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ETF – ACT EU Priority Action on Clinical Trials in Public Health Emergencies

Workshop report

21-22 November 2024

An agency of the European Union

Strengthening collaboration between Regulatory Authorities and Ethics Committees

Introduction

The COVID-19 and Mpox Public Health Emergencies (PHEs) highlighted significant challenges in the rapid set up and initiation of large, multinational clinical trials (CTs), emphasizing the need to improve the way CTs are conducted in the European Union (EU) during crises. In order to increase the effectiveness of the response in preparedness and during emergencies in the EU, the Member States (MSs) and relevant Union bodies, launched several legislative and non-legislative measures.

An Emergency Task Force (ETF) was established by Regulation (EU) 2022/123 as the EMA expert group to manage PHEs, as well as preparedness. In this role, the ETF is mandated to provide scientific advice to developers including on the main aspects of CTs and clinical trial protocols submitted, or intended to be submitted, in a clinical trial application (CTA). The ETF is also required to obtain from developers' information on the MSs where an application for authorisation of a CT is submitted, or is intended to be submitted, and to involve those national competent authorities in the preparation of said scientific advice (SA).

The Accelerating Clinical Trials in the EU (ACT EU) programme, initiated by the European Commission, the European Medicines Agency (EMA) and the Heads of Medicines Agencies (HMA), aims to create a favourable environment for all clinical research and development of medicines through harmonisation, innovation and collaboration among CTs stakeholders in the EU. The ACT EU programme features a 'priority action' with the aim to facilitate large multinational clinical trials in the EU during PHEs. To fulfil this objective, a group of experts from the regulatory, ethics and academic fields have been working on crucial aspects to support the rapid approval, start and conduct of adequately powered CTs in preparedness for, and during PHEs, that are coordinated in an effective manner.

The role of Medical Research Ethics Committees (MRECs) is essential to ensure the protection and well-being of patients and participants in CTs, as well as to enable a rapid response and approval of CTs during PHEs. Therefore, one of the main objectives of the ACT EU priority action on CTs in PHEs has been to set up a public health emergency ethics advisory group (PHE EAG) with the role to provide expertise and support to the ETF assessment of SA applications covering aspects of CTs in preparedness and during emergencies. Ultimately, the PHE EAG will gain experience on the involvement of MRECs in SA for CTs during emergencies, which will inform future policy recommendations of the ACT EU priority action on CT in PHEs.

The joint workshop on 21-22 November 2024 brought the ETF, ACT EU priority action on CTs in PHEs and the PHE EAG together for the first time, with the objective to discuss topics relevant to improving preparedness and cooperation during PHEs and to explore policy options to accelerate CTs in the EU. The event emphasized fostering collaboration, streamlining processes, and addressing challenges in order to improve and expedite the set up and initiation of CTs in PHEs in the EU.

Strengthening collaboration between regulatory authorities and ethics bodies to facilitate clinical trials in preparedness and during public health emergencies

The workshop kicked off with an overview of the ACT EU priority action on CTs in PHEs and the role of the ETF in crisis scenarios. The priority action focuses on three main objectives:

strengthening the involvement and collaboration of ethics committees; developing a simplified CTA package in a PHE; and developing a fit-for-purpose regulatory flexibility toolkit for the assessment and conduct of CTs in PHEs. To support the first objective, the PHE EAG has been set up, currently composed of experts from 11 MSs. Additionally, the merits and obstacles of an EU central ethics committee for the assessment of clinical trials in PHE are being discussed. Both in preparedness and during PHEs, the ETF provides formal scientific and regulatory recommendations through SA procedures with input from representatives of National Agencies with expertise in CTs as the Members of the Clinical Trials Coordination Group (CTCG). The involvement of PHE EAG in ETF SA would be critical to capture the thinking of ethics experts and foster harmonisation of EMA, clinical trial units and ethics committees' perspectives in EU. The participants discussed the best approach to test this collaboration.

Exploring the best framework for an overarching approach to facilitate the conduct of clinical trials during emergencies in the EU.

Different areas have been identified where harmonisation and simplification of the CTA package to be submitted for assessment in case of PHE, could be beneficial, while adhering to national law specifications and requirements. In the context of emergencies, the main priorities include having a set of minimum required documents for dossier content, reducing administrative burden and improving coordination.

In order to accelerate the start of clinical trials in PHEs, prepositioning of core protocols that are agreed with regulatory authorities and ethics committees without including the full set of medicines to be investigated in an emergency in a platform trial, has been considered as a valid strategy. The current legislation allows for partial submission of applications provided that at least one investigational medicinal product (IMP) is included. A syndromic approach as well as recycling successful protocols could be particularly valuable in this context. The World Health Organization (WHO) has identified 12 viral families and is organizing collaborative consortia for each to develop core protocols that can be pre-approved for prototype medicines and vaccines, allowing the drafting of legal agreements and facilitating funding. This approach has already been put in place for the recent Marburg outbreak in Rwanda. Both the syndromic and pathogen approaches are valuable and could complement each other.

Another relevant aspect is funding. Working on preparedness poses additional challenges in securing funds and sponsorship for a potential emergency that may not occur. To address this, the European Commission together with MSs and EMA has developed a CT coordination mechanism to identify and prioritise investigational medicines targeting high-priority threats, to create a landscape of warm-based trials and strategic cohorts, and foster alignment between EU and national funding to support such initiatives. The warm-based approach was strongly supported by the participants of the workshop.

The lessons learned from the RECOVERY trial, a successful pragmatic trial conducted in the UK during COVID-19, were discussed. This large-scale trial that used a platform design and factorial randomization, provided crucial information into the performance of several drugs and contributed to defining optimal treatment approaches. Several factors were critical to its success, and it was agreed that this experience could be applied to clinical trials in the EU. Key elements for success included:

- adopting a pragmatic approach,
- using pre-engineered contracts and cost frameworks to minimize time and expenses,
- establishing streamlined protocols and easily adaptable templates,

- avoiding fragmentation and adopting a prioritization approach that all sites had to follow,
- using centralised regulatory and ethics assessments, safety reporting and granularity proportional to the scenario to reduce unnecessary costs and burdens for investigators.

Ethical issues and considerations for placebo-controlled clinical trials in public health emergencies

The main ethical aspects for placebo-controlled CTs and controlled human infection models (CHIM) were discussed.

The discussions touched upon important criticalities such as conducting placebo-controlled CTs in these situations: i) high-risk populations where an approved comparator is available, ii) when the approved comparator is not available in the MS, iii) immunobridging approaches for updating medicines targeting rapidly evolving pathogens, and iv) during outbreaks of pathogens with high morbidity and mortality. Agreement on the level of equipoise coming from prior knowledge of the agents to be investigated is a crucial aspect. However, defining a clear framework is challenging given the complexity of how ethics committees reach their decisions, which, for instance, are based on the collective evaluation of all members. While the expertise of the PHE EAG to support the work of the ETF would be extremely valuable, their views may not necessarily and fully reflect what would be the recommendation of a specific Ethics Committee. The Ethics Committee's opinion stays within the competence of the specific MS concerned.

Ethical issues and considerations for controlled human infection models studies in public health emergencies

The CHIM studies and their contribution to the development and authorisation of medicines were discussed. Volunteers' participation needs to be safeguarded. CHIM studies could play a significant role in preparedness while during emergencies, their role is limited because of time constraints and aspects related to the lack of knowledge around the pathogen involved including possible lack of treatment. The fact that the selected participants are healthy volunteers, which may not necessarily reflect the situation in the at-risk population, may reduce their scientific value. Furthermore, CHIM studies can only be performed for treatable or self-limiting diseases and when results of a CHIM study can lead to regulatory decision-making.

When to accelerate clinical trials approval and how to prevent fragmentation

The discussion explored on how to formally trigger emergency procedures to accelerate clinical trial approval before the formal declaration of a public health emergency in the EU, and how to prevent fragmentation in research with multiple underpowered clinical trials by merging initiatives to generate the most impactful evidence. There is currently no clear legal framework to activate emergency procedures during the period between preparedness and the formal declaration of an emergency. Possibilities are currently being explored within the context of the mpox emergency. As an outcome of the 2023 EMA/ETF workshop on lessons learned on CT in PHE[1], a proposal for a Clinical Trials Coordination Mechanism aimed at identifying and prioritizing financial support for trials based on their robustness and likelihood of providing critical data has been developed by the European Commission. A potential 'activation mechanism' could involve a recommendation from the ETF, to be taken up by the coordination mechanism for clinical research and funding. Warm-based networks with trials integrated into

clinical practice were seen as the best opportunity to prevent fragmentation. Adequate and timely funding is crucial along with enhanced engagement of all Member States in the initiatives.

Experts encouraged innovative thinking and challenged the *status quo* to identify the most effective interventions for PHEs, highlighting the need for efficient mechanisms to facilitate the rapid initiation of CTs while preventing fragmentation and duplication of efforts. Furthermore, open communication between regulators, ethics representatives, developers and investigators are essential to identifying optimal solutions. These actions require strong collaboration, targeted training and transparency.

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