

Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic

Version 2 (27/03/2020)

Key changes from v1 (20-03-2020): additional clarification on obtaining informed consent; link to methodological guidance on statistical considerations in relation to COVID-19 pandemic; advice on IMP stocks, safety reporting, conduct of audits; temporary halts

The European Medicines Agency (EMA), Good Clinical Practice (GCP) Inspectors Working Group, the Clinical Trials Facilitation and Coordination Group (CTFG, a working group of the Heads of Medicines Agency (HMA)), the Clinical Trials Expert Group (CTEG, a working group of the European Commission representing Ethics Committees and National Competent Authorities) and the European Commission (EC) acknowledge the impact of COVID-19 on the health system and broader society, and the impact it may have on clinical trials and trial participants¹. Extraordinary measures may need to be implemented and trials adjusted due to e.g. trial participants being in self-isolation/quarantine, limited access to public places (including hospitals) due to the risk of spreading infections, and health care professionals being committed to critical tasks. Therefore, EMA, EC and HMA strongly support the efforts of the GCP Inspectors' Working Group for developing a harmonised EU/EEA-level guidance to mitigate the negative effects of the COVID-19 pandemic on the conduct of clinical trials.

The situation is evolving, and pragmatic actions may be required to deal with the challenges of conducting research, and in ensuring the rights, safety and wellbeing of participants. The points mentioned below are intended to provide guidance for all parties involved in clinical trials during this time.

Due to the urgency, this guidance is issued without prior public consultation. The sponsors should note that due to the rapidly evolving situation further updates to this guidance are possible and likely.

Sponsors and investigators need to take into account that there might be specific national legislation and guidance in place², which they should consult and which can be used to complement this guidance, or, with respect to particular matters may take priority over these recommendations. This document is however seeking to include most of the current guidance across Member States with the aim to serve as an EU-level harmonised set of recommendations. Hence, this guidance is agreed by the Clinical Trials Expert Group (CTEG) of the European Commission supported by the EMA, the Clinical Trials Facilitation and Coordination Group (CTFG) of the Heads of Medicines Agencies (HMA) and the GCP Inspectors' Working Group coordinated by the EMA.

¹The word « participant » is used in this text as a synonym for the term “subject”, defined in Directive 2001/20/EC as “an individual who participates in a clinical trial as a recipient of the investigational medicinal product or a control”.

² Links to national recommendations can be found at CTFG website (<https://www.hma.eu/ctfg.html>)

1. Introduction

Various challenges exist which result in restrictions of visits to healthcare facilities, increased demands on the health service and changes to trial staff availability. Participants may also be required to self-isolate, which introduces difficulties for Investigators to maintain their medical oversight. These challenges could have an impact on the conduct of trials, such as the completion of trial assessments, completion of trial visits and the provision of Investigational Medicinal Products (IMPs).

The impact of COVID-19 on ongoing trials, on opening a new trial site in an existing trial, ongoing recruitment and continued involvement of participants in the trial, or on starting of new trials needs to be considered. This evaluation should take into account national recommendations and restrictive measures including travel restrictions and confinements of trial participants and trial staff and the availability of trial staff to perform visits, enter data in the Case Report Form (CRF), notify serious adverse events and, more generally, follow the protocol. The ability to confirm eligibility and to conduct key safety assessments and trial evaluation is of particular importance. Actions should be proportionate and based on benefit-risk considerations, on contingency provisions taken nationally and locally by the authorities with priority given to the impact on the health and safety of the trial participant. Where a trial participant is unable to attend the site, other measures, such as home nursing, if possible given social distancing needs, or contact via phone or telemedicine means, may be required to identify adverse events and ensure continuous medical care and oversight. However, the limitations and risks of such methods and the requirements for data protection should be taken into account and such alternative arrangements need to be adequately documented.

The International Committee of Medical Journal Editors has made clear that in the event of public health emergencies, information with immediate public health implications should be disseminated without concern that this will preclude subsequent consideration for publication in a journal.³

2. Initiating new trials

The feasibility of starting a new clinical trial or including new trial participants in an ongoing trial should be critically assessed by sponsors. Additional risks to participants should be addressed in the risk benefit section of the protocol along with risk mitigation measures (see also “risk assessment” below).

3. Changes in ongoing trials

The sponsors should consider in their risk assessment whether the following measures could be the most appropriate during COVID-19. Measures should generally be agreed with investigators and could be:

- Conversion of physical visits into phone or video visits, postponement or complete cancellation of visits to ensure that only strictly necessary visits are performed at sites;
- A temporary halt of the trial at some or all trial sites;
- Suspension or slowing down of recruitment of new trial participants;
- Extension of the duration of the trial;
- Postponement of trials or activation of sites that have not yet been initiated;

³ <http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/overlapping-publications.html>

- 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 safety and well-being of patients already participating and data validity;
- If unavoidable (it should be justified that this is a truly exceptional situation based on the personal risk-benefit ratio for the individual trial participant), transfer of participants to investigational sites away from risk zones, or closer to their home, to sites already participating in the trial, or new ones could occur. Initiation of new trial sites is generally not expected in the current situation unless no other solution exists for the trial participant. If there is an urgent need to open a new trial site for critical trial visits for example outside the hospital, this may be implemented as an urgent safety measure (USM) first, with a substantial amendment (SA) application submitted later as for the approval and initiation of an additional site later. The exceptional situation could involve e.g. a trial participant who urgently needs to stay in the trial and for whom no other sites are available. In such cases, it is important that trial participants as well as investigators (both receiving and sending) are in agreement about the transfer and that the receiving site has the possibility to access previously collected information/collected data for the trial participant and that any eCRF can be adjusted accordingly to allow the receiving site to enter new data. The impact on trial participants should be considered and arrangements made to e.g. appropriate transportation; transport;
- There may be a need for critical laboratory tests, imaging or other diagnostic tests to be performed for trial participant safety. In case the trial participant cannot reach the site to have these performed, it is acceptable that laboratory, imaging or other diagnostic tests are done at a local laboratory (or relevant clinical facility for other tests) authorised/certified (as legally required nationally) to perform such tests routinely (e.g. blood cell count, liver function test, X-ray, ECG etc.), if this can be done within local restrictions on social distancing. The sites should inform the sponsor about such cases. Local analysis can be used for safety decisions. If this is a trial endpoint and the samples cannot be shipped to the central lab, analysis should be performed locally and then explained, assessed and reported in the clinical study report following ICH E3.

The changes above may also be initiated by the investigator sites contacting the sponsor. There might also be cases where the current principal investigator (PI) of a site is indisposed for a period and may need to delegate parts of his/her duties temporarily to e.g. a sub-investigator. Any permanent changes in PI should be submitted to the National Competent Authority (NCA) and Ethics Committees as appropriate and as soon as possible.

When changes in ongoing trials are considered, the overall well-being and best interests of the participant should be also considered, for example in trials for patients with life-threatening or severely debilitating conditions, when participants require to stay on trial treatment. In cases, when trial halt, even if temporary only, can potentially compromise the overall well-being and best interest of trial participants, all measures need to be considered and taken to avoid this.

Changes should be well balanced, taking into account in particular the legitimate interest of trial sites in avoiding further burden in terms of time and staffing during the COVID-19 pandemic.

Please note that prospective protocol waivers remain unacceptable and that patients should not be included in trials without proper eligibility assessment, including performance of planned tests, and written informed consent according to national laws and regulations.

Compliance with the trial protocol should be ensured to such an extent that an ongoing benefit-risk assessment for the clinical trial and its participants is still possible. 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. A relevant guidance on the implications of Coronavirus disease (COVID-19) on methodological aspects of ongoing clinical trialtrialtrialtrial by the CHMP Biostats working party was published on March 25 2020⁴.

4. Safety Reporting

Sponsors are expected to continue safety reporting in adherence to EU and national legal frameworks (Directive 2001/20⁵; CT-3⁶). When per protocol physical visits are reduced or postponed, it is important that the investigator continue collecting adverse events from the participant through alternative means , e.g. by phone.

5. Risk assessment

The safety of the participant is of primary importance, and risks of involvement in the trial, in particular with added challenges due to COVID-19, should be weighed against anticipated benefit for the participant and society (ref: principle 2.2 of ICH GCP).

All decisions to adjust clinical trial conduct should be based on a risk assessment by the sponsor (ICH GCP section 5.0). It is expected that the sponsor performs a risk assessment of each individual ongoing trial and the investigator of each individual participant and implements measures which prioritise subject safety and data validity. **In case these two conflict, subject safety always prevails.** These risk assessments should be based on relevant parties' input and should be documented on an ongoing basis. It is important that sponsors in their risk assessment consider prioritisation of critical tasks in the clinical trial and how these are best maintained.

The sponsor should reassess risks as the situation develops. This reassessment should also be documented.

It is possible that with the escalation of the pandemic, 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 (and communicated to the sponsor).

Regarding participants enrolled in ongoing clinical trials who may be determined as being a risk group for COVID-19 or who are in trials involving treatments, which may increase such risk, the potential impact of COVID-19 on these participantgroups should be carefully considered when deciding to start or continue such trials.

⁴ <https://www.ema.europa.eu/en/implications-coronavirus-disease-covid-19-methodological-aspects-ongoing-clinical-trials>

⁵ Directive 2001/20/EC (OJ L 121, 1.5.2001) https://ec.europa.eu/health/documents/eudralex/vol-10_en

⁶ Communication from the Commission ('CT-3'; 2011/C 172/01) https://ec.europa.eu/health/documents/eudralex/vol-10_en

6. Communication with authorities

Priority is given to any (new) clinical trial applications for the treatment or prevention of COVID-19 infection, and/or substantial amendment applications to existing clinical trials necessary as a result of COVID-19.

In case the risk assessment leads to actions that affect the trial as described below in a) and b), the relevant competent authorities and Ethics Committees must be informed in accordance with the Directive 2001/20/EC and national laws:

a) When a new event is likely to have a serious effect on the benefit-risk balance of the trial, it is possible that immediate actions are required by the sponsor and investigator to protect the subjects against immediate hazard. These, urgent safety measures may be taken without prior notification, but the information needs to be provided *ex post* to the National Competent Authority (NCA) and the Ethics Committee as soon as possible (CT-1⁷: EC 2010/C82/01; 3.9). In this communication, the sponsor is expected to provide adequate information on the cause, the measures taken and the plan for further actions;

b) If changes are likely to affect the safety or well-being of the participants and/or the scientific value of the trial, but do not require immediate action from sponsor or investigator, it should be possible to submit them as substantial amendment applications. Sponsors are encouraged to take into account the limited capacity of assessors, and submit only high quality, complete applications containing only the necessary changes. Over-reporting should be avoided (Art. 11b of Directive 2001/20/EC CT-1section 3.9).

c) When a trial is put on hold for reasons not linked to participant safety (as covered by a) and b)), e.g. to avoid unnecessary strain on health care professionals, the sponsor is not expected to notify NCAs and Ethics Committees, unless nationally required.⁸ If later, it is decided not to restart the trial, the sponsor is expected to declare the premature end of trial to the concerned NCAs and Ethics Committees.

Aggregated submission to National Competent Authorities and Ethics Committees are encouraged.

Unless otherwise advised by relevant authorities, it is recommended to mark any contact clearly with 'COVID-19' in the subject field.

7. Agreement with and communication to sites and participants

Changes to trial conduct should be agreed with and communicated clearly to investigator sites. To support implementation by sites, it is important that changes and local implications are made clear, including marking of changed documents with track changes. Agreements may be documented as e-mail exchange.

In addition, trial participants should be informed by the investigator, in time, about changes in the conduct of the clinical trial relevant to participants (e.g. cancellation of visits, change in laboratory testing, delivery of IMP).

⁷ Communication from the Commission - ('CT-1') (2010/C 82/01)

⁸ Links to national recommendations can be found at CTFG website (<https://www.hma.eu/ctfg.html>)

8. Changes to informed consent

The informed consent procedure in all trials needs to remain compliant with the trial protocol as well as with EU and national rules. It is acknowledged that national provisions and approaches differ.

Sponsors should be mindful of the current pressure on the medical profession and should carefully assess the pertinence of adding new subjects in ongoing clinical trials. Absolute priority should be given to clinical trials for the prevention or treatment of COVID-19 and COVID19- related illnesses, or trials on serious diseases with no satisfactory treatment option. In case a sponsor plans to initiate a trial aiming to test new treatments for COVID-19, advice should be sought on alternative procedures to obtain informed consent, as it is likely that the physical consent cannot leave the isolation room, and therefore is not appropriate as trial documentation.

However, the following specific aspects should be taken into account with trials involving COVID-19 patients.

If written consent by the trial participant is not possible (for example because of physical isolation due to COVID-19 infection), consent could be given orally by the trial participant (Art 2(j) of Directive 2001/20/EC) in the presence of an impartial witness. In such cases, the witness is required to sign and date the informed consent document and the investigator is expected to record how the impartial witness was selected.

In addition, it could be considered that the trial participant and the person obtaining consent sign and date separate informed consent forms. In either case, all relevant records should be archived in the investigator site's Trial Master File. A correctly signed and dated informed consent form should be obtained from the trial participant later, as soon as possible.

Where potential COVID-19 trial participants lack capacity to consent due to the severity of their medical condition, or when minors are included, consent has to be obtained from the legal representative(s) according to the Articles 4 and 5 of Directive 2001/20/EC and national rules.

In case of acute life-threatening situations, where it is not possible within the therapeutic window to obtain prior informed consent from the patient (or her/his legal representatives(s)), informed consent will need to be acquired later, when this is allowed in national legislation. In these cases, the investigator is expected to record why it was not possible to obtain consent from the participant prior to enrollment.

For other ongoing trials, there may be a need to re-consent already included trial participants. However, avoid the need for trial participants to visit investigator sites for the sole purpose of obtaining re-consent. If re-consents are necessary for the implementation of new urgent changes in trial conduct (mainly expected for reasons related to COVID-19), alternative ways of obtaining such re-consents should be considered during the pandemic e.g. contacting the trial participants via phone or video-calls and obtaining oral consents supplemented with email confirmation. Approved updated patient information sheet and consent form should be provided to trial participants by e-mail, mail or courier before re-consent is obtained. Any consent obtained this way should be documented and confirmed by way of normal consent procedures at the earliest opportunity when the trial participants will be back at the regular sites.

Any validated and secure electronic system already used in the trial in the particular member state for obtaining informed consent can be used as per usual practice and if in compliance with national legislation.

9. Changes in the distribution of the IMP

Changes in the distribution of the IMP may be necessary to remove avoidable visits to sites and to provide the trial participants with needed treatments. Sponsors must assess the risks relating to the product and consider any alternative shipping and storage arrangements.

Such measures raise various practical considerations, including whether the IMP is appropriate for administration and general storage at the trial participant's home, how the stability of the product will be maintained during transit (especially for cold chain product), how safe custody of product will be ensured and how IMP accountability and the evaluation of compliance to treatment (if appropriate) will be managed.

The overriding objective of all changes in distribution is to provide trial participants with the IMP and other medications categorised as non-IMPs as needed according to the trial protocol to ensure the right, safety and well-being of trial participants as well as the integrity of the clinical trial.

Changes in distribution of IMP may include:

- The following measures could be considered provided that they do not create shortages of marketed medicinal products:
 - Larger amounts of trial medications than normally foreseen can be provided to the participant (in particular IMP, when prepared specifically for the purposes of the trial). This is to sustain the trial participant for a longer period and thereby avoid non-critical visits by the participant to the investigator site. This may be done providing that the continuation of treatment is under adequate supervision of the responsible investigator.
 - It is recommended for all IMPs and non-IMPs in clinical trials that appropriate stock is maintained to ensure treatment in case of distribution failure;
- In case of urgent shortage of IMP at some sites or transfer of trial participants from one site to another clinical trial site, there might be a need to potentially re-distribute the IMP between sites in accordance with GMP annex 13 (section 47). This should only be considered in cases where a direct distribution of the IMP to a trial site by the usual distributor is not possible or in the exceptional circumstance where a trial participant is transferred from one site to another. Sponsors should assess whether sites can handle and control such a re-distribution process, especially in case of restricted conditions for storage such as the need for specific conditions other than room temperature (e.g. +2-8° C). Re-distribution should follow a written procedure established in cooperation with the Qualified Person or the person responsible for distribution of the IMP, and sites should be provided with sufficient information to ensure that the process can be performed securely. Associated records should be included in the transfer;
- In line with the reduction of physical site visits, we foresee that there will be a need for delivery of the IMP directly to trial participants during the COVID-19 pandemic to avoid that the trial participant has to reach the site with the consequent risk of spreading/acquiring infection. The delivery is generally expected to happen from investigator sites to trial participants.

- Direct from sponsor to trial participant IMP delivery is accepted only in a few Member States and strictly during this emergency situation. The sponsor should check the NCA guidance regarding the possibility of direct sponsor to trial participant shipment, as it is likely that such measures can only be implemented under specified conditions (e.g. agreement with sites, dedicated couriers with procedures to only allow delivery directly to a trial participant or his/her carer, solid shipment and receipt procedures, informed consent provisions if necessary for the sponsor's third party to handle personal information etc.), and for a limited period.

Alternative shipping and storage arrangements should not compromise the treatment blinding.

Changes in IMP distribution are often associated with additional changes (e.g. in the visits schedule per protocol or replacement of physical visits with virtual ones (eg. through telephone calls)). Such changes need to be reflected in the protocol and communicated to regulatory bodies as described in section 6.

10. Changes in the distribution of in vitro diagnostic and medical devices

It is important to ensure the availability of those in vitro diagnostic devices and medical devices, which are essential for the conduct of the clinical trial (for example to allow enrolment, monitoring trial participants' safety 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 can be done without posing any risk to the treatment of patients outside of the trial under standard clinical care. In addition, changes in the distribution of these devices between trial sites may be necessary.

11. Changes to monitoring

Certain sponsor oversight responsibilities, such as monitoring and quality assurance activities (including the conduct of planned audits) need to be re-assessed and temporary, alternative proportionate mechanisms of oversight may be required. The extent of on-site monitoring, if it remains feasible, should take into account national and local restrictions, the urgency (e.g. source data verification can often be postponed) and the availability of site staff, and should only be performed as agreed with investigator sites. The burden of the introduction of any alternative measures for the site staff and facilities should also be considered in order to strike an acceptable balance between appropriate oversight and the capacity of and possibilities at the site. Possible temporary, alternative measures could include:

- Cancelling or postponing of on-site monitoring visits and planned audits and extending of the period between monitoring visit;
- Implementing phone and video visits (without increased burden to the investigator site and taking into account trial participant integrity and the applicable Directive and legislation thereon/on privacy);
- Adapting the on-site monitoring plan when it is impossible to follow, supplementing it with (additional/increased) centralised monitoring and central review of data if possible and meaningful;
- Remote site selection visits and investigator training for critical trials (without unnecessarily increased burden to the investigator site).

Results of adjusted monitoring/review measures should be reported to the sponsor in monitoring reports and in the clinical study report.

It is essential that robust follow-up measures are planned and ready to be implemented when the situation is normalized. This should likely include increased on-site monitoring for a period that is sufficient to ensure that the impact of the reduced monitoring could be rectified and problems resolved or properly documented for reporting in the clinical study report.

So-called remote source data verification (e.g. providing sponsor with copies of medical records or remote access to electronic medical records) is currently not allowed in most member states as it might infringe trial participants' rights. In addition, provision of redacted/ de-identified pdfs files will not be acceptable as it puts disproportionate burden on site staff.

Nevertheless, since the coronavirus emergency situation and containment measures are likely to last for a prolonged period, several NCAs have started to look into ~~possible~~ temporary options ~~solutions~~ related to remote access and conditions for such, providing that methods can be used that restricts access to participants' trial records, in line with the principles of necessity and proportionality. This should however also be clarified with other relevant authorities in this area (such as, without limitation, Ethics Committees and data protection agencies) and is consequently not allowed unless a member state has given specific guidance allowing this.

12. Changes to auditing

In the current situation, audits should in general be avoided or postponed. Audits should only be conducted if permitted under national, local and/or organizational social distancing restrictions. For critical trials, on-site visits 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 non-compliance.

13. Protocol deviations

We acknowledge that the COVID-19 situation is likely to introduce more protocol deviations than normal. We expect that the sponsor escalates and manages such protocol deviations in accordance with their standard procedures. A proportionate approach will be taken by the GCP inspectors when such deviations are reviewed during inspections, in particular where the best interest of the participant is maintained, and the participant is not put at risk.

An increase in protocol deviations in relation to the COVID-19 situation will in itself not trigger the actions required by GCP § 5.20. They will however need to be assessed and reported in the clinical study report, following ICH E3.

14. Reimbursement of exceptional expenses

Taking into account this exceptional situation, if, in order to implement urgent measures for the protection of participants involved in a clinical trial, expenses may arise which may be borne initially by the participants, these should typically be compensated subsequently by the sponsor via the investigator. If additional financial compensation is provided to sites/investigators (e.g. to cover the cost of using couriers for IMP delivery), this needs to be documented and performed according to national legislation. Handling of reimbursement of such expenses should follow national legislation and/or guidance.

15. Initiation of new trials aiming to test new treatments for COVID-19

The Member States support the submission of large, multinational trial protocols for the investigation of new treatments for COVID-19⁹.

In addition, sponsors are encouraged to consider the submission of such applications for an accelerated Voluntary Harmonisation Procedure¹⁰ (VHP) assessment when possible. In order to avoid or minimise delays due to the harmonised review, sponsors are recommended to prospectively contact the proposed Ref NCA to explore the feasibility of an accelerated VHP (plus) process.

It should be noted that the developers of medicines or vaccines are invited to contact EMA as soon as possible with information about their proposed development by emailing to 2019-ncov@ema.europa.eu. EMA provides a full fee waiver and a fast-track procedure for scientific advice¹¹.

⁹<https://www.ema.europa.eu/en/news/call-pool-research-resources-large-multi-centre-multi-arm-clinical-trials-generate-sound-evidence>

¹⁰https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2016_06_CTFG_VHP_guidance_for_sponsor_v4.pdf

¹¹<https://www.ema.europa.eu/en/news/covid-19-developers-medicines-vaccines-benefit-free-scientific-advice>