Opinion of SÚKL's Department of Clinical Trials on Medicinal Products on Ongoing Clinical Trials and To-Be-Commenced Clinical Trials in Light of the COVID-19 Epidemiological Situation of 3 April 2020, added 6. 4. 2020
(This opinion supersedes the opinions of ~~12~~03 March ~~and 16 March~~ 2020)

With reference to numerous repeatedly asked questions regarding the conduct of ongoing clinical trials or to-be-commenced clinical trials in view of the current coronavirus epidemiological situation, SÚKL hereby provides its general recommendations for those cases when the sponsors propose and plan measures aimed at patient/trial subject safety in relation to the globally serious situation:

Always ascertain the trial subject's situation in advance by phone

- Whether the patient is not in quarantine because he/she visited a risk region (for an updated list of risk regions, please refer to: https://koronavirus.mzcr.cz/staty-sveta-s-vysokym-rizikem-prenosu-nakazy/) or whether he/she has not been in contact with a person with confirmed coronavirus infection or weather he/she doesn´t wait for test result
- Whether coronavirus infection has not been confirmed for him/her (this information should be written into the medical records and CRF)
- Whether he/she does not share household with a quarantined person
- Whether he/she agrees to the proposed course of action (a telephone visit, sending of study medication by a courier with confirmed receipt of shipment by phone and verification of data accuracy, control laboratory sampling…)

Control visits

SÚKL strongly recommends, if it is possible, a change of a physical follow-up visit of a trial subject in order to ensure the subject's safety or due to closed healthcare facilities or the Goverment's recommendation to restrict the movement of persons to a telephone visit. The phone visit has to be documented with a rationale referring to the current situation. In case a follow-up visit is completely omitted, it has to be documented and thereafter evaluated in terms of its impact upon the validity and quality of data from the clinical trial.

In case of a trial subject's visit to the trial site it is necessary to:

- Arrange for the visit beforehand by phone, so as to prevent any patient accumulation; dedicate specific time for healthcare staff to conduct follow-up visits – this should apply only to visits that are necessary and cannot be handled "online".
- Provide personal protective equipment for healthcare staff as well as for trial subjects; this is essential for immunosuppressed patients (such as patients on long-term corticosteroid therapy or on any immunosuppressive therapy, i.e. especially cancer patients and any post-transplantation patients).

Investigational Medicinal Products (IMP) – study medication (including AMP-auxiliary medicinal product required by the Protocol and supplied by the sponsor)

1) **Investigational Medicinal Products (hereinafter referred to as the "IMPs") – stored at room temperature, any pharmaceutical forms except for parenterally administered IMPs (e.g. tablets, capsules, etc.)**:
   - Possibility to provide the supply of study medication to patients during the upcoming visit for a longer period of time than originally planned.
   - In case it is not practicable to supply the study medication directly to the patient during the upcoming visit, it is possible, as an emergency situation, to send the study medication

by courier service. The courier service would collect the medicinal products at the trial site, from the investigator who is responsible for the investigational medicinal products and this fact would be recorded by the investigator in the trial subject's documentation. The courier service would deliver the study medication to the patient's (= trial subject's) home, i.e. to the address provided by the investigator to the courier service. Thereafter, the investigator would make sure by phone that the patient has received the study medication and would record this fact to the trial subject's documentation.

- In case the courier service is to carry several medicinal products at one time, the investigator must also make sure that the trial subject received the correct medicinal product (by the IMP code or trial subject code), as in blinded clinical trials there are several medicinal products; the major purpose of the telephone check is to avoid confusion of medicinal products. The patient should start taking the therapy only after the investigator endorses the correctness of the shipment.
- Further option is delivering IMP to the trial subject by his/her family member, who has been previously determined by the trial subject to investigator over the phone. The investigator records it all in source data and CRF.

2) <u>IMPs – sterile pharmaceutical forms (except for intravenously administered IMPs) such as parenteral administration, subcutaneous administration, eye drops, etc. self-applied by trial subjects at home:</u>

- Procedures outlined under Section 1) shall apply.
- In this case, it is necessary to respect also the requirements for the storage of the study medication; mostly, this concerns products to be stored at temperatures between 2–8° C. In such a case it is essential to arrange for transportation of the products in cooler boxes meeting this requirement. For the duration of transport, continuous temperature monitoring has to be ensured and documented in the clinical trial documentation. The courier service should be organised – and paid for – by the sponsor who is responsible for the quality of the IMP. It is, however, necessary, that the investigator who is fully responsible for the trial subjects from the respective trial site, agrees to this course of action.

3) **<u>IMP – parenteral administration – i.v. – in the form of bolus or infusion, applied by the doctor at the trial site:</u>**

- If permissible with a view to the protocol, SÚKL recommends to postpone the visit as well as the application of the IMP. Protocols typically offer the possibility to postpone the administration of products by 14 days.
- If the product administration cannot be postponed or it has already been postponed by the maximum period permissible, the following may be arranged for:
    - Administration at the trial site while observing the aforementioned safety hygienic rules.
    - In emergencies, if necessary, administration of the IMP at the patient's home; such administration shall be carried out by adequately qualified healthcare staff trained for this purpose.
    - Should the sponsor consider using the services of a specialised company licensed for the conduct of medical home care within the territory of the Czech Republic via qualified and properly trained paramedical staff, it is necessary to obtain the approval of the investigator from the respective trial site for this course of action, as the investigator is fully responsible for the trial subject and organisation of treatment for him/her. This course of action should be approved by the provider of healthcare services of the respective trial site. The question is how the clinical

trial insurance covers this service, how compensation for injury to health caused by a procedure conducted by "medical home care" staff would be handled. In such a case, the IMP has to be dispensed by the study staff at the trial site. Where infusions requiring preparation by pharmacy are concerned, they would be dispensed to an employee of the trial site on a request form and thereafter dispensed by the investigator or appointed trial site employee to the medical home care employee.

- Injections that may be reconstituted prior to administration: proceed as per manufacturer's instructions and, if permissible, reconstitute immediately prior to administration at the patient's, observing all of the procedures prescribed by the pharmaceutical manual.
- Infusions that were prepared by the pharmacy have to be transported under strictly observed storage conditions for the reconstituted product – i.e. under continuous temperature monitoring during transport and in compliance with other conditions prescribed by the Protocol or Pharmaceutical Manual, as applicable.
- In case of administration of IMPs presenting the risk of anaphylactic reaction, these IMPs should be administered exclusively at the trial site where intensive and resuscitation care may be arranged for.

4) Sending of study medication directly from the sponsor, albeit via third party, is not acceptable (the sponsor must not know trial subject's identification, his/her address….).

~~4)~~5) As for the return of study medication by the patient to the investigator at the trial site by courier service: in this case, SÚKL considers the sending of unused study medication by courier service inappropriate and requires that the patient keep the unused study medication and return all medication, i.e. for control purposes, used and unused medication, only after safety measures are lifted; the medication is to be returned directly to the investigator during the trial subject's next personal visit to the trial site, when the investigator shall record everything in the trial subject's documentation.

The administration of study medication that influences the immune system is not possible/is contraindicated for trial subjects with confirmed coronavirus infection.

Control laboratory sampling

If the trial subjects need to complete necessary control laboratory assessments prior to the IMP administration – such as blood count, biochemistry, urinalysis – and the IMP administration cannot be postponed, it is necessary to:

- Arrange the date (as well as the time) of the visit to the trial site and completion of the control sampling beforehand over the phone.
- Arrange for the conduct of the control sampling at trial subject's home either by contract laboratory staff or contract medical home care service availing of appropriately qualified and trained staff and means, proceeding in compliance with any other aforementioned safety measures (respirators for healthcare staff, masks for trial subjects, …) and exclude those trial subjects who have been quarantined or share a household with a person who has been quarantined or in whom coronavirus infection has been confirmed.

Informed Consent Form / Patient Information Sheet

In the case that the trial subject should be informed, we do not recommend delivering the information through „personal contact“, but the information should be communicated by phone or email (an acknowledgment of an email is necessary), and recorded in source documentation and CRF.

Investigators - changes of investigators

In the case of investigator´s /principal investigator´s illness his duties may be temporarily taken over by his representative (co-investigator). If the investigator does not have any representative, his duties and activities may be delegated to an investigator from another trial site. The next option could be the approval of a new investigator by the local Ethics Committee (EC).

Closure of the trial site / opening of a new substitute trial site

In the case of the closure of the trial site in relation to the current emergency (all staff in quarantine etc..) is possible as follows:

- halt of activities of this trial site for the required time. Temporarily transfer of the trial subjects to another trial site is possible with the agreement of both – the sponsor and the investigator. The trial subject has to agree with this change.
- or if the design of the clinical trial allows it, to halt temporarily the clinical trial
- or if there is no other option, to end the clinical trial in the trial site and transfer the trial subjects from this trial site to another trial site or to stop their participation in this clinical trial. In this case, the investigator should inform trial subjects about their further treatment, if the treatment is necessary.

If necessary, a new, substitute trial site may be opened; all GCP requirements and requirements stipulated by effective legislation must be met (such as approval by the local ethics committee, agreement concluded by and between the sponsor and the healthcare service provider, etc.). For SÚKL and MEC (multicentric ethics committee) the only notification is required (CTA form update); it is not classified as substantial amendment and reimbursement of costs for SÚKL is not required.

Monitoring

Changes to the monitoring plan involving a change of a site visit to remote monitoring or change of dates of monitoring do not have to be reported to SÚKL or to the ethics committee by the sponsor, yet everything has to be documented and justified in the clinical trial dossier. SÚKL does not provide its opinion on the organisation of monitoring when authorising clinical trials, either, and it does not have to be included in the annual progress report for the clinical trial.

In response to frequent questions regarding the possibility of alternative ensuring of monitoring, please find below the position of SÚKL (Department of Clinical Trials and GCP inspectors):

1) Centralised monitoring is permitted.
2) Remote monitoring – source data are currently in paper form. **Remote monitoring** fusing **copying or scanning of reports or medical documentation, making and use of de-identified certified copies or certified copies of de-identified source documents is not acceptable.** SÚKL's position, i.e. the position of the Department of Clinical Trials as well as that of GCP inspectors is unanimous; SÚKL would consider monitoring organized as described above a breach of GCP and legal regulations.
3) In case the reduced frequency of monitoring posed a hazard in respect of a particular CT, SÚKL would accept an alternative approach, such as central monitoring + teleconference monitoring, if feasible with regard to the workload of healthcare staff at the trial site, i.e. an

appointed study team member would read the source data and the monitor would check them against the CRFs within the scope of the TC. Nevertheless, after the emergency situation passes, data obtained in this manner would have to be verified by standard process, and for this reason, this alternative approach should only be employed in justified cases identified by risk analysis.

4) A combination of centralised + teleconference monitoring is permissible.
5) In case of videoconference monitoring, the representatives of the sponsor/CRO must not make any photocopies of the documents. (pictures, printscreens etc.). Videoconference monitoring must be ensured by secured transmission. It must be ensured verifiably that only monitor (authorized person) could consult the documentation, not any unauthorized person could have attend the videoconference. Sponsor has to establish standard procedure for such type of monitoring. It is necessary to follow GDPR requirements as well as the Law 110/2019 on personal data processing.

Initiation of newly authorised clinical trials / recruitment of new trial subjects (patients)

SÚKL STRONGLY DISCOURAGES the commencement of newly authorised clinical trials and the enrolment of new trial subject (patients) in ongoing clinical trials!

To protect the safety of the trial subjects, SÚKL recommends not to:

- Commence new clinical trials or enrol new patients/trial subjects in ongoing clinical trials wherever practicable;
- Conduct clinical trials involving healthy volunteers or "healthy patients", i.e. such clinical trials that do not provide therapeutic benefit to the enrolled trial subjects, such as bioequivalence or pharmacokinetic studies;
- Commence clinical trials involving, in particular, therapies that affect/influence the immune system.

Due to the variability of clinical trials, it is not feasible to cover all potential situations. **Trial subject safety in ensuring data validity, and hence the quality of the clinical trial conduct, is the responsibility of the sponsor; trial subject safety at the trial site is the responsibility of the investigator or principal investigator who is also responsible for the entire study team.**

Act No 378/2007 Coll., on Pharmaceuticals
Section 56(3):
Where any new fact relating to the conduct of the clinical trial or the development of the investigational medicinal product arises which may affect the safety of the trial subjects, the sponsor and the investigator shall be obliged to take urgent measures to protect the trial subjects against any immediate hazard. Provisions of paragraphs 1 and 2 shall not be prejudiced hereby. The sponsor shall forthwith inform the Institute and the concerned ethics committees of these new facts and of the measures taken.

The SÚKL will not approve or acknowledge the method of securing the evaluated products (IPMs) to the trial subjects; the sponsor is only obliged to inform SÚKL and ECs (see citations of the Act on Pharmaceuticals above).

The sponsors are asked to notify SUKL and ECs of all emergency measures concerning ongoing and approved but non-initiated clinical trials in the Czech Republic. SUKL records all these measures. SÚKL

will not consider notification of emergency measures as substantial amendment and will not require the reimbursement of costs.

In case the sponsor needs SÚKL acknowledgment about emergency measures, we will provide it on the request.

Emergency measures cannot be effective indefinitely; SÚKL will inform about the termination of the possibility to apply such emergency measures in due time.

Should you have any further questions, please contact MUDr. Alice Němcová, Director of Department of Clinical Trials on Medicinal Products (272 185 817, alice.nemcova@sukl.cz) or MUDr. Ondřej Palán, Head of Clinical Trials on Pharmaceuticals Unit (272 185 327, ondrej.palan@sukl.cz).

Department of Clinical Trials on Medicinal Products
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