Information on the continuity of clinical trials under COVID-19 (coronavirus) - 25.03.2020

The European Medicines Agency (EMA), Good Clinical Practice (GCP) Inspectors Working Group, the Clinical Trials Facilitation and Coordination Group (CTFG), a working group of the Heads of Medicines Agency (HMA), the Clinical Trials Expert Group (CTEG), a working group of the European Commission representing Ethics Committees and National Competent Authorities) and the European Commission (EC) have developed a harmonised EU/EAA-level Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic

https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf.

This national recomendation can be used with the European guidance document.

Extraordinary measures already implemented to inhibit spreading infections may have an impact on the conduct of clinical trials and some changes may be required however continuity of clinical trials must be provided especially for those patients for whom the continuation of the treatment is especially important (e.g. oncology patients).

General considerations

A thorough risk assessment of ongoing investigations should be carried out considering restrictions already applied and expected (quarantine, visitation ban in healthcare institutions, increased burden of the healthcare system, possible supply problems for medicines — IMP and non-IMP, etc.) and measures should be put in place to prioritise patient safety and data validation. In the event of conflict between these two objectives, patient safety should be prioritised.

All decisions must follow ICH GCP and EU and Hungarian legislation, inclusive of GDPR.

It is important to emphasise that patient safety is the top priority and that, consequently, any changes should be proportionate and based on a thorough risk assessment (benefit-risk assessment, impact on the health and safety of the impacts). The risk assessment shall be repeated and properly documented, depending on the evolution of the situation. Any deviation from current practice should be proportionate, verifiable and clearly documented (see ICH GCP 5.0.4).

Changes to trial conduct should be agreed with and communicated clearly to investigational sites. To support implementation by sites, it is important that changes and local implications are made clear, including marking of changed documents with track changes.

In cases when obtaining wet ink signature is difficult, agreements may be documented with alternative methods e.g. e-mail exchange.

During the transition period, the number of protocol deviations may increase. It is important that these deviations are clearly documented (see ICH GCP 4.5.3). The authorities will take a fair approach when reviewing deviations if they are in the interests of participants and do not expose them to undue risk.

In case of ongoing studies with populations particularly at risk of coronavirus (immunosuppressant treatment, over 60 years of age, chronic diseases), special considerations should be made regarding the continuation of the study.

In general, it is considered prudent to stop the enrolment of patients during this period.

In case of temporary halt of recruitment due to COVID-19 notification shall be sufficient and the restart of recruitment is not considered as a substantial amendment either. Notifications can be made within one letter even in case of more clinical studies.

Authorization procedure

The new clinical trial applications and substantial amendment requests should be sent to the OGYÉI client gate. In cases that concern the Ethics Committee as well, the electronic communication has been solved, so we don't need any CDs. In case of new clinical trial applications – considering that the documentation takes up much space, there is an opportunity to upload the documents by CESP. Since not all applicants have a CESP access, there are other submission opportunities, such as Eudralink, or transfer (https://transfer.ogyei.gov.hu/). Detailed information can be found on our website about this

https://ogyei.gov.hu/tajekoztato_a_koronavirus_jarvany_miatt_elrendelt_digitalis_munkarendben_torteno_iratfogadasrol__20200318.

In the current crisis situation, the Medical Research Council - Ethics Committee for Clinical Pharmacology (MRC – ECCP) cannot ensure the proper issue of official position statements, but they bear full responsibility for their content. The National Institute of Pharmacy and Nutrition issues decisions according to the official position statements. Hereby we note, that since these are enclosed to our decisions, they are electronically authentic documents as well.

When substantial modifications of the study are required in order to ensure the patient's continued participation, sponsor may do so as an "urgent safety measure" (USM). The change will take effect immediately. The urgent safety measure should be sent to the authority and the amendment should be subsequently, officially authorised in accordance with the usual procedure.

Patient information

Considering the current situation with its restrictions, in case of ongoing trials, a new informed consent form may be necessary and patients may have to be re-informed. Alternative opportunities for this re-information should be considered, e.g. contacting enrolled subjects via telephone or video-call, and obtaining oral consent followed by confirmation via e-mail. Every consent obtained this way must be documented, and confirmed by the participants with wet-ink signatures as soon as possible, when attending the study site again.

In Hungary, electronic patient information sheets and informed consent forms are not permitted, according to the law that must be followed in the current extraordinary situation as well.

Study visits

Sponsor, in agreement with the investigator-in-charge, shall consider converting or deferring on-site visits to telephone visits or terminating them on the basis of the risk assessment, in order to ensure that it is strictly necessary visits to the test sites.

Currently, our Institute does not support visits carried out at the patient’s home, because of its limited availability, its negative effect on the spread of the virus, and the disproportionate burden of the investigational staff.

If the epidemiological situation subsequently so requires, consideration should be given to the transfer of subjects to existing or new test sites. Such relocation may only be carried out with the agreement of the subjects and the principal investigators (transfer and host), by appropriately transferring the eCRF to ensure that the new test site has access to all information and previously collected data, and to record new data. The relocation agreement should be documented in the TMF (e.g. by e-mail).

The performance of critical laboratory tests, imaging procedures or other diagnostic tests may be needed for patient safety. If the participant cannot attend the site, then it is acceptable to perform the laboratory, imaging or other diagnostic procedures in accredited local laboratories, taking the epidemiological restrictions into account. The site needs to inform the sponsor about the change. The examinations carried

out in the local laboratory can be used for decisions regarding patient safety. If laboratory tests serve as endpoints in the trial, and biological samples cannot be transported to the central laboratory, this fact must be documented in the Clinical Study Report at the evaluation of the results, according to ICH E3.

If it is not possible to continue the study at a test site, it shall be suspended and everything that follows should ensure patient safety and data adequacy.

If the continuation of the study is not possible at the investigational site any more, and the relocation of the site also meets with difficulties, subjects should be informed in the simplest way, via telephone. Similarly to telephone visits, this must be documented as well, and –considering the risk-benefit assessment – decision should be made whether the sponsor puts the study on hold or terminates it. Our Institute should be informed about this decision subsequently giving the reasons and the exact time points.

In every case, when the principal investigators cannot complete their tasks due to protective measures or illnesses, the sub-investigator previously delegated to the study can take over their role. This also needs to be documented, and our Institute should be informed about the change subsequently, when the situation has normalized.

Currently, we do not know about sites that have been closed, only relocation of sites. If any site moves to another settlement of the institute, or other health care institute due to the evolved crisis, and there the study is continued, the Institute only needs to be informed subsequently giving the exact dates of the address change. There is also an opportunity for the investigator to move the patient care to a private surgery that has not been marked as a satellite-site before, but the Institute and the Ethics Committee needs to be informed, and subsequently it needs to be submitted as an amendment.

Monitoring

In order to reduce on-site monitoring, appropriate alternative methods should be selected. Alternative methods shall be decided on the basis of a risk analysis taking into account patient and data security in agreement with the study sites and amended Monitoring Plan on the basis of accepted changes. The choice of alternative methods shall take into account that they do not place a disproportionate burden on the test site and staff.

Implementing phone and video visits can be considered without unnecessary burden to the investigator site and taking into account trial participant integrity.

Remote and central monitoring through an EDC system may be an appropriate alternative, while this will not cover the review of source documentation, this process can still alert the CRA to the following:

- medical history, scales, ePROs, eDiaries, physical exam findings and concomitant medications
- protocol non-compliance with visit windows, gaps in investigational product administration, dose taper and dose titrations, SAE reporting, adherence to withdrawal criteria, etc.
- Safety concerns through the assessment of labs, AEs and other assessments reported in the EDC system (or lack there-of)

Sharing of patient data and the remote access of the Sponsor's representative to the electronic database of healthcare institutions is not acceptable due to the protection of particularly sensitive data and ethical considerations. The upload of patient documentation to a cloud-based solution would infringe trial participants' rights and/or, considering the current situation, it puts disproportionate burden on site staff.

It is important to stress out that proper follow-up of these transitional measures after the normalization of the situation is essential and includes, for example, an increase in the frequency and/or time of on-the-spot monitoring in order to identify and address the possible negative effects of the transitional measures.

IMP management

Measures to address problems with access to investigational medicinal products and other medicinal products used in the clinical trial (non-IMP) shall be taken in accordance with the procedure laid down in Article 13 of The GMP. It shall be established in accordance with the procedure referred to in Article 10(2) of the processes may be carried out by a qualified and delegated person on the basis of written regulations.

The transfer of IMPs between sites, the patient's increased supply with IMPs during on –site visits, or the dispatch of IMP from the site to the patient's home may arise.

In case of trials where the patient self administer the medication at home, transport of IMP and non-IMP (rescue-medication) to patients' home can be an considered.

In cases like this the responsibility remains with PI. Transportation of IMPs from the site/institution pharmacy is preferred. The person who performs the transportation of IMPs must know the guidelines with regard of

IMP handling. Special storage conditions must be documented all the time, but there is no need to inform National Competent Authority about this change.

Any transitional measure shall be designed in such a way as to ensure that

- the prescribed conditions for transport/storage of the product in question during transport and storage in the patient's home, especially in special circumstances (e.g. 2-8 °C),
- safe custody of preparations
- and the relevant documentation of the accounts.

To avoid IMP/non-IMP shortage an adequate supply maintenance is recommended for those cases when transportation of IMPs to investigation sites is faced with difficulties. Direct IMP delivery from sponsor to trial participant's home is not accepted as sensitive data may be revealed.

Hungarian National Competent Authority agrees to make accelerated assessment in case of submissions of COVID-19 clinical trial applications.

Hungarian National Competent Authority is ready to give support to parties involved in clinical trials. This information is updated regularly, please come back forfurther updates.

Budapest, 25.03.2020