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3 Guidance on the conduct of clinical trials during public 4 health emergencies

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Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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Guidance on the conduct of clinical trials during public health emergencies

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1. General considerations

In case of serious cross-border threats that endanger public health in the European Union (EU), as defined in Article 3(1) of Regulation (EU) 2022/2371 -including pandemic situations-, the European Commission may declare a public health emergency (PHE) at EU level. Serious cross-border threats can be of biological, chemical, environmental or unknown origin, or may correspond to public health emergencies of international concern under the International Health Regulations, as described in Article 2 of Regulation (EU) 2022/2371.

Before declaring a PHE, the European Commission will consider expert opinions from the European Centre for Disease Prevention and Control, and from other relevant bodies, such as Commission expert groups, EU Agencies and the Advisory Committee established under Regulation (EU) 2022/2371. The Commission will also liaise with the World Health Organization to share its analysis and inform it of a planned declaration of a PHE at EU level.

The EU legislation (Regulation (EU) No. 536/2014, referred to hereafter as the CTR), and revised or new international guidance (e.g. ICH E6(R3), ICH E8(R1), ICH E19) that became applicable after the COVID-19 pandemic, support a risk proportionate approach in the design and conduct of clinical trials.

This guidance is intended for sponsors and all stakeholders involved in the design and conduct of clinical trials. In the absence of available EU legislation related to PHEs, the provisions described in this document apply to the extent permitted by national legislation.

A key lesson learnt from the COVID19 pandemic is that small, isolated clinical trials or compassionate use programmes in individual Member States may not generate sufficiently robust evidence for clear medical and public health recommendations. This underlines the need to prioritise the inclusion of trial participants in well-designed clinical trials over off-label or compassionate use in order to strengthen the scientific basis for decision making.

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.

It is the responsibility of the sponsor to take into consideration potential risks to the proper conduct of a clinical trial addressing a PHE and to update their risk management plan accordingly. The effort required to implement regulatory flexibilities in clinical trial documentation and conduct should be balanced against the expected public health benefits of earlier access to clinical trial results and uninterrupted continuation of ongoing studies. This document outlines such regulatory flexibilities and discusses the impact of a PHE on key aspects of the conduct of clinical trials.

The concepts of risk management and 'critical to quality' factors (as defined in ICH E8(R1)) should be embedded in the general clinical trial design, as they are essential for ensuring robustness and reliability of clinical trial data and results during a PHE. Such an approach is part of the preparedness strategy for any crisis situation and should be aligned with the regulatory flexibilities outlined in this guidance.

The ethical principles of the Declaration of Helsinki shall be fully upheld during a PHE, ensuring that urgency does not compromise research standards. Apart from detailing possible new provisions related to regulatory submissions and flexibilities in clinical trial conduct, this document does not aim to present a 'one size-fits-all' model for adapting clinical trials during a PHE. It is therefore very important that business continuity plans/emergency preparedness plans that can support robust trial designs and

associated methods and technologies are identified and ready to be implemented as soon as a PHE starts to impact the normal conduct of a clinical trial. This helps manage disruptions effectively and enables stakeholders involved in clinical trials to take immediate action to safeguard participant safety and the integrity and reliability of the data collected.

The publication of the summary of trial results, also in lay terms, should comply with the clinical trials information system (CTIS) transparency rules. Availability of trial results is especially important during a PHE to avoid duplication and to keep the general public informed of the collaborative efforts made by the academia, industry and regulators.

This document will be kept up to date in line with future EU legislation or guidance related to PHE and will be revised once the CTR amendments under the European Biotech Act are adopted.

2. Initiating clinical trials

During a public health emergency, the timely generation of robust and reliable evidence is essential to inform effective public health interventions and regulatory decision-making. In such circumstances, national competent authorities (NCAs) should prioritise the assessment of clinical trials that are essential for understanding, mitigating, or addressing the PHE, while, where necessary, temporarily placing less urgent clinical trials on hold to safeguard regulatory capacity. To enable an efficient and proportionate regulatory response, clinical trials initiated to investigate the cause or direct consequences of the PHE, to address urgent medical needs, or trials forming part of ongoing development programmes should be evaluated based on their relevance and criticality to the PHE.

Regardless of their specific objectives, the initiation and conduct of clinical trials during a PHE should ensure that the trial design, procedures and oversight are fit for purpose and take into account the nature and scale of the emergency. They must also adhere to the principles of ICH E6(R3), including the protection of trial participants, data integrity and the reliability of results.

Sponsors are encouraged to seek scientific advice from the Emergency Task Force (ETF) to streamline the authorisation of clinical trials addressing a PHE.

This guidance applies to:

1. Clinical trials initiated in response to the PHE to evaluate preventive or therapeutic interventions relevant to the emergency itself; and
2. Clinical trials addressing other serious or life-threatening medical needs, and, where feasible, other ongoing or planned clinical development activities that may appropriately continue during a PHE, provided that the safety of trial participants and data integrity can be maintained.

In all cases, the rights, safety and well-being of trial participants take precedence, and the generation of scientifically reliable evidence should remain central to any decision to initiate (or continue) a trial.

Sponsors should assess the feasibility and proportionality of initiating new trials during a PHE, considering the available infrastructure and opportunities for collaboration. Coordination at national and EU level is important to avoid unnecessary duplication, ensure optimal use of resources, and facilitate the generation of meaningful trial results.

Different methodological approaches may be appropriate depending on the type of PHE. For example, large-scale platform or adaptive trial designs may be efficient in widespread outbreaks, whereas smaller or localised emergencies may require different approaches. Such approaches should be scientifically justified, proportionate to the level of uncertainty and risk, aligned with applicable ethical

and regulatory standards, and avoid unnecessary burden for trial participants and investigators. When initiating a new clinical trial during a PHE, sponsors should identify and mitigate potential risks to trial participants, trial integrity and operational feasibility, including but not limited to:

(a) Logistical feasibility

- Availability and capacity of investigator sites and staff;
- Accessibility limitations due to public health or movement restrictions;
- Continuity of supply chains for investigational and supportive materials.

(b) Participant safety

- Maintenance of appropriate safety oversight and adverse event reporting mechanisms.

(c) Evidence generation

- Where possible, sponsors should explore collaboration or integration with existing coordinated trial infrastructures (for example, established platform trials or master protocols) to maximise efficiency and reduce duplication;
- Early and transparent interaction with NCAs and Ethics Committees to ensure compliance with applicable legal and ethical requirements.

3. Changes to ongoing clinical trials

During a PHE, regulators may provide sponsors with specific communication channels to facilitate clarification on requests for information (RFIs) received during the evaluation of substantial modifications (SMs) to an initial clinical trial application. This aims to ensure that all RFIs are well understood and may help avoid conditional approval or rejection of the proposed SMs. If the questions concern ethical aspects, the Reporting Member State (RMS) should coordinate, as appropriate, with the relevant Ethics Committees of the Member States Concerned for the trial. This would facilitate a timely assessment and a faster approval process.

3.1. Substantial modifications to include the investigation of the prevention or treatment of medical conditions related to the PHE

Every effort should be made to adapt ongoing clinical trials, or those already authorised before the start of the PHE, to obtain relevant clinical trial results as fast as possible. Attention should be given to platform trials, because of their ability to efficiently incorporate adaptations. Proposed modifications should be related to the investigation of the prevention or treatment of medical conditions related to the PHE. Sponsors should carefully assess whether adapting an existing clinical trial would be resource-efficient and would reduce the time needed to obtain clinical trial results compared to initiating a new clinical trial. Examples of such adaptations are:

- 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 PHE;
- Adapting the randomisation to reflect the PHE needs;
- Expanding recruitment - shortening time to analysis.

In these cases, the aforementioned changes will be considered substantial, as by definition these will have a potential impact on the safety or physical integrity of the trial participants and, moreover, have a substantial impact on the data generated in the clinical trial and subsequent analyses.

Nevertheless, these SMs could, in many cases, also include changes as described in section 3.2 of this guidance document, and would have to be limited to what is allowed within the boundaries set by EU legislation related to PHE situations.

Measures taken during the PHE would, in most cases, consist of SMs directly linked to the prevention and treatment of the medical conditions related to the PHE. It is therefore essential that such changes can be implemented as fast as possible. These SMs would undergo an expedited process once submitted.

Sponsors are encouraged to seek scientific advice from the ETF on one or multiple proposed SMs that are urgent and have impact on the safety of the trial participants, the robustness and reliability of clinical trial results and/or on changes that are exceptionally relevant to the PHE or could have a significant impact on the PHE. This type of scientific advice can streamline the approval of such SMs.

3.2 Modifications to adapt an ongoing clinical trial as a consequence of the PHE

During a PHE, SMs are likely to be required to enable the clinical trials to continue.

Sponsors should apply only those measures that are essential, appropriate and conditional for the continuation of a clinical trial during a PHE, without jeopardising trial participant safety, data integrity and reliability or personal data protection. Measures should also minimise the introduction of bias into the trial results. Where relevant, these measures should be included as SMs to ongoing trials.

Several measures are listed below as examples. However, this does not represent an exhaustive list:

- Adjustments to the informed consent process, such as implementing remote consent;
- Changes to the schedule or arrangement of the study visits;
- Temporary halt of the clinical trial at some, or at all, investigator sites;
- Adjusting the process of recruiting trial participants;
- Extension of the duration of the clinical trial;
- Postponement of the activation of sites;
- Closing of sites;
- Discontinuation of participation: adapted measures for follow-up;
- Transfer of trial participants to investigator sites away from risk zones, including data transfer/access to all information;
- Initiation of new investigator sites away from risk zones;
- Inclusion of additional critical laboratory tests, imaging and other diagnostic tests, if justified;
- Shipment of investigational products (IP) directly from the study centre to participants;
- Permanent or temporary change of the principal investigator;
- Implementation of remote source data verification (SDV);
- Inclusion of an independent data monitoring committee, if not involved before, and revision of the data monitoring center charter;
- Other changes introducing decentralised elements into clinical trials, in accordance with the Recommendation paper on decentralised elements in clinical trials;

To ensure the ongoing safety, well-being and rights of trial participants during the entire duration of a clinical trial, the following substantial changes are **not** acceptable:

- Disproportionate or non-essential changes to the protocol that are unrelated to the PHE;
- 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).

It is the sponsor's responsibility to assess whether a proposed modification is to be considered substantial or non-substantial. In this regard, guidance is available in Annex IV of the Q&A on the CTR. If the proposed modification is not captured in the Q&A, the evaluation of the substantiality of the proposed modification should always be risk-based and justified, and this assessment should be documented. Communication with NCAs and Ethics Committees regarding the nature of the proposed modification before implementation is always possible and encouraged, especially for modifications that are not described in the aforementioned Annex IV of the Q&A on the CTR.

Once submitted, SMs that are a direct consequence of the PHE will undergo an expedited assessment process.

During a PHE, sponsors are encouraged to seek scientific advice from the ETF on one or multiple proposed SMs that are urgent and have an impact on the safety of the trial participants, clinical trial result robustness and reliability and/or changes that are exceptionally relevant to the PHE or could have a significant impact on the PHE. This type of scientific advice can streamline the approval of such SMs.

In exceptional cases, where immediate action is required (e.g. when the safety of the trial participants would be severely impacted) sponsors may implement changes to an ongoing clinical trial without prior approval, to ensure the safety of the trial participants or the robustness/reliability of the trial data. Such urgent actions can be communicated to the Member States Concerned for the trial making use of the existing Urgent Safety Measure (USM) procedure available in CTIS. In the context of a PHE, the scope of this USM procedure can be extended also to issues directly linked to the PHE, however not concerning *per se* the safety of the IP directly. In such cases, the sponsor can contact the RMS of the ongoing trial and agree to submit in CTIS an USM notification which includes the commitment to submit one, or several SMs if required within the context of the proposed change and directly implement the changes to the ongoing trial. This prior agreement between the sponsor and the RMS ensures that the proper mitigating measures (which may include additional measures related to the context of the PHE) are included in the USM notification and implemented in the trial.

3.3 Modifications unrelated to the PHE

SMs for clinical trials with primary goals or endpoints that are unrelated to the PHE will be assessed according to normal timelines. However, they may be reviewed in an expedited manner if combined with other SMs related to the PHE described in the above sections.

To ensure maximum efficiency of assessment of the proposed modifications, and to allow optimal allocation of resources, when a sponsor decides to group SMs that are both related and unrelated to the PHE, prior agreement with the RMS of the clinical trial should be obtained. It is the sponsor's responsibility to assess whether a proposed modification is to be considered substantial or non-substantial. In this regard, guidance is available in Annex IV of the Q&A on the CTR. If the proposed modification is not captured in the Q&A, the evaluation of the substantiality of the proposed modification should always be risk-based and justified, and this assessment should be documented for evaluation during future GCP inspections. Communication with NCAs regarding the nature of the proposed

modification before implementation is always possible and encouraged, especially for modifications that are not described in the aforementioned Annex IV of the Q&A on the CTR. To ensure maximum efficiency and optimal allocation of resources and to reduce the workload for sponsors and regulators, the number of submitted SMs modifications that are unrelated to the PHE should be kept to a minimum. Therefore, during a PHE, the fulfilment of a previous part I condition for a clinical trial can be accepted by the RMS during the validation phase of a dedicated submission. This allows the RMS to check if the submitted modifications are limited to what was requested in the condition.

4. Adaptations to key aspects of the conduct of clinical trials

4.1. Informed consent

Obtaining and documenting informed consent (in paper or electronic format) is a critical process in the conduct of clinical trials. Despite the exceptional circumstances of a PHE, compliance with applicable legal and regulatory requirements-including adherence to GCP and ethical principles during the informed consent process-remains a fundamental consideration. From an ethical perspective, a major crisis such as a PHE may render potential trial participants more vulnerable than under normal circumstances. Therefore, in case of PHE it is even more important that the informed consent process is conducted fully in line with ethical and regulatory requirements. ICH E6(R3) supports the use of remote informed consent, which could be a mitigation measure to address the operational constraints arising from a PHE. If informed consent is obtained remotely, the process may be conducted electronically, using consent materials provided in digital format, and by documenting the informed consent, including signatures, via secure applications on electronic devices (e.g. mobile phones, tablets, or computers).

The process should allow verification of the identity of the trial participant and of the person conducting the informed consent discussion, including all signatories to the informed consent form, particularly where no prior interaction has occurred. During a remote electronic informed consent process, the interview conducted by the investigator, or a person appropriately qualified and designated by the investigator, should take place using secure, real-time audio-visual communication. This interaction should support participant understanding, allow questions to be asked and addressed, and ensure confidentiality. The informed consent process, including any key steps applied under remote conditions, should be sufficiently described in the protocol or other protocol-related documents to enable appropriate ethical and regulatory review.

Documenting informed consent, including those obtained remotely through electronic means, is essential to support ethical compliance, trial integrity and audit or inspection readiness. The documentation approach should allow retrospective reconstruction of the process and include appropriate technical and organisational measures, such as access controls, authentication, and audit trails, proportionate to the risks and necessary for the conduct and oversight of the clinical trial.

Where elements of the process are adapted or streamlined due to the PHE, the rationale should be documented in a manner proportionate to the associated risks. The informed consent form should be signed and personally dated by at least two natural persons: the trial participant or the trial participant's legally acceptable representative, and the person who conducted the informed consent discussion. Where electronic signatures are used, the selected solution should support identity verification and the integrity of the signed document, considering applicable electronic identification and trust frameworks, such as the electronic Identification, Authentication and trust Services Regulation, as well as national requirements.

In addition to the ethical requirement for informed consent under the clinical trials framework, trial participants should receive appropriate information on the processing of their personal data in accordance with applicable data protection legislation. This includes information on the categories of data collected, the purposes of processing, parties with access to the data, and relevant participant rights. Appropriate technical and organisational measures should be implemented to safeguard confidentiality and data security, including where remote access to identifiable health data is foreseen.

4.2. Safety monitoring, safety data collection and reporting

The purpose of safety monitoring during a clinical trial is to protect the safety and wellbeing of trial participants and to establish the risk profile of the IP.

If the PHE affects the collection of safety data on-site, for example, if protocol-scheduled on-site visits need to be reduced or cancelled, it is important that investigators continue to collect adverse events from the trial participants through alternative means, such as phone calls, telemedicine visits and electronic reporting, as appropriate.

If there are changes implemented to the location or to the service providers for trial specific interventions (e.g. blood samples, ECG), the sponsor should ensure that appropriate arrangements are put in place. The integration of digital health technologies to collect safety data in a fit-for-purpose manner is supported by ICH E6(3) also outside PHE situations.

Furthermore, it is important that the safety information collected remotely through audio or video means is captured electronically or on paper and transferred into the case report forms or medical records of the trial participant, as appropriate.

The adaptations to safety data collection during a PHE depend also on the type of clinical trial, i.e. whether the trial directly addresses the causes of a PHE, or whether it is unrelated to it. For clinical trials targeting life-threatening or very serious outcomes associated with the PHE (e.g. COVID-19), the urgent public health need may justify limiting safety data collection to serious or otherwise critical events, in line with the risk-based principles of ICH E19 (sections 2.4 and 2.5). Non-serious adverse events, various types of laboratory monitoring, physical examinations and vital sign data may be waived if their collection would significantly divert resources, without compromising participant safety or the interpretability of trial results.

For clinical trials not addressing the causes of the PHE, safety data collection should continue to follow the standard ICH E19 principles, as well as any risk-proportionate approaches implemented before the crisis, in accordance with the provisions of Article 41(2) of the Regulation (EU) 536/2014.

Regulation (EU) 536/2014 includes provisions for applying a risk proportionate approach to safety reporting. When risk adaptations to safety reporting includes alternative methods of collecting adverse events, sponsors should ensure that any duplicate reports are identified, and double reporting is avoided.

As also applicable outside a PHE, and in line with the recommendations described in ICH E6(R3), the sponsor should assess whether information on emerging safety concerns related to the PHE-associated medical condition could affect a trial participant's willingness to continue their participation in the clinical trial and if re-consent is required. If re-consent is needed, the new information should be clearly identified in the revised informed consent materials.

4.3. Investigational product management

4.3.1. Distribution, traceability and accountability

During a PHE, it is critically important to maintain the trial participants' access to IP.

The provisions for the management of IPs, including the roles and responsibilities of the investigator and of the sponsor are described in sections 2.10 and 3.15 of ICH E6(R3), respectively. These cover the manufacturing, distribution, handling and storage, dispensing, administration, accountability, return and destruction of the IPs.

All steps of the IP management process should ensure the safety and rights of the trial participants, the integrity of the IP, as well as the reliability of the trial results.

4.3.1.1. Direct shipment of investigational products to the trial participant's place of residence

Section 2.10.8 of the ICH E6(R3) guideline describes the possibility for an IP to be shipped to the trial participant's place of residence, or to a location easily accessible to them (e.g. to a local pharmacy or to a local healthcare centre). This is particularly useful during a PHE, when the access to the investigator sites might be limited or temporarily suspended. The overall aim is to minimise interruptions in the continuity of the treatment.

While responsibility for IP management lies with the investigator, the sponsor may facilitate direct shipment of the IP to the trial participant's place of residence. In this case, the sponsor should set up a written agreement with the service provider undertaking this direct shipment of the IP to the trial participant's place of residence, which covers at least the following provisions:

- Data privacy: The personal data of the trial participants required for the delivery of the IP should be used in accordance with the general data protection regulation, i.e. it should be accessible only to those involved in the delivery of the IP and not made available to the sponsor.
- Delivery of the IP only to authorised persons: When delivering the IP, it should be handed over to the trial participant (or to their appropriate authorised designee, such as a caregiver, if applicable) or to a healthcare professional involved in the trial, if present at the time of the delivery at the trial participant's place of residence.

Dispensing of the IP or its administration may be delegated by the investigator to a pharmacist or to a healthcare professional, respectively in line with national legislation. Nevertheless, the oversight for all IP dispensing and administration activities, as well as the related drug accountability remains the responsibility of the investigator.

If the IP to be provided to the trial participant has a marketing authorisation in the EU/EEA, in case of a PHE its distribution could be performed via the routine care supply chain (e.g. through pharmacies close to the trial participant's place of residence or through online pharmacies), provided that the integrity of the IP and its traceability are preserved.

If the IP is not authorised in the EU/EEA, stricter instructions, controls and traceability in the storage, distribution and dispensing to trial participants (or to their authorised designee) may apply due to higher safety risks for the trial participants, including potential unauthorised access and use.

With regards to the administration of the IP at trial participant's place of residence, this can be done either by the trial participant or by their caregivers, if the pharmaceutical form, the route of administration and the level of complexity of the administration procedure, as well as the safety profile of the IP permit this approach. This is usually the case for IPs with marketing authorisation, which are not restricted to hospital administration. If, however, the self-administration by the trial participant is not considered an adequate approach by the investigator, a healthcare professional would need to administer the IP at the trial participant's place of residence.

If the IP needs reconstitution before administration, the trial participant or their care giver should be instructed in advance on how to perform this task.

Where appropriate, there should be clear instructions on the steps to be followed, including on the dosing. These instructions are in addition to the information already available in the product information of the IP and should be adapted to the needs of the individual trial participant. The use of electronic step-by-step instructions which are easily and promptly accessible (such as links to product websites, online tutorials, electronic information brochures, visual aids), could be considered. Depending on the complexity of the IP handling and storage and administration, the investigator/pharmacist at the investigator site should contact the trial participant after the first delivery of the IP to ensure their proper handling.

The sponsor should provide the trial participant with additional equipment necessary for the safe administration, use and destruction of the IP. This requirement should be described in the protocol or other protocol-related documents (e.g. pharmacy manual), including the documents provided to the trial participant. The delivery of this equipment should follow the same standards as described for the IP delivery.

The intention to ship the IP to the trial participant's place of residence should be communicated to the relevant NCAs and Ethics Committees through submission of a SM to the trial protocol (see chapter 3).

Any communication with the trial participants regarding delivery or (self-)administration of the IP to their place of residence should occur be channelled through the investigator site and not directly through the sponsor.

The recommendations for IP delivery and administration at place of residence also apply to auxiliary medicinal products (AxMP).

4.3.1.2. Distribution and dispensing of investigational products for trial participants transferred to sites unaffected by the public health emergency.

If the impact of the PHE is limited to certain regions within a country or to certain countries, the transfer of trial participants to sites not affected by the PHE and located within the EU/EEA could be a measure to ensure that the trial participants can continue their participation in the trial.

If the IP is dispensed to trial participants who are transferred to other sites, it should ideally be sourced from the stock allocated to the sites they were enrolled at, and which became (temporarily) non-operational due to the PHE. This approach would ensure that the trial participants continue the same treatment they started at the original site and, equally important, the IP would be labelled in the native language of the trial participants. See also section 4.3.2.

If the IP cannot be supplied from the stock allocated to the (initial) site which became inoperable due to the PHE, the trial participant would receive their medication from the stock available at the site they were transferred to.

For blinded IPs, unblinding during the shipment to other sites should be avoided through the implementation of appropriate measures. See section 4.1 of the ICH E6(R3) guideline.

In case of the transfer of trial participants, the provisions related to the labelling of the IP and the instructions for storage and administration should be communicated to the concerned NCAs and to the Ethics Committees through the submission of a SM to the trial protocol. See also sections 3 and 4.3.2. of this guidance document.

4.3.1.3. Redistribution of investigational products between active sites

In case of shortages of IPs at certain sites, or when trial participants are transferred from one investigator site to another site not affected by the PHE (see sub-chapter 4.3.1.2), there may be a need to redistribute IPs between sites to ensure access of trial participants to trial medication and thus, treatment continuity.

Redistribution of IPs between sites should only be considered when direct distribution to an investigator site is not possible, or in the exceptional circumstance where trial participants are transferred from one site to another. In case of redistribution, this needs to be performed in accordance with the provisions of Regulation (EU) No. 536/2014 and of the guideline on the responsibilities of the sponsor regarding handling and shipping of investigational medicinal products for human use in accordance with Good Clinical Practice and Good Manufacturing Practice. Therefore, redistribution should follow written procedures established in cooperation with the Qualified Person. Appropriate records documenting the transfer should be maintained.

The above-described requirements for IP redistribution apply also to the redistribution of AxMP used in the clinical trial.

4.3.1.4. Traceability and accountability

The activities outlined in sections 4.3.1.1. to 4.3.1.3. may impact the level of detail and scope of IP accountability records that need to be maintained. Regardless, the drug accountability records should enable a reasonable reconstruction of the IP's transport, receipt, storage, dispensing, handling, administration, return and destruction, as applicable.

Where unauthorised medicinal products are used as IPs, comprehensive accountability records covering all the elements described above are usually required.

For IPs with marketing authorisation, drug accountability records on IP's transport, receipt, storage, dispensing, handling and administration may be sufficient.

4.3.2. Labelling and instructions for use for redistributed IPs

In relation to the language in which the IP labelling and instructions for use (as applicable) are made available to the trial participants and considering that a risk-based approach would be applied during a PHE, the IPs can be classified into:

- IPs intended for self-administration

In this case, the labelling and instructions for use should be provided in the participant's mother tongue or language of the originating country. If this is not possible, and if IP re-labelling in a good manufacturing practice environment cannot be performed during the PHE, the sponsor may provide the trial participants with a printed or with an electronic version of the labelling and instructions for use in the participant's mother tongue, so that the correct understanding and administration by the trial participant (or their authorised designee) are ensured.

IPs administered by investigator site staff or healthcare professionals at the trial participant's place of residence.

In this scenario, the labelling and instructions for use may be in the language of the EU Member State where the site is located, so that trial staff can safely handle and administer the IP. Alternatively, the labelling could be available in English or in a language understood by the trial staff who is administering the IP.

- IPs administered exclusively at the investigator site

For these types of IPs, if labelling is not available in the language of the EU Member State where the site is located, it could be provided in English or in a language understood by the trial staff who is administering the IP.

Risk proportionate approaches to the labelling requirements for authorised IPs and AxMPs are described in Article 67 of Regulation (EU) No. 536/2014 and are also applicable outside a PHE. Furthermore, the

Commission Delegated Regulation (EU) 2022/2239 allows for the period of use (expiry date or retest date) to be omitted from the immediate packaging of unauthorised IPs and of AxMPs in order to prevent safety risks and delays associated with the relabelling process.

4.4. Distribution of in vitro diagnostics and medical devices used for testing for medical conditions related to the public health emergency

It is important to ensure the availability of those in vitro diagnostic devices and medical devices that are essential to the conduct of the clinical trial (e.g. to allow enrolment, monitoring the safety of trial participants and treatment efficacy, providing data for trial endpoints). Therefore, it is recommended that appropriate stock of these devices is maintained in case of distribution failure, if this is possible without posing any risk to patients undergoing standard medical care and not participating in the clinical trial. In addition, redistribution of these devices between investigator sites may be necessary.

In case the IPs are distributed directly to the trial participants' place of residence, it is acknowledged that the AxMPs (if any), and other products or devices normally provided to the trial participants during on-site trial visits, as defined in the protocol, should also be distributed together with the IP.

As referred to in section 4.3.1.3 above and in line with the guidance available in section 4 of the Recommendation paper on decentralised elements in clinical trials, these recommendations also apply to AxMPs and other products or devices normally provided to the trial participants during on-site trial visits, as defined in the protocol.

4.5. Trial management

4.5.1. Auditing

As a general rule, and in accordance with ICH E6(R3), audits should be conducted in a manner that is proportionate to the risks associated with the conduct of the trial.

During a PHE, on-site audits should be rationalised to minimise burden on clinical trial staff and to ensure the safety of all those involved in the audit, should the PHE be linked to social distancing restrictions. For critical trials or sites with higher rates of data anomalies identified during monitoring, on-site audits as well as remote audits can be considered, after agreement with the investigator and if the audits are assessed as essential, e.g. triggered audits with the purpose of investigating serious deviations from the trial protocol or from the applicable legislation.

4.5.2. Monitoring

Depending on the monitoring strategy and the clinical trial design, monitoring includes site monitoring (performed on-site and/or remotely) and/or centralised monitoring.

Major disruptions, such as PHEs may require adaptations to the planned monitoring strategy to address newly emerging risks.

The priority when considering any change in the monitoring strategy is to protect the rights, safety and well-being of trial participants. A risk-based approach to monitoring should be taken, focusing on those sites, data points and processes which are critical to ensuring the rights, safety and well-being of trial participants and the integrity of the trial (and trial data).

The sponsor should determine the extent and nature of monitoring appropriate for each specific trial during the PHE, and balance this against the additional burden that alternative measures may impose on site staff and facilities.

The monitoring plan should be revised in accordance with these considerations to strike an acceptable balance between appropriate oversight and the capacity of the investigator site.

The adjusted monitoring or review strategy, where applicable, and their outcome and impact should be summarised in the clinical trial report.

The following measures can apply during a PHE:

Site monitoring

On-site monitoring

During a PHE, cancellation or postponement of on-site monitoring visits and extensions to the interval period between monitoring visits may be necessary. When on-site monitoring remains feasible, it should consider national, local and/or organisational measures implemented due to the PHE, the urgency (e.g. source data verification (SDV) can often be postponed) and the availability of site staff.

Additional measures regarding on-site monitoring may include limited, targeted on-site monitoring identifying higher-risk clinical sites, if not already applicable to the clinical trials of concern. The on-site monitoring plan will need to be adapted, and, more emphasis might be placed on centralised monitoring and remote site monitoring, including source data verification.

Remote monitoring

During a PHE, remote monitoring (as defined in section 3.11.4.1 of ICH E6(R3)) is considered a suitable alternative to on-site monitoring, when the technical means are in place at the site. However, some investigator sites may lack the technical capability to support remote SDV. In justified, exceptional cases, pseudonymised copies of key source records may be shared with monitors. This sharing may be performed electronically, provided the workload remains manageable for site staff.

These cases include clinical trials:

- for the treatment or prevention of the medical condition linked to the PHE;
- for the investigation of serious or life-threatening conditions;
- for which the absence of SDV for critical data may likely pose unacceptable risks to participants' safety or the reliability/integrity of trial results;
- involving particularly vulnerable participants such as children or those temporarily (e.g. trials in emergency situations) or permanently (e.g. clinical trials in patients with advanced dementia) incapable of giving their informed consent; or
- that are pivotal.

As part of the preparedness for any PHE, sponsors should consider outlining the possibility of remote SDV in the data privacy section of the informed consent form.

Remote SDV should focus on the quality control of critical data, such as primary efficacy data and important safety data. Important secondary efficacy data may be monitored simultaneously, provided that this does not result in a need to access additional documents and therefore lead to an increased burden on investigator site staff.

Principal investigators should confirm whether their site can support the chosen remote SDV methods, such as:

- direct controlled remote access to medical records;
- video review of medical records without copying or recording.

For clinical trials initiated during the PHE for the prevention and/or treatment of the medical condition linked to the PHE, when remote SDV is foreseen, it should be described in the initial protocol application (and informed consent form).

For ongoing clinical trials, the introduction of remote SDV should be reflected in a SM to the trial protocol. These provisions should be in line with the principles of necessity and proportionality and in a way that protects the rights of the trial participants and should not place any disproportionate burden on site staff.

Remote SDV should not be carried out if adequate data protection, including data security and protection of personal data even if pseudonymised, is not ensured.

If the monitoring strategy is adjusted during a PHE, the sponsor should consider, once the PHE has ended or whenever it is feasible, to perform more extensive monitoring/re-monitoring of data which was subject to remote monitoring.

Centralised monitoring

If centralised monitoring is not already embedded in the trial design and monitoring activities are performed on site, there is a need to re-assess the monitoring strategy in the context of the limitations and risks brought by the PHE.

Centralised monitoring of data acquired through electronic data capture systems (e.g. electronic data capture systems: electronic case report forms, central laboratory or ECG / imaging data, electronic patient-reported outcomes etc.) that are in place, or could be put in place, provides additional monitoring capabilities that can supplement and temporarily replace on-site monitoring through a centralised evaluation of ongoing and/or cumulative data collected from investigator sites in a timely manner.

4.5.3. Protocol deviations and serious breaches

A PHE is likely to introduce more protocol deviations than normal. The sponsor should manage such protocol deviations in accordance with their standard procedures. The sponsor should perform an analysis of the number and type of deviations periodically, to assess whether a protocol amendment or other modifications are needed. A proportionate approach will be taken by GCP inspectors when such deviations are reviewed, recognising that the best interest of the trial participants is maintained, and the trial participants are not put at risk.

Examples of protocol deviations arising from the impact of a PHE on the conduct of a clinical trial could be: missed or delayed study visits (other or of greater delay than initially foreseen), visits conducted remotely (video or telephone visits), inclusion of remote clinical outcome assessments, like physical examination e.g. weight, blood pressure, etc., provided that these are not primary efficacy endpoints, in which case it would lead to study discontinuation due to the PHE.

Important protocol deviations should be assessed and reported in the clinical study report, in line with the provisions of ICH E3.

According to Article 52 of the CTR, a serious breach is defined as a breach likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated in the clinical trial.

Sponsors should notify Member States through CTIS about a serious breach without undue delay and no later than seven days of becoming aware of that serious breach. Please refer to the following document for further details on reporting serious breaches: Guideline for the notification of serious breaches of Regulation (EU) No 536/2014 or the clinical trial protocol. Slight delays in the reporting timelines due to the PHE need to be justified.

4.6. Trial documentation

4.6.1. Essential records/content of the Trial Master File

Essential records are defined in ICH E6 (R3). These essential records should be maintained in the trial master file (TMF). Guidance on the content of the TMF is provided in the Guideline on the content, management and archiving of the clinical trial master file.

Article 57 of the CTR, ICH E6 (R3), as well as the aforementioned guideline support the implementation of a risk-based approach with regards to the content of the TMF.

5. Trial-related procedures

5.1. Decentralised and pragmatic elements of trial conduct

During a PHE, decentralised elements in clinical trial conduct, including trial-related procedures performed outside the investigator site, such as at trial participant's place of residence, may be used to mitigate risks associated with continuing on-site activities or when on-site procedures cannot be fulfilled. Further guidance on this topic is provided in the Recommendation paper on decentralised elements in clinical trials.

5.2. Transfer of trial participants

The rights, safety and well-being of trial participants are the most important considerations in a clinical trial. Therefore, the primary objective for trial participants affected by a PHE is to ensure their further participation in the clinical trial by making it possible to have continuous access to the investigational treatment. In such situations sponsors are encouraged to make necessary arrangements to allow transfer of trial participants to other investigator sites within the EU/EEA, to facilitate delivery of IPs to trial participants' place of residence, or to enable IP redistribution from one clinical site to another site, as mentioned in section 4.3.

To ensure treatment continuity, trial participants enrolled in a site impacted by the PHE may be transferred to another site within the same country, or in an EU/EEA Member State where the trial is ongoing operationally.

If trial participants need to be transferred to other sites, the sponsor should provide relevant NCAs with an up-to-date overview of all investigator sites and their recruitment status to allow assessment of site suitability.

Sponsors should verify that the receiving clinical sites have sufficient capacity and can assume medical responsibility for the continued treatment of the transferred trial participants before relocation occurs. Transfer should only occur if epidemiological risks can be appropriately managed and if the move does not negatively impact public health, including transmission of the PHE-related disease to patients or trial participants at the receiving sites.

Sponsors should ensure that data previously collected from the transferred participants is available at the receiving site and that the data-collection tools are fully operational.

Appropriate measures for sample management should be foreseen, including risk mitigations to prevent unblinding of samples.

Any required amendments to the clinical trial agreement (contract) with investigators and/or institutions receiving transferred participants should be considered, including updated related to medical responsibilities.

Participants should be fully informed about the change of site as soon as the receiving sites are available and a transfer becomes feasible.

All communication with trial participants regarding transfer arrangements should be channelled through the investigator site and not through the sponsor.

Transfer requires obtaining renewed informed consent from the trial participant for the continuation of their participation in the trial.

6. Methodological aspects

A PHE may significantly impact recruitment, data collection, analysis and interpretation of trial results. Therefore, sponsors should conduct a thorough assessment for each affected clinical trial and determine how any gaps in data collection, data loss, challenges in locking databases, protocol modifications etc may impact the statistical analyses. A detailed assessment of the reasons for data loss can support the identification and mitigation of bias, the conduct of robust analysis, and any additional data gathering.

The former Biostatistics Working Party issued, in June 2020, the paper: Points to consider on implications of Coronavirus disease (COVID-19) on methodological aspects of ongoing clinical trials. The recommendations described in this document are generally applicable during PHEs and other major disruptions to the conduct of clinical trials.

Another relevant reference document is: Points to consider on the impact of the war in Ukraine on methodological aspects of ongoing clinical trials, published in April 2022. Although not specific to a PHE, this document addresses major disruptions to clinical trial conduct resulting from military conflicts. In this regard, the considerations relating to transfer of trial participants to investigator sites located in other countries may be useful when a PHE affects only one or several countries and it is not extended across Europe or globally.

7. GCP inspections

The GCP Inspectors Working Group has issued specific guidance on conducting GCP inspections during crisis situations, including PHEs. Relevant guidance is provided in the documents: Guidance on remote GCP inspections during public health threats emergencies and crisis situations (europa.eu).

8. Communication

During and PHE, sponsors should communicate any changes in trial conduct resulting from PHE-related disruptions to investigators and trial participants in a timely manner.

Regulatory authorities and institutional review boards and independent Ethics committees, including those outside the EU, should collaborate to mitigate PHE-related disruptions and work toward a harmonised approach that supports the conduct of global clinical trials during such challenging periods.

9. References

1. ICH E6 (R3) Guideline on good clinical practice (GCP) Step 5
2. ICH guideline E8(R1) Step 5 on general considerations for clinical studies
3. ICH guideline E19 Step 5 on optimisation of safety data collection
4. WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Participants – WMA – The World Medical Association
5. Recommendation paper on decentralised elements in clinical trials
6. Questions and Answers Document – Regulation (EU) 536/2014
7. Guidance on remote GCP inspections during public health threats emergencies and crisis situations (europa.eu)
8. Guideline for the notification of serious breaches of Regulation (EU) No 536/2014 or the clinical trial protocol
9. Points to consider on the impact of the war in Ukraine on methodological aspects of ongoing clinical trials
10. EMA GCP IWG points to consider regarding the management of ongoing clinical trials impacted by political conflicts, natural disasters or other major disruptions
11. Points to consider on implications of Coronavirus disease (COVID-19) on methodological aspects of ongoing clinical trials
12. Guideline on the content, management and archiving of the clinical trial master file
13. Guideline on the responsibilities of the sponsor with regard to handling and shipping of investigational medicinal products for human use in accordance with Good Clinical Practice and Good Manufacturing Practice
14. Proposal for a Regulation to establish measures to strengthen the Union's biotechnology and biomanufacturing sectors (European Biotech Act)

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AxMP	Auxiliary medicinal product
CTIS	Clinical Trials Information System
CTR	Clinical Trials Regulation
ETF	Emergency Task Force
EU	European Union
EU/EEA	European Union/European Economic Area
GCP	Good clinical practice
ICH	International Council for Harmonisation
IP	Investigational product
NCA	National competent authority
PHE	Public health emergency
RFI	Request for information
RMS	Reporting Member State
SM	Substantial modification
TMF	Trial master file
USM	Urgent safety measure

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