Exceptional measures applicable to clinical trials to manage the problems derived from the COVID-19 emergence

- These measures are intended to guarantee the clinical trial activity, the safety and well-being of the patient and the traceability of the implemented actions.
- Their application does not require AEMPS or CEIm approval, but they must be communicated once the health crisis of COVID-19 is passed.

The Spanish Agency of Medicinal Products and Medical Devices (AEMPS), as the national competent authority in the authorization of clinical trials, proposes several recommendations for exceptional application during the duration of the COVID-19 crisis in Spain. These measures are aimed to preserve the activities of the clinical trials as much as possible, guaranteeing the healthcare of the patients, protecting their safety and well-being, and preserving the traceability of the actions implemented in this health emergency.

It is essential to maintain the health system at maximum capacity, reducing the risk of infection for the population. Also, it is necessary to consider the measures applied in the different autonomous communities after the declaration of the state of alert by the Government.

In this context, the scheduled follow-up visits, access of external personnel to the sites and monitoring of the trial in situ may be compromised. In some cases, it may be necessary to transfer a patient from one site to another to facilitate their healthcare. On the other hand, there may be a decrease in the staff of the Sponsor monitoring the trial.

It is important that the Sponsor together with the investigator make a risk analysis and prioritize the activities that are critical and how they need to be carried out. Both must evaluate the application of these measures in a proportional way for each clinical trial with its particularities, the organization of each site, and the epidemiological characteristics of COVID-19 in it. These measures may be updated to adapt to epidemiological developments as determined by the Ministry of Health.

Any of these exceptional measures taken, it should be documented in the Clinical Trial Master File. However, its application does not require prior approval on a case-by-case basis as a specific modification by AEMPS or by the Ethics Committee (CEIm), nor the individual notification of protocol serious breaches, except specifically required in the point 2. In the four months following the date in which the COVID-19 crisis is considered ended in Spain, the Sponsor must communicate for each clinical trial a report on the exceptional measures set that must be sent to the Agency and the CEIm.

1. **Patients' on-site visits scheduled in a clinical trial:** The Sponsor together with the investigator should consider the possibility and convenience of postponing these visits or change them into phone visits, rescheduling them within the visit frame of the clinical trial. It should be ensured the critical scheduled on-site visits are carried out. In case of rescheduling visits, these protocol deviations will not be considered serious breaches, unless they put the patient´s safety at risk.
2. **Recruitment of new patients:** Planned protocol deviations on a prospective basis are not acceptable, and it is expected that all the subjects included in a clinical trial meet all the selection criteria. The Sponsor, together with the investigator, based on a benefit/risk assessment that considers the characteristics of the trial and the circumstances of the participating sites, may interrupt the recruitment and even interrupt the treatment of the study patients to avoid

unnecessary risks and guarantee the best possible healthcare services for patients. This analysis is especially pertinent in clinical trials involving immunosuppressant treatment, and therefore, an increased risk of infection, with no benefit for participants expected. In the case of an interruption of the clinical trial leading to the hold of treatment for part of the patients, the Sponsor would have to notify these measures as "urgent safety measures" explaining the measures adopted to guarantee the alternative treatment of the patients by sending an Ad Hoc report for both the AEMPS and CEIm within 15 days following the interruption or termination of the study.

3. **Access to the Clinical Trial treatment:** patients must be guaranteed access to trial medication in the same conditions in which it was being given. It is recommended that the researcher assesses the possibility and the convenience of, when the patient comes to a scheduled visit, he receives an amount of medication covering a longer period of treatment.

   The Pharmacy Department of the hospitals may take the measures they deem necessary, for example, it would be considered appropriate to dispense the drug to a person authorized by the patient for a treatment that must be taken at home or the shipment from the Pharmacy to the domicile of the patient when the circumstances make it recommendable. Concerning the described above, the preservation of the drug treatment during transportation and the communication with the patient must be ensured to allow the reception and proper administration of the treatment. Section 10 of the document “Q&A: Good clinical practice (GCP)” - GCP Matters” must be considered. The situation in each case must be assessed by the Sponsor, the principal investigator, and the Pharmacy Department.

4. **Monitoring visits:** The sponsor is recommended to update the trial monitoring plans for the next four months, prioritizing centralized monitoring and remote monitoring of the participating sites that do not entail overloading the site staff with tasks or the review of source data and postponing as far as possible the verification of source data until you can access the medical history in person. The sponsor will agree with the participating sites and teams the conditions for such monitoring.

5. **Transfer of patients to other sites:** if it is necessary to transfer a patient from one trial site to another, it may be carried out provided that: a) a transfer agreement is signed between sites, b) the new site have access to the data collection Case Report Form and the patient's medical records (or the original site will send you a copy of the patient´s medical records); c) the original site sends a transfer report summarizing the most relevant medical data of the patient in relation to the trial to facilitate patient´s follow-up by the new site; d) the transfer of the patient is documented in the trial master file of the two sites.

6. **Clinical trials related to the investigation of new drugs against coronavirus:** AEMPS is prioritizing, together with the CEIm, the evaluation of the clinical trials to treat or prevent the coronavirus disease. Sponsors or investigators, who have a research project on this topic should send a message to the Clinical Trials Area indicating in the subject: *Urgente nuevo EC COVID19* (Urgent new EC COVID19). An answer will be provided the same day.