UNOFFICIAL ENGLISH TRANSLATION

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COVID-19: Exceptional measures regarding clinical trials execution during the period of risk to public health

Following an International Public Health emergency, declared by the World Health Organization on 30/01/2020 due to SARS-CoV-2 (new coronavirus 2019) infection, and also regarding clinical trials conduction in Portugal, INFARMED, I.P. admits that sponsors, clinical trial sites and clinical research staff consider it necessary to introduce changes to the approved terms in the current Clinical Trial Authorization, in order to safeguard the safety, protection and rights of clinical trials subjects.

In the emergency context, it is also important to simultaneously reduce the risk of spreading infection among the population and to ensure the availability of health professionals for priority tasks.

Without prejudice to the harmonized guidelines published by the European Commission, regarding the clinical trials conduction in the various Member States in the context of a pandemic, follows below the specific recommendations that should be followed, although these might be updated in the future.

In the public health emergency context, t**he measures' set presented below can be implemented immediately, without requiring prior notification or approval of a substantial amendment, exception to point 1.A "Interruption of Treatment", which should be notified as an urgent safety measure.**

It is expected that the sponsor and the Investigator make mutual decisions regarding the measures to be taken proportionately and appropriately, based on a risk analysis for each clinical trial, considering the trial characteristics, the trial site and the trial epidemiological risk.

For each clinical trial, during the pandemic crisis, if Sponsor and Investigator consider necessary to adopt measures that might consist in protocol violations and in changes to protocol predefined procedures, in order to protect the subjects, sponsor must notify Infarmed, up to 4 months after this period, with a systematic report containing the set of measures implemented, the deviations that had occurred, as well as an evaluation of the implementation of these measures and their impact on the study after the resolution of the

current epidemic outbreak, i.e. when there is a consensus that the COVID-19 pandemic period in the EU/EEA has been overcome.

This present guideline refers to the implementation of immediate measures in the context of COVID-19, to safeguard the immediate subjects' safety. Therefore, the Sponsor should submit a substantial alteration if these changes may impact the safety and well-being of subjects, **but not require an immediate intervention** by the investigator and the sponsor.

Other recommendations are also presented, related with the availability of experimental, non experimental drugs, and medical devices used in the context of clinical trials.

These recommendations are also applicable to clinical studies with intervention of medical or cosmetic devices, under law n. º 21/2014, of 16 April, in current wording.

1. Measures of immediate implementation:

A. Treatment Interruption

The necessity of immediate interruption of study treatment may be a possibility, whenever the subjects' safety is a concern.

In such cases, of which we particularly highlight clinical trials involving immunosuppressive populations due to treatment instituted, as well as other therapies that may constitute an intolerable risk, whenever the treatment is interrupted, in some or in all subjects, sponsor must submit as soon as possible an "urgent safety measure" to Infarmed, with detailed explanation of the context and of the measures taken to guarantee the alternative treatment to subjects.

For the other "urgent safety measures", not related to the current pandemic situation, the current procedure remains in force, provided on the Note to Guide "Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial" published on Volume X of Eudralex.

B. Suspension of recruitment

As referred, due to the current pandemic situation, it is expected that the Sponsor and the investigator make mutual decisions regarding the measures to be taken proportionately and appropriately to new clinical trials and to those already ongoing. The subjects' recruitment for clinical trials should be based on the sponsor's feasibility analysis regarding the initiation of a new clinical trial in the current conditions.
This should take in account, based on a risk analysis for each clinical trial, the trial characteristics, the population to be included or already included, the clinical trial site and its epidemiological risk.

Therefore, it is recommended to suspend the recruitment activity, whenever this represents a justified additional risk of SARS-CoV-2 infection for the subjects to be recruited.

C. Scheduled visits - clinical evaluation and study procedures using telematics methods

Sponsor must evaluate if protocol visits' schedule should be reviewed in terms of:

- Adjust the visits' frequency during the period considered necessary
- Adjust the level of information collected at each visit

Remote visits, using telephone calls or other technological methods (telematic), are allowed and should be assured the collection and documentation of all information requested for the visit in question (including the method in which visit was performed and also the identification of the site staff who performed the visit).

It must be ensured that subject allows the use of telematic method and that only the strictly required information is collected.

This consent can be obtained verbally, registered on trial site documentation by the site staff responsible for collecting it, or, for example, by email (video or sound record is accepted). It should be confirmed by the subject signature, whenever the current situation is normalized.

D. Centralized monitoring and source data review

Sponsor must assess if the monitoring plan implemented should be reviewed in order to:

- Postpone on-site monitoring visits
- Centralized monitoring visits, based on a risk assessment, are permitted and encouraged.
- To reduce the monitoring activities to whatever it is possible to do remotely, even if this implies delaying the source data review, for when it is possible to have access in person and in agreement with the trial site and principal investigator.

Centralized monitoring cannot imply the retention of source documents or access to personal data by unauthorized persons. Furthermore, the remote access to patients' clinical data, registered on informatics systems belonging to the trial site can be acceded if compliance with Good Clinical Practices and the General Data Protection Regulation is guaranteed. Exceptions to these requirements should be properly analysed by the Data Protection Officers of the involved entities and should be communicated to CEIC and CNPD, within the framework of their competences and compliant with their guidelines, on the context of public emergency.

E. Direct dispensing at home of investigational products

Considering the exceptional circumstances, the dispensing at home may be accepted, based on the following premises, and should be complemented by the Circular Normative N.º 005/CD/555.20.001 of 07/04/2020, related to the "Guideline on the proximity access to dispensed medicines of hospital pharmacy for outpatient treatment on the context of COVID-19", especially in what refers to the items 1.1, 2, 2.1.1, 2.1.2 and 2.3, with the due adjustments

to guarantee the control of access to subjects' personal data and, when applicable, the blinding maintenance of the clinical trial:

- Ensure that the Principal Investigator and clinical research team (including the hospital pharmacy) maintain the supervision of this process, ensuring communication channels that allow subjects to clarify doubts.
- Guarantee that access to personal information (name and address) is allowed by the subject.
- Maintain records to allow the track of transportation from the point of departure (trial site) until the subject´s delivery.
- Maintain the storage methods registered.
- Guarantee that temperature/humidity records are registered during the transportation.
- In cases when reconstitution is necessary, the drug stability period between the time of reconstitution until the administration must be considered; this possibility is applicable only in cases when the administration does not require the intervention of a health professional *
- Ensure that the subject receives all the information and is informed about the administration and surveillance process, as well as he has the necessary contacts to communicate adverse events / serious adverse events
- Safeguard the breaks of the blinding, when applicable.

* in cases when the administration requires the intervention of a health professional and it is not possible to guarantee that this will be carried out at the subject´s home (ensuring all safety conditions for the patient and for the health professional, as well as all technical means necessary) should be considered to transfer the patient to another alternative clinical trial site. If the transfer it is not possible, it must be carried out interruption of treatment as seen in point A or the closure of the research site, with the completion of all end-of-study procedures, safeguarding the safety and well-being of the subjects. Subject´s follow-up after premature trial completion at the research site must be followed in accordance with study protocol for these cases

Also, should be considered the section 10 provisions of document "Q&A: Good clinical practice (GCP)" – GCP Matters".

F. Transfer conditions between trial sites:

Given the exceptional circumstances, the transfer between trial sites may be accepted, and this must be in accordance with Good Clinical Practices, General Data Protection Regulation, aspects related to the circulation of health information arising from law no. 12/2005, of January 26, as well as the other deontological aspects for the transfer of documents between health institutions.

If it is necessary to transfer the investigational product stock (when applicable), sponsor must ensure that:

- Records are maintained to allow the track of transportation from the point of departure (sponsor or trial site) to the new site delivery.

- The storage methods are registered and maintained.
- That temperature/humidity records are registered during the transportation.

Must be assured that Good Clinical Practices, General Data Protection Regulation, aspects related to the circulation of health information arising from law no. 12/2005, of January 26, as well as the other deontological aspects for the transfer of documents between healthcare institutions were followed.

2. Other recommendations:

A. Communication with Infarmed

The main email contact is: ensaios.clinicos@infarmed.pt

All the submissions related to processes prior to the implementation of RNEC, must during this time be submitted by email.

B. Interruption of investigational drug provision

To guarantee stock for subjects for at least 3 months.
In case of impossibility to guarantee reserve of stock:

- evaluate the possibility to suspend the subjects' recruitment
- evaluate the necessity to suspend the clinical trial, according to the criticality of the subjects' health status, therapeutic indications and risks of discontinuation (e.g. cytotoxic)

The importation/exportation of investigational products for use by a specific participant, in line with the provision on section 1.E., shall be preceded by anticipated notification to Infarmed (dil-ins@infarmed), with a description of the situation, including: identification of trial site, identification of investigational product and quantities to be shipped, and a declaration by the principal investigator that the therapy is indispensable for that specific participant, assuring that will be used exclusively by that participant and that the conditions required for maintaining the remote treatment are met.

C. Interruption of Non-Investigational Medicine Products (NIMPs) provision / Interruption of medical devices required to administration or manipulation of investigational product provision

To assess if they belong to the Strategic Medicines Reserve, published in Diário da República, Order No. 3219/2020 available at: https://dre.pt/web/guest/pesquisa/-/search/130112149/details/normal?l=1. If not, guarantee reserve of stock to the subjects, for at least 3 months.

D. Protocol deviations

Protocol deviations that may occur must be properly registered in sponsor´s Quality Management System.

E. Evaluation of clinical trials of new drugs for Covid-19 disease

Infarmed will prioritize the evaluation of new clinical trials aimed to treating or preventing the disease by the new coronavirus (SARS-CoV-2).

The applicants must submit the study through RNEC, clearly identifying the scope of the disease Covid19, and send an email to Infarmed (ensaios.clinicos@infarmed.pt) and CEIC (ceic@ceic.pt), in order to streamline the process with a view to an expeditious approval.