

# Guidance on clinical trial management in the context of COVID-19 pandemic

## State Agency of Medicines

**01.04.2020**

The Government of Estonia has declared an Emergency Situation until 1 May, 2020 due to the pandemic of COVID-19. The following guidance is intended to provide regulatory clarification for all concerned parties in clinical trials. The guidance is in effect until the end of the emergency situation and will be updated as the situation progresses.

The State Agency of Medicines acknowledges that due to the pandemic of COVID-19 and the restrictions imposed by the emergency situation, it may be necessary for sponsors and investigators of clinical trials to diverge from approved study plans in order to ensure the safety of trial subjects and the continuation of study procedures.

### **General guidance:**

- All decisions to adjust clinical trial conduct should be based on risk assessment by the sponsor in cooperation with principal investigators. It is expected that the sponsor performs a risk assessment of each individual ongoing trial and implements measures that prioritise patient safety and data validity. In case these two conflict, patient safety should take priority. The sponsor should reassess risk as the situation develops. This reassessment should also be documented and included in any amendments to the trial.
- The sponsors are recommended to consider temporary halt of recruitment to ongoing clinical trials. Trials that have been approved but have not yet started recruitment should be postponed. Opening additional sites to existing studies should also be postponed. Temporary halt of ongoing trials or withdrawal of individual trial subjects may be appropriate methods of risk mitigation in certain cases.
- All protocol deviations must be carefully documented.
- Where a substantial amendment to the study plan is required due to temporary measures, the amendment should be in the form of a local or global sub-protocol or annex to the existing protocol. There is no need to update the entire protocol. This will hopefully add flexibility to the planning of the trial and help speed up the evaluation process.
- The State Agency of Medicines and the national ethics committees are prepared to evaluate amendments to the study plans in an expedited manner.
- All notifications to the State Agency of Medicines should be sent to [trials@ravimiamet.ee](mailto:trials@ravimiamet.ee) and „COVID-19“ should clearly be written in the subject line.

**NB!** *Any reported changes to the trial conduct must be specific and applicable to Estonian study sites and Estonian trial subjects. We do not accept general descriptions of possible measures that may or may not be used in Estonia.*

### **Changes that require a substantial amendment:**

***NB!** A regular substantial amendment should be submitted. The amendment will be reviewed in an expedited manner*

**Changes to the frequency of visits** – Due to possible restrictions of visits to health care institutions, self-isolation of patients and changes to trial staff availability, it might be necessary to change the frequency of study visits. This would be considered an important change in the conduct of the trial with possible implications to the safety of trial subjects. Therefore, a substantial amendment is considered necessary.

**Switching from face-to-face meetings to telemedicine** – Where appropriate, the use of telemedicine or phone calls instead of face-to-face meetings might be acceptable. However, this constitutes a major change in the conduction of the trial and therefore, prior approval of a substantial amendment is necessary.

**Changes to assessment/measurement methodology** - When possible, some assessments or measurements that would normally be done by health care professionals during study visits, might temporarily be done by the trial subjects themselves (e.g. blood pressure and weight measurements, PRO questionnaires, measurement of body temperature etc.). The sponsor should assess the feasibility and appropriateness of such methods. A substantial amendment is required.

**The use of home health care** – In the case of trial site quarantine or self-isolation by trial subjects, certain study procedures such as blood sampling or i.v. infusion administration or physical examinations might be jeopardised. In this case, sponsors might be tempted to use home health care. Instead, trial site relocation or other measures might be more appropriate. However, if the sponsor is adamant about using home health care, this should be sufficiently justified and described in detail in a substantial amendment.

### **Changes that do not require a substantial amendment:**

**NB!** A notification of the changes via email is required. The email must contain justification for the changes. The notification must be sent as soon as possible.

**Centralised Source Data Verification** – Certain oversight duties, such as monitoring and quality assurance activities might need to be reassessed and alternative proportionate mechanisms of oversight introduced. On-site monitoring can be performed to the extent possible and as agreed with investigator sites. The burden of the introduction of such measures on the site staff and facilities should also be considered, and a proportionate approach should be taken, balancing appropriate oversight with the capacity of the site.

Possible alternative measures could include:

- Cancelling of onsite monitoring visits
- Implementing phone and video visits (without unnecessarily increased burden to the investigator site)
- If it is not possible to follow the on-site monitoring plan, monitoring should be supplemented with centralized monitoring and central review of data if possible and meaningful. Results of adjusted monitoring/review measures should be reported.

It is essential that robust follow-up measures are planned for 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 has been established and handled.

So-called remote SDV (providing sponsor with copies of medical records or remote access to electronic medical records) is not allowed as it jeopardizes trial participants' rights. In addition, provision of redacted/de-identified PDF files will not be acceptable as it puts disproportionate burden on site staff.

**Transfer of IMP between investigational sites** - In case of risk of shortage or related to the transfer of participants (records of the type of packaging, expeditions, transport and reception should be ensured), this would be considered acceptable on the condition that storage and transportation conditions are met and appropriate records are kept. As an urgent and temporary measure, no amendment to the study plan is necessary.

**Moving patients from one study site to another** - We foresee many possible problems with moving patients from one study site to another. For one, alternative study sites might not be as well acquainted with the subjects and their medical history. This might impair treatment quality. Also, having parallel study sites might adversely affect the quality of documentation. There is also the risk of over-burdening certain sites. These risks should carefully be considered by the sponsor and weighed against risks of not moving the patients and other possible measures. Temporarily moving trial subjects between sites is not considered a substantial amendment.

**Adding COVID-19 testing to study plan** - When the sponsor or investigator considers it necessary for the protection of trial subjects, COVID-19 testing can be added to the study plan. Any additional testing must be carefully documented. There is no need for a substantial amendment or notification.

**Direct supply to patient of IMP/NIMP (site to subject)** – Due to logistical problems, study site or subject quarantine or travel restrictions, the shipping of IMP/NIMP directly to the patient may be necessary. The shipment is usually expected to be sent only from the study site to the subject. IMP-specific storage and transportation conditions must strictly be adhered to and taken into consideration when assessing the viability of direct to patient supply. Records must be kept of transfer/storage details. This option is generally considered appropriate only for self-administered treatment. The sponsor should contemplate supplying the IMP/NIMP for a longer period than would normally be considered necessary. Although a significant change in the trial conduct, under current exceptional conditions, the decision to supply IMP/NIMP from the study site directly to the patient does not require a substantial amendment (or prior approval).

**Changes that do not require a formal substantial amendment but where prior approval is still mandatory:**

**Direct supply to patient of IMP/NIMP (sponsor to subject)** - Under exceptional conditions, having exhausted all other options, with every measure taken to ensure that the subjects' personal data are protected and that blinding procedures remain intact, under the supervision of the principal investigator and with proper documentation of the responsibilities of all parties involved (e.g. SOP, contract between the courier and the sponsor), direct shipments of IMP/NIMP from the sponsor to trial subjects may be allowed. However, this arrangement would require **prior approval** from the State Agency of Medicines. The sponsor must, in an email to the Agency, describe:

- Shipping arrangements
- Means of re-consenting the subjects
- Measures of protecting the subjects' personal data from the sponsor (i.e. address, contact details)
- Measures of ensuring that the blind remains intact (if applicable)

If considered acceptable, the sponsor will receive an email with permission to proceed with direct from sponsor to subject shipments. No formal substantial amendment is required. Hopefully, this measure will ensure that the rights of trial subjects are not compromised while also providing some flexibility to the sponsor in making rearrangements.

## **Electronic procedures:**

**General** - Please note that electronic procedures in clinical trials are regulated by the same guidelines as regular procedures, such as **ICH E6 Good Clinical Practice** document. Some of the relevant points are:

**2.10** All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.

- a. Systems with procedures that assure the quality of every aspect of the trial should be implemented.

**5.5.3** When using electronic trial data handling and/or remote electronic trial data systems, the sponsor should:

- a. Ensure and document that the electronic data processing system(s) conforms to the sponsor's established requirements for completeness, accuracy, reliability, and consistent intended performance (i.e., validation).
- b. Maintain SOPs for using these systems.
- c. Ensure that the systems are designed to permit data changes in such a way that the data changes are documented and that there is no deletion of entered data (i.e., maintain an audit trail, data trail, edit trail).
- d. Maintain a security system that prevents unauthorized access to the data.
- e. Maintain a list of the individuals who are authorized to make data changes (see 4.1.5 and 4.9.3).
- f. Maintain adequate backup of the data.
- g. Safeguard the blinding, if any (e.g., maintain the blinding during data entry and processing).
- h. Ensure the integrity of the data including any data that describe the context, content, and structure. This is particularly important when making changes to the computerized systems, such as software upgrades or migration of data.

**Electronic signatures** - The informed consent document may be signed by an electronic signature as long as it meets the requirements for a qualified electronic signature set out in Article 3 (12) of Regulation (EU) No. 910/2014 of the European Parliament and of the Council. Electronic signatures are subject to the following EU and national regulation:

1) [Regulation \(EU\) No. 910/2014 of the European Parliament and of the Council](#)

2) [Electronic Identification and Trust Services for Electronic Transactions Act](#)

The following electronic signature methods are widely used and acceptable in Estonia:

The	National	ID-card	
The	Mobile-ID	method	
The	Smart	ID	method

More information about these methods can be found [here](#).

### **Versions of the document:**

**Version 1** (dated 18.03.2020)

**Version 2** (dated 27.03.2020) Information regarding the direct shipment of IMP to the patient was updated. Clarifications of reporting requirements were added. Grammar corrections.

**Version 3** (dated 01.04.2020) A separate category of changes to trial conduct was created (no SA but prior approval still required). This is to reflect the need to allow for direct from sponsor to subjects shipping of IMP/NIMP while also ensuring proper oversight. Information regarding centralised source data verification was updated.