significant impact on the feasibility and conduct of clinical trials, particularly innovative trials with multiple arms where modifications are expected by design. A substantial modification can take over 3 months for approval, therefore only allowing four substantial modifications per year.

Flexibility in the legislation (and in the CTIS) to allow the lifecycle of trials to continue without interruption by **allowing parallel substantial modifications**, where appropriate, would enhance the attractiveness of the EU ecosystem. A related issue is the inability to incorporate other countries' feedback during the EU assessment process to enable one global protocol to be implemented at study start, rather than require a substantial modification after approval to align.

Similarly, **facilitating minor updates to all aspects** of a CTA via non-substantial modifications would reduce workload for both, MSs and sponsors and ensure uninterrupted treatment for trial participants. The ACT EU initiative aims to identify gaps, issues and bottlenecks that present challenges for non-commercial sponsors in the conduct of multinational clinical trials. From a regulatory process perspective, the current **Investigational Medicinal Product Dossier-Quality (IMPD-Q) only process**, essential for co-sponsored trials and collaborations between non-commercial and commercial sponsors is seen as cumbersome and not scalable to support the EU ambition to have more multinational trials.

Another blocker to innovation in the EU is the growing number of challenges for studies at the **interface of the EU CTR and other legislation** required for research approvals. For example, issues regarding the In Vitro Diagnostic Regulation (IVDR) and the Medical Device Regulation (MDR), have been identified in our EFPIA survey conducted in March 2023. Another example is the development of innovative radiopharmaceuticals for therapy (rather than diagnostic purposes) that is hampered by the absence of a clear exemption from holding a manufacturer's licence for reconstitution and radiolabelling of radiopharmaceuticals from kits, and by the national legislation relevant to radiotherapies.

There is a need to review both the EU Clinical Trial Regulation text and the CTIS processes and ensure they are fit-for-purpose and future-proof, enabling innovation to occur more easily in the EU. Opportunities for communication between sponsors, Member States and Ethics Committees should be available and established throughout the entire process to contribute to the effective implementation of the regulation.

Conclusions

It appears that previous national best practices under the Clinical Trial Directive, in terms of risk proportionality, pragmatism, flexibility, and timelines (particularly for phase 1 trials), have been diluted under the EU Clinical Trial Regulation via a **'lowest common denominator'** approach. Whilst EFPIA truly appreciates the efforts of the Clinical Trials Coordination Group (CTCG) and its Chairs to support harmonisation and pragmatism, the experience of sponsors to date is that the intended benefits of a coordinated, harmonised, and streamlined framework have not been delivered.

Radical and urgent action is needed to **simplify and harmonise the EU regulatory framework**, unfettering innovation from the constraints of inflexible systems and processes, and empowering timely, pragmatic and risk proportionate decisions. Serious consideration should be given to rationalising and clarifying the review responsibilities of Member States, clarifying and bolstering the role of the Reporting Member State as a rapporteur - with centralised support to provide transparency and consistency on decision making - and establishing mechanisms to coordinate Ethics Committee reviews on an EU level, while maintaining their crucial independence.

We consider that a **holistic approach** is needed for the review of clinical trials related legislation. Navigating the multiple and varied EU and national frameworks required to obtain research approval in the EU serves as a disincentive to innovation, which ultimately affects the benefit to our patients. We would also encourage the Commission to consider aspects beyond regulation when reviewing the EU clinical trials landscape as set out in Advancing Clinical Trials for European Patients since these issues need to be approached and dealt with in the round.

The Commission's review should not be limited in its ambition and a **'building from the ground up' approach** could be considered to fully integrate the regulatory pathways for clinical research and to consider learnings from global best practices, such as the FDA Investigational New Drug (IND) system to fully harness the opportunity to supercharge innovation in the EU.

EFPIA stands ready to support the Commission in its study on the implementation of the EU CTR and would welcome opportunities to provide input to the Commission, the European Medicines Agency and Member States to help address these issues, providing further details on the examples above as necessary, and urgently accelerate the outputs of the ACT EU program and the COMBINE priorities, so that a truly holistic and fit-for-future approach to improving the EU regulatory framework for clinical research is achieved.

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