Notice

**Clinical trials' management in Italy during the COVID-19 (*coronavirus disease 19*) emergency**

Following the number of requests received by the Clinical Trial Office/Pre-Authorization Area and by the GCP Inspections Office from the various stakeholders, the Italian Medicines Agency provides indications regarding the management of clinical trials in Italy during the COVID-19 (coronavirus disease 19) emergency, valid until further notice.

**Submission of clinical trials and substantial amendments**

Considering the recent precautionary measures adopted by the Italian Council of Ministers and by the Ministry of Health, and acknowledging that, as a consequence of the afore-mentioned measures, many pharmaceutical companies, no-profit Sponsors and CROs have consequently applied or extended smart-working in order to continue their activities related to clinical trials and to assure at the same time the highest possible protection of the personnel involved, AIFA informs you as follows.

As regards authorization requests of clinical trials and substantial amendments submitted by the OsSC, the postponement of paper documentation and CD-rom sending referred to in the AIFA communication of 1st August 2019 (https://www.aifa.gov.it/-/aggiornamento-lettere-per-l-autorizzazione-di-sperimentazioni-cliniche-e-relativi-emendamenti-sostanziali) is allowed.

It is anyway recommended, whenever possible, to apply the stamp duty on the transmission letter by virtual payment (except in the cases provided for in article 17 of the legislative decree n° 460/1997 and in article 82, par. 5 of the legislative decree n° 117/2017) and to digitally sign the letter uploaded in the OsSC.

Paper documentation and CD-rom will have to be sent to the Clinical Trial Office as soon as possible.

In case the submission via OsSC is not possible and paper transmission is needed as provided for in the AIFA communication of 2nd October 2018 (https://www.aifa.gov.it/-/attivazione-nuova-piattaforma-ossc-aggiornamento-02-10-2018-), transmission by e-mail will not be accepted.

Exception is made only for the submission of clinical trials regarding treatment of COVID-19 (coronavirus disease 19): authorization requests are allowed to be submitted by mail to apa@pec.aifa.gov.it and related documentation can be sent via Eudralink or similar ways within the same e-mail.

Please note that, in this case, the whole authorization process of such requests will continue by e-mail and the Applicant is requested to return in the OsSC as soon as possible, as provided for the temporary paper management (AIFA communication of 6th August 2018: https://www.aifa.gov.it/documents/20142/871583/comunicazione_OsSC_06.08.18.pdf/20bdd0c0-d754-817c-93ac-ca7b0476f1e5).

**Ethics Committees evaluations of clinical trials/substantial amendments**

Without prejudice to the current legislation and internal procedures of each single Ethics Committee, their meetings may also be held by web-conferences or other telematic ways, with the appropriate frequency to manage urgencies due to the current emergency.

**Management of clinical trial activities outside investigational sites**

In the case it is necessary – where feasible –, in order to limit the risk of coronavirus infection, and in case of patients facing with difficulties in reaching trial sites or of trial sites that have suspended outpatient activities, to supply patients with the investigational drug(s) so as to avoid them going to the hospital (thus ensuring treatment continuity), or carry out other activities related to the clinical trial (e.g. visits and exams or adverse reactions management) at patient's home or in a site different from the investigational clinical site, Applicants/Sponsors will have to notify a substantial amendment for immediate implementation only to the Ethics Committees involved, indicating its urgency due to the current emergency.

In this regard, taking into account provisions set down by DPCMs (decrees of the Italian President of the Council of Ministers) concerning the urgent measures for the containment and management of the epidemiological emergency from COVID-19 and by specific ordinances issued by Regions, Sponsors/CROs are invited to draw up a risk evaluation plan and implement an action plan for the maximum protection of experimental subjects, also in view of the urgent need to minimize contacts between patients and investigational staff, and not to overload healthcare facilities.

In particular, limited to the coronavirus emergency period, the following exemptions are provided:

1. Investigational medicinal product (IMP) management
   If possible, when the patient goes to the study site for a visit, it may be useful to provide an amount of medicinal product covering a longer period of time than is normally estimated.
   According to current legislation (article 7 of the Ministerial Decree 21st December 2007), the Sponsors must send investigational drugs needed for the trial to the pharmacy of the investigational site, that is in charge for their registration, appropriate storage and delivery to the investigator. Therefore, considering the COVID-19 serious emergency, even if the priority mode remains the delivery to the hospital pharmacy that then proceeds to the subsequent delivery to the investigational centre, direct deliveries from the hospital pharmacy to the trial subjects also through dedicated couriers can be arranged, upon indications of both the hospital pharmacy Director and the Principal Investigator (PI). It is intended that the hospital pharmacy is responsible for the process supervision; the pharmacy and the PI must be constantly informed on the delivery, according to procedures established for the correct conduction of the trial and by the above-said risk plan, that must take into account the IMP typology, administration methods, conservation and transport. Adequate remote communication ways with involved subjects must be implemented to replace the information that will no longer be provided in person. Depending on the case, telephone and/or video call can be used to inform the patient, where deemed necessary. Adequate tracking of what is being implemented in this

emergency situation is recommended. All this without prejudice, if possible, to conditions set out in FAQ 10 of the EMA Document "Q&A: Good clinicalpractice (GCP)" – GCP Matters (https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-clinical-practice/qa-good-clinical-practice-gcp).
If the CRA of the study is not able to carry out the control on the final accounting of the investigational medicinal product for the purpose of reconciliation, and this operation is considered as impossible to be postponed, it can be carried out by a pharmacist of the hospital pharmacy or by the study coordinator/data manager, appropriately trained. The IMP can be returned to the Sponsor directly by the hospital pharmacy.

2. Clinical examinations
   Being aware of the need to have haematological tests performed in laboratories near to the patient's home, they will have to be carried out in public health structures. The use of private sites not recognized eligible pursuant to the Ministerial Decree of 19th March 1998 yet, will have to be carefully taken into consideration and chosen only in the case it represents the unique possibility for the patient's protection; the use of such data for regulatory purposes will have to be discussed when submitting data.

3. Sites closing
   If a site is closed to the public for COVID-19 containment measures, it should be carefully assessed if the clinical trial staff is able to guarantee the continuity of the trial itself. In case the site is unable to follow the patients undergoing the trial, the study should be temporarily halted or, where possible, enrolled patients should be transferred to the nearest active trial site. Information exchange between PIs must be assured, as well as the transmission of clinical documentation and other trial material (e.g. IMPs) between sites. Contacts between Sponsor and health structures involved must be updated according to new agreements.
   A site not authorized to participate in the specific clinical trial is not considered as suitable as back-up, since it is not active, it does not know the trial and could not ensure a proper therapeutic continuity for the patient.

4. Clinical trial monitoring
   By analogy with what stated in the previous paragraph, Sponsors are invited to draw up a risk evalutation plan and implement an action plan taking into account the need to reduce unnecessary contacts in this period of COVID-19 epidemiological emergency. First of all, it should be assessed whether in-situ monitoring visits can be replaced by an enhanced centralised monitoring or whether such local visits can be postponed.
   Exceptional methods such as telephone contacts or, even better, videoconferences with the trial site staff can be implemented for the purpose of source data verification. These methods must be described in a specific SOP by the Sponsor/CRO and must be evaluated and approved by the Personal Data Protection Officer of the trial site.
   Other unusual monitoring methods involving more risky ways of accessing sensitive data, such as video recording of source document or making available to monitors original documents in shared electronic areas, must always be agreed with the Personal Data Protection Officer of the hospital, but it is considered appropriate that a specific opinion by the Italian Data Protection Authority be obtained.

5. Possibility for the Sponsor to sign contracts directly with specialized service agencies/companies (e.g. home nursing services) to carry out activities related to clinical management of patients falling under the Principal Investigator's (PI) responsibility
   In reiterating that such measures should be intended as extraordinary and limited to the coronavirus emergency period, by way of derogation from the FAQ 11 of the EMA document "Q&A: Good clinicalpractice (GCP)"–GCP Matters (https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-clinical-practice/qa-good-clinical-practice-gcp), the Sponsor is allowed to sign contracts directly with such specialized agencies/companies. All other indications in the afore-mentioned FAQ remain applicable, such as for example:
   - the need that the PI remains responsible for the supervision
   - that efficient communication contacts are established between the staff in charge and the PI
   - that the staff in charge is suitably trained and that duties and responsibilities are stated in the contract and/or delegation log
   - that the protection of data confidentiality is assured.

6. Possibility of exceptional expenses reimbursement
   Taking into account this exceptional situation, if, in order to implement urgent measures for the protection of subjects involved in a clinical trial, expenses are foreseen to be charged to these subjects, similarly to what is already allowed in extraordinary cases (e.g. trials on rare diseases), the Sponsor is allowed to reimburse such expenses directly to the subjects, keeping appropriate supporting documentation.