Overview of the content of the draft guidance on the conduct of clinical trials during public health emergencies

Romee Reijsenbach de Haan (EMA)

ACT EU

Delivering benefits to clinical trial stakeholders across key areas [ACT EU website]

Implementation of the Clinical Trials Regulation

Multinational clinical trials by non-commercial sponsors

Multi-stakeholder platform

Good clinical practice modernisation

Clinical trials analytics

Consolidated advice on clinical trials

Clinical Trials methodologies

Clinical trials safety

Clinical trials training curriculum

Clinical trials in public health emergencies

European Commission | EMA HMA Heads of Medicines Agencies

Draft guidance on the conduct of clinical trials during public health emergencies

- Complementary to other guidance documents being developed under the ACT EU priority action
- First consolidated guidance document specifically addressing how to run clinical trials in a public health emergency – building on lessons learnt
- Based on the HMA/EMA/EC COVID-19 guidance (Feb 2022), grounded in existing frameworks: CTR (EU 536/2014), ICH E6(R3), ICH E8(R1), ICH E19
- Will evolve with the European Biotech Act amendments

What does the guidance cover?

1. General considerations
2. Initiating clinical trials
3. Changes to ongoing clinical trials - three types of substantial modifications
4. Adaptations to key aspects of the conduct of clinical trials *(Informed consent; Safety monitoring, safety data collection and reporting; Investigational product management; Distribution of in vitrio diagnostics and medical devices used for testing for medical conditions related to the public health emergency; Trial management; Trial documentation)*
5. Trial-related procedures
6. Methodological aspects
7. Good clinical practice inspections
8. Communication

Overarching principle

A PHE necessitates prompt action to adapt the conduct of clinical trials. Justifiable regulatory flexibilities need to be implemented to ensure that the safety of trial participants is prioritised, while minimising risks to data integrity and reliability. These regulatory flexibilities must be counterbalanced by the foreseeable benefits to public health resulting from the clinical trials. With regard to new clinical trials, which need to be appropriately powered to provide meaningful data, the aim is to initiate them in a timely and safe manner, giving priority to those trials focused on the diagnosis, prevention and treatment of the medical condition associated with the PHE.

- Public consultation until 30 April 2026

Thank you

Initiating clinical trials

Jeroen De Roeck (AFMPS FAGG)

Initiating clinical trials

Timely generation of **robust and reliable evidence-based data** is essential to **inform effective public health interventions** and **regulatory decision-making.**

Rights, safety and wellbeing of trial participants should at all times be **safeguarded**.
ICH E6(R3)

Initiating clinical trials

Prioritization of trials that are related to the **cause** or **direct consequences** of Public Health Emergencies

Making sure human, regulatory, infrastructural, … **capacity** is optimally used

Urgent medical needs, **ongoing development programmes** etc. should be evaluated based on **relevace and criticality to Public Health Emergencies**

Initiating clinical trials

Decision to initiate clinical trial should be tested against **feasibility** and **proportionality** of initiating new trials during a public health emergency, considering the **available infrastructure** and **opportunities for collaboration**.

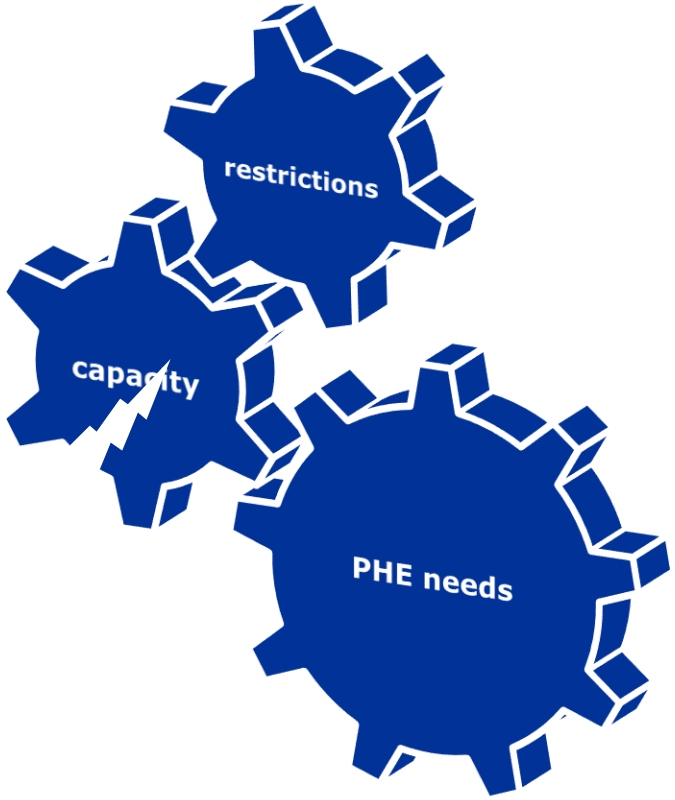
Public health needs;

Industry capacity;

Regulatory capacity;

Public health emergency restrictions;

…;



Initiating clinical trials

Coordination and **collaboration** at national and EU level to avoid unnecessary duplication, ensure optimal use of resources, and facilitate the generation of meaningful trial results.

Regulatory advice from **Emergency Task Force** (ETF)*

> regulatory advice and agreement on trial design, endpoints, in/exclusion criteria, Investigational medicinal product, … could lead to **expedited assessment**

* *Regulation on EMA's Reinforced Role (Regulation (EU) 2022/123)*

Initiating clinical trials

Identification and mitigation of potential risks during trial design!

Logistical feasibility

- *availability/capacity* ***investigator sites and staff****;*
- ***accessibility*** *limitations;*
- *continuity of* ***supply chains****;*

Participant safety

- ***safety oversight*** *and* ***adverse event reporting*** *mechanisms;*

Evidence generation

- ***collaboration*** *or* ***integration*** *with existing coordinated trial infrastructures (e.g. established platform trials or master protocols);*
- *interaction with* ***National Competent Authorities*** *and* ***Ethics Committees*** *to ensure compliance;*

Changes to ongoing clinical trials

Jeroen De Roeck (AFMPS FAGG)

Changes to ongoing trials

To verify if a proposed change is **substantial**

- *Annex IV CTR Q&A;*
- *Check with reporting member state;*

Sponsors are encouraged to seek **scientific advice** from **Ethics Task Forces** to streamline the approval process

- *urgent;*
- *impact on safety of participants;*
- *trial results reliability/robustness;*
- *exceptionally relevant to public health emergencies;*

Specific communication channels to facilitate **clarifications** on **requests for information** (RFIs)

Changes to ongoing trials

3.1. Substantial modifications to **include** the **investigation** of the **prevention** or **treatment** of medical conditions **related to the Public Health Emergency**

3.2 Modifications to **adapt** an ongoing clinical trial **as a consequence of the Public Health Emergency**

3.3 Modifications **unrelated to the Public Health Emergency**

Changes to ongoing trials

3.1. Substantial modifications to include the investigation of the prevention or treatment of medical conditions related to the public health emergency (p.5-6)

Adapting ongoing/authorized clinical trials

Special attention to platform trials

Consideration: **reduced time obtaining results** vs **initiating new trials**

Expedited assessment

Changes to ongoing trials

3.1. Substantial modifications to include the investigation of the prevention or treatment of medical conditions related to the public health emergency (p.5-6)

Examples adaptations

- Adjusting the **trial design** to target the emerging relevant aspects, e.g. endpoints;
- Including a **new cohort** with a different indication;
- Adding **new trial arms** with additional investigational agents;
- Putting **on hold or terminating arms** that are not related to the circumstances of the public health emergency;
- Adapting the **randomisation** to reflect the public health emergency needs;
- Expanding **recruitment** - shortening time to analysis;
- …;

Changes to ongoing trials

3.2 Modifications to adapt an ongoing clinical trial as a consequence of the public health emergency (p.6-7)

Existing trials could be modified because of

- limited participant mobility (lockdowns);
- manufacturing and investigational medicinal product transport constraints;
- interaction public health emergency – existing in- and exclusion criteria;
- …;

Modifications have to be **essential**, **appropriate** and **conditional for the continuation of the clinical trial** without jeopardising trial **participant safety**, **data integrity** and **reliability or personal data protection,**

Changes to ongoing trials

3.2 Modifications to adapt an ongoing clinical trial as a consequence of the public health emergency (p.6-7)

Examples of possible measures (non-exhaustive list):

- Adjustments to the **informed consent process**, such as implementing remote consent;
- Changes to the **schedule or arrangement** and/or **recruiting activities** and processes of the study visits;
- **Temporary halt** of the clinical trial at some, or at all, investigator sites, **postponement of activation** or **closing of sites**;
- **Extension of the duration** of the clinical trial;
- **Transfer of trial participants** to investigator sites away from risk zones, including data transfer/access to all information;
- …;

Changes to ongoing trials

3.2 Modifications to adapt an ongoing clinical trial as a consequence of the public health emergency (p.6-7)

Some changes are **never** acceptable:

- **Disproportionate** or **non-essential changes** to the protocol that are **unrelated to the public health emergencies**;
- Prospective **protocol waivers**;
- Waiving of scientifically validated **eligibility assessments**;
- Waiving of the obligation to obtain and document **informed consent**;
- Postponement or cancellation of **strictly necessary tests** described in the protocol which ensure trial data reliability or robustness and/or the safety of trial participants;
- Omitting or not including the **evaluation by the Ethics Committee(s)**;

Changes to ongoing trials

3.2 Modifications to adapt an ongoing clinical trial as a consequence of the public health emergency (p.6-7)

Expedited assessment

Urgent and **exceptional** changes can be immediately implemented via the **Urgent Safety Measure** (USM) procedure

- *extended scope USM;*
- *prior agreement with reporting member state;*

Changes to ongoing trials

3.3 Modifications unrelated to the public health emergency (p.7-8)

Limit as much as possible!

Evaluation according to **normal timelines** unless **combined** with other substantial modificatiions related to public health emergency

- *prior agreement with reporting member state required*

Fulfillment of Part I condition(s) could be expedited

Thank you

Adaptation of key aspects of the conduct of clinical trials

Informed consent; safety monitoring & reporting; trial monitoring

Gabriele Schwarz (BfArM)

1. Informed consent

Informed Consent in Public Health Emergencies (PHEs)

Core Principles

- Informed consent remains a critical process in clinical trials, including during PHEs.
- Applicable legal, regulatory and GCP requirements remain fully in place.
- Participants may be more vulnerable than under normal circumstances, requiring particular ethical attention

Process Considerations in Public Health Emergencies

- Remote informed consent may be applied as a mitigation measure to address operational constraints.
- The process, including any adaptations, should be described in the protocol or related documents.
- Adaptations or streamlining due to the public health emergency should be justified proportionate to the associated risks.

Remote and Documented Consent in PHEs

Remote Consent (ICH E6(R3))

- Remote informed consent may be used to address operational constraints.
- Conducted via electronic tools; paper-based options remain available.
- Requires real-time audio-visual interaction to support understanding and questions.

Key Requirements

- Identity verification of all parties involved.
- Confidentiality and data protection ensured.
- Consent documented via signed and dated forms (electronic or paper).

Documentation & Oversight

- Process allows retrospective reconstruction (e.g. audit trails).
- Proportionate justification of any adaptations due to the public health emergency.
- Implementation of technical and organisational safeguards for data security.

2. Safety monitoring, safety data collection and reporting

Safety Monitoring and Safety Data Collection during PHE

- **Objective:** To protect participant wellbeing and establish/complement the Investigational Product (IP) safety profile.
- **Alternative Safety Data Collection:** If on-site visits are reduced or cancelled due to a public health emergency, investigators should collect adverse events via alternative means (e.g. phone calls, telemedicine, or electronic reporting).
- **Safety Monitoring Adaptations:** For trial-specific interventions (e.g. blood samples, ECG) moved to new locations or providers, sponsors are expected to ensure appropriate arrangements are in place.
- **Use of Digital Health Technologies (DHTs):** The use of fit-for-purpose DHTs for safety data collection is supported by ICH E6(R3), both during and outside PHE situations.
- **Documentation:** Safety information captured remotely via audio or video should be recorded (electronically or on paper) and transferred into the Case Report Forms (CRFs) or medical records.

Risk-Proportionate Approaches to Safety Data Collection & Monitoring

PHE-Related Trials (Targeting PHE Causes):

- Reduced Safety Data Collection: Urgent public health needs may justify limiting collection to SAEs, Important Medical Events, events leading to trial medication discontinuation, medication errors/overdose, pregnancy/lactation outcomes, and protocol-defined Adverse Events of Special Interest (see ICH E19, Section 2.4).
- Resource Prioritisation: Non-serious Adverse Events, routine lab monitoring, or physical exams may be omitted if they divert resources, provided participant safety and trial results remain valid.

Non-PHE Trials (Unrelated to PHE Causes):

- Standard ICH E19 principles (pertaining to safety reporting) and pre-established risk-proportionate approaches (per EU 536/2014) continue to apply.

Operational Integrity & Re-Consent:

- Sponsor Responsibility: Ensure alternative methods that avoid double reporting/duplicates.
- Participation: Assess if public health emergency related safety concerns affect willingness to continue.
- Re-Consent: If required, new information must be clearly identified in revised materials.

3. Trial Monitoring

Trial Monitoring during PHE

- **Trial monitoring may include on-site, remote and/or centralised monitoring depending on the monitoring strategy and trial design.**
- During a public health emergency, monitoring strategies may require **adaptation** to address emerging risks. The primary consideration in any adaptation is the protection of the rights, safety and well-being of trial participants, as well as the integrity of the trial and trial data.
- The sponsor should determine the **appropriate extent and nature of monitoring** for the specific trial during a public health emergency and balance this against the operational burden on investigator sites, ensuring an **appropriate balance between oversight and site capacity**.
- A **risk-based approach** should be applied, focusing monitoring activities on critical sites, processes and data. Where not already embedded, centralised monitoring of electronic data (e.g. eCRFs, central laboratory, imaging or ePRO data) may supplement or temporarily replace on-site monitoring during a public health emergency.
- The **adjusted monitoring strategy and its impact should be documented** in the clinical trial report.

Remote Monitoring & Source Data Verification during PHE

- Trial monitoring during a public health emergency follows a **risk-proportionate approach in line with ICH E6(R3)**.
- Remote monitoring may be used where appropriate technical capabilities are available.
- In **justified and exceptional cases**, **pseudonymised source data may be shared with monitors** electronically, provided that workload at investigator sites remains manageable and data protection requirements are ensured.
- **Remote Source Data Verification (SDV)** should focus on critical data, including primary efficacy endpoints and important safety data. Secondary efficacy data may be included where this does not increase site burden or require access to additional documents.
- Remote SDV may be particularly relevant for trials involving public health emergency related interventions, serious or life-threatening conditions, vulnerable participants, or pivotal trials.
- Remote SDV arrangements should be described in the protocol or protocol amendments and implemented **in line with the principles of necessity, proportionality and data protection**.

Protocol Deviations and Serious Breaches during Public Health Emergencies

- A public health emergency may increase protocol deviations. The sponsor should manage deviations according to standard procedures and periodically assess their nature and frequency to determine whether protocol modicications are required.
- The sponsor should assess and report **Important Protocol Deviations** in the clinical trial report **in line with ICH E3**.
- A **Serious Breach**, as defined in Regulation (EU) No 536/2014, should be notified via CTIS without undue delay and no later than seven days after becoming aware. Any delays due to the public health emergency should be justified.

Adaptation of key aspects of the conduct of clinical trials

Investigational product management; transfer of patients to other sites

Sarah T'Kindt (AFMPS FAGG)

Context and scope

- Public health emergencies require rapid and proportionate adaptations to clinical trial conduct
- The draft guidance introduces regulatory flexibility under Regulation (EU) 536/2014
- Focus of this presentation:
    - Investigational product management
    - Labelling and instructions for use
    - Transfer of trial participants

Investigational product management

4.3.1.1 Direct Shipment of Investigational Products

- Direct shipment of investigational products to participants' homes may be used during a Public Health Emergency
- Objective: ensure treatment continuity when access to sites is limited
- Considerations on feasibility (IP nature – opinion investigator)
- The investigator remains responsible for IP management, administration and accountability (~ oversight)
- Delivery of IP only to authorised persons
- Includes also Auxiliary Medicinal Product and medical devices
- Data privacy and communication to National Competent Authorities and EC are required

Investigational product management

4.3.1.2: Investigational Product distribution for transferred participants

- IP distribution should be sourced from:
  - the stock allocated to the sites they were enrolled at
  - the stock available at the site they were transferred to
- The provisions related to the labelling of the IP and the instructions for storage and administration should be communicated to the concerned National Competent Authorities and to the Ethics Committees through the submission of a substantial modification to the trial protocol
- Provisions on the transfer of the participants, see section 5.2

Investigational product management

4.3.1.3: IP redistribution between active sites

- Redistribution between sites may be necessary due to shortages or site closures
- Only acceptable when direct supply is not feasible
- Applies also to the Auxiliary Medicinal Product and applicable medical devices

4.3.1.4: Traceability and accountability

- Accountability records must allow full reconstruction of the investigational product lifecycle
- Risk based approaches possible for authorised products

Investigational product management

4.3.2: Labelling

- Risk-based flexibility applies to language requirements during a public health emergency, depending on the investigational product administrator
  - Self-administered IP
  - IP administration by the professional at home
  - IP administration at the investigator site
- If relabelling is not feasible, translated paper or electronic instructions may be provided
- IP administered by professionals may be labelled in a language understood by staff or English

Trial-related procedures

5.2: Transfer of trial participants

- Primary principle: protection of participants' rights, safety and well-being to enable further trial participation
- Participants may be transferred to other EU/EEA sites to ensure treatment continuity
- The sponsor should perform a risk assessment for those transfers and must verify site capacity and medical responsibility
- Data accessibility, operational data-collection tools and prevention of unblinding must be ensured
- Participants must be fully informed

Communication and informed consent

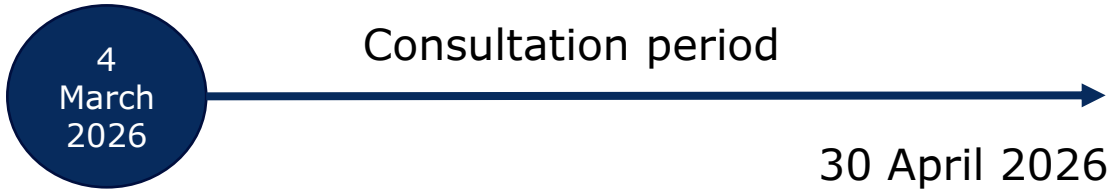
- All communication with participants must occur via the investigator site
- Sponsors should not communicate directly with participants
- Renewed informed consent is required for continuation at a new site
- National competent authorities must be informed of updated site information and investigational product shipment to the participant's home.

Key take-home messages

- The guidance introduces pragmatic flexibility during public health emergencies
- Fundamental good clinical practice principles remain unchanged
- Participant protection and data integrity always prevail

Thank you

How to submit your comments



All stakeholders are invited to provide comments

How to submit comments

- Download the official comments template (Excel) and insert your comments following the instructions in the template
- Email the completed template to: acteu@ema.europa.eu

Key documents

- Consultation page: New guidance on the conduct of clinical trials during public health emergencies in the EU | European Medicines Agency (EMA)
- Draft guidance: Guidance on the conduct of clinical trials in public health emergencies
- **Excel file:** **Template for submission of comments - Draft guidance on the conduct of clinical trials during public health emergencies**

European Commission | EMA HMA Heads of Medicines Agencies

Thank you

ACTEU@ema.europa.eu