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 ~~25 June 2020~~06 November 2020 (fully superseding opinions of ~~14 May~~28 August 2020) ~~added 1 July 2020; last updated 28. August 2020~~.

With regard to the conduct of ongoing clinical trials or to-be-commenced clinical trials in view of the current coronavirus epidemiological situation, the unpredictability of the future development, announcement ~~and the lifting~~ of emergency measures imposed by the government and their subsequent lifting, SÚKL hereby provides its updated general recommendations.

Due to the ~~fact that there are still locations with an increased occurrence of coronavirus infections in the Czech Republic (currently e.g. Karviná, Prague…), the termination of~~ development of the situation in the Czech Republic, emergency measures permitted by SÚKL ~~for locations with an increased COVID-19 occurrence is postponed by~~may be applied within the entire territory of the Czech Republic until 31 December 2020. ~~To ensure the provability of the fact that at a particular time, the location was affected by an increased COVID-19 occurrence, the sponsor should PROVABLY document this fact in the documentation of the respective trial site, e.g. through information from the website of the Czech Ministry of Health: COVID-19: Overview of current situation in the Czech Republic – Overview of COVID-19 occurrence evidenced by laboratory testing by region.~~

~~(The locality with an increased occurrence of COVID-19, where emergency measures can still be applied, is considered to be a place with an incidence of 10 or more patients per 100,000 inhabitants; the exception is Prague, due to the large number of inhabitants and other people commuting here daily for work, where extraordinary measures can be applied even in the presence of 3 or more patients per 100,000 inhabitants).~~

~~In respect of clinical trials in other locations, the termination of emergency measures as of 30 June 2020 shall apply, as stipulated by the previous SÚKL opinion of 14 May 2020. In these cases, the s~~Sponsors may~~should~~ return to normal conduct in those locations where practicable with regard to the coronavirus epidemiological situation and personnel conditions at trial sites~~without the application of emergency measures~~. Good Clinical Practice inspections may review the observance as well as termination of the measures.

Updated SÚKL recommendations that continue to be effective after 30 June 2020:

In respect of all clinical trials, it is still recommended to always ascertain the trial subject's situation in advance by phone or by e-mail:

- Whether the patient is in quarantine because he/she visited a risk region (or whether he/she has been in contact with a person with confirmed coronavirus infection or weather he/she waits for test result)
- Whether coronavirus infection has been confirmed for him/her (this information should be written into the medical records and CRF)
- Whether he/she shares household with a quarantined person
- Add the coronavirus medical history both to source documentation and the CRFs
    - Evidenced COVID-19 disease (in such a case, add also other details regarding hospitalisation/home care/treatment…, its duration, recovery…)
    - Reasons for quarantine
    - COVID-19 evidenced in another member of the patient's household
- The aforementioned is absolutely necessary for trial sites in areas with increased COVID-19 occurrence. If the sponsor, having regard to trial subject safety, applies any emergency measures in such areas, it is advisable to find out and document that the trial subject agrees to the proposed course of action (e.g. a phone visit, sending of study medication by courier

service, or collection of study medication by a relative with phone confirmation of receipt of the supply and verification of data accuracy, conduct of control laboratory sampling …).

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Applications for new clinical trials

Applications for authorisation/notification of clinical trials on COVID-19 shall continue to be assessed as a priority in abbreviated timelines. Moreover, multicentric ethics committees have promised to assess such applications over a shorter period of time.
We are fully involved in VHP procedures and we accept involvement in all of those to which we have been or will be invited to. Until further notice, we do not accept involvement as the Reference Member State~~We also participate as the Reference Member State. Acceptance of our involvement as a Reference Member State depends on our current capacities and workload of all of SÚKL's concerned assessors at the time of the submission of the application~~.

Any other applications for clinical trial authorisation/notification are assessed as usual.

Recommendations for ongoing or authorised clinical trials ~~after 30 June 2020~~in respect of which normal conduct may be resumed:

Control visits

Sponsors ~~should~~ may resume the normal regimen of follow-up visits at trial sites where practicable with regard to the epidemiological situation~~in accordance with the approved clinical trial protocol, without the application of emergency measures employed at the time of the coronavirus pandemics~~ and the personnel conditions of the study team. Where the emergency measures were incorporated by the sponsor into a clinical trial amendment and the amendment was approved by SÚKL and by the ethics committee, it shall be applicable without limitations until the end of 2020.~~only at the time of an increased occurrence of coronavirus infections at the trial site location, which has to be evidenced in the documentation (e.g. through information from the website of the Czech Ministry of Health – see above). In case of a new infection outburst in the concerned trial site location, emergency measures as per the approved amendment may be resumed. Any new infection outburst has to be documented.~~

In respect of the normal regimen of clinical trial conduct, SÚKL hereby issues the following recommendations:

1) Trial subject **visits** to the trial site are to be agreed in advance by phone, so as to avoid patient accumulation and so as to allow study site personnel to dedicate time for control visits. Furthermore, it is advisable to complete a COVID-19 questionnaire with the trial subject (in the form of a questionnaire or an affidavit regarding the trial subject's condition of health in the past 14 days and his/her COVID-19 history) and choose the visit date accordingly.
2) In compliance with the measure issued by the Czech Ministry of Health, as long as the measure is effective and until it is lifted, the obligation to safeguard protective aids (masks, respirators or protective shields) for the staff as well as for trial subjects shall remain applicable. The protective aids should be safeguarded by the sponsor.
3) **Commencement of clinical trials and inclusion of new trial subjects** may be carried out in compliance with the approved documentation without any further limitations, if practicable with regard to the epidemiological situation.~~.~~ The sponsor should always act with a view to the situation of the respective healthcare service provider (staffing capacities), the overall situation in the institution, and the current government resolutions applicable to healthcare service providers (currently effective Government Resolution No 1101 of 26 October 2020 that may be subject to amendments). Clinical trials where treatment delay would imply worsening

of the disease prognosis and treatment should be initiated immediately, shall form an exception.

4) **Study medication** (IMPs and AMPs prescribed by the clinical trial protocol) shall be dispensed by the investigator or a person authorised thereby (such as the sub-investigator or pharmacist) at the trial site during the trial subject's visit. ~~After 30 June 2020, the s~~Sending of study medication ~~shall no longer be permissible, except for trial sites provably located in areas with an increased COVID-19 occurrence (see below)~~at investigator's discretion and as per the situation at the trial site. Returns of unused or left-over medication by trial subjects shall take place at the trial site.
5) **Control laboratory testing** shall be organised at the trial site as per the original clinical trial plan.
6) **Safety reporting** shall be undertaken by the sponsor in accordance with the original plan pursuant to Guideline KHL-21 and Guideline CT-3. Furthermore, sponsors shall report to SÚKL also trial subject deaths not meeting the definition of a SUSAR. Investigators shall report adverse drug reactions also according to the original plan.
   ~~a.~~ Safety reports should include also information associated with coronavirus and COVID-19. As of 4 May 2020, new codes have been introduced to the MedDRA terminology that may be used for SAE reporting – new codes (the list of codes is provided under the article in separate annexes). The coronavirus history should be added for all trial subjects enrolled in ongoing clinical trials and it should form part of the baseline assessment for newly enrolled trial subjects (patients as well as healthy volunteers).
7) **Patient Information Sheet / Informed Consent Forms**
   Trial subjects should be provided with the Patient Information Sheet/Informed Consent Form as usual, at the trial site where the trial subject should be given the opportunity to read the text of the document. This should be followed by an interview with the doctor or an appointed study team member (e.g. the sub-investigator) in whose presence the trial subject and the investigator should sign the document.
8) **Clinical trial monitoring**
   If practicable with regard to the situation at the trial site, c~~C~~linical trial monitoring should be carried out in accordance with the original plan, or the plan amended with regard to the emergency measures. The permissible monitoring methods shall be: 1) monitoring directly at the trial site; 2) centralised monitoring; or a combination of both.
   ~~For trial sites located in areas where there is no longer an increased coronavirus occurrence, the sponsor should not avail of~~With a view to the adverse development of the epidemiological situation, this may be combined also with teleconference or videoconference monitoring ~~permitted as part of emergency measures~~.
9) **The conduct of clinical trials enrolling healthy volunteers or "healthy patients"**, i.e. clinical trials that do not offer any therapeutic benefit for the enrolled trial subjects, such as bioequivalence or pharmacokinetics studies, shall be permissible providing safety measures for trial subjects are adopted. Recommended safety measures during the commencement of clinical trials with healthy volunteers or clinical trials without therapeutic benefit for enrolled trial subjects:
   a. Collection of the potential trial subject's COVID history no longer than 4 days prior to invitation to the trial site;
   b. Completion of the RT-PCR test to evidence SARS-CoV-2 and the evaluation of its result prior to the trial subject's enrolment; (The RT-PCR test is mandatory only for volunteers living or working in a locality with an increased occurrence of COVID-19 (see above). For other volunteers the RT-PCR test is not mandatory.)
   c. Safety measures during the conduct of the clinical trial:
      i. During hospitalisation, reduce the number of trial subjects in one room to the lowest practicable count, no more than 4 persons.

nastavil formátování: Písmo:

Naformátováno: Normální, Odsazení: Vlevo: 1,25 cm, Bez odrážek a číslování

ii. Provide protective aids for the personnel – single-use masks; in the course of sampling: single-use gowns, respirators or single-use masks + protective shields, gloves to be exchanged after each trial subject sampling by the staff.
iii. Minimise trial subject accumulation at the trial site; obligation to wear masks while moving around the trial site.
iv. During meals, define trial subject groups that shall remain unchanged for the duration of the clinical trial (e.g. by rooms). A single table may be occupied by trial subjects from the same room.
v. Provide disinfection in corridors and in the rooms.
vi. Tighter hygienic and disinfection rules, particularly for restrooms and common premises.

10) Possibility to **utilise "Home care"** in the conduct of clinical trials ~~also in areas where there is no longer an increased coronavirus occurrence and outside the period of the COVID-19 pandemics~~.

"Home Care" may be included, if the following conditions are met:

- The utilisation of "Home Care" is justified by the patient's diagnosis or condition
- The investigator/principal investigator who is responsible for the conduct of the clinical trial at the particular trial site must agree to it
- Trial subjects must not be exposed to a higher risk than that posed by the completion of the same procedures at the trial site (a documented risk analysis is expected)
- The utilisation of "Home Care" must be clearly described in the clinical trial protocol and in the informed consent that were approved by SÚKL and by the ethics committee
- The patient must also agree to the utilisation of "Home Care" as it is a rather significant interference in the patient's private life.
- Medical decisions – such as changes to medication, AE/SAE review – continue to be the responsibility of the investigator/sub-investigator
- The clinical trial protocol (or related documentation) must predefine and describe an effective system of timely communication between the investigator/sub-investigator and "Home Care" staff ensuring that the investigator is informed about the completed visits in a continuous and timely manner (particularly in terms of trial subject safety – e.g. SAE occurrence and timely reporting by the investigator to the sponsor)
- The procedures conducted within the scope of "Home Care" must be adequately documented and the relevant source documents must be stored as part of clinical trial documentation kept by the investigator at the trial site and investigator's supervision must be documented (the investigator shall forthwith review records from "Home Care" visits and attach his/her signature on the source documents as confirmation that the review was completed)
- The "Home Care" staff who are to be involved in the clinical trial in question must be engaged as external co-workers of the study team, i.e. they must be included in the Delegation Log, including their responsibilities and competencies, documented qualification, completion of training by the principal investigator/sub-investigator in the activities they are to perform
- "Home Care" must be covered by the insurance of the clinical trial
- The "Home Care" provider cannot be engaged by the sponsor; the sponsor shall pay for "Home Care", but there must be a written contract between the provider of the healthcare services where the concerned trial site is located, and the "Home Care" provider. Such contract must specify the responsibilities and competencies of the "Home Care" provider in the clinical trial, and also contain a list of names of "Home Care" staff to be involved in

the clinical trial (may be included in the form of an annex). The listed staff shall be included also in the investigator's Delegation Log at the trial site.

- (Note: *"Home Care" cannot be utilised for the purposes of administration of products to be applied under the supervision of a medical doctor or by a medical doctor, after which the patient is to be followed up for a particular period of time (as specified by the Protocol or by the SmPC, e.g. for 1-2 hours). "Home Care" cannot be utilised for the application of a phase II product where a first-in-human study is concerned.)*

For all sites in the Czech Republic~~that are provably located in in areas with increased COVID-19 occurrence~~ (which has to be documented in the CT dossier), the below specified emergency measures may continue to be applied until 31 December 2020:

1) It is still possible to change~~, in justified cases,~~ physical follow-up visit of a trial subject in order to ensure the subject's safety or due to closed healthcare facilities 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 in order to ensure trial subject safety, it has to be documented and thereafter evaluated in terms of its impact upon the validity and quality of data from the clinical trial.

2) 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. Furthermore, a COVID-19 questionnaire should be completed with the trial subject (in the form of a questionnaire or an affidavit regarding the trial subject's condition of health in the last 14 days and his/her COVID-19 history), and on the basis thereof, select a date and time for the visit.
- Provide personal protective equipment for healthcare staff as well as for trial subjects. Protective equipment should be safeguarded by the sponsor.

3) Initiation visits for trial subjects newly enrolled in ongoing clinical trials

- Where the sponsor evaluates the risk/benefit ratio for newly enrolled patients as favourable for enrolment in the study and the situation in the trial site ~~is also favourable~~allows to do so (sufficient study staff capacity), the initiation visit has to be organised at the trial site, taking into account all of the aforementioned conditions (COVID-19 medical history, phone arrangements for the time of the visit, provision of protective equipment to the patient and healthcare staff…). During the initiation visit to the trial site, the investigator, in an interview with the patient, shall explain everything regarding the clinical trial and shall obtained a signed informed consent from the patient. The informed consent may be sent in advance (e.g. by e-mail) and the interview with the investigator conducted as a teleconference, so as to reduce the visit to the trial site to the necessary minimum.

4) The initiation of COVID-19 clinical trials and the enrolment of new trial subjects to such clinical trials shall be conducted in compliance with the approved documentation without further limitations.

Investigational Medicinal Products (IMP) – study medication (including AMP-auxiliary medicinal product required by the Protocol and supplied by the sponsor) – the below-listed ways of providing the study medication to trial subjects may be employed until 31 December 2020:

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.
   - The courier service should be organised by the sponsor, or, after an agreement with the sponsor, it may be organised by a study team member. The engagement of a courier service has to be covered by a contract which shall form part of the clinical trial documentation. Another option is to keep the courier service in the Delegation Log as part of the team (whereas confidentiality issues must be covered). The costs of courier service shall be covered by the sponsor.
   - When sending investigational medicinal products containing narcotic or psychotropic substances by a courier service, it is recommended to pack each shipment for the trial subject into a box or another container that will be sealed by a study team member with an adhesive tape bearing a stamp or signature of the study team member. On confirmation of shipment take-over by the trial subject, the courier shall ask the trial subject to confirm that the shipment was delivered sealed and its integrity was not compromised.
   - Another option is to have the IMP delivered to the trial subject by his/her family member, who has been previously appointed by the trial subject in phone conversation with the investigator. The investigator shall record this change of IMP dispensing in source data and CRF.

2) 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:
   - 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, agree to this course of action.

- The courier service should be organised by the sponsor, or, after an agreement with the sponsor, it may be arranged for by a study team member. The engagement of a courier service has to be covered by a contract which shall form part of the clinical trial documentation. Another option is to keep the courier service in the Delegation Log as part of the team (whereas confidentiality issues must be covered). The costs of courier service shall be covered by the sponsor.
- When sending investigational medicinal products containing narcotic or psychotropic substances by a courier service, it is recommended to pack each shipment for the trial subject into a box or another container that will be sealed by a study team member with an adhesive tape bearing a stamp or signature of the study team member. On confirmation of shipment take-over by the trial subject, the courier shall ask the trial subject to confirm that the shipment was delivered sealed and its integrity was not compromised.

3) **IMP – parenteral administration – i.v. – in the form of bolus or infusion, applied by the doctor at the trial site:**
   - If permissible with a view to the protocol and the patient's condition of health, 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 (see above).
     - 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….).

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. If a trial subject's participation in a clinical trial is terminated (early termination or regular completion) and the patient is not to come to the trial site any more, it is possible to organise the collection of unused study medication from the trial subject by a courier service. Everything has to be properly recorded in the clinical trial documentation.

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:

a. 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.
b. 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.
c. Arrange for sampling in a nearby local laboratory or with the general practitioner, if they agree to this. In such a case, the costs of the assessment shall be borne by the sponsor and they cannot be reported to the health insurance company.

Arranging for control laboratory sampling in the manner specified under points b) and c) contrary to the original protocol may be employed **until 31 December 2020**.

Safety reporting

The sponsor shall safeguard the submission of the Suspected Unexpected Serious Adverse Reaction (hereinafter referred to as "SUSAR") reports to the EudraVigilance database and of the Development Safety Update Report (hereinafter referred to as "DSUR") to SÚKL on an ongoing basis as per the original plan, in compliance with guideline KHL-21 and guideline CT-3. Furthermore, the sponsor shall report to SÚKL any death of a trial subject not meeting the SUSAR definition.
The investigator shall also report adverse drug reactions as per the original plan.
Safety reports should also include information pertaining to coronavirus and COVID-19. As of 4 May 2020, new codes have been established in the MedDRA terminology that may be used for SAE reporting – new codes. The coronavirus history should be added for all enrolled trial subjects in

ongoing clinical trials and it should also form part of the baseline assessment for newly enrolled trial subjects (patients as well as healthy volunteers).

Informed Consent Form / Patient Information Sheet

In case that the trial subject should be informed, it is still possible to deliver the information also through ways other than "personal contact", e.g.:

- Communicating the information by phone and documenting it in the source documentation and in the CRF;
- In the form of written email information, with trial subject's acknowledgment of the email and a record thereof made to the source documentation and CRF.
- In case an amendment to the Patient Information Sheet/Informed Consent Form (hereinafter referred to as the "PIS/ICF amendment") or an **updated version of the Patient Information Sheet/Informed Consent Form** (hereinafter referred to as the "PIS/ICF") is issued, it is necessary to submit this PIS/ICF amendment or updated version of the PIS/ICF to SÚKL and to the ethics committee for approval prior to its use in the clinical trial. An exception to this rule shall be PIS/ICF amendments or PIS/ICF updated versions containing safety information that need to be communicated to trial subjects as soon as practicable. In such a case, PIS/ICF amendments or PIS/ICF updated versions shall be presented to trial subjects as soon as possible and thereafter shall be notified to SÚKL and to the ethics committee.
- A PIS/ICF amendment or updated version may be sent to the trial subject by e-mail or post, but it is not possible to require that a document delivered in this manner be signed and the signed document be returned by post or a scan of the signed document be returned by e-mail. In case e-mail is used, the investigator/study team member shall ask the trial subject to acknowledge the receipt of the document and shall enter this fact to the CRF, and shall add the e-mail to source documentation. If the document is sent by post, the investigator/study team member shall check the receipt of the document by phone and shall enter this fact into the CRF and source documentation. During the next visit, the trial subject shall sign the PIS/ICF amendment or updated version, date it with the study visit date, and confirm that he/she had been previously familiarised with this document.

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's representative cannot take over the investigator's responsibilities, either, his duties and activities may be delegated to and coordinated by an investigator from another trial site. Another option could be the approval of a new investigator by the Ethics Committee.

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

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

- suspend the activities of this trial site for the required time. Temporarily transfer the trial subjects to another trial site, if agreed both with the sponsor and the investigator. The trial subject has to agree with this change;
- or, if possible with regard to the design of the clinical trial, temporarily suspend the clinical trial;
- or, if there is no other option, end the clinical trial at 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, where a chronic or continued condition is concerned, the investigator should inform trial subjects about their further treatment.

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), only notification is required (CTA form update); it is not classified as substantial amendment and reimbursement of costs for SÚKL is not required.

Clinical Trial 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** using **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. Furthermore, it must be verifiably ensured that only the monitor (authorized person) may consult the documentation and that no unauthorized person shall be allowed to attend the videoconference. The sponsor has to establish a standard procedure for such type of monitoring. It is necessary to follow GDPR requirements as well as those of Act No 110/2019 on personal data processing.

With regard to the lifting of emergency measures, it is appropriate to go back to the original clinical monitoring plan, wherever possible with a view to the study team capacity, favourable epidemiological situation in the given locality and at the concerned healthcare service provider.

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

Always ascertain the current situation at the concerned trial site with the principal investigator/investigator beforehand (by phone, e-mail):

- What is the current situation at the given healthcare facility, whether any limiting measures have been imposed therein in relation to the COVID-19 situation;
- What is the personnel situation in the study team conducting the clinical trial or appointed to conduct the clinical trial in question.

To protect the safety of the trial subjects:

- When commencing new clinical trials or enrolling new patients/trial subjects in ongoing clinical trials, it is necessary to assess the epidemiological situation at the particular healthcare facility (the condition of health of the CT team members, their capacity available for the conduct of the clinical trial, and, if applicable, imposed restrictions in the particular healthcare facility).
- The sponsor shall forthwith notify SÚKL and the ethics committees of the commencement of a new clinical trial by means of a letter (Section 55(6) of Act No 378/2007 Coll., on Pharmaceuticals, as amended; Section 15(1) of Decree No 226/2008 Coll., on Good Clinical Practice). The letter may be sent to SÚKL electronically, always with the clinical trial identification by the EudraCT Number of SÚKL's file number "sp.zn. sukls". (Via data mailbox or e-mail: posta@sukl.cz).
- Where the enrolment of new patients to clinical trials is resumed, the sponsor shall be obliged to send this information to SÚKL and to the ethics committee together. The notification is not subject to reimbursement for expert activities. SÚKL shall confirm (take note of) the receipt of this information.

Sponsors are notified to check the validity of SÚKL's authorisation/approval for to-date not initiated clinical trials. In case the expiry of the authorisation/approval of a notified clinical trial is approaching (i.e. 1 year of the date of issue of the authorisation/approval of the clinical trial), it is necessary to re-apply for the issue of the authorisation/approval of a notified clinical trial with SÚKL prior to the expiry date of the application. The handling of such application shall be considered a substantial amendment and is subject to fee.
In case an authorisation/approval of notified clinical trial expires, SÚKL shall not re-issue a backdated authorisation/approval of notified clinical trial and the sponsor will have to submit an application for the issue of a new authorisation/approval of notified clinical trial (resubmission) and cover the full fee for expert activities.

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.

~~SÚKL will not approve or acknowledge the method of securing the investigational medicinal products (IPMs) for trial subjects; the sponsor is only obliged to inform SÚKL and ECs (see citations of the Act on Pharmaceuticals above). Sponsors are asked to notify SÚKL and ECs of all emergency measures concerning ongoing and approved but non-initiated clinical trials in the Czech Republic. SÚKL records all of these measures and enters them in CT documentation. SÚKL will not consider notification of emergency measures as a substantial amendment and will not require the reimbursement of costs.~~

In case the sponsor submits to SÚKL clinical trial amendments (incl. also Dear Doctor Letters (DDL) or Dear Investigator Letters (DIL) specifying the emergency measures that have been or are to be implemented at the respective trial site, in order to provide for a uniform approach, these documents shall be assessed as a substantial amendment subjected to reimbursement of costs. ~~needs SÚKL's acknowledgment of the emergency measures notified to SÚKL, we will provide it electronically upon request (by e-mail or scan of the confirmation enclosed by the sponsor).~~

Emergency measures applicable in areas with increased COVID-19 occurrence shall not be effective indefinitely; SÚKL hereby defines the date of termination of the possibility to apply such emergency measures as 31 December 2020 or until new emergency measures are established. After this date, it will no longer be possible to apply the aforementioned emergency measures.

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~~Eva Hrušková Reinová, Head of Clinical Trials on Pharmaceuticals Unit (272 185 ~~327~~317, eva.hruskovareinova@sukl.cz~~ondrej.palan@sukl.cz~~).

Department of Clinical Trials on Medicinal Products
Date: ~~25 June 2020, added 1 July 2020, last updated 28 August 2020~~… November 2020