AIDFMCETERA
ACADEMIC CONSULTING RESEARCH ORGANIZATION

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CEIC information regarding clinical trials or intervention studies with MD in view of the current conjecture of Covid-19

The pandemic situation for the new coronavirus (SARS-CoV-2) may have an impact on the conduct of clinical trials and other clinical studies on subjects' visits at the trial sites, provision of investigational product and monitoring activities, among other aspects.

During this period, subjects may be advised by health authorities not to do hospital visits/health facilities or be limited to other movement restrictions (self-isolation, for example).

The protocol should continue to be the guiding document for all study specific activities, and, due to the above mentioned constraints, actions must be taken to allow minimize major deviations (remote visits, sending investigational product instead face to face dispensation, remote monitoring, for example). Safety monitoring of subjects already enrolled and their access to investigational product should be priority over the recruitment of new subjects.

It is therefore important to establish some rules and procedures regarding notification or submission to CEIC, considering the different recommendations available in this matter and the different questions asked by the applicants.

Despite the European Commission's harmonized recommendations, CEIC informs:

1. Regarding subject´s visits at research sites and other sites for execution of complementary diagnostics
    i. As an alternative to the face-to-face subject´s visits, it is possible to perform telephone visits or by video call.
    ii. For site initiation visits, the adequacy and timeliness of these should be considered and/or their realization not in person, given the current situation.
    iii. When foreseen and financially supported by the sponsor, the patients commute to local laboratories and other external clinics for the execution of clinical analysis and/or examinations is acceptable, as long as the entities are properly certified and the DGS measures for the prevention of infection by Covid-19 are, as far as possible, confirmed.
        - The selection of laboratories and/or external sites should be prepared through the trial site and Principal Investigator (PI).
        - The adoption of not in person visits to patients and/or execution of laboratory tests and/or examinations in other places outside the trial site, should be notified to CEIC as a non-substantial amendment (NSA) integrated in the sponsor action plans or as deviations, if considered major by the sponsor.

2. Regarding monitoring activities (of quality)

i. Those activities can be conducted through alternative and proportional mechanisms, remotely and/or centrally, such as telephone calls, video calls, etc., in order to guarantee the continuous safety and well-being of the participants;
ii. The risk of impact on monitoring deviations should always be assessed by the sponsor, considering the prioritization of critical activities, such as adverse reactions, safety reports, among others;
iii. Alternative monitoring ways and timelines must be properly documented;
iv. For CRA monitoring visits, monitors will be able to access remotely, as they often do, safeguarding the audit trail and the confidentiality of participants' data.
v. The validation of the subject's signature on the informed consent can be executed through the confirmation by the Investigator during a remote monitoring visit, and subsequent verification.
    - Monitoring is restricted to encrypted data that subject´s has already consented to share outside the site.
    - Remote monitoring does not include remote access to the subject´s health records (except if the subject´s privacy is properly taken care of and the applicable regulation requirements are met)
    - The delivery of source documents by fax and/or e-mail to the CRA (for remote revision) is allowed, when properly anonymised and codified through randomisation number or other equivalent mechanism.

3. Regarding supply of the Investigational Product (IP)

It may be acceptable shipping investigational product to subjects through the sites, in compliance with Good Clinical Practices and other applicable legislation and verified the following:

i. Supply of investigational product to the subject, through the site, if they cannot go to the Hospital (trial site), and when clinically appropriate/necessary;
    - The direct supply to the patient (or his/her selected delegate), from the trial site, since it constitutes a change to the IP circuit, must be notified to CEIC as NSA, in addition to being properly registered in the study documentation;
ii. Temporary and/or permanent discontinuation can be considered, if clinically appropriate/necessary;
iii. The IP redistribution between sites is allowed, as long as properly traceable and all the transportation measures are safeguarded.
iv. IP transport services must comply with the good distribution practices issued by Infarmed, I.P., now applicable to the context of investigational products;
v. The IP return from the subjects to the trial site can be executed by mail or other transport company, as long as required by the site and with reimbursement of the related costs to the subject;
vi. Whenever the study medication, provided at home, requires administration by a nurse or other qualified person, this must be included in the site staff team.
    - Whenever the protocol already expects for "home nursing" services, including biological products collection, these may be extended to IP provision and/or administration, once the safety of the intervention is safeguarded, and it is only necessary to notify CEIC as NSA.
    - Whenever not expected in the protocol, or has not been approved by CEIC, this possibility must be submitted to CEIC as PSA, despite the possibility of direct implementation and subsequent notification, once properly justified by the Principal Investigator (PI) and patients' safety and confidentiality are ensured.

4. Regarding Informed Consent

Alternative procedures for the acquisition of the subject's consent can be necessary for already enrolled subjects in clinical trials or for the inclusion of new subjects. Therefore:

i. For ongoing studies, the acquisition of the re-consent for the implementation of the urgent alterations to the conduct of studies in relation to the Covid-19 situation, can be executed upon oral consent through telephone or video calls and, if possible, confirmed by e-mail after the subject received the new amended consent.
   - Not all the procedures alterations resulting from the Covid-19 situation require formal and prior re-consent, as for example the delivery of IP to the subject's residence.
   - Informed consent alterations for accommodation of procedures alterations resulting from Covid-19 do not require immediate notification (NSA) to CEIC, as long as they are not considered major protocol alterations (see point 7.v).
   - Once the normal state is restored, the subjects consent should be obtained by the usual channels and as soon as the subject returns to the site, and CEIC should be notified (NSA) in time of the last version of the informed consent.

ii. When the sponsor is planning to initiate the trial in Covid-19 patients, alternative procedures for the acquisition of the subject's consent can be considered.
   - Whenever the written consent cannot be obtained, due to the patient's physical isolation, the oral consent can be obtained in the presence of an impartial testimony.
   - Additionally, the patients consent can be obtained upon the subject's signature and of the physician who obtained the consent in independent documents.
   - It is up to CEIC to evaluate and authorize the proposed alternative procedures at the time of the trial submission.

5. Regarding materials for subjects and/or patients
   i. The supply of explanatory leaflet(s) to the patient for the administration of medication, must be notified to CEIC (NSA);
   ii. Explanatory leaflets or other information materials for subjects regarding the new coronavirus infection, should be given, preferably to the patient, by the Principal Investigator/Sub Investigator, and notified to CEIC as NSA.

6. Regarding protocol deviations
   i. In order to allow an appropriate and expedited assessment (if applicable), each sponsor must ensure that protocol deviations are properly documented, since an increase of those deviations is expected;
   ii. Protocol deviations justified by Covid19, do not constitute a major violation, in the first place, unless the subjects have been placed at risk;
   iii. Protocol deviations, such as related with subject´s eligibility for studies, justified by the difficulties in evaluating the subjects and performing tests, are not acceptable;
   iv. It will be sponsor's responsibility to classify the protocol deviations, and in this context, to notify CEIC, according to the impact on the safety and well-being of the participants.
      - The notification of major deviations shall be made in an aggregated structure, by study, with site and patient and/or adjusted visit discrimination, in a maximum time of 30 days between the identification of the deviation and the information to CEIC (notwithstanding a possible alteration to this notification timelines).

7. Regarding study activation, recruitment of new subjects and/or continuation of the study

The suspension and/or postponing of trial site activation procedures and/or of already approved new sites shall be address/considered, as well as the temporary suspension of the active recruitment sites. Therefore:

i. No subject can be enrolled in the study if it is not possible to verify the necessary procedures to fully comply with the protocol inclusion and exclusion criteria;
ii. New subjects should also not be included if there is no guarantee that there are conditions to comply with the study protocol;
iii. Whenever the subject safety is at risk, because he cannot complete the main study assessments or follow the critical mitigation steps, the possibility of study discontinuation should be discussed;
iv. Urgent security measures to mitigate the risk of subjects are kept at the disposal of any investigator and/or sponsor, as well as the tools for temporary interruption of the study and/or recruitment;
v. If it is necessary to transfer a patient from one trial site to another, based on an individual risk-benefit assessment, it must be notified to CEIC as urgent safety measure (NSA);

- Any temporary interruption of the study, including for logistical reasons, such as the unavailability of the study team, should be considered as an urgent safety measure, and then notified to CEIC (NSA).
- The purpose of the majority of observed changes is to ensure the patients' safety and well-being, and are not considered protocol alterations.
- The waiver of compliance with the protocol remains unacceptable.
- Major changes to the protocol with impact in patients' safety and well-being, which imply consent alterations and therefore re-consent, must be submitted as PSA, which will be evaluated in an expedited manner.

8. Regarding the risk / benefit of conducting some clinical trials

Clinical trials that may have an additional risk of infection with no possible benefit for the subject, should be carefully re-evaluated on their beginning and/or continuation, such as clinical trials with drugs that act as immunosuppressants in healthy volunteers, where there is no therapeutic benefit to the volunteer.

- CEIC should be notified (NSA) about those decisions.

9. Regarding Sponsors contingency plans

The contingency plans developed by the sponsors must be notified to CEIC (NSA), respecting the applicable general guidelines, as well as the specific procedures requested by CEIC and/or Infarmed in this scope.

i. These contingency plans – Sponsor orientations – when applicable to two or more clinical trials, can be notified together with precise indication of the EudraCT number which the Requirement letters apply.

10. Regarding subjects infected by the new coronavirus

i. The trial subject infection by the new coronavirus should be considered as an adverse effect and reported to CEIC (NSA);
ii. Health authorities' guidelines regarding infection with the new coronavirus should be followed;

iii. If the patient maintains, as far as possible, compliance with the study procedures, all records should be kept, and the patient's risk-benefit assessment should remain a priority.
   - CEIC must be notified (NSA) of the decision to keep the patient in the study, as soon as possible

11. Regarding extraordinary expenses
    i. All the additional expenses resulting from implemented procedures due to Covid-19 situation shall be ensured by the sponsor, preferentially in advance.
    ii. Any additional expense payed by the subjects and resulting from the Covid-19 situation, shall be reimbursed through the sites, as usual.

12. Regarding validity and signature of CEIC documents

    It may not be possible for CEIC to sign the approval documents in an expedited and timely manner, as well as to issue documents on letterhead. Therefore:

    i. The sponsors/claimants must consider as valid the alternative methods of communication, such as confirmation by email and/or information/communication via RNEC, of the decisions of CEIC.
    ii. All documentation (letters requesting additional information and/or approval, or others), once signed, will be sent later, by the usual channels.

13. Regarding clinical trials evaluation of new drugs for Covid-19 disease

CEIC has developed expedite procedures for the evaluation of new clinical trials aimed for treating or preventing disease by the new coronavirus (SARS-CoV-2).
- Applicants must submit the study through RNEC, clearly identifying the scope of the Covid-19 disease in the subject, and send an email to CEIC (ceic@ceic.pt), in order to streamline the process as an expedited approval.
- Depending on the nature of the study in question and of the time needed for additional clarification requests, CEIC predicts a response time (between submission and final decision) between 48 and 72h (on workdays).

All requests for protocol substantial amendments, due to changes of procedures as a result of Covid-19, **will be evaluated in an expeditious manner by CEIC**, since submitted by usual means and **communicated via e-mail to** ceic@ceic.pt.

All changes to procedures from clinical studies previously approved, whenever **they do not require submission to CEIC as PSA**, according to this information, **must be** properly documented, and **notified to CEIC**, for monitoring the clinical trial by this Commission. The applicant may perform a single submission, through RNEC, regarding more than one study (for various EudraCT), whenever applicable for equal procedures.

The adoption of these direct implementation procedures; that is, without prior approval by CEIC, it must respect their proportionality and serve the best interest of the clinical trials participants (sick or not).

When considered appropriate, CEIC will continue to require changes and/or suspension of procedures to adapt to the context of Covid-19, adopted by sponsors and/or applicants.

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