European Commission

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EUROPEAN MEDICINES AGENCY

HMA
Heads of Medicines Agencies

ACT EU multi-stakeholder platform

Kick-off workshop report

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Contents

Introduction

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Excellent clinical trials are core to the generation of clinical evidence. In turn, robust clinical evidence is critical to the development of new medicines and the safe and effective use of medicines already on the market. The European Union (EU) has a long tradition and a strong academic base in clinical trials. However, in recent years, increasing complexity within the clinical research environment and fragmentation across the EU clinical trials landscape have led to fewer impactful clinical trials being conducted in the EU, relative to some other regions of the world.

Accelerating Clinical Trials in the EU (ACT EU) is a joint initiative of the European Commission, Heads of Medicines Agencies (HMA) and the European Medicines Agency (EMA). ACT EU's vision is to make the EU a competitive centre for innovative clinical research, building on the new Clinical Trials Regulation (CTR) and the Clinical Trials Information System (CTIS) launched on 31 January 2022.

Smarter, often larger and more impactful clinical trials can only be achieved by empowering, engaging and supporting all stakeholders. ACT EU foresees the establishment of a neutral multi-stakeholder platform (MSP) enabling all key players to come together to discuss challenges, share experience, and work together towards improving evidence generation and innovating trials. The MSP is expected to be a mechanism for responding to stakeholder needs and promoting better communication among key stakeholders.

On 22 and 23 June 2023, the European Commission, HMA and EMA organised a kick-off workshop to present the scope of this platform and listen to stakeholder feedback on the EU clinical trials landscape. The workshop aimed to gain a stronger understanding of stakeholders' priorities and perspectives on how to transform the EU environment for clinical trials, and to present and discuss a proposed model for the establishment of the MSP.

Session 1

Setting the scene

Moderators: Peter Arlett (EMA) and Björn Eriksson (HMA)

Key messages

- The EU Clinical Trials Regulation (CTR) represents an important step towards full harmonisation across clinical trial regulation and processes within the EU.
- ACT EU aims to support the ongoing transformation of the EU clinical trials environment to ensure people in the EU have faster access to innovative medicines.
- To invigorate the EU clinical trials landscape, stakeholders emphasise the importance of reducing bureaucracy by simplifying guidance and procedures, as well as the need for increased patient centricity and involvement of all key actors involved in a medicine's lifecycle.

Over the last two decades, the EU clinical trials environment has undergone a number of changes to simplify and harmonise the administrative provisions governing EU clinical trials and to tackle obstacles that hamper the conduct of multinational trials in the EU. Further progress has been made with the recent application of the EU CTR and the related launch of the single EU portal and clinical trial database, CTIS.

Building on the momentum of the CTR and CTIS, the ACT EU initiative aims to support further transformation of the clinical trials environment in the EU. With a number of priority actions covering different aspects of clinical trials, the main goal of ACT EU is to contribute to the health of EU citizens through faster access to innovative medicines and optimised use of medicines on the market.

At the start of 2023, a public consultation was held to gain insight into the priorities of all the stakeholders involved in clinical trials and on the proposal for establishing a multi-stakeholder platform (MSP). Respondents confirmed the importance of all ACT EU priority actions, with a focus on the successful and timely implementation of the CTR and methodological guidance on topics such as decentralised trials and the interface between the CTR and the *in vitro* diagnostic medical device and medical device regulations (IVDR/MDR).

In terms of the MSP proposal, respondents flagged the need to ensure adequate representation of key stakeholder groups in such a platform, including patients, clinicians, academia and sponsors.

The panel and audience discussion focused on how the EU clinical trials environment could flourish. The discussion pointed to a need for simplification, targeted trainings (especially to increase understanding of the CTR and CTIS) and adequate patient involvement at different stages of the clinical trials.

Session 2

Discussion on priority areas

Moderators: Stan van Belkum (HMA/CCMO) and Harald Mische (European Commission)

Key messages

- The CTR has improved the regulatory system, promoting greater harmonisation and transparency. To ensure successful implementation, stakeholders would benefit from closer engagement and additional guidance on CTIS, the interplay between the CTR and other legislations (MDR/IVDR), and the use of patient data.
- Efficient implementation of the CTR requires greater collaboration between ethics committees within and across Member States. An EU platform for ethics committees would help increase alignment and allow the sharing of best practices.
- ACT EU should facilitate purposeful and timely transparency, which is key to maintaining patients' and citizens' trust and promoting clinical trial innovation.

Clinical trial regulation implementation update

The CTR replaced Directive 2001/20/EC and provides a new regulatory framework for clinical trials. It aims to minimise divergent approaches and promote harmonisation across EU Member States, while maintaining the highest standards of patient safety, data integrity and transparency.

In collaboration with Member States and the European Commission, EMA set up the Clinical Trials Information System (CTIS) to streamline and facilitate the flow of information between sponsors and Member States and between Member States themselves.

Comprehensive guidance on the CTR application has been provided by the Commission in the form of a Q&A[1], which was developed with the pivotal contribution of experts and endorsed by the Clinical Trials Coordination and Advisory Group (CTAG). The scope of this document is to inform on the technical aspects of the CTR to facilitate its implementation.

In 2022, stakeholders were consulted through a survey to understand their first experience with the application of the CTR and the use of CTIS, and the challenges identified are actively being addressed. A new survey will be launched in September 2023 to identify further hurdles and seek feedback on progress made to date.

Member States support to the CTR implementation

Member States are closely involved in various aspects of the CTR implementation. As well as assessing clinical trial applications, individual Member States have been working to define the

[1] Note: only the European Court of Justice can give an authoritative interpretation of Community law.

national implementation of the CTR, set up transparent fee structures and, most importantly, support collaboration between national competent authorities (NCAs) and medical research ethics committees (MRECs) to achieve a consolidated decision for each clinical trial application.

During the session, sponsors were reminded that, under the CTR framework, trials that are expected to end in the EU after 30 January 2025 must be transitioned to CTIS before that date. To streamline the process, the Clinical Trial Coordination Group (CTCG) established by the HMA developed guidance for sponsors to facilitate the expedited administrative procedure. This guidance was updated and published in July 2023 (see CTCG Best Practice Guide for sponsors of multinational clinical trials under CTD transitioned to CTR) and the Commission has provided additional clarifications in an *ad hoc* guidance document (see Guidance for the transition of clinical trials from the Clinical Trials Directive to the Clinical Trials Regulation (europa.eu)).

During the panel discussion, stakeholders commented on their contribution to the successful implementation of the CTR. They flagged the need for more flexibility to ensure the successful transition of affected clinical trials to CTIS and to enable submission of parallel substantial modifications. Panellists also called for more guidance, for example to ensure a more effective interplay between the CTR and the IVDR/MDR and to allow a more flexible interpretation of low-intervention trials.

Other important topics raised during the discussion included adaptations to CTIS so that newer forms of trial design, such as platform trials, are supported, as well as the need for a platform where academia could share best practices and exchange experiences. Further issues to address were the need for alignment between parts I and II of the clinical trial application, the harmonisation of the ethics review and the role of the General Data Protection Regulation (GDPR) within the CTR, particularly when it comes to informed consent. From the patient perspective, patient-reported outcome measures (PROMs) were highlighted as important sources of information for clinical trials and the development of new medicines. To capture PROMs effectively, patient organisations need support, for example by developing standards for data collection and ensuring that information is available to patients. Patient organisations also require support to manage patient registry data collection.

The role of ethics committees in clinical trials

With the introduction of a single clinical trial application dossier, the CTR has brought about a new way of working in the EU, requiring greater collaboration between NCAs and MRECs, but also between MRECs themselves.

Ethics committees play an important role in ensuring that the rights and wellbeing of trial participants are protected. As such, MRECs are key to maintaining the EU as an attractive region for conducting scientifically and ethically sound clinical trials.

There was support for an EU platform for ethics committee to achieve better alignment and collaboration between the different MRECs structures in the EU. With representatives from different Member State MRECs, such a platform would give insight into differences between systems, but would also provide an opportunity to discuss how to increase alignment and to share best practices. Such an EU ethics committee platform could provide a coordinated voice from MRECs in the EU.

Transparency of clinical trials

Publicly available information contributes to protecting public health and fostering innovation in European medical research, while recognising the legitimate economic interests of sponsors. With around 18 months of experience with CTIS to date, a revision of the CTIS transparency rules is underway. A public consultation was conducted to collect views from system users and stakeholders and discuss the best approach to balancing transparency of clinical trials information in CTIS and confidentiality requirements. While ensuring that the CTIS transparency rules remain fully in line with the CTR, the ongoing revision will lead to modifications of the existing rules, such as those on the publication of deferred trials, and to an update to the CTIS functionalities. The appendix on disclosure, defining the current transparency rules for CTIS, will also be replaced by a new, concise document on the technical aspects of the CTIS transparency rules.

Transparency regarding clinical trial data is welcome and the panel presentations raised a number of important points on the topic. Stakeholders recognised the importance of transparency for clinical trial data as a way to promote patient trust and drive innovation. Transparency can help healthcare providers give optimal advice to patients, build patient trust and drive innovation, and this includes transparency on negative trial results. However, transparency should be purposeful, focusing on the patient's needs and offering opportunity to improve public health, while also respecting the integrity of the trial.

Session 3

Discussion on priority areas

Moderators: Jane Moseley (EMA) and Gunilla Andrew-Nielsen (HMA/CTCG)

Key messages

- Clinical trials conducted by non-commercial sponsors make up a large proportion of the clinical trials in the EU and are central for changing practice and improving standards of care. A flexible definition of non-commercial clinical trials is needed to optimise the use of these trials in medicine approval in the EU.
- ACT EU seeks to enable non-commercial trials in the EU by working to remove bottlenecks faced by sponsors. Further training and guidance are needed for key stakeholders, along with better alignment between the level and duration of funding and the clinical trial timelines, particularly for multinational trials.
- Greater coordination between the scientific advice procedures for clinical trials and for marketing authorisation applications can be achieved by enhancing the exchange of information and developing a more consolidated approach to the scientific advice process. Early involvement of patients, ethics committees and health technology assessment (HTA) bodies would be optimal, along with further support for academia and small and medium-sized enterprises (SMEs).
- ACT EU seeks to facilitate alignment and optimisation of EU methodology guidance.
- During a public health emergency, better coordination of clinical trial assessment and authorisation and further harmonisation of national regulations would facilitate the setting up and conduct of effective clinical trials in the EU.

Supporting non-commercial clinical trials

Non-commercial clinical trials make up a large proportion of the clinical trials in the EU and are often supported by public funding or grants. According to a survey carried out by the CTCG, the definition of a non-commercial trial varies between Member States. The definition often relying on the purpose of the trial, in particular whether the data collected are used for regulatory or marketing authorisation purposes. Definitions further include elements such as the nature of the sponsor, ownership and source of funding. It was agreed that the definition of non-commercial trials represents an important challenge and needs further discussion, as definitions do not adequately reflect how evidence generated in non-commercial clinical trials is used. There was also a strong consensus that all evidence, whether generated by a commercial or non-commercial sponsor, should be included in the assessment of medicines.

According to stakeholders, to ensure the EU is an attractive and patient-centred environment for clinical trials, all types of trials, including non-commercial ones, should be facilitated and promoted. Non-commercial trials are central for changing practice and improving standards of care, and complement those from commercial sponsors.

Non-commercial trial sponsors often require infrastructure support and capacity to get the trial through all the regulatory steps at the national or multinational level. It is therefore important to encourage capacity building, involving funding bodies and those driving the non-commercial research agenda. It was noted that funding of multinational non-commercial trials should reflect the long-term nature of clinical research and should match the needs of a multinational study in terms of both duration and level of financing.

Sponsors of multinational academic trials as well as patient organisations working in the field of rare diseases often face challenges when it comes to navigating the complexities of national regulations. There is a need for further harmonisation of national requirements and guidance on how to interact with regulators, as well as methodological guidance. To achieve this, existing infrastructures supporting clinical trial management should be strengthened and developed at national and EU level. In addition, panellists proposed navigation support at EU level as well as an EU-level network to help and improve stakeholder initiatives in non-commercial clinical research. The value of data from non-commercial clinical trials for modifying existing therapeutic indications (e.g., extension of indication/repurposing) was acknowledged by the stakeholders.

Stakeholders agreed that ACT EU should enable non-commercial clinical trials by facilitating interactions and removing bottlenecks faced by academic sponsors. The approach should involve all stakeholders, with a common goal and a shared responsibility, recognising that flexibility is needed. The MSP could facilitate the sharing of best practices and guidance relating to non-commercial clinical trials, especially when it comes to multinational trials.

Reinforcing coordination between scientific advice and clinical trial approval

ACT EU aims to strengthen coordination between scientific advice and clinical trial approval by enhancing the exchange of information within the network and by developing a more consolidated approach to the scientific advice process.

General agreement was reached on the need to provide more support, especially to patients, academia and small and medium-sized enterprises (SMEs), who may not always be familiar with the regulatory language and requirements. In this context, participants proposed workshops and clearer guidance, including guidance on scientific advice for different trial types, such as drug repurposing studies.

Stakeholders also recognised the benefit of earlier involvement of patients (with a more prominent role for PROMs in the scientific advice process), ethics committees and health technology assessment (HTA) bodies, including in the ongoing simultaneous national scientific advice (SNSA) pilot.

Harmonisation of scientific advice procedures and timelines, together with early involvement of HTA bodies and payers, would further enhance the current scientific advice activities. The increased consolidation of national scientific advice facilitated by the SNSA pilot was welcomed and participants reported positive experiences to date while noting opportunities for further development of the procedure and bringing it closer to EMA scientific advice. Greater continuity between the scientific advice provided prior to clinical trial application and the clinical trial approval could be achieved by involving clinical trial experts in the scientific advice. In terms of medical devices, *in vitro* medical devices or companion diagnostics, for the performance studies a more coordinated scientific advice procedure involving notified bodies would be welcomed. A further suggestion for a more consolidated approach to scientific advice was involving the MREC in the SNSA, while considering the implementation of Regulation (EU) 2023/2282 on HTA.

Optimising the EU infrastructure for methodology guidance

The European Medicines Regulatory Network (EMRN) requires excellent coordination to work together efficiently and make the most of opportunities for synergies. At the core of the EMRN's activities lie clinical trials. Within ACT EU, work is underway to better align guidance on clinical trials across the EU network. Based on a broad definition of methodology guidance, an overview of key existing, ongoing and planned guidance activities is being put together to clarify the guidance landscape. This will be complemented by a multi-stakeholder workshop in November 2023 to further consolidate guidance development by identifying priority topics, defining best practices for developing guidance and setting out a process for coordinated guidance development.

During the discussion it was highlighted that the methodology guidance should be flexible to accommodate different needs. Proposals for priority topics included digital health data, innovative trial designs such as complex trials, and decentralised trials and drug repurposing.

Lessons-learned workshop on clinical trials in public health emergencies

In the face of a public health emergency (PHE) there is a need for large, fast and well-coordinated clinical trials, both within the EU and globally. During a recent workshop, participants discussed lessons learned from the COVID-19 and mpox public health emergencies and possible actions to secure faster clinical trial approval across multiple countries in a PHE setting.

EMA's Emergency Task Force (ETF), which was set up during the COVID-19 pandemic, now has a formal legal mandate as an advisory and support body on medicines for PHEs and preparedness. As such, the ETF plays an important role in providing scientific advice and support to large multinational clinical trials that could be key during a PHE. The ETF scientific advice procedure involves the CTCG and patients, healthcare professionals and ethics committee representatives and also incorporates input from clinical trial experts at NCAs so that trial sponsors receive feedback in one go. This will facilitate rapid approval of clinical trial protocols at national level.

The workshop considered some of the obstacles to conducting large and fast clinical trials during a PHE. These included a lack of coordinated decision-making at EU level on which products and clinical trials to pursue, and insufficient coordination among the Member States and between NCAs and ethics committees, resulting in slow assessment and authorisation of clinical trial applications. Other issues related to a lack of harmonisation of national regulations in the case of multinational trials and a lack of flexibility in the CTR to accommodate the approval process.

Possible actions to facilitate regulatory approval of clinical trials in the EU during a PHE include setting up cooperation mechanisms between ethics committees at EU level, continuing ETF's role as a *one-stop-shop* for the coordination of clinical trial protocol reviews with the reference Member State, CTCG and MRECs, and further improving the functionality of CTIS to ensure that the EU has the necessary agility for clinical trials conducted during a PHE.

Funding-related issues were also identified as potential obstacles to clinical trials in the EU during PHEs. It was noted that there is a lack of flexible funding mechanisms for larger, multinational trials, with slow and uncertain mobilisation of the necessary funds. A coordinating committee could support rapid decisions on which study is needed and which clinical trial network or platform should be used in an emergency. These recommendations would be linked to funding, taking into account ETF feedback and the envisaged clinical trial authorisation process.

Session 4

Building a multi-stakeholder platform for Europe

Moderators: Melanie Carr (EMA) and Maria Lamas (HMA)

Key messages

- Ongoing dialogue among all stakeholders is vital to keep up with advances in regulation, methodologies and technology and to facilitate multinational clinical trials in the EU.
- The ACT EU multi-stakeholder platform will bring together all stakeholders in a neutral forum to share perspectives and promote innovation.

The CTR has intensified the need for dialogue among stakeholders to ensure more multinational clinical trials are conducted in the EU and to keep up with advances in regulation, methodologies and technology. The MSP will aim to accelerate innovation, connect stakeholders in a neutral forum, and build trust and drive transparency by sharing perspectives and outcomes.

Following public consultation on the initial proposal for the MSP, a revised proposal is being drawn up, based on clear guiding principles. The proposed model builds on the existing ACT EU structure, with an advisory group forming the strategic link between ACT EU and the stakeholder communities. The advisory group will include representation from key stakeholder groups and ACT EU, enabling bidirectional exchange. The advisory group will identify stakeholder priorities and advise on how stakeholders can contribute most effectively. It will also facilitate topic-specific workshops and review groups and advise on stakeholder engagement and communication.

Based on input from participants at this MSP kick-off workshop, the next step will be to define the selection criteria for the advisory group, put out a call for nominations and draft the mandate and rules for procedure for the advisory group.

The MSP initiative was welcomed by stakeholders as a vehicle through which stakeholders and ACT EU can come together, connected through participation in ACT EU priority action multi-stakeholder events, and under the guidance of the MSP advisory group and related governance. Panellists agreed that the MSP should be able to capture the views from all stakeholders, including decision makers, and highlighted the importance of having concrete goals for the MSP and ensuring that priority topics are discussed with relevant experts from all stakeholder groups.

Patients called for the MSP to be committed to creating a patient-centred framework for clinical trials in the EU, through early patient involvement in research and through patient education and empowerment. The platform can also support meaningful patient involvement in the development of new methodologies and initiatives, such as the EU health data space, which are key to providing powerful data.

From the healthcare professional perspective, the MSP should help change the way evidence is generated to ensure there are impactful, high quality clinical trials in the EU that reach the patients and reflect the patient populations treated post approval.

The needs of academia should also be reflected in the MSP, which could contribute to the development of suitable trainings and guidance materials for these stakeholders. The MSP should further ensure that clinical trials not only focus on new treatments, but also inform clinical practice for existing therapies.

Closing remarks

Moderators: Björn Eriksson (HMA), Sylvain Giraud (European Commission) and Peter Arlett (EMA)

The clinical trials landscape in the EU is complex and challenging, but there is now a robust regulatory framework in place that will support innovation, greater harmonisation and robust data generation, while also ensuring the safety of clinical trial participants. ACT EU was set up to help stakeholders maximise the opportunities for clinical trials in the EU, harnessing flexibilities in the CTR to ensure convergence and minimise divergence.

The workshop confirmed stakeholders' support for an advisory group that includes key stakeholder representatives, which would guide the multi-stakeholder platform activities within the existing ACT EU structure. The advisory group should become a hub of meaningful cooperation between all stakeholders, with an inclusive approach, ensuring representativeness, and with the common purpose of advancing and supporting a thriving clinical trials ecosystem in the EU which places patients at the centre. The crucial collaboration seen at this kick-off workshop will continue, with topic-specific workshops to follow later in 2023 and calls for nominations for members of the ACT EU advisory group planned in the autumn of 2023.

Glossary

ACT EU	Accelerating Clinical Trials in the EU
ATMP	Advanced therapy medicinal products
CCMO	Central Committee on Research Involving Human Subjects
CTAG	Clinical Trials Coordination Advisory Group
CTCG	Clinical Trials Coordination Group
CTIS	Clinical Trials Information System
CTR	Clinical Trials Regulation
EMA	European Medicines Agency
EMRN	European Medicines Regulatory Network
GDPR	General Data Protection Regulation
HMA	Heads of Medicines Agencies
HTA	Health technology assessment
IVDR	Regulation on *in vitro* diagnostic medical devices
MDR	Regulation on medical devices
MREC	Medical research ethics committee
MSP	Multistakeholder platform
NCA	National competent authority
PROM	Patient-reported outcome measure
PHE	Public health emergencies
SME	Small and medium-sized enterprises

More information

The Accelerating Clinical Trials in the EU (ACT EU) initiative aims to develop the European Union further as a competitive centre for innovative clinical research. ACT EU seeks to deliver on the clinical trial innovation recommendations of the European medicines agencies network strategy and the European Commission's Pharmaceutical strategy for Europe.

ACT EU builds on the Clinical Trials Regulation (CTR) and Clinical Trials Information System (CTIS) launched on 31 January 2022. The European Commission, EMA and Heads of Medicines Agencies launched ACT EU in January 2022 and run the initiative together, establishing a steering group in March 2022. The programme's strategy paper features ten priority action (PA) areas that are the basis for the ACT EU workplan.

The ACT EU workplan was published in August 2022 and sets out deliverables and timelines for the programme for 2022-26. The deliverables for 2023 include:

- Establishing a process to support academic sponsors in enabling large multinational clinical trials
- Supporting clinical trial sponsors to make best use of available CTIS and CTR training activities
- Setting up a multi-stakeholder platform to facilitate dialogue between clinical trial stakeholders, including patients, healthcare professionals and academia
- Modernising good clinical practice by supporting the adoption and implementation of revised EU guidelines in clinical trial design
- Facilitating innovation in clinical trial methods by publishing a methodology roadmap and further developing guidance on decentralised clinical trials.

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