NOTA INFORMATIVA

Exceptional measures applicable to clinical trials to manage problems arising from the COVID-19 emergency

Date of update: 1st July 2020
Category: medicinal products of human use, COVID-19
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- **These measures are aimed at guaranteeing the trial activity, the safety and well-being of the patient and the traceability of the actions implemented**
- **They are complementary measures to those adopted recently in the EU and include the specific aspects which are applicable in Spain**
- **This document has been updated in section 60 of Instruction document of the Spanish Agency of Medicines and Medical Devices for conducting clinical trials in Spain with respect to clinical trials where remote monitoring with source data verification may be considered during this pandemia and the report to be provided to AEMPS and the CEIm on the adopted exceptional measures**

The Agencia Española de Medicamentos y Productos Sanitarios [Spanish Agency of Medicines and Medical Devices], as competent national authority in the authorisation of clinical trials, underlines the importance of the measures approved in the EU Council of Health Ministers on 27 April 2020 of exceptional application during the period which the COVID-19 crisis lasts in Spain, and indicates the specific aspects of its implementation in our country. These measures are intended to preserve the trial activities as far as possible, guaranteeing healthcare to the patients, protecting their safety and well-being and preserving the traceability of actions implemented in this health emergency situation.

On 4 May, this note has been updated with the aim of referring to the measures recently published in the EU[1] and clarifies the aspects of its application specific to Spain, in particular with regard to the process of obtaining the informed consent, the distribution of study drugs to the home of the patient, the remote monitoring of source data and form of communication of these measures to the AEMPS and the Ethics Committees for Investigation with medicinal products (CEIm).

On 29th June this note has been updated with respect to points 5 and 7 in section 60 of Instrucciones de la AEMPS para la realización de ensayos clínicos en España.

It is essential to maintain as much as possible the capacity of the health system, reducing the risk of infection for the population. Also, the measures taken in the different Autonomous Communities following the declaration of the state of alarm by the Government must be taken into account.

In this context, the scheduled follow-up visits and the access of non-site staff and in situ monitoring could be affected. In some cases, it might be necessary to transfer a patient

[1] https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf

from one site to another to facilitate their healthcare or send the trial drugs to their home. Meanwhile, there could be a reduction in sponsor's staff entrusted with trial follow-up.

It is important that the sponsor, together with the investigator, carries out a risk analysis and prioritises critical activities and the way they must be carried out. Both of them must also evaluate the application of these measures proportionately to each clinical trial considering its particularities, the organisation of each site and the epidemiological characteristics of COVID-19 at each site. These measures could be updated to adapt to epidemiological evolution according to the decisions of the Ministry of Health.

1. Scheduled in-person visits for clinical trial patients

The sponsor, together with the investigator, must consider the advisability of postponing said visits, or turning them into telephone visits, re-scheduling them on the clinical trial schedule of visits. It must be guaranteed that the critical scheduled in situ visits are carried out. In the case of rescheduling visits, these protocol deviations will not be considered serious non-compliance unless they put the patient's safety at risk.

2. Recruitment of new patients

Expected prospective protocol deviations are unacceptable and it is expected that all subjects included in a clinical trial comply with all selection criteria. The sponsor together with the investigator, based on a risk/benefit assessment, which takes into consideration the characteristics of the trial and circumstances of the participating sites, shall be able to cease recruitment and even discontinue the treatment of trial patients with the aim of avoiding unnecessary risks and guaranteeing the best possible healthcare for the patients. This analysis is especially pertinent in clinical trials that involve treatment with immunosuppressants and therefore a greater risk of infection, without any expectation of benefit for the participants.

3. Access to trial treatment

Patients' access to the trial medicines must be guaranteed in the same conditions in which they were being given. It is recommended that the investigator assesses the possibility and advisability that, when the patient attends a scheduled visit, he/she receives an amount of the medicinal product to cover a longer period of treatment.

The Hospital Pharmacy department will be able to take the measures they consider necessary, for example, the dispensing to a person authorised by the trial patient of a treatment which must be taken at home or the sending from the Hospital Pharmacy department of the treatment to the patient's home when his/her circumstances make it advisable. With regard to the latter, it must be ensured preservation of the treatment during transport, and communication with the patient, allowing treatment reception and appropriate administration of it.

In the exceptional case that, being necessary, the Pharmacy Department cannot send the trial treatment to the patient's home, said Department might consider other alternatives and entrust the sponsor to organise the delivery via an authorised medicinal products distributor.

The situation must be assessed in each particular case by the sponsor, the principal investigator and the Pharmacy Department following the instructions and directives of the UE1 and section four of order SND/293/2020[2] .

In the case of a temporary halt of the trial due to shortage of trial medication, the sponsor must adopt the necessary measures to guarantee the alternative treatment of the patients. This discontinuation and the measures adopted will be communicated by sending an ad hoc report to both the AEMPS and the CEIm in the 15 days following the temporary halt.

4. Informed Consent

Obtaining consent in COVID-19 studies

Consent must be obtained preferably in writing. However, to guarantee that the process of obtaining the informed consent is carried out avoiding the risk of contagion, allowing the recording of the patient's willingness, and in line with the current ethical and legal recommendations, the consent can be obtained orally and preferably before a witness[3], documenting it in the patient's medical records and ratifying it later in writing by means of the patient's signature and that of the investigator, as far as possible and making a reasonable effort to obtain it.

In the case of a patient without the capacity to consent or a minor, the consent must be obtained from their legal representative. If the subject's condition so permits, and in any event if the minor is aged twelve or more, he/she will also give his/her consent to participate in the study.

In the case of emergency situations, article 7 of Royal Decree 1090/2015 will apply.

Obtention of informed consent in studies already underway to continue the study

Consent must be obtained preferably in writing. However, taking into account the epidemiological situation of the pandemic, and to avoid the patient having to go to the sites to sign the consent, it is permissible to get the consent orally (for example, by telephone or video-call), documenting it in the patient's medical record and ratifying it later in writing by means of the patient's signature and that of the investigator.

The principal investigator or the person who has been designated by him/her must send the patient information leaflet (PIL) to the patient by email or courier. The later ratification in writing by means of the patient's signature and that of the investigator can be carried out by mail, by audiovisual means or digital images. The patient can send the scanned, signed PIL by email, or can take a photo of the signed consent and send it to a telephone only accessible to the research team. This image file must be printed out and maintained in the investigator's file as proof of signature.

[2] Order SND/293/2020, of 25 March
[3] Provided the epidemiological situation of the pandemic allows it.

5. Monitoring visits

It is advisable for the sponsor to update the trial monitoring plans for the next four months, prioritising the centralised monitoring and remote monitoring of the participating sites that do not involve giving excessive work to site staff and postponing, as far as possible, the verification of source data until access to the medical records in person is possible. The sponsor will agree conditions for said monitoring with the participating sites and teams.

Remote verification of source data shall be considered only for clinical trials that investigate the prevention or treatment of COVID-19 and for the final preparation of data prior to the therapies. In any case, it will be carried out with all the safeguards and precautions shown in closure of the database of pivotal trials investigating treatments for serious diseases without alternative the UE guidance[1] and therefore shall require the prior approval of each site with the approval of his/her data protection delegate.

It will not be required the previous approval of a substantial amendment by the CEIm nor the authorisation of the AEMPS. Neither will it be necessary to have the patient's express consent to carry out the verification of source data during remote monitoring, given that this activity is legally regulated as a necessary activity in the trial. For that reason, the informed consent given to participate in the trial implies that it is carried out in the terms established in the regulations which govern it, and they establish that the monitor can access the necessary clinical information for the proper execution of the trial[4].

The changes adopted in the monitoring data plan together with the acceptance on the part of the principal investigator of the site where the remote monitoring with verification of source data will be carried out and the acceptance on the part of the data protection delegates of the sponsor and the research site will be adequately documented and will be kept in the clinical trial file. Also, they will be made available to the AEMPS if required.

6. Transfer of patients from one site to another

If it were necessary to transfer a patient from one trial site to another trial site, this could be carried out as long as:

a) a transfer agreement between sites is signed,

b) the new site has access to the case record form and the medical records of the patient (or, failing that, the original site sends them a copy of the same)

c) the original site sends a transfer report summarising the most relevant medical data of the patient with regard to the trial to facilitate their follow-up at the new site

d) the transfer of the patient is documented in the trial file of both sites. No prior acceptance of this change by the CEIm is required

The opening of a new trial site requires the prior approval of a substantial amendment by the CEIm and for clinical trials in COVID-19, depending on the urgency, presentation of reduced documentation is being accepted. Said approval will be notified later to the AEMPS as an extension of sites so that the new site can be published in the REec [Spanish Clinical Trials Registry].

[4] Non-requirement for consent has been confirmed with the Spanish Data Protection Agency.

7. Notifications to the CEIm and the AEMPS

Any of the exceptional measures adopted due to these recommendations must be duly documented in the trial archive. However, their application does not require prior approval on a case-by-case basis as a substantial amendment by the AEMPS or CEIm and neither the individual notification of serious non-compliance they involve. Those changes carried out in the studies which do not affect the welfare and/or safety of the patients, or the quality of the data should not be processed as substantial amendments either.

As for urgent measures, the following shall not require individual notification within the period of 15 days:

- The dispatch of study drugs to the patient's home. This dispatch in all cases must be approved by the site's Pharmacy Department.
- The carrying out of tests in a local laboratory instead of at the expected site.
- The transfer of patients from one trial site to another trial site.

The sponsor must prepare, for each trial, a report about all the exceptional measures adopted, together with the risk assessment carried out and its justification which will be sent to the Agency and the CEIm in the four months following the date in which it is considered that the COVID-19 crisis has ended in Spain, via the ECM Portal as E ii) Report on trial progress.

For any consultation to the AEMPS related to these recommendations, please write to:

- Department of Medicinal Products of Human Use: Área de Ensayos Clínicos
- Department of Inspection and Control of Medicinal Products: Área BPC y BPFC