IMPROVING THE EU CLINICAL TRIAL ENVIRONMENT

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EU clinical trials continue to decrease even after EU Clinical Trials Regulation (CTR) entering in 2022[1]:

- EFPIA survey estimated up to 420 trials could be **delayed by 6-12 months** over 3 years, **impacting as many as 42,000 EU patients**, the majority being cancer patients.[2]
- EFPIA/IQVIA report determined that clinical trials initiated in the European Economic Area (EEA) **dropped by 10% over the last decade** (2013-2023)[3]. Resulting in **60,000 fewer patients** having access to trials and **20,000 less trial sites available**.[4]

RECOMMENDATIONS FOR CTR IMPLEMENTATION IMPROVEMENT

Unless EU policymakers and regulators take pragmatic approaches to resolve CTR implementation issues and improve the CT application (CTA) approval timelines, **EU patients will continue to miss out** on early access to innovative medicines. To increase clinical trials in the EU, policymakers should:

1. **Enhance CTA review efficiency** to become more competitive with the timelines of other countries. Companies have experienced diverging CTR interpretation by Member States, which result in a fragmented system. EU policymakers must diminish unique additional Member States obligations and improve CTA review timelines.

2. **Establish informal dialogue** between CT sponsor and Member States to resolve minor CTA issues. During CTA review, if Reporting Member State (RMS) has an inquiry for the CT sponsor, there are no mechanisms to discuss and resolve the issue – often minor such as updating template – before issuance of a conditional approval (or a rejection of the CT) adding a 3-month delay.

3. **Address overlapping legislative complexities** particularly the **EU In-Vitro Diagnostic Regulation (IVDR)**. There is a lack of coordination in authorizing the use of diagnostic tests for CTs in Member States. EU **Oncology** and **Neurology** trials – which often use diagnostics – have fallen consistently since 2021[5]. IVDR implementation policies can be improved today as well through Commission's implementing acts "*to resolve issues of divergent interpretation and practical application*" (**see below proposals**).

The IVDR update should foster a **risk-based framework for regulation of IVDs** used in therapeutic clinical trials while ensuring appropriate oversight for patient safety. Lilly proposes:

HARMONIZED INTERPRETATION OF IVDR

- Apply a risk-based approach to IVDs used specifically in clinical trials by removing the need for a PSA for assays used in medicinal product research, where the analytical and clinical validity of the test is not being evaluated and there is no IVD commercial development study intended.

[1] Clinical Trials Regulation | European Medicines Agency (EMA)
[2] SLIDE 5-6 - efpia_ivdr-survey-slides.pdf
[3] SLIDE 16 - efpia_ve_iqvia_assessing-the-clinical-trial-ct-ecosystem.pdf
[4] SLIDE 39 - efpia_ve_iqvia_assessing-the-clinical-trial-ct-ecosystem.pdf
[5] SLIDE 20 - efpia_ve_iqvia_assessing-the-clinical-trial-ct-ecosystem.pdf

- The risk/benefit evaluation and analytical validation of IVD can be integrated into the overall assessment of the clinical trial application, allowing the same reviewers and Ethics Committee to assess the quality and risk of investigational IVD use in the medicinal product clinical study.

- Align on least burdensome interpretation of "invasive sample-taking" which currently requires additional requirements to be met for performance studies
  - *e.g.,* Exclude routine blood draw from definition

- Allow: (1) a unified submission of combined studies (CTA and PSA) for evaluation by regulators and (2) a single Ethics Committee review of the CTA and PSA at the member state level which will streamline study review and approval whenever IVD commercial development is intended
  - Harmonization of IVDR interpretation and PSA documentation requirements among Member States without country-by-country variability

IVDR LEGISLATIVE CHANGES

- Update IVDR Article 5 (5) to allow tests that are manufactured and processed outside of the EU to fall under "in-house test" IVDR exemption, as well as tests developed and utilized at central laboratories within the EU (e.g. CROs, commercial laboratories that serve health institution patients but are not located within a health institution).
  - Currently, there are differing requirements for in-house tests with similar analytical and/or clinical performance based solely upon geography and not based on risk to patients—reducing EU patients testing options (e.g. rare diseases tests or rare monitoring tests not available in EU).
- **An all-encompassing solution would be an EU Centralized Procedure for medicinal product CTA and IVD PSA with commercial intent (*e.g.* CDx development) allowing a unified review of both studies, as well as an EU Centralized Ethics Committee opinion—eliminating country-by-country Ethics Committee review.**

Lilly Alzheimer's Trials

- There are currently no in-house IVDs or CE marked tests available in the EU for Alzheimer's. Under IVDR, Performance Study Applications (PSAs) are required to be submitted for the diagnostic test used.
- Lilly may not be able to enroll EU patients in a global, competitive Phase 3 study due to additional timelines (an added 4-12 months) driven by the need to submit PSA on country-by-country basis.

Lilly Oncology Trials

- To select patients for oncology trials, Lilly often uses results from local lab tests done as part of routine clinical practice. This reduces enrolment delays, prevents additional tissue biopsy, and allows more patients to access lifesaving treatments. IVDR has made this approach very burdensome.
- Lilly has been requested to prospectively provide a Competent Authority (CA) with the in-house IVDs compliance documentation during CTA review. This information is often not readily available due to tests being run as part of routine clinical practice - not for the study. Being unable to supply this information prior to trial start has resulted in study rejection by that Member State.