

Joint Guidance of Swissmedic and swissethics on the management of clinical trials with medicinal drug products in Switzerland during the COVID-19 pandemic

(Version 2.4, 17.12.2020)

Changes from version 2.3 (04.11.2020): clarifications made to the sections “Monitoring”

Swissmedic and swissethics recognize the impact the COVID-19 pandemic may have on the management and conduct of clinical trials. In the following, guidance is provided to the parties involved in clinical research activities during the COVID-19 pandemic. Due to the rapidly evolving situation, further updates to this guidance are possible and likely.

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Clinical trials with medicinal drug products to treat COVID-19:

Applications for clinical trials with medicinal drug products to treat COVID-19 or substantial amendment applications to existing clinical trials necessary as a result of COVID-19 are prioritised by the authorities. The sponsors are requested to submit high quality and complete dossiers to the authorities in order to allow for a most efficient review.

Important: In acknowledgment of the current situation during which applicants may work from home office, dossiers may be submitted electronically to Swissmedic (see section “Communication with Swissmedic”).

Dossiers to the ethics committee must be submitted electronically via the portal BASEC (see section “Communication with the ethics committees”).

In the following, guidance is provided with respect to the management of clinical trials with medicinal drug products during the COVID-19 pandemic in Switzerland. The procedures described are aligned to the requirements laid down in the Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic (version 3 (28/04/2020) 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).

Risk assessment:

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

The sponsors should critically assess which measures could be the most appropriate during the COVID-19 pandemic in order to ensure subject safety. The impact of COVID-19 on ongoing trials, opening a new trial site in an existing trial, ongoing recruitment and continued involvement of participants in the trial, or on starting new trials needs to be considered. Actions should be proportionate and based on benefit-risk considerations with priority given to the impact on the health and safety of the trial participant. Measures may be to suspend the recruitment of new trial participants, to extend the duration of a trial, a temporary halt of the trial, postponement of trials or activation of trials that have not been initiated yet. Measures should generally be agreed with investigators who are responsible for all trial related medical decisions. Changes to trial conduct should be communicated clearly to investigator sites. To support implementation by sites, it is important that changes and local implications are made clear.

All decisions to adjust clinical trial conduct should be based on a risk assessment by the sponsor (ICH GCP 5.0). It is expected that the sponsor performs a risk assessment of each individual ongoing trial and implements measures prioritising subject safety and data validity. **In case these two conflict, subject safety always prevails.** These risk assessments should be documented on an ongoing basis. The sponsor should reassess risks as the situation develops. 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).

Changes in the distribution of the study medication (= investigational medicinal drug products, IMPs): Direct to the patient delivery:

The implementation of changes in the distribution of IMPs is strictly limited to the COVID-19 pandemic period.

The sponsor must assess the risk relating to the product and the appropriateness of storing and administering the IMP at the study participants' home. It lies within the responsibility of the investigator to assess, whether the administration of the study medication at the patients' home is medically justified and ensures best patient safety. Therefore, a change in the distribution may only be introduced in agreement with the investigator.

The procedure is only permitted for IMPs, which are suitable for use at home. The study participants have to be informed appropriately upfront. Please use the new addendum to the study patient information made available by swissethics on [swissethics.ch / covid-19](https://www.swissethics.ch/covid-19).

The sponsor should establish written procedures in order to ensure the stability of the IMPs during the transport and the storage at home. The receipt of the IMP should be confirmed by the study patient to the investigator. The requirements with respect to the drug accountability as defined in ICH GCP E6(R2) have to be fulfilled.

The delivery of the study medication **may only be made from the trial site to the study patient**. The distribution of study medication from the manufacturer/warehouse to the study patients is not allowed. It must be assured by appropriate measures that personal data of the study participants (e.g.: name, address, phone number) are not transmitted to the sponsor for the purpose of IMP delivery.

Changes in the distribution of the study medication have to be notified to Swissmedic and to the Lead ethics committees for information. The authorities reserve the right to contact the sponsor for further clarifications if needed.

Swissmedic: The sponsors are requested to confirm in writing (using the form “Submission of Changes to a Clinical Trial and Answer to Conditions”) that the only change is the shipment of the IMPs from the trial sites to the patients’ home. Swissmedic will issue an acknowledgement of receipt, but the change can be implemented before this acknowledgement is issued.

Lead ethics committees: The “silent acknowledgement” procedure applies.

Monitoring:

The monitoring strategy may be adapted in response to the COVID-19 pandemic, which is currently persisting and unfolding in waves.

A risk-based approach to monitoring should be taken, focusing on trial sites, data points and processes that are critical to ensure the rights, safety and well-being of trial participants and the integrity of the 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

On-site monitoring:

Cancelling or postponing of on-site monitoring visits and extending of the period between monitoring visits may be necessary. To the extent on-site monitoring remains feasible, it should take into account cantonal and/or organisational social distancing restrictions, the urgency of on-site visits and the availability of site staff and should only be performed as agreed with trial sites. The on-site monitoring plan will need to be adapted and alternative measures put in place (centralised monitoring, off-site monitoring, and remote source data verification).

Centralised monitoring and central review of data collected:

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.

Off-site monitoring:

Additional off-site monitoring activities could include phone calls or e-mails 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.

Remote source data verification (SDV):

Remote SDV may be considered only during the public health crisis. It should focus on the quality control of critical data such as primary efficacy data and important safety data. Important secondary efficacy data may be monitored simultaneously, provided this does not result in a need to access additional documents and therefore in an increased burden for trial site staff. The sponsor should carefully weigh the extent and nature of remote SDV and weigh it against the extra burden that introduction of any alternative measures would put on site staff.

The principal investigators should make their own determination, without undue pressure, as to whether or not the situation at their clinical site allows any of the following options for remote SDV:

- Direct, controlled remote access to trial participants' electronic medical records (EMR), without the monitor recording images during the review.
- Sharing coded copies in digital format of trial related source documents with the monitor; this may be done through secure channels, and end-to-end encryption

The sharing of coded copies in paper format (e.g.: via courier or postal mail) as well as video review of medical records by using Zoom, Skype or other comparable tools are not allowed.

For clinical trials starting now, when remote SDV is foreseen, it should be described in the initial protocol application and specified in the monitoring plan.

The following requirements apply for remote SDV:

- Remote SDV may only take place from a (remote) monitoring location within Switzerland. However, If remote SDV is planned to take place from a location outside Switzerland, prior written informed consent must be obtained from the study participants. **An amendment with an updated informed consent form has to be submitted to the Lead Ethics Committee for prior approval.**
- 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. The sponsor should identify critical data for which remote SDV needs to be performed in a monitoring plan.
- The Principal Investigator has to confirm his agreement to the conduct of remote SDV in writing.
- The site staff and monitors must be trained on the remote SDV process.
- 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.
- Monitors should sign a written confidentiality agreement committing to securely destroy any copy of redacted documents, as soon as they have been used for source data verification and committing not to make any copy of any non-coded document.

If the 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 (e.g. VPN (Virtual Private Network)) read-only access to the EMR system, including all modules relevant for review. This access must be restricted to the records of only those patients who participate in the trial.
- 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.
- The monitor must not make local copies (e.g. by means of print-screens or taking photographs of the screen) of trial participants' health records.

If the remote SDV process involves redaction by the site staff (coding) 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. code 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 coded copies available to the monitor using a secure mechanism (e.g. electronically by encrypted end-to-end communication). The redacted copies should be kept in the investigator's site master file with records of their communication to the monitor. It lies within the responsibility of the investigator to overview the source documentation provided to the monitors for the purpose of remote source data verification.
- The monitor should access the records securely and complete the monitoring task.
- Following completion of the monitoring task, the monitor must securely delete the digital records and provide a certificate of destruction to the trial site. If print-outs of coded health records are made by the monitor, they must be either destroyed or alternatively may be returned to the trial site.
- Once on-site monitoring visits are again feasible, the monitor should verify at the earliest opportunity that the provided coded data are indeed data related to the trial participant with the provided code.

For the above-mentioned procedures, no separate informed consent form (ICF) has to be signed by the patient. The current ICF template of swissethics informs the patient that only very few people (i.e. including monitors) may inspect the uncoded patients' data for the purposes of monitoring in strict compliance with the principle of confidentiality. No extra risk of data protection violation is expected, if the requirements for remote SDV as outlined in this guidance paper are fulfilled.

The Monitoring Plan should be adapted by the temporary measures taken in response to the ongoing COVID-19 pandemic. 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 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.

Adapted Monitoring Plans have to be submitted to the Lead Ethics Committee for silent acknowledgement. A delayed submission is acceptable.

Conduct of study visits:

Transfer of study participants to other trial sites:

In view of the measures imposed by the Federal Council, the transfer of study participants to other trial sites is not allowed unless it is critical in order to ensure patient safety.

The Lead Ethics Committee has to be notified for silent acknowledgement. The Lead Ethics Committees reserve the right to contact the sponsors for further clarifications if needed.

Conversion of physical visits into phone or video visits:

Where a trial participant is unable to attend the site, other measures, such as 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 study participants must be informed accordingly. Please use the new addendum template from swissethics available on [swissethics.ch / covid-19](http://swissethics.ch/covid-19).

Amendments to the conduct of physical visits as outlined above have to be provided to the Lead Ethics Committee for information.

A delayed submission, and consequently a delayed approval of the addendum to the patient information, is acceptable. See next section “Informed Consent Procedure” for the procedure to follow in such case.

Administration of the IMPs at patients’ home:

If the medical condition of the study participants require staying on trial treatments while participants should not travel to the trial site any more, it is acceptable that a trained nurse/investigator may administer the study medication at the study participant’s home. It lies within the responsibility of the investigator to assess, whether the administration of the study medication at the patient’s home is medically justified and ensures patient safety and well-being. The decision of administering IMPs at home must be taken by the investigator and must be documented in the patient file. The study participants have to be informed appropriately. Please use the new addendum available on the website [swissethics.ch / covid-19](http://swissethics.ch/covid-19).

A delayed submission and consequently a delayed approval of the addendum to the patient information by the Lead Ethics Committee, is acceptable.

Study specific assessments:

There may be a need for critical laboratory tests, imaging or other diagnostic test to be performed for patient safety. In case the trial participant cannot reach the site to have these performed, it is acceptable that safety relevant assessments are performed by the family doctor/laboratory/institution which is authorised/certified 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. This should only be done in agreement with the investigator and be limited to rather simple procedures. 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 Lead Ethics Committee has to be notified for silent acknowledgement. The Lead Ethics Committees reserve the right to contact the sponsors for further clarifications if needed.

Informed Consent Procedure:

Obtaining initial consent for participation in a clinical trial:

In general, it is expected that no patients be recruited in clinical trials during the COVID-19 pandemic. Exceptions may be the enrolment of patients with life threatening diseases for whom there are no other treatment options. The informed consent procedure has to be approved and conducted according to the existing legal requirements (art 16(2) HRA [Federal Act on Research involving Human Beings], section 3 ClinO).

Obtaining re-consent from trial-participants already included in the trial for new urgent changes in trial conduct (mainly expected for reasons related to COVID-19):

Avoid the need for trial participants to visit investigator sites for the sole purpose of obtaining re-consent. 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. Any consent obtained this way should be documented by the investigator in the source documents and confirmed by way of normal consent procedures at the earliest opportunity when the trial participants will be back at the investigational sites. Written informed consent may be obtained based on an addendum to the patient information document. (templates are published on the swissethics website: swissethics.ch / covid-19)

The addendum to the patient information has to be submitted to the Lead Ethics Committee for approval. A delayed submission is acceptable.

Protocol deviations:

The protocol deviations are to be assessed by sponsors in accordance with their standard procedures. 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.

Safety Reporting:

The sponsors are expected to continue safety reporting to Swissmedic/the ethics committees in adherence to the Swiss legal requirements (i.e.: section 5, chapter 2 ClinO). When per protocol physical visits are reduced or postponed, it is important that the investigators continue collecting adverse events from the trial participants through alternative means, e.g. by phone.

COVID-19 infections in study patients do not need to be reported to Swissmedic unless they were classified as a SUSAR by the investigator/sponsor, or required immediate safety and protective measures. In this case, the legal requirements as defined in ClinO apply. If the

infection qualifies as SUSAR, or required immediate safety and protective measures, the deadlines for reporting as defined in ClinO apply.

COVID-19 infections in study patients do not need to be reported to the Lead Ethic Committees unless they were classified as a SAE, resp. SE, or a SUSAR by the investigator/sponsor/project leader, or required immediate safety and protective measures. In this case, the legal requirements as defined in ClinO, resp. Human Research Ordinance (HRO), apply. If the infection qualifies as SUSAR, SAE, resp. SE, or required immediate safety and protective measures, the deadlines for reporting as defined in ClinO, resp. HRO, apply. Mild symptomatic COVID-19 infections, which do not require hospitalisation of a study participant, do not qualify as SAE unless defined otherwise in the clinical trial protocol.

Reporting of changes in study implementation due to COVID-19 to the authorities:

If the sponsor decides to temporarily interrupt or to definitively discontinue a clinical trial, this must be notified to the Ethics Committee and to Swissmedic within 15 days respectively (art 38(2), art 38(5) ClinO [Ordinance on Clinical Trials in Human Research]).

A recruitment hold does not have to be reported if already enrolled patients continue to be treated in the respective clinical trial.

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. Immediate and protective measures taken are to be reported within 7 days to the Ethics Committee and to Swissmedic respectively (art 37(1), art 37(3) ClinO).

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 (art 29, art 33 ClinO).

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 the existing legal requirements.

This does not need to be approved by the ethics committee.

Communication with Swissmedic:

Bulk submissions for several clinical trials of a sponsor are accepted. Due to the current COVID-19 situation, it is possible to submit clinical trial documentation electronically to Swissmedic. Applications for new clinical trials may also be submitted electronically.

Please send the documentation to the following email address:

ct.medicinalproducts@swissmedic.ch.

Please contact Swissmedic in case the documents can't be sent by email for technical reasons. The program FileTransfer Service can be used in this case. An invitation will be needed for the upload of the documents.

Please make sure that the documents are submitted with the corresponding accompanying form, otherwise the submission will not be accepted. To facilitate the processing of the submission, please add the number of the corresponding file section 1-10 in the filename of each document. The sponsors are requested to mark any correspondence clearly with 'COVID-19' in the subject field/line.

In addition, the subject line of the email should state the reason for the message. Therefore, please use the following information in the subject line:

Subject line		To use with the following emails:
a.	Submission_CTA_xxxxxxx	Application for approval of a new clinical trial
b.	Submission_Changes_xxxxDRxxxx	Request for change / fulfill of conditions of an ongoing clinical trial, blue form
c.	Submission_Reporting_xxxxDRxxxx	Reporting on an ongoing clinical trial, green form
d.	Submission_admin-changes_xxxxDRxxxx	Administrative Change to an ongoing clinical trial, Administrative Change form
e.	Question xxxxx	Questions for the Swissmedic Clinical Trials Division

For further information regarding the correct submission of documents, please see our website www.swissmedic.ch > Human medicines > Clinical trials on medicinal products. Please contact us should you encounter problems with the document transmission by email.

Important: The sponsors are requested to provide the entire documentation also in paper format to Swissmedic at the earliest opportunity. The paper documentation should be accompanied by a cover letter in which the sponsor confirms that the documentation has been transmitted electronically previously.

The subsequent submission must include the following:

- Form with original signature (wet ink)
- Cover letter with reference to initial submission by e-mail
- Printouts: 2 pages per sheet, double-sided print

Communication with the ethics committees:

Bulk submission for several clinical trials of a sponsor are accepted. One single information letter is sufficient. Ideally, the letter should be uploaded to all concerned clinical trials in BASEC. It is recommended to contact the Lead ethics committee before doing so. The sponsors are requested to mark the correspondence clearly with 'COVID-19'

Resumption of clinical trials activities following the COVID-19 pandemic:

Relaxation of the transitional measures put in place due to the COVID-19 pandemic is only allowed as long as the spread of the virus decreases and as long as the investigators and the investigational sites can guarantee trial participants and site staff safety.

The resumption of clinical trials must always be assessed in light of the medical need of trial participants, the specificities of the clinical trial and of the investigational site(s) (site staff availability, local pandemic context) and the potential risks for the trial participants and site staff inherent to the COVID-19 pandemic. In all cases, the sponsor must take responsibility to ensure that it has full and complete capacity to monitor and follow up the clinical trial in conjunction with the investigators and the investigational sites. The assessment for the resumption must be filed in the Trial Master File.

The clinical trial can only resume according to the latest version of the protocol as it was authorised by Swissmedic and by the Lead-Ethics committee. A resumption of the clinical trial with an amended protocol is subject to authorization by Swissmedic and the Lead Ethics committee.

Other accompanying measures, which are not amendments to the protocol, that were put in place to guarantee trial participants and site staff safety should continue as long as the investigators and the investigational sites deem so necessary. The sponsors as well as the investigators should document the measures put in place if they affect the trial conduct (ICH GCP 2.10).

The resumption of the clinical trial, conducted as authorized by Swissmedic and by the Lead Ethics committee, must be notified to the Lead Ethics Committee for silent acknowledgement. Swissmedic has to be informed about the resumption by using the form "Submission of Changes to a Clinical Trial and Answer to Conditions". The submission of the notification has to be done separately from other changes. As long as the applicants work from home due to the current situation, dossiers may be submitted electronically to Swissmedic (see section "Communication with Swissmedic"). The sponsors are requested to provide the entire documentation also in paper format to Swissmedic at the earliest opportunity. The paper documentation should be accompanied by a cover letter in which the sponsor confirms that the documentation has been transmitted electronically previously. Swissmedic will issue an acknowledgement of receipt, but the change can be implemented before this acknowledgement is issued.

Swissmedic and the Lead Ethics Committees reserve the right to contact the sponsors for further clarifications if needed.

In the event of an (unexpected) increase in the spread of the virus, or an increase of hospital admissions and/or deaths, or any other circumstances that in the opinion of the investigational sites and investigators might jeopardise trial participants and site staff safety, the relaxation of the rules should be adapted to the new circumstances, or reversed. In this case, the sponsors are requested to follow the guidance as described in the previous sections.