



GUIDANCE ON THE MANAGEMENT OF CLINICAL TRIALS DURING THE COVID-19 (CORONAVIRUS) PANDEMIC

Version 5

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Key changes from v4 (04-02-2021): updated with references to the Clinical Trials Regulation

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The European Medicines Agency (EMA), Good Clinical Practice (GCP) Inspectors Working Group (GCP IWG), 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 (NCA)) 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, among others, to trial participants being in self-isolation/quarantine, limited access to public places (including hospitals) due to the risk of spreading infection, and health care professionals being committed to critical tasks.

The COVID-19 pandemic has been continuously putting national health care systems under high pressure. In some Member States the capacity of the health-care system has been at its limits since the beginning of the pandemic. Against this background, pragmatic and harmonised actions are required to ensure the necessary flexibility and procedural simplifications needed to maintain the integrity of the trials, to ensure the rights, safety and wellbeing of trial participants and the protection and safety of clinical trial staff during this prolonged global public health crisis. The points mentioned below are intended to provide guidance and clarity for all parties involved in clinical trials during this time. **It should be noted that the simplification measures proposed in this document will only last during the current public health crisis until the revocation of this Guidance, when there is a consensus that the period of the COVID-19 outbreak in the EU/EEA, has passed.**

Sponsors² and investigators should note that due to the rapidly evolving situation further updates to this guidance might be possible and likely. This current version takes into account that as of 31 January 2022, clinical trials can be authorised both under the Clinical Trials Directive (2001/20/EC) and the Clinical Trials Regulation ((EU) No. 536/2014). Regulatory flexibilities in this guidance linked with additional risk adaptations are therefore applicable also for clinical trials that have been authorised under the Clinical Trials Regulation ('CTR').

Member States are encouraged to implement the harmonised guidance to the maximum possible extent to mitigate and slow down the disruption of clinical research in Europe during the public health crisis. At the same time, sponsors and investigators need to take into account that national legislation and derogations cannot be superseded. Member States shall complement this guidance to create additional clarity on specific national legal requirements and derogations to them³.

This document sets out to include most of the current guidance across Member States with the aim of serving as a harmonised EU-level set of recommendations. Hence, this guidance was drafted and supported by the CTEG, EMA, the CTFG of the HMA and the GCP IWG coordinated by the EMA.

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. Trial

¹The word "trial 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".

²Sponsors should be read in this context as "sponsor and/or CRO".

³Links to national guidance documents are collected here:

https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2020_03_CTFG_Link_to_National_guidance_on_CT_managment_during_the_COVID-19_pandemia.pdf

participants may also be required to self-isolate, which can make it difficult 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 new trial sites in an existing trial, on ongoing recruitment and continued involvement of participants in a trial, or on starting of new trials needs to be considered. This evaluation should take into account national recommendations and 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 evaluations 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, 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 journal⁴.

2. INITIATING NEW TRIALS

The feasibility and immediate necessity of starting a new clinical trial should be critically assessed by sponsors, in close collaboration with other relevant parties, in particular the investigators. Additional risks to trial participants should be addressed in the benefit-risk section of the protocol along with risk mitigation measures (see chapter 5).

3. CHANGES TO ONGOING TRIALS

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;

⁴ <http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/overlapping-publications.html>

- Interruption or slowing down of recruitment of new trial participants – the feasibility of including new trial participants in an ongoing trial needs to be critically assessed;
- Extension of the duration of the trial;
- Postponement of 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 and well-being of trial participants and data validity;
- If unavoidable (it should be justified that this is a truly exceptional situation based on the personal benefit-risk ratio for the individual trial participant), transfer of trial 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, followed later by a substantial amendment (SA) application (see below in chapter 6) for the approval and initiation of this additional site. In such cases, it is important that trial participants as well as investigators (both receiving and sending) are in agreement about the transfer, that the receiving site has the possibility to access previously collected information/collected data (including necessary medical records) 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 such as providing adequate transportation;
- There may be a need for critical laboratory tests, imaging or other diagnostic tests to be performed, (e.g. blood cell count, liver function test, X-ray, CT, MRI, ultrasonography, ECG etc.), e.g. for trial participant safety or the integrity of the trial. 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 authorised/certified (as legally required nationally) to perform such tests routinely, 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 biological samples cannot be shipped to the central laboratory, analysis should be performed locally and then explained with detailed justification, assessed and reported in the clinical study report following ICH E3. In these cases, it is important 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.

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 NCA and/or Ethics Committees (in line with chapter 6).

When changes in ongoing trials are considered, the overall well-being and best interests of the trial participants have to be prioritised, for example in trials for patients with life-threatening or severely debilitating conditions, when trial participants need to stay on trial treatment. When a trial is halted, even if temporarily only, this 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 and proportionate, 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. Alternative arrangements, consistent with the protocol to the extent possible, should be fully documented with a well-reasoned rationale as to how they will ensure trial participant safety, data integrity and protection of personal data.

Please note that prospective protocol waivers remain unacceptable and that potential trial participants 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 trials by the CHMP Biostatistics Working Party was published on 25 March 2020⁵.

4. SAFETY REPORTING

Sponsors are expected to continue safety reporting in adherence to EU and national legal frameworks (Directive 2001/20/EC⁶; CT-3⁷ and Regulation (EU) No. 536/2014). When per protocol physical visits are reduced or postponed, it is important that the investigators continue collecting adverse events from the trial participant through alternative means, e.g. by phone calls or telemedicine visits, as appropriate.

Sponsors can consider to introduce risk adaptations in the protocol of clinical trials regarding safety reporting by investigators to the sponsor in accordance with Article 41.1 and 2 of the Clinical Trials Regulation as well as with Article 16.1 of Directive 2001/20/EC and Article 4 of the CT-3. Recommendations for procedural aspects are in Chapter 4.2 of the guidance for Risk proportionate approaches in clinical trials⁸.

⁵ <https://www.ema.europa.eu/en/implications-coronavirus-disease-covid-19-methodological-aspects-ongoing-clinical-trials>

⁶ Directive 2001/20/EC (OJ L 121, 1.5.2001) https://ec.europa.eu/health/documents/eudralex/vol-10_en

⁷ Communication from the Commission ('CT-3'; 2011/C 172/01) https://ec.europa.eu/health/documents/eudralex/vol-10_en

⁸ https://ec.europa.eu/health/system/files/2017-08/2017_04_25_risk_proportionate_approaches_in_ct_0.pdf

Participants' and patients' safety oversight will be reinforced by the Implementing Regulation 2022/20 setting up the rules and procedures for the cooperation of the Member States in the safety assessment of clinical trials⁹.

5. RISK ASSESSMENT

The safety of the trial participants 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 trial participants 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 trial participant and implement measures, which prioritise trial participant safety and data validity. **In case these two conflict, trial participant 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 as part of the sponsor's trial master file.

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. This assessment should be documented in the investigator's site master file and communicated to the sponsor.

The potential impact of COVID-19 on trial participants who may be determined as being part of a-risk group for COVID-19 or who are in trials involving treatments, which may increase such risks, should be carefully considered when deciding to start or continue such clinical trials.

6. COMMUNICATION WITH AUTHORITIES

Priority is given to any (new) clinical trial application for the treatment or prevention of COVID-19 infection, and/or substantial amendment ['substantial modification'¹⁰ as referred to in Regulation (EU) No. 536/2014] applications to existing clinical trials necessary as a result of COVID-19.

For ongoing trials, the guidance given by EC CT-1¹¹ on substantial amendments and the provisions in Regulation (EU) No. 536/2014 remain applicable. A single submission by the same sponsor with the list of concerned trials and an aggregated list of changes is

⁹ https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.L_.2022.005.01.0014.01.ENG

¹⁰ Article 2(13) of Clinical Trials Regulation (EU)536/2014

¹¹ Communication from the Commission - ('CT-1') (2010/C 82/01) [https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52010XC0330\(01\)](https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52010XC0330(01))

acceptable and encouraged in case of substantial amendments as well as of urgent safety measures.

Two important aspects need to be taken into account:

- 1) It is up to the sponsor to assess whether an amendment is to be regarded as ‘substantial’. A change is substantial when it has a potential impact on the safety or physical or mental integrity of the clinical trial participant, or on the scientific value of the trial (CT-1 section 3.3, CT-2 section 5¹²) or when it is likely to have a substantial impact on the safety or rights of the subject or on the reliability and the robustness of the data generated in the clinical trial (Article 2.2.13 of the Regulation (EU) No. 536/2014). Substantial amendments relate to amendments of documents/information that are part of the clinical trial application dossier.
- 2) Submission of information is only obligatory if the amendment is a substantial amendment. Directive 2001/20/EC or the Regulation (EU) No. 536/2014 does not require notification, or immediate submission of information on non-substantial amendments. In other words, the only communication mechanism of substantial changes to information in the protocol or clinical trial dossier is through the submission of a substantial amendment [modification]. Non-substantial amendments, or changes that do not relate to information submitted in the clinical trial application dossier should be recorded in the documentation when it is subsequently submitted, for example in the subsequent submission of a substantial amendment (CT-1 section 3.1).

In case the risk assessment leads to actions that affect the trial as described below in a), b), and c), the relevant NCA and/or Ethics Committees must be informed in accordance with Directive 2001/20/EC and national laws or a notification needs to be submitted through CTIS to the Member States concerned in accordance with the Regulation (EU) No. 536/2014:

- a) It is possible that urgent actions are required by the sponsor and investigator to protect the trial participants against immediate hazard. These urgent safety measures do not need prior notification. Due to specific local or national circumstances related to the COVID-19 Pandemic, submission to the relevant authorities could take longer than usual, but the information needs to be provided to the NCA and the Ethics Committee as soon as possible (CT-1, Art 3.9). The sponsor needs to document the justification for this delay in the trial master file. In communication with authorities, the sponsor is expected to provide adequate information on the cause, measures taken and the plan for further actions.
- b) If changes, which are substantial amendments, do not require immediate action from the sponsor or investigator, these should be submitted as substantial amendment applications. Sponsors are encouraged to take into account the limited capacity of regulatory authority assessors and Ethics Committees, 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-1 article 3.9).
- c) Certain procedural or other changes might become necessary to address global or local consequences of the pandemic (e.g. related to social distancing or to avoid unnecessary strain on health care professionals). If these changes are justifiable,

¹²Detailed guidance from the Commission ('CT-2') (2006) https://ec.europa.eu/health/system/files/2020-02/12_ec_guideline_20060216_en_0.pdf

COVID-19 related changes, not related to trial participants' safety and do not have a serious effect on the benefit-risk balance for the trial participants and the scientific value of the trial, they can be notified as soon as possible taking into account national and local circumstances. In these cases, sponsors are expected to submit to the relevant NCA and Ethics Committee the list of all changes with appropriate risk assessment and justification as well as follow-up actions when necessary. Cumulative changes must not have a negative impact on trial participants' safety and/or on the integrity of the trial. Relevant protocol deviations are sufficient to be recorded according to chapter 13.

Sponsors of clinical trials authorised under the Regulation (EU) No. 536/2014 will need to submit the above-mentioned notifications through the Clinical Trials Information System (CTIS) as other safety notifications according to Article 53, urgent safety measures according to Article 54 or as substantial modifications in accordance with Chapter III of that Regulation.

The sponsor is expected to maintain appropriate records, in a timely manner, of all changes described in the chapter above in the trial master file.

Communication under the Directive 2001/20/EC should be clearly marked with 'COVID-19' in the subject field or in the trial title under Regulation (EU)536/2014.

The following table provides a non-exhaustive list of examples for the classification of different mitigating measures – more information on specific approaches can be found in the chapters 3, 9 and 11 below, and/or in the national recommendations, where applicable.

| Urgent safety measures (a) (in light of the conditions described above) | Substantial amendments/modifications (b) (in light of the conditions described above) | Other measures (c) (in light of the conditions described above) |
|--|---|---|
| Temporary halt due to shortage of trial medication | | Temporary halting of a trial, when it is not linked to the safety of trial participants |
| Direct distribution of IMP to trial participants/carer home or residence by a distributor in case of exceptional emergency situations (please refer to chapter 9 for more detail) | Direct distribution of IMP to trial participants/carer home or residence by a distributor (please refer to chapter 9) | |
| Testing is performed in local laboratories instead of at the trial site | | |
| | Introducing remote SDV (in exceptional cases, see chapter 11) | |
| Transfer of trial participants to another trial site, but treatment is continued | | |

| | | |
|---|---|---|
| Temporary de-activation of the trial site with discontinuation of treatment | | |
| | Changes to the as per protocol informed consent process | |
| Opening of new trial sites or relocation to existing trial sites to accommodate for the transfer of existing trial participants in case of emergency situations | | |
| | | Supplying trial participants with larger amounts of IMP under the supervision of the investigator |

7. AGREEMENT WITH AND COMMUNICATION BETWEEN SPONSORS, TRIAL SITES AND TRIAL PARTICIPANTS

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

Vice versa, investigators may initiate changes to trial conduct as urgent safety measures. These should be reported as soon as possible by the investigator to the sponsor as well as by the latter to the competent authorities and ethics committees, in line with the principles described in chapter 6.

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

8. CHANGES TO INFORMED CONSENT

Unless linked to the implementation of urgent safety measures, changes in informed consent procedures will need to be reviewed and approved by the relevant ethics committee in advance.

The informed consent procedure in all trials needs to remain compliant with the trial protocol as well as with EU and national legal framework. 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 enrolling new trial participants in ongoing clinical trials. Absolute priority should be given to clinical trials for the prevention or treatment of COVID-19 and COVID-19-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, in case 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 and Article 29.1 of Regulation (EU) No. 536/2014) in the presence of an impartial witness. In such cases, the witness is required to sign and date the informed consent form 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's site 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 are incapacitated adults not able to give informed legal 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 Articles 4 and 5 of Directive 2001/20/EC or Articles 31 and 32 of Regulation (EU) No. 536/2014 or according to 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 trial participant (or her/his legal representative(s)), informed consent will need to be acquired later, when this is allowed by national legislation. In these cases, the investigator is expected to record why it was not possible to obtain consent from the trial participant prior to enrolment. The procedure for trials authorised under the Regulation (EU) No. 536/2014 needs to be compliant with Article 35 of the Regulation.

There may be a need to re-consent already included trial participants. However, it should be avoided that trial participants visit trial sites for the sole purpose of obtaining re-consent. If re-consent is necessary for the implementation of **new urgent changes in trial conduct** (mainly expected for reasons related to COVID-19 or important safety issues for other trials), alternative ways of obtaining such re-consent should be considered during the pandemic. These could comprise contacting the trial participants via phone or video-calls and obtaining oral consents, to be documented in the trial participants' medical records, supplemented with e-mail confirmation. Approved updated patient information sheet and consent form should be provided to trial participants by the investigator 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 are 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 INVESTIGATIONAL MEDICINAL PRODUCTS

The recommendations in this section of the guidance also apply to "non-investigational medicinal products" (NIMP), auxiliary medicinal products (AxMPs) and other products or devices normally provided to the trial participants during on-site trial visits, as defined in the protocol.

Changes in the distribution of the investigational medicinal products (IMP) may be necessary to prevent 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 a cold chain product), how safe custody of products will be ensured and how IMP accountability and the evaluation of compliance to treatment (as defined in the protocol) will be managed.

The overriding objective of all changes in distribution is to provide trial participants with the IMP as needed according to the trial protocol and to avoid treatment interruptions, in order to maintain a positive benefit-risk balance and to protect the rights, safety and well-being of trial participants as well as the integrity of the data collected during the clinical trial. The continuation of treatment should be under adequate supervision of the responsible investigator.

Changes in distribution of IMP may include the following:

- Provided that such measures do not create shortages of marketed medicinal products:
 - Larger amounts of IMP than normally foreseen can be provided to the trial participant. This is to sustain the trial participant for a longer period and thereby avoid non-critical visits by the trial participant to the investigator site.
 - 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 clinical trial site to another site, there might be a need to potentially re-distribute the IMP between sites in accordance with GMP annex 13 (section 47) or the Regulation (EU) No. 536/2014. 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. -20°C, +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 enough information to ensure that the process can be

performed securely. Appropriate associated records should be included in the transfer and retained. Adequate documentation of the transfer needs to be included in the investigators' and the sponsor's trial master file.

- 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' homes 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 following should be considered for the direct shipment of IMP to trial participants:
 - It should also be determined whether further education or training of the trial participants will be necessary for IMP receipt, handling and self-administration. Written information on the dose regimen needs to be provided to trial participants along with contact information to site for any questions they may have. The same contact should be used for trial participant to inform the investigator if there is any damage to the IMP packaging, containers or the IMP itself.
 - The delivery should be done from trial sites (hospital pharmacies as applicable) to trial participants. The sponsor should bear the cost of the shipment and should provide logistical assistance to the trial site if needed, for instance for the selection of an appropriate courier or transporter.
 - If, due to the COVID-19 pandemic, a trial site is not able to handle the additional burden of IMP shipment to trial participants, the IMP may as an exception be shipped to the trial participants by a distributor¹³ independent from and acting on behalf of the sponsor in line with national law or temporary national emergency measures¹⁴. The following then applies:
 - IMP shipment to the trial participants should be described in a contract between the sponsor and the distributor. The contract should identify all involved investigators/ trial sites. The contract should set out what documents or other materials are permitted to be supplied to the site. The contract and procedures involved should be documented in the sponsor trial master file.
 - The IMP may only be dispatched to trial participants after agreement with the investigator and on the basis of the investigator's prescription. The agreement and the procedure should be recorded in the investigator site file;
 - The investigator should explain the process to the trial participant or carer orally and should obtain her/his oral consent before agreeing with the sponsor, including for the investigator to provide the trial participant's name, address and contact details (phone and or e-mail) to the distributor. When possible, consent should be confirmed in writing by e-mail, mail or letter sent via a courier. The oral or written consent should be documented in the trial participant's medical records;

¹³A distributor is a third party located in the EU/EEA contracted by the sponsor to store the IMP and distribute it to the trial sites and, in the current exceptional circumstances, to the home of the trial participant.

¹⁴The provision of IMP directly from an independent distributor to participants under specific conditions was shared with the health ministers and no concern was raised in the videoconference of Ministers of Health of 27 April 2020.

- The distributor should not store the personal data of the trial participant for a longer period than is required for the purpose of dispatching the IMP (should be destroyed as soon as no longer needed and in no case longer than the duration of the public health crisis) **and should only use this information for the purpose of making the IMP deliveries during the period of the pandemic**. It should not be used for any other purpose or disclosed to a third party for another purpose, other than monitors, auditors or inspectors verifying the conduct of the trial. This should be set out in the contract between the sponsor and distributor.
 - The trial participants' names, address and contact details should never be provided to the sponsor, and the distributor should not have access to the trial participants' health information.
- The organisational measures agreed between the sponsor and the contracted distributor should protect blinding and ensure compliance with the randomisation.
- Dedicated couriers should be contracted for IMP shipment with procedures in place. These procedures should ensure timely delivery directly to the trial participant or her/his designated caregiver to avoid that e.g. the IMP is handed over to the neighbour etc. The investigator should receive confirmation of all deliveries by the courier and confirm the receipt with the trial participant/caregiver by e.g. phone-call or e-mail. The investigator is responsible for proper IMP administration.
- The shipment should be done under conditions that safeguard the integrity of the IMP, whether physically or with regards to temperature. Temperature records should be maintained during shipment for temperature-sensitive products. The investigator should be immediately informed in case the temperature departs from the specified conditions and should advise the trial participant at the earliest on the possibility to use or not the IMP, after consultation with the sponsor.
- The courier should be informed of, and commit to, the shipment conditions (in particular regarding temperature) and maximum duration.
- Procedures for the accountability of the IMP must be in place (among others for compliance monitoring). Accountability of the IMP should be maintained. Clear records of shipment from the trial site or from the distributor should be kept in the investigator site file, itemising the medication being delivered and the quantity involved. Documentation of receipt by the trial participant should be kept. Participants should retain unused IMP and containers and return them to the investigator when they next have a visit to the investigator site

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).

Such changes need to be communicated to regulatory bodies as described in section 6.

Importantly, risk proportionate labelling requirements for authorised IMPs and AxMPs are established in Article 67 of the Clinical Trials Regulation.

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 (e.g. 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 clinical trial under standard medical 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 need to be re-assessed and temporarily, alternative proportionate mechanisms of oversight may be required.

The first priority when considering any change is to protect the rights, safety and well-being of trial participants.

As part of the risk assessment outlined in chapter 5, a risk-based approach to monitoring should be taken, focusing on certain sites, certain data points and certain processes that are critical to ensure the rights, safety and well-being of trial participants and the integrity of the trial (and trial data). The sponsor should consider the extent and nature of monitoring that would be eligible in each specific trial under this **exceptional** situation, and weigh this against the extra burden that introduction of any alternative measures would put on site staff and facilities. The monitoring plan should then be revised in accordance with these considerations, in order to strike an acceptable balance between appropriate oversight and the capacity of the trial site.

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

It is essential that robust follow-up measures are planned and ready to be implemented when the situation is normalised. This should include increased on-site monitoring for a period that is sufficient to ensure that the impact of the reduced monitoring can be rectified, and problems resolved or properly documented. Data subject to remote source data verification are likely to require re-monitoring, in particular if it was based on pseudonymised documents, which cannot be considered as source documents, and considering that remote monitoring is expected to only have focused on the most critical information.

Adjusting monitoring activities may include a combination of the following:

a) On-site monitoring

Cancelling or postponing of on-site monitoring visits and extending of the period between monitoring visits are likely to be necessary.

To the extent on-site monitoring remains feasible, it should take into account national, local and/or organisational social distancing 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 trial sites.

Additional measures regarding on-site monitoring may include limited, targeted on-site monitoring identifying higher risk clinical sites, if not already applicable for the trials of concern.

The on-site monitoring plan will need to be adapted and alternative measures (like those outlined in b), c) and d) below) put in place, or relied on to a greater extent if already present.

b) Centralised monitoring and central review of data collected

Centralised monitoring is an established method under ICH GCP E6. 5.18.3 (Addendum). In the context of the pandemic, the role of centralised monitoring has an increasing importance. Centralised monitoring of data acquired by electronic data capture systems (e.g. eCRFs, central laboratory or ECG / imaging data, ePROs 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 remote evaluation of ongoing and/or cumulative data collected from trial sites, in a timely manner. Centralised monitoring should not be confused with remote source data verification (see 11.d. below).

c) Off-site monitoring

Additional off-site monitoring activities could include phone calls, video visits, e-mails or other online tools in order to discuss the trial with the investigator and site staff. These activities could be used to get information on the clinical trial progress, to exchange information on the resolution of problems, review of procedures, trial participant status as well as to facilitate remote site selection and investigator training for critical trials.

d) Remote source data verification

In addition to the above mentioned, established methods (11.a-c), and taking into account the continuing nature of the COVID-19 pandemic and the need to ensure the quality of clinical trial data and to protect the rights, safety and well-being of the participants in the EU/EEA, remote source data verification (rSDV) can be justified in clinical trials. Remote SDV can be considered only during the COVID-19 pandemic related public health crisis and when in line with EU and national law (or temporary national emergency measures)¹⁵. Remote SDV may be considered for trials:

- involving COVID-19 treatment or prevention;
- investigating serious or life-threatening conditions;
- where 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. trials in patients with advanced dementia) incapable of giving their informed consent or
- in pivotal trials.

Remote SDV should focus on the quality control of critical data such as primary efficacy data, important safety data. Important secondary efficacy data may be monitored

¹⁵ The initial provision for source data verification to take place remotely in the case of trials with (1) COVID-19 treatments and (2) medicines for treatment of serious or life-threatening conditions with no satisfactory treatment option, provided that certain conditions are met to protect trial participants' rights was shared with the health ministers and no concern was raised in the videoconference of Ministers of Health of 27 April 2020. The scope for rSDV was further extended in February, 2021 (v4) due to the prolonged nature of the pandemic.

simultaneously, provided this does not result in a need to access additional documents and therefore in an increased burden for trial site staff. The sponsor should determine the extent and nature of remote SDV that they consider needed for each trial under this exceptional situation and should carefully weigh it against the extra burden that introduction of any alternative measures would put on site staff and facilities.

In the case of these trials, principal investigators should make their own determination as to whether or not the situation at their clinical site allows any of the following options for remote SDV:

- Sharing pseudonymised copies of trial related source documents with the monitor; this may be done electronically where manageable by the site staff;
- Direct, suitably controlled remote access to trial participants' electronic medical records;
- Video review of medical records with clinical site team support, without sending any copy to the monitor and without the monitor recording images during the review.

For COVID-19 trials starting now, when remote SDV is foreseen, it should be described in the initial protocol application (and informed consent form). In case of ongoing trials introduction of remote source data verification should be submitted, in line with national law or temporary national emergency measures, via a substantial amendment. These provisions should be in line with the principles of necessity and proportionality and in a way that protects trial participants' rights and should not place any disproportionate burden on site staff as determined by the investigator and trial site staff.

Remote SDV can be carried out only in agreement with the investigators who should not be put under undue pressure to accept remote SDV and should always give priority to the care to be given to trial participants and other patients.

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. Refer to Annex 1 for controls that, where applicable, can protect trial participants' rights while permitting remote SDV.

12. CHANGES TO AUDITING

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

13. PROTOCOL DEVIATIONS

The COVID-19 situation is likely to introduce more protocol deviations than normal. It is expected that the sponsor manages 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 the 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.

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

Please also refer to the guidance on the implications of Coronavirus disease (COVID-19) on methodological aspects of ongoing clinical trials⁵ by the CHMP Biostatistics Working Party, published on 25 March 2020.

A Guideline for the notification of serious breaches of Regulation (EU) No. 536/2014 or the clinical trial protocol^{16,17} provides detailed information to support sponsors in the process of identification and reporting of serious breaches.

14. REIMBURSEMENT OF EXCEPTIONAL EXPENSES

Taking into account this exceptional situation, the implementation of urgent safety measures may create unplanned expenses. These expenses should be borne by the sponsor, preferably directly. If expenses nevertheless arise which have to be borne initially by the trial 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-19¹⁸.

In order to benefit from coordinated national and multi-national assessments with fixed maximum timelines, sponsors of large, multi-national clinical trials for COVID-19 therapeutics or vaccines are encouraged to submit their clinical trial application under the Regulation (EU) No. 536/2014 or consider early transition of their ongoing clinical trial to the Regulation (EU) No. 536/2014. Importantly, Member States concerned need to organise the scientific and ethics assessments of the applications internally and notify the sponsor of their single decision on each application. Applications for multinational COVID-19 therapeutic trials submitted in CTIS can be considered for fast-tracked assessment within the EU4Health joint action ‘CT-CURE’¹⁹.

The developers of medicines or vaccines are invited to contact EMA as soon as possible using the e-mail address 2019-nCoV@ema.europa.eu (or following relevant updated indications on the EMA web portal) for advice on the main aspects of clinical trials and clinical trial protocols submitted or intended to be submitted in a clinical trial application by developers. EMA provides a full fee waiver and a fast-track procedure for such scientific

¹⁶ [Guideline on reporting serious breaches \(europa.eu\)](#)

¹⁷ [2014-clinical-trial-protocol_en.docx \(live.com\)](#)

¹⁸ <https://www.ema.europa.eu/en/news/call-pool-research-resources-large-multi-centre-multi-arm-clinical-trials-generate-sound-evidence>

¹⁹ https://ec.europa.eu/health/events/joint-action-support-coordinated-and-expedited-assessment-clinical-trials-covid-19-therapeutics_en

advice²⁰, on clinical trials of medicinal products that have the potential to address the public health emergency. This centralised expedited scientific advice is provided by the Emergency Task Force of EMA with the involvement of clinical trials experts from Member States²¹.

²⁰ <https://www.ema.europa.eu/en/news/covid-19-developers-medicines-vaccines-benefit-free-scientific-advice>

²¹ <https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52020PC0725>

Annex 1: Protection of trial participants' rights during remote source data verification

The implementation of the following controls can help to appropriately protect trial participants' rights while permitting remote source data verification (SDV). Remote SDV should follow the principles laid out in Section 11.d.

- The principal investigator (PI)/PI's institution and the sponsor may be jointly responsible as controllers for ensuring information is safeguarded²². Remote SDV of medical records of EU/EEA trial participants may generally take place from a (remote) monitoring location within EU/EEA. In case the data are transferred/processed outside the EU/EEA, one of the transfer tools under the General Data Protection Regulation (GDPR)²³ needs to be in place; in practice, unless an adequacy decision adopted by the European Commission applies, it should be contractually ensured that a level of data protection essentially equivalent to Union data protection legislation will be applied.
- A documented risk assessment should be performed to establish the risk to the trial participants and to the trial if SDV cannot be performed in the near future. **Critical data for which SDV needs to be performed should be identified by the sponsor in a monitoring plan and should be focused on primary efficacy data and important secondary efficacy data if they are documented on the same source document and important safety data.** It is important to ensure that only the data that is necessary for this purpose is accessed.
- The sponsor should consult with their data protection officer (DPO) and with the PI at each site to establish whether remote SDV would be allowed, feasible and manageable for this site and what the practicalities could be.
- If the PI/PI's institution, in consultation with their DPO, confirms their agreement to the conduct of remote SDV in writing, a substantial amendment should be submitted to the Ethics Committee and/or NCA where required before proceeding, with a justification of the urgency of the remote SDV and their risk assessment.
- Site staff and monitors should be trained on the remote SDV process.
- Site staff should inform each trial participant or designated legal representative and ensure that they do not object to the remote review of their records for trial purposes and document this process in the trial participant's medical records. If a trial participant objects to remote review of their records, no remote SDV will occur for that trial participant.
- Performance of remote SDV by the monitor may only occur in locations that prevent viewing by any unauthorised person, through a secure internet connection and on a computer appropriately protected against unauthorised access to the data.

²² See also [European Data Protection Board Guidelines 07/2020 on the concepts of controller and processor in the GDPR – version for public consultation](#), p. 21-22.

²³ Regulation (EU) 2016/679, [OJ L 119 4.5.2016, p. 1](#)

- Monitors should sign a written confidentiality agreement committing to securely destroy any copy of redacted documents, whether paper or electronic, as soon as they have been used for source data verification and committing not to make any copy (or recording in the case of video access) of any non-pseudonymised document.
- If the agreed remote SDV process involves redaction by the site staff (pseudonymisation) of source records:
 - The monitor should provide a written request to the site for the specific participant's specific trial records required for SDV.
 - Site staff should create copies of the requested trial participant's records, redact (i.e. pseudonymise and mask any unnecessary private information unrelated to the trial) the copies, identify them with the trial participant identification code in the trial, have a second person perform and document a quality control to ensure that all identifying information has been redacted and is no longer readable, and make the pseudonymised copies available to the monitor using a secure mechanism. The redacted copies should be kept in the investigator's site master file with records of their communication to the monitor.
 - The monitor should access the records securely, complete the monitoring task, securely destroy any copy made locally and provide a certificate of destruction to the trial site.
 - Once on-site monitoring visits are again feasible, the monitor should verify at the earliest opportunity that the provided pseudonymised (coded) data are indeed data related to the trial participant with the provided code.
- If the agreed remote SDV process involves a video review of records:
 - The quality of the video should be adequate to enable reading, without risk of confusion between similar characters, and to avoid a negative impact on the visual health of the monitors.
 - The video review of documents may include site staff sharing the screen of their computer with the monitor using a secure video conference application hosted on their computer. Videoconferencing solutions where data may be captured on third country servers may not be acceptable.
 - The video review of documents is likely to necessitate the presence of a member of the trial site staff at all times in order to change the document being viewed or to scroll the document on a computer screen. Sponsors and investigators should be aware of the importance of the burden that such SDV methods may represent for trial sites and hence the review should be restricted to a minimum of critical data in critical trials.
 - The transmission of the data should be adequately protected against unauthorised third party access.
- If the agreed remote SDV process involves the site providing the monitor remote access to the site electronic medical record (EMR) system:
 - The monitor should be provided with a secure, read-only access to the EMR system, including all modules relevant for review. This access should be restricted to the records of only those patients who participate in the trial and who did not object against remote access to their medical records as outlined above.

- A list of the monitors to whom remote access has been granted should be maintained. In order to prevent unauthorised access, access rights should be revoked once remote SDV tasks have been completed for the trial.
 - The EMR system should have an audit trail and be able to log information on who accessed data and when.
 - Remote access to the EMR should only be possible using a two-factor authentication.
- It should not be possible to make local copies of trial participants' health records. Users should be aware of the automatic creation of temporary files on their computer when reviewing trial participant data, and should securely delete such files immediately after each source data verification session.