

To:

Emer Cooke, Executive Director, European Medicines Agency
Sandra Gallina, Director-General, European Commission, DG SANTE
Karl Broich, Management Group Chair, Heads of Medicines Agencies

Cc:

Peter Arlett, Head Data Analytics and Methods Task Force, European Medicines Agency
Harald Mische, Deputy Head of Unit, Medical Products, European Commission, DG SANTE
Bjorn Eriksson, HMA Clinical Trials Lead, MPA
Marianne Lunzer, CTCG Chair, Safety Assessor at AGES
Monique Al, CTCG Vice-Chair, Special Advisor CCMO
Olga Tkachenko, Co-Chair of MDCG IVG group and COMBINE project, European Commission, DG SANTE
Isabelle Clamou, Co-Chair of COMBINE project, European Commission, DG SANTE
Bitte Zerlang Christensen, COMBINE Project Manager, Danish Medicines Agency

Issues at the IVDR/CTR interface need to be prioritised under ACT-EU

Dear Executive Director Cooke, dear Director-General Gallina and dear Prof. Dr. Broich,

We are writing to you as a community of stakeholders to reiterate our concerns about the unforeseen impact of Regulation (EU) 2017/746 (the In Vitro Diagnostics Regulation, hereinafter IVDR) on patient access to clinical trials using in-vitro diagnostics. As you know, challenges with the implementation of IVDR have led to delays, and reduced access to clinical trials for European patients, thereby adversely impacting the vision of flagship initiatives like ACT-EU and Europe's Beating Cancer Plan. A survey conducted by the European Federation of Pharmaceutical Industries and Associations (EFPIA) confirms the very negative impact the IVDR is currently having on clinical trials in the EU.^{i&ii}

We warmly welcome the launch of the "COMBINE" projectⁱⁱⁱ by the Medical Device Coordination Group and the Clinical Trials Coordination Group, with the support of other relevant clinical trial groups, as a very important step that has elevated the IVDR/CTR interface issues as a priority. Our community of stakeholders strongly supports this project. As expressed by many ACT-EU stakeholders, **we believe that the IVDR/CTR interface, hence the deliverables of the COMBINE project, should be developed in connection with the ACT-EU initiative.**

We welcome the support from the Head of Medicines Agencies to facilitate coordination across Member States of the review of IVDR performance study applications, to maximize efficiency and prevent delayed launch of clinical trials in Europe. This coordination will require urgent dedicated efforts and multi-stakeholder discussions to develop an appropriate procedure that would execute this vision and involve all stakeholders interested.

Accordingly, we would like to kindly ask you to:

- agree that the IVDR/CTR interface for combined studies could also be elevated as one of the ACT-EU priorities in 2023 and 2024 to allow mapping the deliverables of the COMBINE project in the ACT-EU workplan 2023-2024;
- establish a feedback mechanism between the COMBINE project group and the ACT-EU Stakeholders' Advisory Group;
- organise, in Q4 2023 before the end of the first phase of the COMBINE project, an ACT-EU workshop with key stakeholders, to have an in-depth discussion and get input to the COMBINE

project's first phase outcomes and allow to start implementing its proposed solutions, including setting up an optimal voluntary coordination process.

We thank you for considering our proposals and are looking forward to your feedback.

Respectfully yours,

Signatories below

		
		
		
		
		
		
		
		

ⁱ EFPIA: New European legislation designed to protect patients is delaying clinical trials for thousands of people with cancer and rare diseases, March 20, 2023. <https://www.efpia.eu/news-events/the-efpia-view/statements-press-releases/new-european-legislation-designed-to-protect-patients-is-delaying-clinical-trials-for-thousands-of-people-with-cancer-and-rare-diseases/>.

ⁱⁱ Problem statement: Under the IVDR, a performance study authorisation is expected prior to use of a diagnostic in a clinical study if the test results may influence patient medical management or involve invasive sampling procedures, and the test is not yet available in the EU in compliance with the IVDR. This is in addition to other requirements, such as authorisation of a clinical trial application for the medicinal product study under the Clinical Trial Regulation (CTR), ethics committee approval and, for certain ATMPs, GMO applications. This interplay between the IVDR and the CTR submission, requirements, and reviews is not well-defined, which adds complexity and delays to study approval.

The IVDR describes a process for coordinated assessment of the performance study protocol – sponsors would submit the protocol into EUDAMED, then a single Member State could coordinate feedback for European clinical trials, review, and approve the performance study to proceed. Unfortunately, neither the coordinated process, infrastructure, nor necessary guidance are available to enable this streamlined option. As a result, the study sponsor must submit an application to every Member State involved in the clinical trial independently. The fragmented process, different interpretations, and lack of guidance to both sponsors and Member States, is regrettably causing delayed launch of clinical trials in Europe and a reduced access to these trials for European patients. In addition, the unpredictable and uncoordinated IVDR process is also pushing some sponsors to rethink the inclusion of EU sites in upcoming trials.

ⁱⁱⁱ As per EMA’s communication dated 11 August 2023, the Medical Device Coordination Group (MDCG) and relevant EU clinical trial groups CTCG, CTEG, CTAG are launching the first phase of the ‘COMBINE’ project to address the challenges for combined studies relevant to the interface of the three regulations: CTR, IVDR and MDR. Combined studies are to be understood as a clinical trial of a medicinal product together with a performance study of an IVD or a clinical investigation of a medical device. The analysis phase of this project will run until December 2023/January 2024 and is expected to deliver:

1. Issue list: identify and clarify problems that cause delays for the conduct of combined studies in terms of ‘scientific, procedural, legal’ issues.
2. Mapping of ongoing work: mapping of work potentially related to the CTR/IVDR/MDR interface taking place in existing structures (e.g. development of Q&A on performance studies).
3. Mapping CTR/IVDR/MDR EU landscape: Mapping of competent authorities for the different regulations on Member State level as well as mapping of relevant aspects of regulatory processes.
4. Developing proposals for solutions: proposal for solutions that could address the identified issues considering the mapping of the landscape and ongoing work.