EMA/340269/2023
Health Threats and Vaccines Strategy

Report of the EMA/ETF workshop on Lessons Learned on Clinical Trials in Public Health Emergencies

1. Executive Summary

Lessons learned from the COVID-19 and Mpox public health emergencies of international Concern have highlighted the need to improve the way Clinical Trials (CTs) are set up and conducted in the EU during crisis times to ensure that sufficient evidence is rapidly gathered from adequately sized clinical trials across multiple Member States to support rapid access to treatments and vaccines.

On the 9th of June 2023, the European Medicines Agency (EMA) hosted a workshop in Amsterdam to collect views and perspectives of the various stakeholders on how to improve clinical trials conduct should future public health emergencies arise in the EU. Academic sponsors of clinical trials, ethics committees' representatives, National Competent Authorities (NCAs), EMA, and the European Commission participated in the discussion.

This summary report provides an overview of the identified issues that hamper a swift set up of clinical trials during public health emergencies (PHE) and summarises possibilities for concrete actions that were presented and discussed by stakeholders present at this workshop. These will serve as a guiding basis for Member States (MSs), the EMA, and the European Commission to define a roadmap towards enabling multinational clinical trials in the EU in emergency contexts.

2. Introduction

The COVID-19 pandemic brought to the fore structural challenges and revealed barriers that hamper the rapid set up and start of large, multinational clinical trials. The fragmented clinical research landscape across the European Union (EU)/European Economic Area (EEA) and competition for the same resources and patient populations was detrimental to early patient access and rapid generation

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of conclusive evidence on safety and efficacy of promising vaccines and treatments. Public health institutions in Europe rapidly highlighted the need to enhance the conduct of larger studies across several European countries and to speed up recruitment and delivery of conclusive results. The ability to set up coordinated studies across Europe has been impaired by the difficulty of activating networks of clinical trial sites across Member States and ensuring timely funding. Finally, the time to gain authorisation to start a clinical trial in multiple Member States appeared to be too slow and burdensome in particular in the context of public health emergency.

As a building block of the European Health Union, the Member States and EU institutions launched legislative and non-legislative measures to make the Union better prepared and to be able to promptly act against future public health emergencies.

On one hand, from a legislative point of view, the mandates of the European Centre for Disease Prevention and Control (ECDC) and of EMA have been extended with Regulation 2022/2370 and 2022/123 respectively. In addition, the Health Emergency Preparedness and Response Authority (HERA) has been established as a new Commission service to strengthen the access and availability of critical medical countermeasures for improved crisis response, including support for accelerated development of safe and effective medications to patients in the European Union. An Emergency Task Force (ETF) was established within the EMA to provide advice on scientific questions related to the development of treatments and vaccines targeting the emergency, including on clinical trial protocols to sponsors, public health bodies, and academia, and on establishing opportunities for coordinating or merging trials with the same or similar objectives with the involvement of EU MSs clinical trials experts. The overall objective of these articles of the legislation is to support the conduct of coordinated, well-designed, and adequately powered randomised controlled clinical trials. Clinical trials conducted during the pandemic were almost exclusively submitted under the former Clinical Trial Directive, whilst starting from January 2023 they have to be submitted under the Clinical Trials Regulation (EU) No 536/2014 (CTR). It can be assumed that this will bring a higher level of harmonisation, predictability, and coordination. Ultimately, decisions on clinical trial applications remain within the competence of the Member States, in accordance with the CTR, but the spirit is to make every effort to avoid divergencies among EU entities that could hamper rapid approval of trials.

Additionally, in January 2022 as a non-legislative measure, the European Commission, the Heads of Medicine Agencies (HMAs) and the EMA launched an EU clinical trials transformation initiative: Accelerating Clinical Trials in the EU (ACT EU) with a comprehensive approach to make the clinical trial research environment flourish.

With respect to funding and coordination of clinical research, several measures have been put in place by Member States and EU institutions such as the set-up of clinical trial networks, e.g., EU-RESPONSE, Ecraid and VACCELERATE. A fora for discussion across clinical research networks have also been set up, e.g., the clinical Trial Coordination Board (TCB) and the Cohort Coordination Board (CCB); as well as the Joint Access Advisory Mechanism (JAAM) for an independent expert assessment of new compounds to be clinically tested.

During a public health emergency recognised at EU level, MSs have to remain compliant with the CTR, which created a regulatory framework for coordinated assessment and authorisation of clinical trials in Europe. Also, the CTR enables sponsors to submit one online application via a single online platform

known as the Clinical Trials Information System (CTIS) for approval to run a clinical trial in several European countries, making it more efficient to carry out such multinational trials.
Nevertheless, the Mpox outbreak proved that several of the issues have persisted and, therefore, complementary solutions must be explored together with the clinical research community.

3. Discussion

The meeting was Chaired by Sandra Gallina, Director General SANTE (Directorate-General for Health and Food Safety) and Marco Cavaleri, Chair of EMA ETF. The EMA Executive Director Emer Cooke, Sandra Gallina and the Vice-chair of HMAs Bjorn Eriksson opened the workshop highlighting unanimously the need to coordinate CTs at speed and at scale avoiding fragmentation of research, to unite forces to make Europe more attractive to research and CTs, and to reassure on the support of the EU bodies and of the MSs in these endeavours.

The morning session of the workshop described the existing European processes for regulatory approval of multinational trials and the lessons learned from the COVID-19 and Mpox crisis. Representatives of European Commission, National Competent Authorities (NCAs) and Ethics Committees (ECs) gave an overview of their respective role and responsibilities in the authorisation of CTs and the EU regulatory framework, with focus on the Clinical Trial Regulation (CTR) and its implementation tool Clinical Trial Information System (CTIS). They considered that the facilitation of multinational assessments submission and assessment under the CTR can still be regarded as burdensome and slow mostly due to the necessity of alignment of national laws. However, it was noted that the CTR does not prevent collaborative approaches on a voluntary basis outside of CTR to accelerate scientific, ethical, and procedural aspects during public health emergencies. In this context, CT-Cure was mentioned, which is a joint action launched by the European Commission in 2021, whose aim is to ensure expedited and harmonised assessment of multinational clinical trials applications, related to COVID-19 therapeutics submitted to CTIS under the CTR. The experience with CT-Cure highlighted the need to simplify part I and II assessment of the Clinical Trial Application (CTA) dossier, to increase clarity on national requirements especially for part II and to introduce the practice of pre-submission meetings to address issues and concerns ahead of submitting CTAs, and to involve, where necessary, the EMA ETF, NCAs and relevant Ethics Committees.

The role of EMA ETF during public health emergencies is essential to advise and support the EMA Scientific Committees in providing scientific advice to developers and sponsors, in supporting the conduct of multinational CT together with the Clinical Trials Coordination Group (CTCG) and the Clinical Trial Advisory Group (CTAG). It also performs scientific reviews of evidence on investigational or repurposed medicines, with the aim to facilitate the authorisation of medicines targeting the emergency. The ETF supports the initiatives of the MSs and of the European Commission, including the newly created HERA, by providing expertise and publishing recommendations on scientific and public health matters and on investigational medicines.

The academic sponsors of the EU-RESPONSE network and of the MOSAIC mpox clinical trial summarised their experiences and challenges encountered in conducting multinational CT during the recent public health emergencies. The main issues relate to excessive CTA documentation, complexity and duration of procedural timelines linked to CTIS and insufficient harmonisation across MSs of the CTA assessment to a high number of requests for additional information. The areas that have been identified as particularly problematic are the approval of part II of CTA dossier, the implementation of substantial modifications (in particular the addition of new sites or change of principal investigators) and the clinical trial site contract finalisation in multiple MSs.
The experience gained in other jurisdictions, such as the global infectious disease network INSIGHT, funded by the U.S (United States) National Institute of Health, underlined the importance of having a large yet agile clinical trial network with the necessary expertise established in advance of emergencies and that can be rapidly activated in case of emergencies. Indeed, there is a need in the EU to have ever-warm CT networks to implement CT during preparedness or inter-epidemic times, established on the basis of clinical research areas and using harmonised protocols. These networks could then be rapidly mobilised or scaled-up when the emergency strikes, using the pre-certified sites that have proven/demonstrated suitability within the network and are familiar with the regulatory aspects to conduct those CTs.

The afternoon session of the workshop focused on the framework for funding and coordinating CTs in the EU, with specific input provided by the Deputy Head of HERA, Laurent Muschel, by the Director of Directorate-General for Research and Innovation (DG RTD), Irene Norstedt, by the consortium preparing for establishing the Pandemic Preparedness Partnership, by ECRIN, by the Clinical Trial Coordination Board (TCB) and by the researchers involved in CTs and CT networks.

The group heard of EU funding through the R&I framework programme Horizon Europe, European Structural and Investment funds (ESI), and EU4Health *inter alia*, and discussed how EU funding can be structured and interconnected with national funding to sustain trial network infrastructure and address public health needs for both emergency response and preparedness purposes. The importance to ensure that medicines going through CTs have demonstrated proof of concept via pre-clinical research and the role of animal models was raised. HERA presented ongoing initiatives to support clinical trials (Mpox, Ebola, Coalition for Epidemic Preparedness Innovations (CEPI), the European & Developing Countries Clinical Trials Partnership (EDCTP)) and additional funding mechanisms under HERA's remit (e.g., EU4Health, HERA Invest) relevant for clinical trials as well as, HERA methodology to identify and prioritise pipeline products. In addition, HERA presented their activities and funding in support of development, production, and procurement (stockpiling) of critical medical countermeasures in preparation for and in case of a crisis. The need for rapid funding strategies in emergencies to avoid fragmentation was highlighted. BE-READY[1], presented the preparations for setting up the European Partnership for Pandemic Preparedness (PPP) that aims to increase coordination of funding for research and innovation among Member States based on a strategic research agenda that includes preparation and reinforcement of CT infrastructure and networks in advance of a pandemic to guarantee an efficient response at the time of a crisis.

The European Clinical Research Infrastructure Network (ECRIN) is a federated organisation to support sponsors with provision of services and advice, and to develop tools and partnerships for multinational CT. The Joint Action Advisory Mechanism (JAAM) provides independent scientific assessment to guide the access of new interventions into platform trials.

The Trial Coordination Board (TCB) is funded through several Horizon 2020 or Horizon Europe funded consortia and led by researchers and sponsors of platform trials. It became a trusted forum during the COVID-19 pandemic to share experiences and knowledge, and act as a facilitator in Europe to increase attractiveness and collaboration for research with other global actors, enabling a sustained engagement between the trial networks and with the European commission. Whereas the TCB is seen as a platform for efficient bottom-up coordination of CTs, there is the need for a more comprehensive and structured coordination to inform rational allocation of funding and structured decision-making models.

Experiences related to coordination and funding were shared by researchers involved in COVID-19 and Mpox CTs and CT networks. The major difficulties included delayed availability of funds during emergency, lengthy negotiations for site contracting, impacted by different requirements in each MS, difficulties in the procurements of investigational products and data management.

There was an agreement that the Health Security Committee (HSC) will need to be involved in the coordination during the entire PPR (Prevention, preparedness, response) cycle.
The afternoon session concluded with the summary from Peter Piot, special advisor to the President of the European Commission Ursula von Der Leyen. Prof. Piot underlined the need for a greater sense of urgency to make Europe a better place for clinical research. The starting point is a set of recommendations from this stakeholder technical workshop to be used by the European Commission, MSs and relevant bodies to set up a concrete roadmap looking into problem solving for identified bottlenecks, coordination committee at the central level and sustainability going forward. Peter Piot concluded that the secretariat of the proposed Coordination Committee should be provided by HERA.
The Director general for DG SANTE, Sandra Gallina, highlighted once more the willingness of the European Commission to push regulatory flexibility bearing in mind the safety of patients, the development of preapproved templates and prequalification of sites among other identified actions and proposed solutions that are listed in the following sections.

4. Proposed actions for further consideration

The following actions were discussed as possible options for consideration by EU institutions and Member States on the way forward.

a. Process and regulatory approval of large, multinational clinical trials in the EU during public health emergencies

Problems & proposed solutions

Foreword

- *The proposed solutions should remain in compliance with the CTR to ensure the validity of the authorisation granted.*
- *It is still possible to envisage solutions on a voluntary basis beside the CTR, which would help foster the CT application assessment and the coordination across the decision makers.*

Problem (1): Insufficient coordination within the Member States (MSs), between national competent authorities (NCAs) and ethics committees; and across Member States in the case of multinational trials, also due to national requirements that lead to dis-harmony.

Proposed actions

1. Increase communication and management efforts to ensure that there is appropriate coordination between the relevant regulatory bodies involved in the implementation of the CTR at national level, including national competent authorities and ethics committees.

2. Ensure that no additional document/data/information in clinical trial applications can be requested on top of CTR requirements, which should already be the norm.

3. Creation of a fit-for-purpose 'emergency' application package compliant with the CTR to gather essential information in the lowest possible number of documents, whilst allowing Member States to evaluate the benefit/risk balance of the trial as well as ensuring generation of reliable and robust data. Use of harmonised templates among EU MSs.

4. Only the MSs' most critical considerations will be sent to the sponsor as Requests For Information (RFIs[1]). When adding a new MS to the clinical trial, this new MS will take into account previous assessment in other Member States.

Problem (2): Slow clinical trial application assessment and authorisation

Proposed actions

1. Setting up an EU level cooperation mechanism between national ethics committees, open to participation from representatives from all MS. Such a cooperation mechanism should provide a forum for consultation by the national ECs to facilitate pre-CTA discussion and assessment.

1 CTTM11_FAQs (europa.eu) Question 1.1. What is a Request for Information (RFI)?

2. ETF should have a role as one stop shop forum to coordinate discussions and advice on critical aspects of CT part I submissions i.e., the clinical trial protocol, involving ethics committees and CTCG representatives, the Reporting Member State (RMS), and the Member State Concerned (MSC), EMA and relevant Commission services (in particular SANTE/HERA/RTD).

3. Setting up pre-submission consultations on specific (individual) clinical trials applications upon request by the sponsor. The sponsors, the ethics committees with expertise in the subject, the proposed RMS, and the MSC should be involved. The aim of the pre-submission consultation is to clarify concerns and gaps in the dossier to expedite the assessments once the application is submitted via CTIS. It should encourage the use of harmonised application templates.

Problem (3) Lack of flexibility in CTR for the approval process

Proposed actions

1. It was agreed that there is the need to reconsider the implementation of the CTR with enhanced flexibility in mind to avoid bureaucracy, and bottlenecks. This should include a simplified template and process for providing a final assessment report.

2. Revise and adapt the HMA/EMA/European Commission COVID-19 flexibilities paper and apply to any public health emergency trial.

3. Discuss with the sponsor starting from very early stages of the outbreaks all relevant questions ahead of the clinical trial application submission via CTIS.

4. Prolong the project period of the EU4Health-funded CT-CURE joint action with 15 EU/EEA Member States to allow sharing experience between all Member States in EU/EEA. The best practice developed for expedited assessment of multinational clinical trial applications in public health emergencies should be the basis for future public health emergencies.

Problem (4) Functioning and knowledge of CTIS

Proposed actions

1. Continue to resolve issues and improve the features of CTIS to enable the necessary agility for public health emergency clinical trials. This discussion should involve sponsors and MSs. For example, more flexibility on the procedures for additional MS and substantial modification submissions. CTIS should support accelerated timelines for the RMS and MSC to manage the expedited assessment.

2. Ensure that sponsors of emergency clinical trials are represented at relevant clinical trials fora including the CTIS Forum and ACT EU Multi-Stakeholder Platform.

3. Continue to disseminate at EU, national, regional, and local level the EMA training material, with ad-hoc communications to non-commercial sponsors and small and medium-sized enterprises.

b. Framework for funding clinical trials during emergencies in the EU

Problems & proposed solutions

Problem (1) Insufficient coordination and fragmentation of clinical trials during emergencies

Proposed actions

- To **establish a Coordinating Committee** for improved coordination for decisions on the prioritisation of clinical trials in Europe.
    - This Coordinating Committee will make recommendations to support rapid decisions on which study is needed and which clinical trial network/platform should be used in an emergency, among those established and kept warm in inter-epidemic periods.
    - These recommendations can be linked to funding, taking into account scientific, including methodological and medical aspects, the envisaged CT authorisation process and ETF regulatory feedback.

- The Coordinating Committee is ruled by a transparent governance that defines clear tasks and responsibilities.

- Starting from currently established fora for discussion (e.g., EMA ETF, TCB, CCB), to **pilot an increased level of collaboration and coordination** to inform the decision-making process by the Coordinating Committee.

Scope of the Coordinating Committee

During crisis:

- Possibly even before there is any formal declaration of public health emergency, the Committee **identifies the clinical trials** that are needed to address the emergency, including which medicinal products should be considered for investigation, and any other relevant

trial/study to address public health needs or to optimise the use of already established medical countermeasures.

During inter-epidemic periods:

- The **Coordinating Committee oversees an appropriate landscape** of perpetual/warm-based trials and strategic cohorts in the EU, covering both vaccines and therapeutics, that are maintained in the interepidemic period, and for which the trial protocols have the in-built ability to pivot rapidly in case of a public health emergency.

- As needed, additional master protocols for Disease X / preparedness studies may be developed by the clinical trial networks, in coordination with the EMA ETF.

- The **Coordinating Committee prioritises investigational medicinal products** targeting the high priority threats (pathogens with pandemic potential, AMR, chemical, biological, radiological and nuclear (CBRN) agents), that can be tested outside of a declared emergency, e.g., antibacterial agents, antiviral agents for respiratory diseases etc.

- Besides clinical trials that could support the pathway to regulatory authorisation of medical countermeasures, i.e., phase 1 to 3 clinical trials, other studies addressing public health needs or optimising the use of medicinal products will be considered as well, e.g., strategy trials or comparative efficacy clinical trials.

- **The Coordinating Committee discusses adequate and sustainable funding** for the selected preparedness trials and cohorts, respecting the governance of contributing funding programmes at Union level.

- Interactions with the private sector are expected to occur, including the options of co-funding of selected clinical trials. The private sector will have direct access to the clinical trial networks.

Participation to the Coordinating Committee

The Coordinating Committee should include at least the following stakeholders:

- Scientific and public health experts with no conflicts of interest
- Representatives of EU institutions and bodies, i.e., the European Commission (HERA, RTD, SANTE, and Directorate-General for Communications Networks, Content and Technology (DG CNECT)), and agencies (EMA ETF, HADEA and ECDC)
- Representation from Member States, especially funding bodies
- Patients' representatives
- Appropriate interaction and communication with international actors will be established
- Representatives of the different main clinical trial networks will attend as observers with measures to avoid conflict of interest in place

The Committee will report its activities back to 1) the Health Crisis Board tasked to ensure the supply of and access to crisis-relevant medical countermeasures during a public health emergency, 2) the Health Security Committee tasked with the overall coordination between Member States for preparedness and response measures to cross border health threats, including research needs, and 3) the Health Programme Committee tasked with coherent research funding.

Problem (2) Lack of consolidated mechanism for investigational products prioritisation

Proposed Actions

- Establish a **process for transparently identifying and ranking products** for clinical trials during emergencies and in inter-epidemic periods for specific intended use; the joint access advisory mechanism (JAAM) could serve as a starting point for this purpose. Prioritisation done by HERA will be taken into consideration. This process entails:
    - A selected group of independent experts assesses candidate products according to criteria for prioritisation as agreed by the Coordinating Committee.
    - Candidate products are proposed by any member of the Coordinating Committee or external parties including industry and clinicians.
    - Interaction of the expert panel with developers ensures that available information is shared to allow proper prioritisation.
    - The selected panel of experts score the products and make a proposal for prioritisation to the Coordinating Committee.

- Within the Coordinating Committee, the prioritised products will be discussed as well against the intended investigational use and the clinical trial conditions that would be most suitable, e.g., post-exposure prophylaxis vs early treatment vs specific populations and clinical settings (e.g., primary care or hospital care).

Problem (3) Lack of flexible funding mechanisms for larger, multinational trials: Mobilisation of the necessary funds is slow and uncertain

There is a need to maintain a flexible but synergistic approach to the allocation of funds from different national and European sources.

Proposed actions:

Set-up efficient and predictable funding mechanisms for high-priority emergency or preparedness trials

1) Funding to support pivoting of the trials in a public health emergency

- During crisis, and possibly before formal emergency declaration, the relevant financial support will be provided mainly under emergency funding (ESI) from the European Union. However, other EU funding mechanisms can also be mobilised as appropriate. Available national funds could complement the EU funds.

- Explore the possibility of rapid release of MS and/or EU funds while ensuring equal treatment of potential beneficiaries, avoiding delays due to the publication of calls, preparation and submission of proposals, evaluation, and grant preparation, and only then funding.

2) Funding to sustain the perpetual trials in the long term

- In inter-epidemic periods and for sustainability of clinical trial networks, aim to establish funding mechanisms that allow longer-term preparedness planning through the conduct of studies that are performed outside of a declared emergency, e.g., assessing antivirals, antibacterial agents addressing antimicrobial resistance (AMR), etc.

- Combined funding by MS and the EU for the perpetual trials could be considered, to better leverage EU (e.g., Horizon Europe, EU4Health) and MS (through the Pandemic Preparedness Partnership) funding sources, for better coordination of funding to increase efficiency and sustainability.

- The already established clinical trial networks in the EU should be expanded to new clinical trial sites and/or new networks compliant with the pre-defined standards can develop to ensure a balanced regional spread across Europe.

Facilitate clinical trial sites contracting and conduction

- Increased harmonisation of trial site contract templates, at least at national level and possibly at EU level: consider use of EU template as condition for funding of large-scale preparedness trials.

- Creation of a network of pre-qualified clinical trial sites with a standard set of qualification documents and a standard contract to be updated as appropriate. Data protection impact assessment (DPIA) process standardisation should also be considered.

- Adequate involvement with trial sites in the network, so they are prepared and committed to participate in the trial.

- Some EU coordination entities are financed to dedicate resources also to address issues related to study start and monitoring (in a 'CRO-like' role). Need of close relationship with the sites and investigators.