

Communication

Management of clinical studies in Italy during the COVID-19 (*coronavirus disease 2019*) emergency

Given the numerous requests received from the various interested parties at the Ufficio Sperimentazione Clinica/Area Pre-Autorizzazione [Clinical Trials/Pre-Authorization Area Office] and at the Ufficio Ispezioni GCP [GCP Inspection Office], the Agenzia Italiana del Farmaco [Italian Medicines Agency] hereby provides recommendations on the management of clinical studies and substantial amendments in Italy during the COVID-19 (*coronavirus disease 2019*) emergency period, valid until new communication.

Procedures of submission of clinical trials and substantial amendments

Considering the recent precautionary measures adopted by the Consiglio dei Ministri [Italian Council of Ministers] and by the Ministero della Salute [Italian Ministry of Health], and acknowledged that, as a result of these precautionary provisions, many Pharmaceutical Companies, *non-profit* Sponsors and CROs have consequently applied or extended the practice of *smart-working* in order not to interrupt the activities connected to clinical trials, and to ensure the maximum protection of the staff involved, we hereby communicate the following.

For applications of authorization of clinical trials and substantial amendments submitted via the OsSC (Osservatorio Nazionale sulla Sperimentazione Clinica dei Medicinali [National Clinical Trials Database]), the deferral of submission of the paper documentation and CD pursuant to the AIFA [Agenzia Italiana del Farmaco] communication of 01/08/2019 is permitted (<https://www.aifa.gov.it/-/aggiornamento-lettere-per-l-autorizzazione-di-sperimentazioni-cliniche-e-relativi-emendamenti-sostanziali>).

Nevertheless, payment of the stamp duty on the cover letter in virtual form is recommended, where possible (excluding cases of exemption from said duty pursuant to Article 17 of Legislative Decree 460/1997 and Article 82, section 5, of Legislative Decree 117/2017), and the application of the digital signature on the same uploaded to the OsSC.

The paper documentation and CD should be sent to the Ufficio Sperimentazione Clinica as soon as possible.

In cases where submission via the OsSC is impeded, and therefore use of the paper transmission method is necessary in accordance with the provisions of the AIFA Communication of 02/10/2018 (<https://www.aifa.gov.it/-/attivazione-nuova-piattaforma-osscc-aggiornamento-02-10-2018->), the transmission via e-mail cannot be accepted.

In express derogation from the above, it is permitted, for the exclusive submission of clinical trials concerning the treatment in general of COVID-19 (*coronavirus disease 2019*), that the submission of requests of authorization is made via the e-mail address apa@pec.aifa.gov.it, and that the documentation supporting the aforementioned requests is submitted via Eudralink or similar procedures within the same e-mail.

Please note that, in that case, the entire authorization process for the aforementioned

authorization applications will be continued by e-mail, and the Applicant will return to the OsSC [portal] as soon as possible, as required for the temporary paper management (AIFA Communication of 06/08/2018:

https://www.aifa.gov.it/documents/20142/871583/comunicazione_OsSC_06.08.18.pdf/20bdd0c0-d754-817c-93ac-ca7b0476f1e5).

Expression of opinions of Ethics Committees on clinical trials/substantial amendments

Without prejudice to the current legislation and internal procedures of individual Ethics Committees, the sessions thereof may also take place using *web conferencing* or another electronic method, with a frequency sufficient to manage the contingencies of the current emergency.

Possibility of managing clinical trial activities outside of the trial site

If, in order to limit the risk of infection from the coronavirus, due to difficulties in moving patients to the trial sites, or from suspension of outpatient activities by some clinical sites, it is necessary - where feasible - to make the medicinal product available to patients without these patients having to come to the hospital (thereby guaranteeing the therapeutic continuity), or to carry out other activities related to clinical trials (for example, performance of visits and tests, management of adverse reactions) at the patient's home or in a facility other than the clinical trial site, a substantial amendment for immediate implementation should be sent for notification to the Ethical Committees of reference only, indicating its urgent nature due to the emergency in question.

In this regard, the Sponsors/CROs are invited, taking account of the guidelines of the DPCM (Decreto del Presidente del Consiglio dei Ministri [Decree of the President of the Council of Ministers]) regarding the urgent measures on the containment and management of the COVID-19 epidemiological emergency, and of the specific Ordinances of the different Regions, to prepare a risk assessment plan and to implement an action plan for the priority protection of trial subjects, and with a view to the minimizing of contact between patients and trial staff in order not to overload the health facilities.

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

1. Investigational Medicinal Product (IMP) Management

Where possible, if the patient comes to the trial site, it may be useful to provide a quantity of medicinal product that covers a time period longer than the period normally estimated. It is recalled that, in accordance with current legislation (Article 7 of the Ministerial Decree of 21 December 2007), medicinal products required for the trial should be sent by the Sponsor to the pharmacy of the health facility where the trial is being conducted; the pharmacy will arrange for the registration, appropriate storage and delivery to the Investigator of the medicinal products. Therefore, in consideration of the serious COVID-19 emergency, even if the priority route remains delivery to the Hospital Pharmacy, which then arranges the subsequent delivery to the trial site, on indication of the Hospital Pharmacy Director and the Principal Investigator, direct deliveries from the Hospital Pharmacy to the trial subjects using dedicated couriers can also be agreed,

without prejudice to the supervision of the process by the Hospital Pharmacy and the constant informing of the same Pharmacy and PI about the successful delivery in the procedures imposed for the correct conduction of the trial and by the aforementioned risk plan, which should take account of the type of IMP, the methods of administration, storage and transport. Appropriate systems of remote communication with the interested subjects should be guaranteed to take the place of information that is no longer provided in person. Depending on the case, the telephone and/or video call may be used if considered necessary to inform the patient. Adequate tracking of what is implemented in this emergency situation is recommended. The conditions listed in FAQ 10 of the EMA document “Q&A: Good clinical practice (GCP) – GCP Matters (<https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-clinical-practice/qa-good-clinical-practice-gcp>) should also be observed, where possible.

If the study CRA is unable to carry out the final medicinal product accountability check for reconciliation purposes, it is considered that this operation, if it cannot be postponed, can be carried out by a pharmacist of the Hospital Pharmacy or by the suitably trained study coordinator/data manager. The IMP can be returned to the Sponsor directly by the Hospital Pharmacy.

2. Clinical tests

With regard to the performance of blood tests, in the awareness of the need to be able to perform the tests in laboratories near the patient’s home, these tests should be performed in public facilities. The use of private facilities not in possession of the recognition of eligibility pursuant to the Ministerial Decree of 19 March 1998, should be carefully evaluated and resorted to only if such use is the sole possibility to protect patient safety; the use of such data for regulatory purposes should be discussed at the time of submission of the data.

3. Site Closure

If a site is “closed” to the public for COVID-19 containment measures, it should be carefully assessed whether the trial staff can guarantee continuity of the trial. If the site is unable to follow the trial patients, the study should be temporarily suspended or, if possible, the patients transferred to the closest trial site of the active sites. Of course, the exchange of information between the PIs and the transmission of trial clinical documentation and other material (e.g., IMP) between sites should be guaranteed. The agreements between the Sponsor and the Health Facilities involved should be updated in accordance with the new agreements.

It is not considered feasible to use as *back-up* a site not authorized to conduct the specific clinical study, as the site is not active, is not familiar with the trial and cannot guarantee a correct therapeutic continuation to the patient.

4. Monitoring of clinical trials

Similarly to what is expressed in the previous paragraph, the Sponsors are invited to prepare a risk assessment plan and to implement an action plan that takes into account the need to reduce unnecessary contacts in this COVID-19 epidemiological emergency period. First and foremost, it should be evaluated if *on site* monitoring visits could be replaced by a reinforcement of centralized monitoring, or if such local visits may be postponed.

Exceptional procedures such as telephone contacts or better video conferences may be implemented with investigational site staff at the end of *source data verification*. These procedures should be described in the appropriate Sponsor/CRO SOP, and should be evaluated and approved by the trial site’s Data Protection Officer.

Other infrequent monitoring methodologies involving more unsafe methods of access to sensitive data, such as by video recording of *source documents* or the making available for the monitors of source documents in shared electronic areas, should always be agreed with the Hospital's Data Protection Officer, but it is considered appropriate that a specific opinion from the Garante per la protezione dei dati personali [Italian Data Protection Authority] be obtained.

5. Possibility for the Sponsor to enter into direct agreements with specialized service agencies/companies (e.g., home nursing services) to conduct activities related to the clinical management of patients who come under the responsibility of the Principal Investigator (PI)

In reiteration that such measures are to be considered extraordinary and limited to the immediate coronavirus emergency period, notwithstanding FAQ 11 of the EMA document "Q&A: Good clinical practice (GCP)"–GCP Matters

(<https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-clinical-practice/qa-good-clinical-practice-gcp>), the possibility for the Sponsor to directly stipulate agreements with such specialized agencies/companies is permitted. All other indications of the aforementioned FAQ remain applicable, such as:

- the requirement that the supervision be maintained by the PI
- that effective communication lines be established between the appointed staff and the PI
- that the appointed staff be appropriately trained and their relative duties and responsibilities be indicated in the agreement and/or *delegation log*
- that the protection of data confidentiality be guaranteed.

6. Possibility of reimbursement of exceptional expenses

In consideration of the exceptional nature of the contingency, if in order to implement urgent measures for the protection of subjects participating in a clinical study, expenses to be borne by such subjects are envisaged, similarly to what is already permitted in extraordinary cases (e.g. studies on rare diseases), it is permitted that the Sponsor arranges to directly reimburse such expenses to the subjects, keeping appropriate supporting documentation.