

European Commission
"Open Public Consultation on the revision of the general pharmaceutical legislation"

Association of Clinical Research Organizations (ACRO)
Supplemental Comment to the Commission's Online Survey Questionnaire

20 December 2021

ACRO EU Transparency Register ID number: 150920420956-26

Contents

In this supplemental comment, ACRO provides feedback on the following three objectives of the EU Pharmaceutical Strategy and Roadmap:

- I. **Objective: Simplify legislation and create regulatory attractiveness with the aim to reduce, where possible, regulatory approval times and regulatory costs while keeping the high standards of robust assessment of quality, safety and efficacy.**
 - a) *Achieving globally competitive timelines for new trial initiation*
 - b) *Horizontal Alignment across EU Regulations:
Ensuring that the General Pharmaceutical Legislation is linked to other EU-level regulations impacting drug development in Europe*
 - c) *Vertical Alignment of EU and Member State Regulation*
 - d) *Increased coordination and communication between drug regulators and data protection regulators*
 - e) *Increasing participation in clinical research in the EU*
 - f) *Patient-Centricity by Design*

- II. **Objective: Introduce flexibility that allows legislative future proofing through adaptability to the innovative ways medicines are developed and evidence is generated**
 - a) *Enabling risk-proportionate, remote SDR and remote SDV in Europe*

- III. **Objective: Revise the legislation to adapt to cutting-edge products, scientific development (e.g., genomics or personalized medicine) and technological transformation (e.g., data analytics and digital tools), provide tailored incentives for innovation**
 - a) *Enabling eConsent and eSignatures throughout Europe in the Interest of Clinical Trial Modernization*

The Association of Clinical Research Organizations (ACRO) represents the world's leading clinical research and technology organizations. Our member companies provide a wide range of specialized services across the entire spectrum of development for new drugs, biologics and medical devices, from pre-clinical, proof of concept and first-in-human studies through post-approval, pharmacovigilance and health data research. In 2019, ACRO member companies managed or otherwise supported a majority of all biopharmaceutical-sponsored clinical investigations worldwide. With more than 150,000 employees, including over 60,000 in Europe, engaged in research activities in 114 countries the member companies of ACRO advance clinical outsourcing to improve the quality, efficiency and safety of biomedical research.

ACRO welcomes and supports the proposed revision of the general pharmaceutical legislation in order to develop a future-proof and crisis-resistant medicines regulatory system. Our comments are particularly focused on two aspects of the consultation on the planned revision: (1) that the current legislative framework may not be fully equipped to respond quickly to innovation, and (2) the inefficiency and administrative burden of regulatory procedures. Both of these aspects have significant consequences for innovation and patient access to novel treatments.

While we recognize that this initiative is targeted specifically at selected content in Directive 2001/83/EC and Regulation (EC) 726/2004, we are concerned that legislation relating to clinical research (specifically Regulation (EU) 536/2014) is not also included, as there is an inseparable association between clinical research and the initial marketing authorization application and subsequent variations of the authorization based on clinical data. Article 8(3)(i) of Directive 2001/83/EC specifies that an application for marketing authorization shall include the results of clinical trials; Annex I Part 4 of this Directive requires that "The clinical particulars to be provided pursuant to Articles 8(3)(i) and 10(1) must enable a sufficiently well-founded and scientifically valid opinion to be formed as to whether the medicinal product satisfies the criteria governing the granting of a marketing authorization. Consequently, an essential requirement is that the results of all clinical trials should be communicated, both favorable and unfavorable" and that "All phases of clinical investigation, including bioavailability and bioequivalence studies, shall be designed, implemented and reported in accordance with good clinical practice." Article 6 of Regulation (EC) 726/2004 confirms that an application for marketing authorization shall contain the information listed in Article 8(3) of Directive 2001/83/EC, and Article 7 requires that the committee responsible for delivering an opinion on the application "shall verify that the particulars and documents submitted in accordance with Article 6 comply with the requirements of Directive 2001/83/EC, and shall examine whether the conditions specified in this Regulation for granting a marketing authorization are satisfied."

At a procedural level, too, there is an intimate association between marketing authorization procedures and clinical research data. For instance, although the EMA does not authorize clinical trials, the new Clinical Trial Information System established by Regulation (EU) 536/2014 will mean that the EMA will host the reports and data supporting clinical trial applications in the EU. As these data are also used to support marketing authorization applications, this provides an opportunity to improve efficiency and streamline overall regulatory processes on the basis of "file once, use often" and make the information available for marketing authorization evaluation without the need for resubmission of reports/data by applicants. This would allow for early, rolling review of pre-clinical data, for instance, which is often finalized while clinical research is still in progress, and help to reduce the overall timeline for evaluation of the marketing authorization application when the clinical data package is complete.

In the clinical research space in which ACRO member companies operate, we have identified key omissions regarding patient focus and innovation in the current legislation that need to be addressed in order to maintain and improve the attractiveness and competitiveness of the EU for clinical research. The manufacture of pharmaceutical products (especially biotechnology medicines and vaccines, and the new generation of patient-specific advanced therapy medicinal products) is closely associated with the location of research and development activities. The resilience of the pharmaceutical industry in the EU is closely linked to the attractiveness of the EU ecosystem for research and development. While the EU Pharmaceuticals Strategy Roadmap acknowledged that the pharmaceutical sector is a major contributor to the EU economy, it is well known that research and development in the EU is losing ground to competitors such as China and the USA, and the EU is in danger of losing its leadership role in medical innovation. We believe that the revision of the general pharmaceutical legislation provides a key opportunity to address this situation. ACRO has organized our feedback in this letter into three sections below.

Section One:

Simplify legislation and create regulatory attractiveness with the aim to reduce, where possible, regulatory approval times and regulatory costs while keeping the high standards of robust assessment of quality, safety and efficacy.

Achieving globally competitive timelines for new trial initiation

Current challenges:

As a result of a lack of harmonization between the Member States, the approval and initiation of new clinical trials in the EU has been subject to variable and inconsistent processes, and takes too long. Member states follow national procedures for the regulatory and ethical approval of clinical trials (and may require additional approvals, e.g., from local/regional bodies), leading to an inconsistency of approach, of requirements and of timelines. As a result, EU countries are often in the second or third rank when a clinical trial is initiated globally, resulting not only to delayed innovation in the EU but also to delays in patient access to participation in clinical trials of novel treatments and, ultimately, delayed patient access to innovative products. It is too early to know to what extent the application of Regulation 536/2014 from end-January 2022 will improve the situation and streamline regulatory and ethics committee approvals for pan-EU clinical trials.

While greater harmonization of the approach and requirements for clinical trial approval and maintenance may be achieved following the application of the EU Clinical Trial Regulation (No. 536/2014), the coordinated assessment procedure provided for in the regulation results in a process that will take something in the order of 8 to 12 weeks from submission to approval of the application. This compares with a typical period of 4 weeks in the USA, where the highest percentage of the world's clinical trials are performed, despite the high cost of performing clinical trials in the USA. It is evident that these costs do not deter sponsors from taking advantage of the faster start-up times for clinical trials in the USA. Until the EU has in place a process that provides a rigorous regulatory and ethical review within similar timelines, it will be difficult for the region to be competitive for clinical research, especially for early phase clinical trials where (rapid) overall timelines have great importance. Additionally, the lack of flexibility around submission and processing of substantial modifications will likely lead to delays in implementation of significant changes required to clinical trials, further reducing the attractiveness of the EU and the opportunities available for innovation and patient access.

In addition to a regulatory approval process that takes too long, the CTIS is structured in such a way as to hamper innovation. The CTIS must be able to adapt to innovation. There are 3 key challenges. First, it is difficult for the CTIS to handle novel clinical trial designs (e.g., platform trials) appropriately. Second, with the exception of specific standardized substance, product, organization and referential (SPOR) data, CTIS is structured for the submission of traditional study reports and does not reflect the increased digitalization of clinical research and the trend towards submission of “data” rather than of “reports.” Third, scientific and technological developments such as advanced therapeutics are testing the limits of the current regulatory system. As clinical trial designs (especially in oncology) become more complex, it is essential that regulatory procedures accommodate this and do not result in yet further delay to trial initiation and patient access because of this complexity.

Proposed solution and request:

ACRO acknowledges the intensive effort that has been put into the development of CTIS but recommends that, as part of the legislation revision, consideration should be given to its adaptation to/replacement by a system that is sufficiently flexible to readily accommodate future innovations in clinical research and the regulation of clinical trials.

- During the COVID-19 pandemic, we saw rolling reviews of data speed up the approval of crucial vaccines. The implementation of the rolling review by the EMA for COVID-19 vaccines marketing authorization applications has demonstrated that this regulatory mechanism has dramatically accelerated availability of medicinal products in the EU, resulting in conditional marketing authorization. This spirit of faster approval, and therefore faster patient access, should be carried over to the revision of the general framework. In particular, we recommend the rolling review should become the standard process rather than an exception.
- Regulatory and ethics committee processes established under Regulation 536/2014 should be further streamlined to match the 4 week timeline for initial approval available in the USA, and provide the ability to handle multiple substantial modifications simultaneously
- CTIS should be redesigned to facilitate processing of novel trial designs and incorporate the submission of study data rather than traditional study reports.

Horizontal Alignment:

Ensuring that the General Pharmaceutical Legislation is linked to other EU-level regulations impacting drug development in Europe

Current challenges:

It is important to recognize that the revision of the general pharmaceutical legislation does not occur in a vacuum, as there are multiple regulations impacting drug development in the EU. It is important to cross-reference the interplay with other regulatory frameworks.

Proposed solution and request:

ACRO asks the Commission to cross-reference – and align – the revision of the basic pharmaceutical legislation (Directive 2001/83/EC and Regulation (EC) No 726/2004) to the following regulations in order to achieve a consistent approach that is harmonized across all EU member states –

- EU Clinical Trial Regulation
- EU General Data Protection Regulation
- Proposed regulation on AI
- Medical Devices Regulation (Regulation (EU) 2017/745)
- In-Vitro Diagnostic Devices Regulation (Regulation (EU) 2017/746)

Vertical Alignment of EU and Member State Regulations

Current challenges:

Clinical studies in the EU are subject to many elements that prevent a single harmonized EU approach to the regulation of clinical research and therefore hinder the conduct of clinical research and the introduction of innovations into clinical research in the EU. These include a variety of national regulations and practices, and differing interpretations of EU law, often involving laws and practices that are not directly related to clinical research. For instance, radiology protection requirements vary between member states and have a significant impact on the acceptance of trial protocols and overall clinical trial approval times, and GDPR implementation varies greatly across the Member States. There are also variations across member states regarding electronic informed consent and electronic signatures. Although patient associations frequently call for the convenience of electronic informed consent in clinical research, the law in some member states requires hand-written consent for health-related matters. During the COVID-19 pandemic, regulatory guidance on obtaining hand-written consent from trial subjects in isolation has demonstrated how difficult this is and that such processes are clearly not in the best interests of patients in these circumstances.

Proposed solution and request:

Member States should be required to review all national legislation (and its implementation) which has an impact on the initiation and conduct of clinical research in order to provide for a harmonized EU position on these matters that protects patients while promoting the EU as a globally attractive, innovative, and patient-focused region for clinical research.

Increased coordination and communication between drug regulators and data protection regulators

Current challenges:

With the increasing digitization of clinical trials and the use of remote technologies, data protection issues are becoming increasingly important. The challenge is to protect the data of clinical trial participants while simultaneously ensuring that necessary privacy protections do not become a barrier to research.

Proposed solution and request:

ACRO asks the Commission to explore possible vehicles to enable ongoing communication and coordination between drug regulators and data protection regulators, both at the pan-European (e.g., EDPS) and Member State (DPA) level.

Increasing participation in clinical research in the EU

Current challenges:

Finding and enrolling patients to participate in clinical trials is more difficult than it needs to be, as is accessing patient data for research purposes. In the current system of patient recruitment, a site cannot cast its net wide enough. This results in slow enrolment, the need to initiate too many sites, increased variability caused by too many sites, and the inability of patients to participate because they do not fall within the small catchment area of a particular site. ACRO recommends that the EU Pharmaceutical Strategy should include the development of a process whereby, using centralized patient records, physicians and clinical investigators should be able to contact patients not directly under their care to offer the opportunity to participate in an appropriate clinical trial (following ethical approval of appropriate outreach). Despite the interest expressed by patients in being informed of appropriate trials, this so-called “Right to Write” does not exist currently in the EU. Instead, there are unnecessary bureaucratic delays and patient access to clinical trials is significantly hampered. In addition, decentralized clinical trials have the potential to increase the investigator site catchment area, and this will require new ways of contacting eligible patients.

Proposed solution and request:

Educating people about clinical research helps build trust and advances the concept that clinical research means better care. The “Right to Write” can help raise the profile of clinical research, catalyze recruitment and improve care for patients. Additionally, clinical care is currently viewed as distinct from clinical research, and healthcare systems typically give greater emphasis to clinical care than to clinical research. This outdated perspective fails to recognize the interconnectedness of clinical care and clinical research, thereby harming the competitiveness of the EU in clinical research. ACRO therefore recommends that the legislative revision should include actions to indicate clearly to all of the stakeholders in healthcare systems across the EU that both clinical care and clinical research are vitally important, and that stakeholders are expected to make meaningful efforts to integrate clinical care and clinical research, for example by presenting clinical trials as a care option, as appropriate, and encouraging the “pre-consent” of individual patients about their willingness to be considered for appropriate clinical research projects upon intake to a healthcare facility. Making clinical research a clear priority for healthcare systems will help increase public awareness and advance the EU’s global competitiveness in clinical research. In addition, there is a need to simplify and distil the consent language to make it more patient-centric. This involves recognition that complex language such as GDPR/ privacy language and insurance language recommended by authorities and ethics committees should be reconsidered.

Patient-Centricity by Design

ACRO welcomes and supports the European Union’s aim to build a holistic, patient-centered, forward-looking EU Pharmaceutical Strategy which covers the whole life-cycle of pharmaceutical products from scientific discovery to authorization and patient access. ACRO supports these objectives but, in the clinical development space in which ACRO member companies operate, we consider that these objectives alone will not address the issues of patient centricity and innovation that the proposed revision of the general pharmaceutical legislation will need to address in order to achieve the stated goals of the strategy.

Current pharmaceutical legislation focuses on ethical considerations and patient safety, but does not reflect modern attitudes and approaches to patient-centricity. We believe that this is a major omission. When the focus is properly on patients, it is easier to overcome the current fragmentation of clinical care and clinical research. The lens of patient centricity helps avoid silos and reminds us of the necessary interconnectedness and interdependence of clinical care and clinical research. We recommend that the legislation incorporates this holistic perspective in order to help ensure that all elements of member states’ healthcare systems are suitably integrated and patient-centered. To this effect, we recommend the adoption and implementation of the concept of “patient-centricity-by-design” (PCbD), in much the same way as quality by design (QbD) underpins product and process development in the medicines and medical devices industries, and data privacy by design (DPbD) underpins the application of the General Data Protection Regulation (GDPR; Regulation (EU) No. 2016/679). One aspect of particular note is the importance of quality of life to cancer patients; clinical trials in this area focus on mortality (or a relevant surrogate measure) as the endpoint for regulatory decisions, when quality of life considerations may be more relevant for individual patients. Accordingly, we recommend that future legislation should promote greater patient involvement and increase the importance of patient-reported outcomes in regulatory decision-making.

Section Two:

Introduce flexibility that allows legislative future proofing through adaptability to the innovative ways medicines are developed and evidence is generated.

When the COVID-19 pandemic hit in the spring of 2020, drug developers were challenged to find ways to keep active, ongoing clinical trials up and running via remote methods in the interest of patients. The emergence of the pandemic necessitated flexibility. In order to be prepared for future pandemics it is vital to institutionalize flexibility and future-proofing for the benefit of clinical trial participants. One of the key areas requiring flexibility is clinical trial monitoring.

Enabling risk-proportionate, remote SDR and remote SDV in Europe

Current Challenges:

European data protection laws may be interpreted as precluding remote source data review (rSDR) and remote source data verification (rSDV) in the EU, even under exigent circumstances. ACRO emphasizes that it is important to distinguish between source data review and source data verification. While SDV focuses on identification of transcription errors, SDR is in many ways the more significant value-added activity because it enables verification of subject eligibility, safety and protocol compliance. Source data review is crucial because of the history in patient notes, which is so important.

Although Version #4 (dated 04 February 2021) of the *EMA Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) Pandemic* contained helpful updates on remote SDV, the guidance does not go far enough and does not specifically make reference to being inclusive of remote source data review. Additionally, the proposed option of utilizing review of pseudonymized data cannot be considered true SDV as it does not meet the full ALCOA+ principles of enabling the recipient to confirm the data is 'attributable' or 'complete.' Consequently, there is a need, per the EMA guidance, to undertake at least some degree of re-monitoring on-site, rendering the activity inefficient and placing a duplicate burden on site staff. In addition to site burden, this slows down research -- and therefore the speed at which new medicines can be brought to patients.

Proposed Solution and Request:

In order to facilitate the use of rSDR and rSDV in Europe – encourage a risk-proportionate approach to monitoring that focuses on critical study site documentation and source data as a best practice, while discouraging 100 percent remote SDV. ACRO requests EU-level legislation that does the following—

- assures stakeholders that “processing operations related to reliability and safety purposes” enables remote review of unredacted data for purposes of source data review or source data verification (SDR/SDV) on the grounds of compliance with a legal obligation to which the controllers (sponsors and/or clinic-institution of the investigators/investigators) are subject under the requirements of Good Clinical Practice
- encourages EU/EEA-wide agreement to the use of common monitoring and risk management plans incorporating rSDR and rSDV across all Member States
- stresses that remote monitoring and rSDR/rSDV must not result in confidential patient information being sent to the sponsor/CRO or being stored by the sponsor/CRO if this has not already been addressed in the participant information sheet. For example, unredacted copies of medical notes, from which individuals may be identified, should not be emailed or posted to the sponsor. Source data verification may be done remotely by electronic means if the necessary security arrangements can be put in place. For example, this could be done by using video calls, via controlled access to relevant electronic health records, or certified copies thereof (e.g., the use of a secure document sharing platform), but sponsors/CROs must not retain any screenshots or electronic records.
- states that the following four conditions shall adequately satisfy requirements for Electronic Health Record systems:
 - read only access
 - audit trail to enable site to confirm that monitor only reviewed trial subject notes
 - requirement for CRA to view in a secure location. For example, from their (home) office, rather than a public area
 - confirmation from the CRA that they will not download, screenshot or screen-print

Section Three:

Revise the legislation to adapt to cutting-edge products, scientific development (e.g., genomics or personalized medicine) and technological transformation (e.g., data analytics and digital tools), provide tailored incentives for innovation

Enabling eConsent and eSignatures throughout Europe in the Interest of Clinical Trial Modernization

Current Challenges:

In order to achieve clinical trial modernization in the 21st century and focus on patient-centeredness, trials must incorporate digital and remote solutions. The lack of harmonization and standardization in Member States' acceptance of eConsent and eSignatures is a key barrier to optimized, 21st century clinical trials that utilize digital, remote solutions to meet the needs of participants. The lack of harmonization and standardization also adds to the cost and complexity of clinical research in Europe. The use of eConsent facilitates and supports ongoing initiatives to make the consent process more comprehensive and inclusive. By facilitating a consent discussion with a participant who is not physically at the site, eConsent expands participation to populations traditionally not afforded clinical research opportunities and helps achieve the important goals of diversity, equity, and inclusion.

ACRO notes that the topic of eConsent and eSignatures is even more timely, given the expected finalization of ICH E6(R3) in 2022. Indeed, the ICH E6(R3) Draft Principles, released on 19 April 2021, explicitly acknowledge the value of technology in the informed consent process. The Draft Principles highlight the importance of technology and their specific potential for the informed consent process (emphasis added):

*The principles are intended to support improved and more efficient approaches to trial design and conduct. For example, **innovative digital health technologies may expand the possible approaches to trial conduct**. Such technologies can be incorporated in existing healthcare infrastructures and enable the use of a variety of relevant data sources in clinical trials. **This will aid in keeping clinical trial conduct in line with advancing science and technological developments**. The use of technology in the conduct of clinical trials should be adapted to fit the participant characteristics and the particular trial design. The use of innovative technologies may help enable those designing and conducting a trial to include relevant patient populations. (page 2)*

3.2

*The process and information provided should be designed to achieve the primary objective of enabling trial participants to make an informed decision on whether or not to participate in the trial. The informed consent process should take into consideration relevant aspects of the trial such as characteristics of the participants, the trial design, anticipated benefit and risk of medical intervention(s), setting and 19 April 2021 4 context in which the trial will be conducted (e.g., trials in emergency situations), **and the potential use of technology to inform participants and obtain informed consent**. (page 3)*

Proposed Solution and Request:

ACRO acknowledges that the varied approaches to eConsent and eSignatures are based on national Member State regulations. However, ACRO recommends the introduction of EU-level legislation to allow the use of eConsent and eSignatures (including the capture of consent) in clinical trials, in order to promote patient-centricity and access to clinical research, reduce the complexity and associated costs of managing clinical trials in multiple Member States, and enhance the perception of the EU as a supporter of innovation in clinical research.

Additionally, although several Member States permit e-consent and e-signature, there is currently little consensus on the standards that should be applied. Consequently, it would be helpful for legislation to provide for a standard approach which:

- states that an acceptable e-signature for clinical trial purposes should be linked to the respective record and include details of the date and time at which the signature was applied.
- states that an e-Signature is acceptable for all clinical trial documents listed in the ICH list of essential documents for which a signature is required.
- describes the following requirements as adequately satisfying an e-consent system:
 - Participants must be informed of the nature, significance, implications and risks of the trial in an interview with the investigator, or another member of the investigating team
 - The interview should involve two-way communication in real time and allow confirmation of the participant's identity
 - Information about the trial does not have to be in writing and can be provided to potential participants using electronic methods. However, special attention should be paid to the information needs of specific patient populations and those of individual participants
 - Informed consent must be recorded 'in writing'. Electronic methods for documenting consent can be considered to be in writing
 - A copy (physical or electronic) of the signed consent form should be provided to the participant
- if consent and signature are both remote, the investigator/designee must implement a method to ensure the identity of the participant (e.g., verification of state identification or other identifying documents or use of personal questions or visual methods).

Thank you for the opportunity to provide this feedback. Please contact ACRO (knoonan@acrohealth.org) if we can answer questions or provide additional details.