

ŠÚKL GUIDANCE FOR THE MANAGEMENT OF CLINICAL TRIALS IN SLOVAKIA DURING THE COVID-19 CRISIS

Version 3 (09/04/2021)

Regarding the ongoing COVID-19 crisis and subsequent restrictive measures for clinical trials in order to ensure the protection of rights, safety and health of the clinical trials participations and to retain adequate data quality from the clinical trials, including the data used in the requests for marketing authorisation for drugs, and also due to the update of European guidance GUIDANCE ON THE MANAGEMENT OF CLINICAL TRIALS DURING THE COVID-19 (CORONAVIRUS) PANDEMIC (Version 4, 04.02.2021) (hereinafter referred to as “European guidance”), ŠÚKL issues the following recommendation:

1. Provision/securing of health care to participants in the clinical trial (hereinafter referred to as “CT”)

- We recommend, if possible, in agreement with the sponsor of the clinical trial, the postponement of the participant's personal visit to the centre of the clinical trial for telephone control due to their safety, closure of the medical facility or recommendations of restricted movement of natural persons issued by the government. The telephone contact should be properly explained to the participant and documented in the medical records, including the reason for contact, epidemiological facts (e.g. a participant of the CT is in quarantine) and consent to a new procedure (e.g. telephone visits, sending the test product by courier, remote monitoring of medical documentation). Informing the participant and confirming the participant's consent to the new procedure can be done by e-mail if possible. Later, when the situation stabilizes and it is possible for the participant to visit the centre of the CT, it is necessary that the participant of the CT confirms their consent to any changes during epidemiological constraints by signing a new version of the Informed consent;
In the case that a follow-up visit to the centre of the CT is postponed or completely omitted with a view to ensuring the safety of participants of the CT, it is necessary to document and subsequently assess the impact on the validity and quality of clinical trial data;
- If a visit to the centre of the CT is necessary and the medical facility allows it, it is necessary to take as many sanitary precautions as possible to avoid accumulation of patients (e.g. telephone ordering, time reserved for follow-up visits outside normal patients) and provide protective equipment for both participants of the CT and medical staff. Necessary or additional required protective equipment is to be provided by the sponsor of the CT (Section 43 (h), point 1 of Act no. 362/2011 Coll.

2. Provision of the investigational medicinal product (hereinafter referred to as “IMP”) to participants of the CT

- One option may be to provide IMP and non-IMP for a longer period of time than originally planned, mostly in case of cancelled CT centre visits;
- In order to minimize visits to medical facilities, we recommend, if possible (e.g. the pharmaceutical form is suitable for home administration and storage), to use an authorized carrier who will arrange the transport of an IMP from the centre of the CT to the participant of the CT to their place of residence. It is the principal investigator who is responsible for the transport of the IMP to the participant of the CT, the costs of which are borne by the sponsor of the CT (contractual arrangement). The sponsor of the CT will also ensure that the personal data of the participant of the CT is protected (contractual conditions), i.e. unauthorized persons, including the sponsor of the CT, will not access the personal data of the participant of the CT (name and address). GDP and GCP requirements for IMP transport and storage should be maintained (e.g. transport temperature control). The transporter/carrier will be ordered by the principal investigator and then the principal investigator will confirm the receipt of the IMP with the participant by telephone, which he/she will record in the source documentation of the participant of the CT. The participant of the CT must be trained to administer and store the IMP. IMP transport should be documented in accordance with GCP requirements. Records from the IMP transport, containing the personal data of the participant of the CT, should be kept at the centre of the CT for traceability. If it is necessary to keep copies of the records of transport of the IMP on the part of the sponsor of the CT in TMF e.g. documentation of protocol deviation, pseudonymized copies will be provided that do not allow identification of the participant of the CT. In case the transport of the IMP from the centre of the CT directly to the participants of the CT represents an enormous burden on the centre of the CT, it is possible to entrust this activity to other trained health care workers from the investigator’s team, while the responsibility remains with the principal investigator (GCP 4.2.5, 4.2.6);
- In case that ensuring the transport of IMP from the CT centre to the place of residence of the CT participant represents an enormous burden for the CT centre, it is possible in necessary cases to use a distributor authorized by the sponsor of the CT. Delivery of IMP to the CT participant directly from the sponsor is not permitted in Slovakia. The possibility of delivering IMP directly to CT participants from such a distributor is enabled by § 2 of Act no. 69/2020 Coll. On emergency measures in connection with the spread of dangerous contagious human disease COVID-19 in the field of health care and by which certain laws are amended. However, the procedure under this provision of the Act is conditioned by the fulfillment of the legal obligation by which the legal entity relieves itself of liability for the committed administrative offense, specifically violation of the provisions of § 38 par. 10, § 43 letter i), j), k) and § 44 letter g), l) of Act no. 362/2011 Coll., By proving that in the mentioned case it was not possible to deliver the tested medicinal product otherwise

without endangering public health. At the same time, all the recommendations given in the previous point should be followed.

- If the participant of the CT is to bring the rest of the unused IMP during the planned visit, it can be instructed not to use the remaining packages and put them as long as they can come to the principal investigator, if applicable;
- Another possibility of the participant of the CT who has ordered restrained movement is for relatives to collect the IMP after telephone verification of such an option by the principal investigator of the centre of the CT with the specific participant of the CT. Subsequent acceptance of the IMP with the participant of the CT will be verified by telephone by the principal investigator and recorded in the source documentation together with information on the previous issue of the IMP to a relative;
- For each study, the sponsor will ensure detailed written instructions for the principal investigator concerning the distribution of the IMP to the participants of the CT and will send them to ŠÚKL for information;
- If the assistance of a physician/doctor or other health care professional is necessary for the administration of the IMP and the participant must visit the centre, we recommend that the personal visit of the participant at the centre be postponed for as long as possible. If it is not possible to postpone the administration of the IMP at the centre of the CT, or it has already been postponed for the maximum possible time, the administration of the IMP at the centre of the CT should be carried out in compliance with the safety hygiene (mentioned above in the provision of health care);
- In case of emergency and necessity to submit the IMP at home to the CT participant with the assistance of medical staff, the investigators may use authorized, trained and authorized persons or a specialized company, while the investigator is responsible for the medical care provided. Similarly to the authorized carrier, the contract with the given persons or any authorized company will be concluded by the contracting authority of the CT, including the preservation of the protection of personal data of the CT participant and possible additional insurance of the CT for this service.

3. Monitoring of the CT

In accordance with the European guideline for management of the CT during the COVID-19 pandemic, we are aware of the significant impact on the performance of the supervisory of the sponsor by a designated person called monitoring. The monitors will not be able to carry out personal monitoring visits to centres of the CT according to the monitoring plans. The sponsor must therefore find alternative options in order to preserve the security of participants of the CT and preserve data in the highest possible integrity and quality.

In line with the current European Guideline, we recommend and complement the local legislative framework as follows:

- Cancellation or postponement of personal monitoring visits to centres of the CT for the period after the COVID-19 pandemic (when the situation stabilizes) and/or extension of intervals between visits to centres of the CT;
- Implementation of telephone or video calls, if this does not represent an increased burden on the centre of the CT and at the same time the rights of participants of the CT in terms of their physical integrity and mental integrity, the right to privacy and the protection of personal data are guaranteed (§30 c) of Act no. 362/2011 Coll.);
- Updating monitoring plans based on new risk assessments, including additional or increased centralized monitoring where possible and meaningful (e.g. centrally generated electronic documents such as pseudonymized ECG, drug laboratory safety results called „drug accountability sheets“). Centralized monitoring in a sense of GCP R2 5.18.3 cannot be replaced with remote source data verification listed below;
- Remote Source Data Verification (hereinafter referred to as remote “SDV”) kept by the principal investigator in writing, whether in the form of identifying the participant of the CT or in a pseudonymized copy of the medical documentation, is commonly not allowed in Slovakia. According to §2 par. 1) and par. 12) Act no. 576/2004 Coll. health care includes, inter alia, biomedical research, which includes clinical trials on a human medicine. In addition, the Act stipulates, in §25, to whom and how the disclosure of the data from the medical records necessary for the SDV are provided. The data is provided in the form of consultation/insight and is stated to whom it is given. Section 2 of that paragraph refers to the possibility of making copies or extracts, but only at the site. Further, in accordance with GCP requirements, the monitor cannot be sure that it has been provided with the CT participant's medical documentation for the remote SDV of pseudonymized source data, whether there was no accidental confusion between the participants of the CT, furthermore, whether he/she has been provided with the complete documentation of the relevant participant of the CT, or whether there was no accidental or deliberate failure to provide all necessary data. Last but not least, remote SDV by means of pseudonymized source data in PDF format would represent an increased burden on the centre of the CT;

Remote SDV during the critical situation is possible only for following CT:

- Clinical trials involving treatment or prevention of COVID-19,
- Clinical trials investigating serious or life-threatening diseases,
- Clinical trials in which the absence of SDV can present unacceptable risk to safety of participants or to the reliability/integrity of trial results,
- Clinical trial involving vulnerable persons, e.g. children or those unable to give informed consent temporarily (e.g. urgent situations) or permanently (e.g. patients with dementia),

- Pivotal (registrational) clinical trial

ŠÚKL derives the legality of such a procedure from the wording of § 2 of Act no. 69/2020 Coll., As before the effectiveness of this Act, such a procedure would violate the provisions of § 43 letter k), l) and § 44 letter i), k), l) of Act no. 362/2011 Coll., But by the fact that a CT monitor, a CT auditor or a GCP inspector of ŠÚKL could not look into the medical documentation in accordance with the provisions of § 25 par. 1 letter c.) and par. 2 of Act no. 576/2004 Coll., there would be a threat to public health;

Remote SDV should be focused on quality control of critical data such as primary efficacy data and important safety data. Important secondary efficacy data can also be the subject of remote SDV, if it does not require further inspection of additional source documentation.

Appropriate forms and methods are those compliant with European guideline, namely:

- remote SDV of pseudonymized copies of source documentation sent directly to the CT monitor,
- direct secured access to the electronic medical records of a healthcare institution,
- checking the medical records through videoconference.

It is the Sponsor's responsibility to assess the appropriate form of SDV to not represent an enormous burden on the investigator and his/her team in the CT centre. Remote SDV can be performed only with the investigator's consent and with the consent of the respective medical facility. Remote SDV shall be performed only by methods which ensure maximal protection of personal data including pseudonymized data. As data controllers, the investigator, the medical facility as well as the Sponsor are responsible for data protection including pseudonymized data.

In case of planned remote SDV for clinical trials mentioned above, the Sponsors shall submit following documentation to ŠÚKL as a part of the initial submission of CT or submission of amendment to CT:

- Protocol or Amendment to the Protocol describing the details of the execution of remote SDV (reasoning including risk assessment, types of remotely verified source data, chosen form of remote SDV, measures taken to ensure the security of CT subject data – protection of personal and pseudonymized data in the scope of the European guideline requirements in Annex 1), or similar document describing relevant details e.g. Monitoring Plan,
- Information for clinical trial participants and Informed consent form or their amendments containing particular forms of remote SDV and measures taken to ensure the security of CT subject data,

- Contract proposal or amendment to contract between the Sponsor and Investigator (or medical facility) containing the assent to perform a particular form of remote SDV,
 - A Statement of The Office for Personal Data Protection of the Slovak Republic (hereinafter referred to as “The Office”) after previous consultation, since the remote SDV represents a high risk for rights of natural persons in case the data controller of personal and/or pseudonymized data does not adopt risk mitigation measures. Pursuant to Paragraph 43(2) of the Law 18/2018: *“Where the Office is of the opinion that the intended processing referred to in paragraph 1 would infringe this Act, in particular where the controller has insufficiently identified or mitigated the risk, the Office shall, within the period of up to eight weeks of receipt of the request for consultation, provide written advice to the controller or to the processor. The Office may, considering the complexity of intended processing of personal data, extend the time period set forth in the previous sentence by six weeks; the Office shall notify the controller or the processor about the extension and its justification within one month of receiving the request for consultation by written form. The period for consultation is suspended until the Office collects the information requested for the purposes of consultation.”*
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- After the end of emergency measures, the sponsor of the CT should take such measures that will mitigate the impact of the reduction of monitoring at the CT centres on the integrity of data, e.g. increased number of monitoring visits to CT centres, remonitoring of source data;
 - During this emergency situation, remote selection visits of the centre of the CT and training activities of the centre of the CT are allowed, if necessary, providing they do not increase the burden on the centre.