Guidance on clinical trial management during the COVID-19 pandemic

State Agency of Medicines

Version 4 (29.09.2020)

The State Agency of Medicines acknowledges that due to the pandemic of COVID-19, 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. The following guidance is intended to specify local requirements for such measures.

General guidance

- This guidance is effective until the end of the pandemic. However, the decision to implement the described measures should be based on the local epidemiological situation and intended to solve COVID-19 related issues in Estonian trial sites.
- All decisions to adjust clinical trial conduct must 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. The implemented measures must prioritise patient safety and data validity. In case these two conflict, patient safety must be given priority. The sponsor must continuously reassess the involved risks. All assessments must be documented and included in any amendments to the trial.
- 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. The amendment is generally expected to include a description of locally applicable changes. Descriptions of global measures alone that may or may not apply locally are discouraged as they tend to produce excessive rounds of communication between the agency and the applicant. The amendments should be sent to trials@ravimiamet.ee and „COVID-19“ should clearly be written in the subject line.
- Given that the aforementioned conditions are met, the State Agency of Medicines is prepared to prioritise the assessment of COVID-19 related amendments.

Changes that require a substantial amendment

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. When changes to visit frequency are foreseen and planned, 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, using telemedicine or phone calls instead of face-to-face meetings might be acceptable. When changes from face-to-face visit to telemedicine are foreseen and planned, 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. The applicant must provide a description of the used technology.

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.

Using home health care – In the case of trial site quarantine or self-isolation by trial subjects, certain study procedures such as blood sampling or IV infusion administration or physical examinations might be jeopardised. In this case, it might be necessary to implement home health care. Prior to such changes, the sponsor is required to apply for a substantial amendment.

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. The sponsor must apply for a substantial amendment where they must 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)

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. The sponsor is required to apply for a substantial amendment.

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.

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).

Remote source data verification – In principle it is not allowed but may only be considered during the public health crisis for trials involving COVID-19 treatment or prevention or in the final data cleaning steps before database lock in pivotal trials investigating serious or life-threatening conditions with no satisfactory treatment option. It must focus on the quality control of critical data such as primary efficacy data and important safety data.

In the case of these very few 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 via a detailed substantial amendment and include updated informed consent form.

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 sections 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 Regulation (EU) No. 910/2014 of the European Parliament and of the Council

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

- National ID-card
- Mobile-ID
- Smart ID

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.

Version 4 (dated 07.10.2020) Major changes to the entire document, incl. the applicability of the document and the categorisation of changes.