EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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EMA GCP IWG points to consider regarding the management of ongoing clinical trials impacted by political conflicts, natural disasters or other major disruptions

Background and Objective

This points to consider document draws from the experience of past major disruptions in society, including the Covid-19 pandemic and the most recent developments of the Russo-Ukrainian War. These are varied in nature but may have similar, multiple consequences on clinical trials performed in the affected geographical areas. This document aims to help sponsors address the resulting challenges and mitigate risks to the rights, safety, dignity, and well-being of trial participants — a particularly vulnerable population — and to the scientific value of the clinical trials.

Scope

The scope of this document is to cover issues that might arise as a result of any political conflict (e.g. armed conflict or political/economic sanctions), either on a national or local level, a natural disaster, a public health threat or any other major disruption in society that threatens the continuity of care and the rights, safety, dignity and well-being of trial participants and may impact the scientific value of the clinical trials (hereafter "major disruption").

This document is complementary to the following guidance documents already published:

- CTCG recommendation to sponsors on managing the impact of the war in Ukraine on clinical trials[1];
- Points to consider on the impact of the war in Ukraine on methodological aspects of ongoing clinical trials[2];
- Covid-19 guidance on the management of clinical trials during the Covid-19 (coronavirus) pandemic[3], current version.

The points highlighted in these documents are endorsed by the GCP IWG.

In addition, the ICH E3 guideline on the Structure and Content of Clinical Study Reports[4] (CSRs) provides a framework for recording and reporting on the actual circumstances of the conduct of a clinical trial, protocol deviations, missed data, or changed approaches to clinical trial conduct, and for analysing and reporting on their impact on trial conclusions. These ICH E3 principles apply in all cases, i.e. how a trial was managed as a result of a major disruption and the effect it had on the data should be described in the CSR.

Risk assessment

All decisions made by the sponsor to adjust clinical trial conduct should follow a risk-based approach. A risk assessment should be routinely performed by the sponsor before the start of the clinical trial (ICH E6[5] section 5.0) and updated as necessary during the clinical trial. In their risk assessment, sponsors should cover the management of potential risks stemming from a major disruption as well as the loss of data. The ethical impact should also be addressed.

If a major disruption occurs, it is expected that the sponsor performs a risk assessment of each individual ongoing clinical trial, that the investigator assesses the risk of each individual trial participant, and that both the sponsor and the investigator implement measures which prioritise trial participant rights, safety, dignity and well-being as well as data validity. Of these considerations, trial participant rights, safety, dignity and well-being should always prevail. Risks of continued participation in the clinical trial should be weighed against the anticipated benefit for the trial participants and society (ref: principle 2.2 of ICH E6).

The risk assessment should be based on input from all relevant parties. It is important that sponsors in their risk assessment consider prioritising critical tasks in the clinical trial and how these are best maintained.

The sponsor should reassess risks as the situation develops, taking the above principles into account. It is possible that the situation develops in a way that local circumstances lead to a local change in risk assessment, therefore the need to implement additional measures may arise and an investigator-driven risk assessment might be necessary.

It is also expected that the risk assessment covers further use of data from trial participants who were transferred to another site and/or another country (see below), to ensure the robustness and integrity of data.

Any risk assessment and re-assessment should be communicated between the sponsor and investigator, documented in the investigator's site file and the trial master file.

General principles/ Potential measures to be implemented

When a trial participant is enrolled in a clinical trial in a country affected by a major disruption, sponsors and investigators should consider in their risk assessment whether any of the following immediate measures could be appropriate. The measures should be agreed between sponsors and investigators, if feasible.

The sponsor should assess whether any changes or arrangements introduced represent an urgent safety measure and/or a substantial amendment to be submitted to National Competent Authorities (NCAs) and/or Ethics Committees, or need to be otherwise notified to NCAs and/or Ethics Committees.

Measures could include:

- Introduction of decentralised elements, e.g. conversion of physical visits into phone or video visits where possible and relevant — please refer to the Recommendation paper on decentralised elements in clinical trials[6], and the Qualification opinion on eSource Direct Data Capture[7];
- Postponement or complete cancellation of visits to ensure that only the most critical visits are performed at sites;
- Temporary halt of the clinical trial at some trial sites;
- Interruption or slowing down of recruitment of new trial participants — the feasibility of including new trial participants in an ongoing clinical trial needs to be critically assessed;
- Extension of the duration of the clinical trial;
- Postponement of clinical trials or of activation of sites that have not yet been initiated;
- Closing of sites; in case it is not feasible for a site to continue participation at all, the sponsor should consider if the trial site should be closed and how this can be done without compromising the rights, safety, dignity and well-being of trial participants and data validity;
- Changes in local laboratory tests and analyses, e.g., performing them at an available (local) laboratory or relevant clinical facility authorised/certified (as required by national legislation) to perform such tests routinely, in case the trial participant cannot reach the trial site. Laboratory tests and analyses performed for safety purposes prevail over those performed for endpoints. It is expected that the sponsor is given access to the normal ranges and certification

information of any additional laboratory used in order to support the use and evaluation of results.

There might also be situations where the Principal Investigator (PI) of a site is indisposed or unavailable for a period and may need to delegate parts of their duties temporarily to e.g., a sub-investigator. If the change needs to become permanent, the information about the change of PI should be submitted to the NCA and/or Ethics Committee(s).

When changes in ongoing clinical trials, such as a temporary halt, are considered, the overall rights, safety, dignity and well-being of the trial participants have to be prioritised, including in terms of continuous access to treatment. All measures need to be considered to reduce the risk to trial participants.

Actions should be well balanced and proportionate. Alternative arrangements — consistent with the protocol to the extent possible — should be fully documented with a rationale.

Prospective protocol waivers (deviations from the inclusion/exclusion criteria of the approved protocol) remain unacceptable and potential trial participants should not be included in clinical trials without a proper eligibility assessment. Any deviations from the protocol need to be reported in accordance with ICH E6 (4.5).

Compliance with the trial protocol should be ensured to an extent that still allows an ongoing benefit-risk assessment of the clinical trial and its participants. The impact of protocol changes on clinical data interpretability needs to be properly assessed by the sponsor and the overall evidence generation package could be subsequently discussed within scientific advice with regulatory authorities. See the Points to consider on implications of Coronavirus disease (COVID-19) on methodological aspects of ongoing clinical trials from the CHMP Biostatistics Working Party (BSWP)[8].

Monitoring always remains a requirement . Site monitoring is usually performed on-site; depending on its purpose and suitability it may be performed off-site (remotely).

It should be possible to monitor, audit and inspect all clinical trials, and it should be taken into account that there may be consequences for a future marketing authorisation application if data cannot be inspected and verified or the integrity and the quality of the reported data cannot be assessed.

Transfer of trial participants to another trial site in the same clinical trial within the country of origin

Based on the benefit-risk ratio for the individual trial participant, transfer of trial participants to investigational sites away from risk zones to sites already participating in the clinical trial, or new sites, could occur. In such cases, it is important that trial participants as well as investigators are in agreement about the transfer. It should be ensured that the site to which the participant transfers is able to access previously collected health information (including necessary medical records) and trial data for the trial participant, and that any eCRF can be adjusted accordingly to allow the site to view previously entered data and enter new data. For blinded clinical trials, measures to avoid the risk of mix-up and unblinding should be taken. The sponsor should consider the impact on trial participants and facilitate arrangements to enable continued participation in the clinical trial.

Transfer of trial participants to an EU/EEA country where the clinical trial is also authorised

When a trial participant is enrolled in a clinical trial in a country affected by a major disruption, the possibility for transfer to another trial site within the country of origin might be limited. As a result, the continuation of participation in the clinical trial in another country, where the clinical trial is also authorised might be an option. This option would need to be assessed on a case-by-case basis.

The following should be considered:

- The overall rights, safety, dignity and well-being of the trial participants, via the established health care system of the country where the participant transfers, have to be prioritised. Local rules should be followed regarding accessibility and right to health care in the country where the participant transfers.
- Consent to continue clinical trial participation in the country where the participant transfers should comply with local rules.
- The PI at the site where the participant transfers should document that the trial participant received all adequate information and that all information obtained and provided was fully understood.
- It should be ensured that translation/interpretation is available both for the information/consent procedure and for all subsequent visits where necessary, with proper documentation in the trial participant's medical files. Medical and administrative care should be provided in a language that is understood by the trial participant during the entire duration of the clinical trial in the country where the participant transfers.
- For investigational medicinal products (IMPs) dispensed and administered at the site where the participant transfers, labelling in the trial participant's language is not required.
  For IMPs managed by the trial participant, the investigator should ensure understanding of the minimum information required by the local labelling requirements. A new label in the trial participant's language may not be necessary if local requirements can be met through the use of accompanying written information and instructions.
- Consideration should be given to the necessary amendments to the Clinical Trial Agreements and to insurance coverage. It should be ensured that the insurance policies cover all trial participants, as well as trial-specific and general liability where relevant.
- The sponsor should consider the impact on trial participants and facilitate arrangements to enable continued participation in the clinical trial.

Transfer of trial participants to an EU/EEA country where the clinical trial is not authorised

If the clinical trial is not authorised in the country of destination, the sponsor is recommended to contact the corresponding NCA or relevant local authority to clarify local law with regard to other potential options for allowing access to investigational treatment for the patient.

Use of data from trial participants transferred to another trial site and/or country

As described in the BSWP points to consider[2], scientific advice on development programmes which are significantly affected is advised. Acting with due diligence at an early stage should minimise the impact on the progress of the development of the concerned medicinal products.

In addition to the BSWP points to consider, the following points should be considered:

- The sponsor will need to determine the impact on the suitability of the data to support decision making for marketing authorisation. This is particularly relevant to data that cannot be verified due to the fact that inspections are impossible (especially if critical data has not been source data verified).
- The sponsor should make every effort to retain data from trial participants in the final statistical analysis. This may require proposing an alternative methodology to deal with missing values and any unforeseen potential sources of bias. Depending on the availability and type of source data, the sponsor could consider measures that can support existing data such that it can be used for product registration, or change to an existing registration.
- Trial participants who cannot be transferred but are no longer able to receive the IMP/continue in the clinical trial should be treated as withdrawn participants, and their data (if available) should be managed as such.

References:

[1] CTCG recommendation to sponsors on managing the impact of the war in Ukraine on clinical trials
[2] Points to consider on the impact of the war in Ukraine on methodological aspects of ongoing clinical trials

[3] Covid-19 guidance on the management of clinical trials during the Covid-19 (coronavirus) pandemic
[4] CPMP/ICH/137/95 - ICH E3 - Structure and content of clinical study reports
[5] EMA/CHMP/ICH/135/1995 - ICH E6 (R2) – Guideline for good clinical practice
[6] Recommendation paper on decentralised elements in clinical trials
[7] Qualification opinion on eSource Direct Data Capture
[8] Points to consider on implications of Coronavirus disease (COVID-19) on methodological aspects of ongoing clinical trials

Additional references:

- EMA/CHMP/ICH/544570/1998 - ICH E8 (R1) – General considerations for clinical studies
- EMA Reflection paper on risk based quality management in clinical trials