ANNEX VII_No.5

GUIDANCES TO MANAGE CLINICAL TRIAL DURING COVID-19

From EMA- Versión 3, 28/04/2020

The European Commission, the European Medicines Agency (EMA) and national Head of Medicines Agencies (HMA) have updated the measures on how to manage the conduct of clinical trial in the context of the coronavirus diseade (COVID-19) pandemic and have emitted the ***Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic Version 3*** **(28/04/2020).**

Key changes from v2 (27-03-2020): distributor to trial participant IMP shipment, monitoring, remote source data verification and communication with authorities.

Extraordinary measures may need to be implemented and trials adjusted due to e.g. trial participants being in self-isolation/quarantine, limited access to public places (including hospitals) due to the risk of spreading infections, and health care professionals being committed to critical tasks.

The COVID-19 pandemic is rapidly escalating putting national health care systems under continuously increasing pressure. In some Member States the capacity of the health-care system has already reached its limits. Against this background, pragmatic and harmonised actions are required to ensure the necessary flexibility and procedural simplifications needed to maintain the integrity of the trials, to ensure the rights, safety and wellbeing of trial participants and the safety of clinical trial staff during this global public health crisis. The points mentioned below are intended to provide guidance and clarity for all parties involved in clinical trials during this time. **It should be noted that the simplification measures proposed in this document will only last during the current public health crisis until the revocation of this Guidance, when there is a consensus that the period of the COVID-19 outbreak in the EU/EEA, has passed.**

Sponsors and/or CRO, and investigators should note that due to the rapidly evolving situation further updates to this guidance are possible and likely.

Member States are encouraged to implement the harmonised guidance to the maximum possible extent to mitigate and slow down the disruption of clinical research in Europe during the public health crisis. At the same time, sponsors and investigators need to take into account that national legislation and derogations cannot be superseded. Member States shall complement this guidance to create additional clarity on specific national legal requirements and derogations to them.

It is attached the ***Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic Version 3 (28/04/2020)***

INTRODUCTION

Various challenges exist which result in:

- *restrictions of visits to healthcare facilities*
- *increased demands on the health service*
- *changes to trial staff availability*
- *participants may also be required to self-isolate, which introduces difficulties for Investigators to maintain their medical oversight*

The challengues could have an impact on the conduct of trials such as the completion of trial assessments, completion of trial visits and the provision of Investigational Medicinal Products (IMPs)

The impact of COVID-19 need to be considered in differents situations:

- *on ongoing trials,*
- *on opening a new trial site in an existing trial,*
- *ongoing recruitment and continued involvement of participants in the trial,*
- *on starting of new trials needs to be considered.*

This evaluation should take into account national recommendations and restrictive measures including:

- *travel restrictions*
- *confinements of trial participants and trial staff*
- *the availability of trial staff to perform visits,*
- *enter data in the Case Report Form (CRF)*
- *notify serious adverse events*
- *follow the protocol, generally*

The ability to confirm eligibility and to conduct key safety assessments and trial evaluation is of particular importance. Actions should be proportionate and based on benefit-risk considerations, on contingency provisions taken nationally and locally by the authorities with priority given to the impact on the health and safety of the trial participant.

Where a trial participant is unable to attend the site, other measures, such as home nursing, if possible given social distancing needs, or contact via phone or telemedicine means, may be required to identify adverse events and ensure continuous medical care and oversight. However, the limitations and risks of such methods and the requirements for data protection should be taken into account and such alternative arrangements need to be adequately documented.

<u>This guidance is focused on the following subjects:</u>

- **Initiating new trials**
- **Changes to ongoing trials**

- **Safety Reporting**
- **Risk assessmentCommunication with authorities**
- **Agreement with and communication between sponsors, trial sites and trialsparticipants**
- **Changes to Informed Consent**
- **Changes in the distribution of the IMP**
- **Changes in the distribution of in vitro diagnostic and medical devices**
- **Changes to monitoring**

  Annex 1: Protection of trial participants' rights during remote source data verification (SDV)
- **Changes to auditing**
- **Protocol deviations**
- **Reimbursement of exceptional expenses**
- **Initiation of new trials aiming to test new treatments for COVID-19**

The recommendations of each Compentent Authorities of the following countries Spain, Italy and Portugal where Leon Resarch maintains its activities are detailed below.

LeonResearch

SPAIN

"Exceptional measures applicable to clinical trials and observational studies to manage problems arising from the emergency by COVID-19" *Date of publication:* ***5 May 2020***

- These measures aim to guarantee trial activity, patient´s safety and well-being and traceability of implemented actions
- They are complementary to the ones recently adopted in the EU and include the specific aspects applicable to Spain.

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).

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

These measures are complementary to the measures recently adopted in the EU and include the specific aspects that are applicable in Spain:

***new text is included in shaded form**.

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 not acceptable and it is expected that all subjects included in a clinical trial meetall 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 which involve treatment with immunosuppressants and therefore an increasedrisk of infection, without any expectation of benefit for the participants.

3. **Access to trial treatment**

Patients' access to the trial drug must be guaranteed in the same conditions in which it was 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 drug to cover a longer period of treatment.

The **Pharmacy Departments of hospitals 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 Pharmacy Department of the treatment to the patient's home** when their 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 of 25 March.

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 (provided the epidemiological situation of the pandemic allows it) , 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.

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

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 necessary, the transfer of one patient from one trial site to another can be carried out provided:

a) a transfer agreement between sites is signed

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

c) the original site sends a transfer report summarising the most relevant medical data of the patient with regard to the trial in order to facilitate their monitoring at the new site;

d) the transfer of the patient is documented in the trial archive 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].

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.

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"Actions of the AEMPS to speed up and promote clinical trials and observational studies on COVID-19" *Date of publication:* ***4 May 2020***

- **Investigators shall consider the possibility of joining ongoing clinical trials before they start a new one.**
- **COVID-19 related trials will be prioritized**
- **Prospective follow-up observational studies will be considered as EPA-AS.**

Clinical trials are an essential tool to identify the way of preventing and treating COVID-19 disease, because of that, the Spanish Agency for Medicines and Medical Devices has established measures in order to ease and streamline the process of clinical trials authorization and observational studies classification.

Clinical trials aimed at investigating new drugs against coronavirus

The situation caused by the COVID-19 crisis is evolving to anew scenario where the number of patients decreases every day. Nonetheless, infections have not disappeared yet, infected patients keep healing in the medical centres, and we have to be prepared for a potential new infections increase during de de-escalation phase or this year´s Winter or Autumn.

In this less demanding healthcare context, it is important to gather efforts around big clinical trials with statistical weight in order to complete the recruiting and obtaining results that may help to take clinical decisions and those decisions necessary to be prepared for a potential increase in the number of infections. Investigator should assess the possibility of joining ongoing clinical trials (see Spanish Registry for Clinical Trials (REec) https://reec.aemps.es/reec/public/web.html) instead of starting new ones

The AEMPS has prioritized, alongside with the CEIm; the evaluation of clinical trials which purpose is to prevent or treat the coronavirus disease. It is also necessary to keep normal activity in those clinical trials studying other conditions that, as long as normal healthcare activities recover, they might recover their normal activity too. Nevertheless, COVID-19 applications are still prioritized and are reviewed as soon as possible in a term no longer than fifteen days.

Sponsors and investigators that might have a clinical trial of these characteristics have to send their application to the CEIm and to the AEMPS through the ECM Portal (see Instrucciones para la realización de ensayos clínicos en España) warning of the presentation with an e-mail to aecaem@aemps.es with the subject "URGENTE COVID-19" identified with the EudraCT number. The trial title has to include the word COVID-19.

In order to check only the particular aspects of the essay before the formal application it is necessary to indicate the particular questions attaching a trial summary and the data justifying the biological plausibility of the drug´s supposed effect given the trials conditions to Área de Ensayos Clínicos, preferably copying the CEIm indicating in the subject: URGENT new EC COVID-19 and the name of the investigational medicine. An answer will be given as soon as possible within a maximum period of fifteen days.

Reminder that to get answers regarding global aspects of new drugs development ,must contact with National Scientific Advisories (aecaem@aemps.es) or the Innovation Support Office (innov_spain@aemps.es).

Clinical trials coming from non-commercial sponsors doesn´t have to pay the tax12. Furthermore, in order to ease their start up, fee exemption and simplification of contracts between the sponsor and the site are recommended. In non-commercial sponsor clinical trials, the contract may be replaced by a document of agreement from the site's management.

It is essential to speed up the analysis of the results of these tests as much as possible and submit them to the AEMPS as soon as they are available.

Observational prospective follow-up studies with coronavirus-related drugs

The subject of the email with the application for observational studies related to coronavirus will be URGENTE COVID-19.

The Classification resolutions for these trials will be sent to the solicitor via email and will be resolved as soon as possible, normally within the very day when the application is sent or within the next to labour days.

Observational non-commercial studies with a prospective purpose, in which the sponsor is an independent organization investigator (Investigation Groups, scientific societies) will be considered as of healthcare interest and identified as EPA-AS. The AEMPS is willing to give methodological support to those investigators that apply for it.

For the evaluation/authorization of EPA-AS from COVID-19, the AEMPS will only ask for, besides the protocol, the favourable opinion of the CEIm and the authorization resolution will be issued no longer than the next 7 natural days starting from the reception of the CEIm decision. Aiming to contribute to the observational investigation about COVID-19 quality and efficiency improvement, the AEMPS will try to help the collaboration among investigators from different centres but with common purposes. For this, we are putting these researchers in contact, in case it is feasible that some kind of collaboration among them and, where appropriate, multicentre studies materialize.

ITALY

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 (AIFA) provides indications regarding the management of clinical trials in Italy and following the exceptional restrictive measures introduced by the Italian government in the context of combating the pandemic from COVID-19 (coronavirus disease 19) valid until further notice and closely related to the state of emergency approved by the Council of Ministers on January 31, 2020.

The conduct of clinical studies must be managed according to common sense principles, in the maximum protection of study participants and maintaining adequate supervision by the Principal investigators (PI). Therefore, please consult the Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic published on the European Commission website, EudraLex Volume 10 Clinical trials ***(https://ec.europa.eu/health/documents/eudralex/vol-10_en).***

"Clinical trials' management in Italy during the COVID-19 (coronavirus disease 19) emergency", Version 2 of April 7,2020. *(Update of the AIFA press release published March 12, 2020)*

1. Procedures for submitting clinical trials and substantial amendments

Following what has already been indicated in the previous press release, it is clarified that, even in the emergency period foreseen for COVID-19 (coronavirus disease 19), the submission of requests for assistance with clinical trials and substantial amendments must take place, in accordance with the current legislation, through OsSC. However, considering that many pharmaceutical companies, non-profit sponsors and CRO have applied the smart-working method, in order to not stop the activities related to clinical trials, AIFA will proceed with the validation / evaluation of the practices received even in the absence of the paper and CD fee associated with the procedures via OsSC, which, however, must be sent as soon as possible.

It is anyway recommended, in applicable cases, 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)

In the event that the method indicated above is not feasible, the stamp must be affixed to the transmission letter and the document must be scanned and loaded into OsSC. For details, refer to the press release "Instances filed with the Italian Medicines Agency: method of payment of stamp duty" published on the institutional website on 26.03.20 *(https://www.aifa.gov.it/-/istanze- presentate-all-agenzia-italiana-del-farmaco-per-via-telematica-modalita-di-assolvimento-dell- imposta-di-bollo)*

If it is not possible to proceed via OsSC, due to blockages or technical constraints of the system, it will be necessary to use the paper transient mode. The submission of requests for authorization of clinical trials and substantial amendments by e-mail is not acceptable, with the exception of studies on COVID-19(coronavirus disease 19) which can be transmitted to apa@pec.aifa.gov.it (in cc to experimentation.clinica@aifa.gov.it) in case of impossibility to proceed via OsSC.

However, it is acceptable to send by e-mail the response documentation to any requests for integration in validation / objections in evaluation. The aforementioned documentation will be assessed without waiting for the paper documentation and the provision will be finalized, it being understood that the paper documentation must be sent as soon as possible.)

2. Procedures for submitting clinical trials and substantial amendments for studies on the treatment of COVID-19

As for the submission of clinical trials relating to the general treatment of COVID-19 (coronavirus disease 19), it is necessary to comply with what is indicated in the circular published on the AIFA website *(https://www.aifa.gov.it/-/circolare-sulle-procedure-semplificate-per-gli-studi-e-gli-usi-compassionevoli-per-l-emergenza-da-covid-19),* as required by art.17 of the Law Decree of 17 March 2020, n. 18 containing "***Measures to strengthen the National Health Service and economic support for families, workers and businesses connected to the epidemiological emergency from COVID-19",*** called **"Cura Italia".**

On the basis of the aforementioned Law Decree, the study protocols are preliminarily evaluated by the AIFA Scientific Technical Commission (CTS) and subsequently approved, after evaluation by the competent Authority AIFA (Clinical Experimentation Office) and by the Ethics Committee of the National Institute for Infectious Diseases Lazzaro Spallanzani of Rome, as the only national Ethics Committee for the evaluation of clinical trials of medicinal products for human use and medical devices for patients with COVID-19 which expresses the national opinion, also based on the evaluation of the AIFA CTS.

Exclusively for the submission of requests for authorization of clinical trials relating to the general treatment of COVID-19 (coronavirus disease 19), where it is not possible to proceed in OsSC, it is acceptable that the submission of requests for authorization takes place through the transitory paper or through the mailbox apa@pec.aifa.gov.it, and that the documentation supporting the aforementioned requests is preferably sent via Eudralink or similar methods (applicable for the secure sending of confidential documentation) within the same email.

It should be noted that, in accordance with Article 17, paragraph 3 of the Law Decree of 17 March 2020, No. 18, the Ethics Committee of the National Institute for Infectious Diseases Lazzaro Spallanzani of Rome, having to issue the single national opinion, must be identified as a Coordinating Ethics Committee and therefore the coordinating site must be identified in the National Institute for Infectious Diseases Lazzaro Spallanzani in Rome. This does not necessarily entail the involvement of the site's PI (only "Ethics Committee" can be indicated instead of Name and Surname of the PI).

We also inform you that, in accordance with paragraph 2, second period of art. 17 of the aforementioned Law Decree, AIFA will take care of sending the protocol and synopsis of the study in question to the Technical Scientific Commission (CTS) for the purposes of its preliminary evaluation.

We also inform you that an accelerated timing is foreseen for the evaluation of COVID-19 studies.

Finally, it is recommended to include the wording "COVID-19" in the title of the clinical studies in question for easier identification of the same, as well as in the subject and text of the e-mail in the event that this transmission route is used.

For the documentation to support the request for authorization of clinical trials relating to the general treatment of COVID-19 (coronavirus disease 19), refer to the document list provided in OsSC (in the event of submission through the paper transitory mode or through the of the *apa@pec.aifa.gov.it* mailbox, in addition to the documentation at the bottom, you must also produce the authorization request form or Appendix 5 and the xml file):

- **Core documentation:**
  - General information (eventual delegation of the Promoter to the Applicant)
  - Protocol information (protocol *, synopsis in Italian *, possible peer review, B / R assessment, assessment on the inclusion of special populations, ethical assessments by the coordinating investigator)
  - IMP information (IB *, alternatively CPR *)

- **Documentation for the competent authority and the national ethics committee:**
  - General information (AIFA transmission letter *, list of Competent Authorities of other countries involved and related decisions, summary of any scientific advice, copy of the EMA decision on a PIP and of the opinion, receipt of payment of the tariff * - NB: in OsSC is required, but - if not applicable - it can be replaced with an explanatory word document)

  - Information relating to IMP (IMPD * or simplified IMPD * or RCP *, GMP authorization for production and import * for the sites involved in production / analysis / packaging, including labeling / import where applicable / release - NB: in OsSC the GMP authorization is required, but - where not applicable - it can be replaced with an explanatory word document, declaration of conformity to the EU GMP of the QP for non-EU sites, IMP analysis certificate if not already included in the IMP, status authorizations applicable to particular IMP type radiopharmaceuticals, drugs and GMO content, TSE certificate of suitability, IMP label in Italian *) (for details see Guide to the compilation of section D of the CTA:

    http://www.agenziafarmaco.gov.it/sites/default/files/Guida_alla_compilazione_Appendice_5_Sezione_D_25.01.2019.pdf)

  - Information related to NIMPs

- **Site-specific documentation (only for the National Ethics Committee:**

  - General information (transmission letter of the Ethics Committee *, receipt of payment of the tariff * - NB: in OsSC it is compulsory, but - if not applicable - it can be replaced with an explanatory word document)

- Information relating to the subjects (form for informed consent *, information leaflet, provisions for recruitment, material for the subjects, letter to the attending physician)
- IMP information (studies / clinical uses and B / R evaluation, if not described in the IB)
- Structures, staff and financial matters (main investigator CV * NB: in OsSC it is compulsory, but - where not applicable - it can be replaced with an explanatory word document, promoter contract-clinical site proposal, insurance certificate *, auxiliary staff, any compensation for failure earnings / reimbursement of participating expenses)

  where * indicates mandatory document)

Please note that for the preliminary assessment, only the protocol and synopsis will be forwarded by the Clinical Trial Office / Pre-Authorization Area, while the IB only on request.

The sites that in addition to the National Institute for Infectious Diseases Lazzaro Spallanzani in Rome will be involved in the study will be included as satellites in section G.2 of the Clinical Trial Application (CTA or Appendix 5) and the related ethical committees of reference, although not formally called to express themselves, they must accept the single opinion of the National Ethics Committee by filling in Appendix 8 if the CTA has been submitted from the start via OsSC.

For COVID-19 studies in OsSC, any substantial amendments to be evaluated must be submitted to AIFA, to the National Ethics Committee for the related opinion and to the other Ethics Committees that will accept the opinion as indicated above.

In particular, as regards the possible addition of sites to already approved clinical trials, since the opinion of the coordinating ethics committee is not envisaged in accordance with Ministerial Decree 21.12.07, but only that of the ethics committee pertaining to the new site intends to involve, exclusively for COVID-19 studies, it is possible to proceed via OsSC through the submission of a substantial "previous" addition of the site so as not to have to acquire the opinion of the Ethics Committee relating to the new site. In this case, the date to be indicated as the date of the opinion of the ethics committee concerned will be the one in which it was decided to include the new site.

For COVID-19 extra-OsSC studies, the substantial amendments to be evaluated must be submitted to AIFA *(apa@pec.aifa.gov.it)* and to the national ethics committee (*committeeetico@inmi.it).*

For multinational studies, we invite you to consider the possibility of a presentation via VHP and to contact the EMA for any Scientific Advice procedure, both in accelerated mode, in accordance with the provisions of the ***"Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic."***

Prospective observational pharmacological studies are also included among the studies to be submitted to AIFA and to the Ethics Committee of the National Institute for Infectious Diseases Lazzaro Spallanzani in Rome.

The observational pharmacological study protocols will be sent simultaneously to AIFA to the mailbox apa@pec.aifa.gov.it (*experimentation.clinica@aifa.gov.it* and *info_rso@aifa.gov.it* in cc), and to the

Ethics Committee national (*comandetico@inmi.it).* They will only be notified to any other ethics committees involved.

3. 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.

4. Methods of communicating deferred measures that modify the execution or management of clinical trials to comply with the measures in place due to Covid -19

In the event that, to limit the risk of contagion from coronavirus, indifferent measures are implemented that modify the execution or management of clinical trials (including temporary changes to the protocol) to comply with the measures in place due to the COVID- 19, a notified substantial amendment must be submitted only to the ethics committees of the sites involved (in which the patients concerned are followed), in order to ensure accurate tracking of all deviations, but also to facilitate the rapid implementation of the measures without determining further burden on the structures concerned.

The notification as a substantial amendment for immediate implementation is also applicable to all the specific cases described later in this press release.

Where possible, the substantial amendment must be notified through the OsSC, otherwise Appendix 9 must be produced to be used for transmission in paper transitory mode. In the case of paper procedures, it is acceptable to send the substantial amendment notified by e-mail (exclusively to the ethics committees involved).

The amendment is necessary both to communicate that emergency measures are being implemented both to communicate its cessation.

In both cases, the amendment must be notified and not submitted for evaluation. To this end, it is suggested to fill in Appendix 9 by selecting Yes in the "D.2.2.3 Other" field and to fill in the "D.2.2.3.1 If other, specify" field. It should not be indicated that this is an urgent security measure, but a notified amendment due to the emergency of COVID-19.

In the event that the Sponsor temporarily suspends enrollment and / or treatment in a clinical trial, to comply with the measures in place due to COVID-19, it will be necessary to notify a substantial amendment to the Ethics Committees of the sites involved (regardless of the their activation) both when the measurement is introduced and when the measurement is canceled.

Also in this case it is suggested to fill in Appendix 9 by selecting Yes in the "D.2.2.3 Other ”and to fill in the field“ D.2.2.3.1 If other, specify ”. This is because if the field "D.2.3.2 is selected in OsSC, the amendment serves to communicate a temporary suspension of the trial", the substantial amendment for the resumption would be automatically submitted for evaluation.

For more details on how to communicate to the competent Authority and to the Ethics Committees

of the actions undertaken / to be undertaken to protect subjects in clinical trials, please refer to point 6. of the "***Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic".***

5. Possibility of managing clinical trial activities outside the experimental center

Investigators and promoters are invited to consider the opportunity to limit visits to those strictly necessary, canceling unnecessary ones and, where possible, also providing for the extension of the duration of the trial.

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, the Sponsors / CRO are invited, taking into account the indications of the DPCM relating to the urgent measures on the containment and management of the pandemic emergency from COVID-19 and the specific Ordinances of the different Regions, to draw up a risk assessment plan and to implement a proportionate to the risk plan, in the pre-eminent protection of the subjects under experimentation, with a view to the urgent need to minimize the contacts between patients and experimental staff and in order to further not to overload health facilities.

The Sponsors are also invited to inform the trial sites and to agree with them on time all the alternative measures, related to the contingent situation, adopted for the management of the subjects in the trials.)

Provided they are compatible with the feasibility at the home of the subject, the carrying out of procedures directly at the patient's home, carried out by the staff of the trial sites or by third parties, may be considered. These home health care activities may include both clinical procedures that cannot be carried out otherwise (e.g. collection of adverse events, vital signs, etc.), and the administration of non-self-administering therapies (e.g. infusions).

In reiterating that these measures must be understood as extraordinary and limited to the strict coronavirus emergency period, in derogation from 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*) it is possible for the Promoter / CRO to directly enter into contracts with these agencies / third-party companies specialized. All other indications of the aforementioned FAQ remain applicable, and compliance with the rules on the protection of personal data, such as:

- the need for supervision to be maintained by the PI
- that efficient lines of communication are established between the staff in charge and the PI
- that the staff in charge is properly trained and the related duties and responsibilities are indicated in the contract and / or delegation log
- that the confidentiality of sensitive personal data is guaranteed
- that the relations between these third parties and the trial sites are governed pursuant to art.
- 28 of the General Regulation on the protection of personal data 2016/679, through a contract or other legal act for the designation to be responsible for data processing.

The Sponsor must ensure that the insurance stipulated for the clinical trial also covers the changes implemented for the coronavirus emergency. It should be noted that, if the trial sites (data controllers) entrust part of the activities aimed at guaranteeing therapeutic continuity to third parties (also through collaboration with the Sponsors), the relations between these third parties and the trial sites must be governed by the pursuant to art. 28 of the General Regulation on the protection of personal data 2016/679, through a contract or other legal act for the designation to be responsible for the processing of personal data.

6. Investigational medicinal product (IMP) management

If possible, when the subject 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 and that has an expiration date that goes beyond the period of treatment provided to avoid erroneous assumptions of expired drug by the subject.

It is also foreseen, in case of difficulty on the part of the subject to go to the clinical site and to limit travel, the possibility that the drug is delivered to a family member or other person (for example a caregiver), who must be in possession of delegation by the subject himself, as established by the law in such cases.

The evaluation of the period to cover the provision of a larger quantity of drug is carried out by the investigating doctor who must maintain constant control over the correct intake by the subject, in accordance with the clinical protocol. In fact, the supply of additional experimental drug corresponds, in this case, to all effects to a prescription by the investigator with all the ethical, clinical and legal responsibilities connected to it.

According to current legislation (article 7 of the Ministerial Decree 21st December 2007), the Sponsors/CRO 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, direct deliveries from the hospital pharmacy to the test subjects can be agreed upon indication of the director of the hospital pharmacy and of the main investigator (PI), also through dedicated couriers) 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).

So, given the serious emergency COVID-19, even if the priority route remains delivery to the hospital pharmacy, direct deliveries from the hospital pharmacy to the test subjects can be agreed upon indication of the director of the hospital pharmacy and of the main investigator (PI), also through dedicated couriers.

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 of the sponsor mentioned in the introduction, that must take into account the IMP typology, administration methods, conservation and transport.

Where the Sponsor/CRO has already identified or has an authorized warehouse, where the drug is stored, given the highly restrictive provisions adopted at national level for the COVID-19 emergency aimed at reducing as much as possible additional travel and passage, source of further risk, direct delivery by the warehouse to the trial subject could be considered only for the period limited to the aforementioned emergency. For this method, procedures for maintaining all guarantees of control and traceability of delivery are to be identified, including transport conditions and agreements in this regard with the trial sites. In this context it is necessary to consider solutions such as the use of a dedicated courier, which operates according to procedures for the direct delivery of the experimental drugs to the participating subjects and which also implements all the measures aimed at guaranteeing the confidentiality of the information relating to the subject, such as the instructions pursuant to art. 29 of the GDPR, which the data controller is required to provide to anyone acting under his authority, or, if applicable, the designation of data controller pursuant to art. 28 of the GDPR.

The GCPs (§§ 5.14.4, 8.2.15 and 8.3.8) require that the Promoter / CRO keep the delivery documentation of the IMP but these points clearly refer only to the shipment from Sponsor/CRO to the hospital pharmacies of the trial sites. Since this is an extraordinary procedure, this does not apply to the direct delivery to the home of the subjects and therefore the relative documentation must be kept directly at the trial site to guarantee the confidentiality of the data.

Adequate remote communication ways with involved subjects must be implemented to allow exchange 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 in order to facilitate the information of the subject or provide detailed instructions), where deemed necessary. It is recommended to keep a documented trace of the communications, of any kind, which occurred in this emergency situation.

All this without prejudice, if possible, to conditions set out 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*)

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, subjects designated for the processing of personal data, pursuant to art. 2-quaterdecies of the Code regarding the protection of personal data, legislative decree 30 June 2003, n. 196 and properly trained. The IMP can be returned to the Sponsor/CRO directly by the hospital pharmacy.

Aimed to limit travel and contacts as much as possible, it is considered acceptable, for those drugs close to the expiry date, to adopt the solution of maintaining, until the emergency is resolved, the drug at the hospital pharmacy, in areas specifically identified and segregated, putting in place the appropriate precautions, foreseen by a specific procedure, aimed at avoiding the erroneous use of expired or deteriorated drug.

7. Clinical examinations

Being aware of the need to have clinical analyzes and / or instrumental investigations (eg CT, MRI, RX) essential for the safety of the subjects), in the awareness of necessity

that these tests are carried out in facilities close to the subject's home, preferably public or private facilities, recognized as suitable for conducting clinical studies pursuant to the Ministerial Decree of 19 March 1998 or private self-certified laboratories pursuant to the AIFA 809/2015 regulation. The use of private structures not in possession of such recognition of suitability or not self-certified, must be carefully evaluated and implemented only if it represents the only possibility to protect the safety of the subjects and the subsequent use of the data produced by these structures, if connected with the study's end-point, should be explained and discussed in the study report.

It should be noted, as mentioned above, that, even in this case, the data controller (trial sites) is required to regulate relations with the aforementioned structures pursuant to art. 28 of the GDPR, if they act in the name and on behalf of the data controller, or if these structures must be considered independent data controllers, pursuant to art. 24 of the aforementioned Regulation.

8. Sites closing

If a site is closed to the public for COVID-19 containment measures, it would be carefully assessed if the clinical trial staff is able to guarantee the continuity of the trial itself. In case the trial staff is unable to follow the patients undergoing the trial, the study should be temporarily halted or, where possible, enrolled patients should be transferred to subjects transferred to the experimental center among the active ones, closer to where the subject is located.

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.

(In this case, the complete transfer of the trial to another site involves the transfer of responsibility to the other PI of the new site. In the case, however, of temporary transfer not of all the trial but of single procedures (for example visits) related to the trial, responsibility for the trial remains with the initial PI.

Contacts between Sponsor/CRO 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 clinical management of the subject.

9. Clinical trial monitoring

By analogy with what stated previously, **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 and alternative methods are accepted for the purpose of source data verification (SDV) such as telephone contacts or better video conferences with the staff of the experimental site

If, in accordance with the Sponsor's risk assessment, the SDV is not deferred and, where appropriately justified by the intent to protect the rights and well-being of the subjects under trial (GCP-ICH § 5.18.1 (a)), other remote monitoring methods, (for example, temporary access to the data contained in the electronic medical records of the healthcare facility relevant for the purposes of the trial), can be considered but must be clearly described in a procedure that must be agreed with all the subjects involved (eg CRO) and having heard their respective Data Protection Officers (DPO), in accordance with the provisions of art. 37 and following of EU Regulation 2016/679.

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.

Solutions that involve a **burden of work for the staff of the trial site are not acceptable** (e.g. the transformation of numerous documents into pdf).

It should be noted that the alternative methods must be implemented in total guarantee that access will only be made to the documentation of the subjects included in the trials, limited to the period of involvement in the trial and for the period of time in which the emergency conditions persist.

In fact, in the presence of suitable guarantees to protect the fundamental rights and freedoms of the interested parties, temporary and alternative monitoring methods can be put in place in consideration

of the urgency or the indifferent need for supervision by the Sponsor/CRO, according to established by the data controller and consistent with the security measures adopted by the data controller that take into account the highest level of risk associated with this method.

It is essential that, when the situation has normalized, robust follow-up measures are planned by the Sponsor/CRO to assess and eventually fill in the gaps due to the reduced frequency of in situ monitoring or the application of alternative measures.

10. Possibility of exceptional expenses reimbursement

Given that from the application of the emergency measures for COVID-19 there must be no additional cost for public finances or for individuals, taking into account the exceptional nature of the contingency, if, in order to implement urgent measures for the protection of participants in a clinical study, expenses are expected to be borne by them, similarly to what is already allowed in extraordinary cases (for example studies on rare diseases), the Sponsor/CRO is allowed to reimburse these expenses to the subjects.

In order to avoid direct contacts between subjects and Sponsor/CRO, the preferable method would be the dispatch of receipts or the delivery (when possible) by the subject to the trial site which will, through its administration, invoice this amount to the Sponsor/CRO and to reimburse expenses. The expenses incurred must be adequately documented and the receipts issued by external structures must clearly indicate the protocol code or the EudraCT number of the study.

11. Exceptions to the method for obtaining Informed Consent

Given the current emergency situation, the inclusion and enrollment of new subjects in clinical trials should be avoided as much as possible except for those cases whose participation in the study is of fundamental necessity, such as in the absence of a valid therapeutic alternative, or of course, in cases of enrollment in studies where COVID-19 drugs are tested. In cases where it is necessary to obtain an informed consent (activation of new studies or, amendment to the informed consent for studies already started or for the implementation of emergency measures referred to in this press release or simply to avoid exchanges of paper material possible source of contagion), where not possible in the usual way, alternative procedures for obtaining it must be considered. The implementation of these alternative procedures (telephone contacts, followed by confirmation e-mails or validated electronic systems) does not exempt from obtaining written consent as soon as the situation permits, on the first occasion in which the subject appears at the site.

The opportunity to obtain consent from the subjects must always be privileged over other solutions, even in cases of subjects who are in isolation conditions, for which cameras or photographs of the documentation taken through the barriers can be used transparent insulation.

In the case of temporary verbal consent, the presence of an impartial witness who certifies the successful administration of the consent and affixes the date and signature on the informed consent

document is required. It is up to the investigator to certify the method of selection of the impartial witness.

In any case, the rules in relation to the discipline on the processing of personal data remain, with particular reference to the acquisition of consent to the processing of the same carried out in the context of clinical trials. According to the principle of accountability, the data controllers are required to identify suitable measures and prove the successful acquisition of a valid consent to the processing of personal data, for example through the voice recording of the telephone consent or the retention of the email.

12. Compliance with the rules on the protection of personal data

Without prejudice to the preliminary indications provided above also in relation to some fulfilments related to the discipline regarding the protection of personal data, it is understood that it is up to each individual data controller to identify, if necessary, the technical and organizational measures necessary to ensure that these methods alternatives for the management of clinical trials comply with the personal data protection discipline set out in Regulation (EU) 2016/679, with the Personal Data Protection Code, with the ethical Rules for processing for statistical or scientific research purposes published pursuant to art. 20, paragraph 4, of Legislative Decree 10 August 2018, n. 101 -

19 December 2018, attachment A5 to the Code, and to the Prescriptions relating to the processing of personal data carried out for scientific research purposes, attachment no. 5 to the Provision containing the provisions relating to the processing of particular categories of data, pursuant to art. 21, paragraph 1 of Legislative Decree 10 August 2018, n. 101, of 5 June 2019. In applying the COVID-19 emergency measures, the principles applicable to the processing of personal data enshrined in Regulation (EU) 2016/679 must be respected, with particular reference to the principles of minimization, of integrity and confidentiality of data (Article 5, paragraph 1, letter c) and f)), according to the solutions deemed, from time to time, more appropriate and suitable for the specific case. To this end, please note that each owner can take advantage of the advice and support of the data protection officer, designated pursuant to art. 37 of the GDPR.

13. General consideration

The measures contained in this press release are of an exceptional nature and a derogation from the applicable rules and practices, therefore a CRO cannot proceed to apply the exceptional measures indicated in this press release without informing the Promoter, who, in accordance with the GCP, remains the person responsible final of the trial.

PORTUGAL

INFARMED

INFARMED, I.P. has updated the guidance with indications regarding to conduct of clinical trial in Portugal during the period of risk to public health.

COVID-19: Exceptional measures within the scope of Clinical Trials during the period of risk to public health (Version 3 dated 11/05/2020)

**new text is included in shaded form.*

Following an international Public Health emergency, declared by the World Health Organization on 30/01/2020 for SARS-CoV-2 infection (new coronavirus 2019), and with regard to conducting clinical trials in Portugal, INFARMED, I.P. admits that sponsors, clinical trial centers and research teams consider necessary to introduce changes to the terms approved in the Clinical Trial Authorization, in order to safeguard the safety, protection and rights of participants in clinical trials.

In the context of emergency, it is also important to simultaneously reduce the risk of spreading infection among the population and ensure the availability of health professionals for priority tasks.

Without prejudice to the publication of harmonized guidelines by the European Commission, regarding the conduct of clinical trials in the various Member States in the context of a pandemic, specific recommendations are described below which should be followed, despite being updated in the future.

In this context of a public health emergency, **the set of measures presented below can be implemented immediately, without requiring prior notification or approval of a substantial amendment, with the exception of point 1.A. "Treatment interruption", which must be notified as an urgent safety measure**.

It is expected that the sponsor, together with the investigator, will make decisions on the measures to be taken proportionately and appropriately, based on a risk analysis for each clinical trial, in which the characteristics of the trial, of the trial center, are considered and the epidemiological risk in it.

For each of the clinical trials, in which during the period of pandemic crisis there is a need to adopt measures that, being violations of the protocol and predefined procedures of the study, were considered necessary by the Sponsor and Investigator to protect the participants, the Sponsor must notify the Infarmed, up to 4 months after this period, with a report that systematically documents the set of measures implemented, the deviations produced as well as an evaluation of the implementation of these measures and their impact on the study after the resolution of the current epidemic outbreak, this means, when there is an agreement that the COVID-19 pandemic period in the EU/EEA has been overcome.

This guideline refers to the immediate measures in the context COVID-19, to immediately safeguard the safety of participants, so if they are changes that may have an impact on the safety and well-being of participants, **but do not require immediate intervention** by the investigator and sponsor, the sponsor must submit a substantial amendment.

Other recommendations are also presented, related to the availability of experimental, non-experimental drugs, and medical devices used in the context of clinical trials.

These recommendations are also applicable to clinical studies with intervention of medical or cosmetic devices, under the provisions of Law No. 21/2014, of 16 April, in its current wording:

1. Immediate implementation measures:

A. Suspension of treatment

There may be a need to immediately interrupt study treatment, whenever that the safety of the participants is at stake.

In these cases, of which we highlight particularly clinical trials that involve, populations in immunosuppression resulting from the treatment instituted, as well as other therapies that may constitute an intolerable risk, whenever an interruption of treatment, in part or in all of the participants, it is up to the sponsor to notify Infarmed, as an "urgent security measure", to be submitted as soon as possible, with a detailed explanation of the context, and of the measures taken to ensure alternative treatment of participants.

For the remaining 'urgent security measures', unrelated to the current situation pandemic, the procedure remains the currently in force, as provided for in published in Volume X of the Eudralex **Detailed guidance for the request for authorization of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial**

B. Suspension of recruitment

As mentioned, it is expected that, in view of the current pandemic situation, the sponsor, together with the investigator, make decisions on the measures to be taken proportionately and suitable for new clinical trials or those that are ongoing. The recruitment of participants to integrate new clinical trials should take into account the analysis of the trial sponsor in view of the feasibility of starting a new clinical study under current conditions. This should take into account, based on a risk analysis for each clinical trial, the characteristics of the test, the population to include or include, the test center and the risk epidemiological data.

In this sense, the suspension of the recruitment activity is allowed, whenever the same justifiably carries an additional risk of SARS-CoV-2 infection for patients to be recruited.

C. Scheduled visits - clinical evaluation and study procedures using telematic methods

The sponsor must assess the need to review the visit plan adopted in the study protocol, in order to:

- Adjust the frequency of visits during the period considered necessary

- Adjust the level of information collected at each visit

Remote visits, using telephone calls or other technological means (telematic), are possible, and the collection and recording of all information provided for the visit in question (including the method of carrying out and identification of the member of the research team responsible for carrying it out) should be ensured.

It must be ensured that the use of telematic means is consented by the participant, and that only the strictly necessary information is collected.

This consent can be obtained by verbal means, being registered in the documentation of the trial center by the team member who collects that consent, or, for example, by email (video or sound registration is also accepted). Must be subject to confirmation by signature of the participant, once the current situation is normalized.

D. Centralized monitoring

The sponsor should assess the need to review the monitoring plan * adopted in order to:

- Postpone face-to-face monitoring visits
- Conducting centralized monitoring visits, based on a risk assessment, is permitted and encouraged.
- Reduce monitoring activities to what is possible remotely, even if this implies delaying the review of source data, for when it is possible to access it in person and in agreement with the trial center and principal investigator.

Centralized monitoring cannot imply the retention of source documents or access to personal data by unauthorized persons. Likewise, remote access to clinical data patients, registered in computer systems belonging to the trial center only can be accessed if they guarantee compliance with Good Clinical Practices in this matter, and of the General Data Protection Regulation. Exceptions to these requirements should be duly analyzed by the Data Protection Officers of the entities involved and communicated to CEIC and CNPD, within the scope of their competences and according to the guidelines of these entities in the context of a public emergency.

E. Direct dispensing at home of experimental drugs

Given the exceptional circumstances, the home dispense may be accepted, based on the assumptions below, and complementary to Normative Circular No.005 / CD / 550.20.001 of 07/04/2020, on "Guidelines on proximity access to medicines dispensed in an outpatient hospital pharmacy regime in the current context pandemic by COVID-19 ", specifically with regard to points 1.1, 2, 2.1.1, 2.1.2 and 2.3, with the necessary adaptations to ensure control of data access personal data of the participants, and, if applicable, maintaining the blinding of the clinical trial.

- Ensure that the Principal Investigator and the research team (including the hospital pharmacy) maintain the supervision of this process, ensuring communication channels that allow participants to clarify doubts.
- Ensure that access to personal information (name and address) is allowed by the participant.

- Records were made to track transport from the point of departure (trial center), until delivery to the participant.
- Records on packaging methods are ensured.
- Guaranteed temperature / humidity records during transport.
- In cases where reconstitution is necessary, the period of stability of the medicine between the time of reconstitution and its administration must be taken into account, this possibility being only applicable in cases where the administration does not require the intervention of a health professional *
- Ensure that the patient receives all the information and is informed about the administration and surveillance process, as well as has the necessary contacts to communicate adverse effects / serious adverse effects
- Ensure that the trial's concealment is not broken, where applicable.

** in cases where the administration requires the intervention of a health professional, if it is not possible to guarantee that this will be carried out at the participant's home (ensuring all safety conditions for the patient and the health professional, as well as all means necessary technicians), the transfer of the patient to another alternative clinical trial center should be pondered.*

If the transfer is not possible, the interruption of treatment as provided for in point A should be considered or must be carried out the closure of the trial center, with the completion of all procedures inherent to the end of the study, safeguarding the safety and well-being of the participants. The follow-up of patients after early trial completion at the trial center should follow the guidelines outlined in the clinical trial protocol for these cases.

The provisions of section 10 of the document must also be considered "Q&A: Good clinical practice (GCP)" – GCP Matters".

F. Conditions for transfer between test centers:

Given the exceptional circumstances, the transfer between trial centers may be accepted, assuring compliance with Good Clinical Practices in this matter and the General Data Protection Regulation, the aspects related to the circulation of health information resulting from Law No. 12/2005, of 26 January, as well as the other ethical aspects for the transfer of documents between health institutions.

In case it is necessary to transfer the stock of experimental medicine (if applicable), to be ensured by the sponsor, the following must be ensure:

- Records were made to track transport from the point of departure (sponsor or trial center), until delivery to the new test center
- Records related to the packaging method are ensured
- Guaranteed temperature / humidity records during transport

Compliance with the Good Clinical Practices in this matter and the General Data Protection Regulation must be guaranteed, aspects related to the circulation of health information resulting from Law No.

12/2005, of January 26, as well as other deontological aspects for the transfer of documents between health institutions.

2. Other recommendations:

A. Communication with Infarmed

The preferred means of contact is email: ensaios.clinicos@infarmed.pt

All submissions related to processes prior to the implementation of RNEC, must at this stage be submitted by email.

B. Disruption of Experimental Medicine supply

Guarantee reserve stock for participants, for at least 3 months. In case of impossibility to guarantee reserve stock:

- evaluate the possibility of suspending the recruitment of participants
- assess the need for suspension of EC, according to the criticality of the participants' health status, therapeutic indications, and risks of discontinuation (eg cytotoxic)

The import/export of experimental medicines for use by a specific participant, in line with the provisions of paragraph 1.E., must be preceded by communication to Infarmed (dil-ins@infarmed), with description of the situation, namely: clinical trial identification, experimental drug identification and quantities to be sent, and statement by the principal investigator on the indispensability of therapy for that specific participant, guarantee that the use will be exclusive by the same participant, and that the conditions are met to keep the experimental treatment at a distance

C. Disruption of supply of NIMPs / Disruption of supply of medical devices necessary for the administration or manipulation of (ME)

Assess whether they belong to the Strategic Medicines Reserve, published in the Diário da República, Dispatch No. 3219/2020 available at: https://dre.pt/web/guest/pesquisa//search/130112149/details/normal?l=1..

If not, guarantee reserve stock for the participants, for at least 3 months.

D. Protocol Deviations

Deviations from the protocol that may occur must be duly registered within the sponsor's QMS.

E. Evaluation of clinical trials of new drugs for Covid disease19

Infarmed will give priority to the evaluation of new clinical trials aimed at treating or preventing the disease by the new coronavirus (SARS-CoV-2).

To this end, applicants must submit the study through RNEC, clearly identifying the scope of the disease Covid19, and send an email to Infarmed (trials.cllinicos@infarmed.pt) and CEIC (ceic@ceic.pt), in order to streamline the process with a view to expeditious approval.

CEIC

The Comision Ethic for Investigation Clinical (CEIC) has updated the indications regarding the management of clinical trials and interventional studies with Medical device in Portugal during the COVID-19 (coronavirus disease 19) emergency, respect to the last document *Información del CEIC about clinical* emitted *"trial and intervetional studies with DM during actual situation with COVID-19", 17 March 2020*

"CEIC Information on Clinical Trials or Intervention Studies with DM in the face of the current conjecture of Covid19", 31 March 2020. (version of march 31 updated on 3 of april)

The pandemic situation for the new coronavirus (SARS-CoV-2) may have an impact on the conduct of clinical trials and other clinical studies with respect to participants' visits to trials centers, provision of experimental medicine and monitoring activities, among other aspects.

During this period, participants can be advised by health authorities not to travel to hospital establishments or be subject to other restrictions of movements (self-isolation, for example).

The protocol should continue to be the guiding document for all specific activities for each study, and, in view of these constraints, measures that allow minimize major deviations to it should be relaxed (remote consultations, shipping rather than presential availability of experimental medication, remote monitoring, for example). Monitoring safety of participants already included and their access to experimental medication should have priority over recruiting new participants.

It is therefore important to establish some rules and procedures regarding notification or submission to CEIC, taking into account the various recommendations available in this matter and the several questions raised by the applicants.

Despite future recommendations, which may be harmonized at the level of the Commission European Union, CEIC informs:

1. On participants' visits to trial centers and to other trial centers to carry out complementary means of diagnosis

i. As an alternative to the face-to-face visits of patients, it is possible to carry out telephone or video calls.

ii. For the **start of study visits**, the adequacy and opportunity of these and / or their realization through non-face-to-face channels should be evaluated, given the current conjecture.

iii. When provided and supported financially by the sponsor, the **displacement of patients** to local laboratories or other **external clinics for carrying out clinical analyzes** and / or examinations **is acceptable,** provided that these entities are duly certified and it is confirmed, as far as possible, that they comply with DGS measures for the prevention of infection by Covid-19;

- The selection and laboratories and / or external centers **must be operationalized via the trial center and Principal Investigator (PI).**

- The adoption of visits to patients through non-face-to-face visits and/or analyzes and/or examinations in other locations, outside the trial center, must be **notified to CEIC**, **as a non-substantial amendment (NSA**) inserted in the **sponsors action plans or as deviations,** if considered major by the sponsor

2. About (quality) monitoring activities

i. These activities can be carried out by alternative and proportional mechanisms**, remotely and / or centrally, such as by telephone calls, video calls**, etc., in order to guarantee the continuous safety and well-being of participants;

ii. The **risk of impact on** deviations from monitoring should always be evaluated by the sponsor, considering the **prioritization of critical activities,** such as **adverse reactions, safety report**s, among others;

iii. Alternative **monitoring paths and timings must be duly documented;**

iv. For **CRA monitoring visits**, monitors will be able to access **remotely,** as they often do, **assuring the audit trail and the confidentiality of participants' data**

v. Validation that the patient has signed informed consent can be done through confirmation by the Investigator during the remote monitoring visit, and subsequent verification;

- **Monitoring is restricted to encrypted data that the participant has already consented to share outside the center.**
- **Remote monitoring does not** include remote access to health records of the participants (unless the privacy of the participant is duly taken care of and complied with the applicable regulations)
- **Sending documents via fax and/or e-mail is allowed exclusively for CRA** (for remote review), when properly anonymized and coded through the randomization number or other equivalent mechanism.

3. On supply of the Experimental Medicine (ME)

It may be acceptable to **send experimental medication to patients through centers**, in compliance with Good Clinical Practices and other applicable legislation and verified the following:

i. Provision of the ME to the participant, through the centers, if they cannot travel to the Hospital (trial center), and when clinically appropriate required.

- **The direct supply** to the patient (or whomever the patient delegates), from the trial center, because it constitutes a change to the ME circuit, in addition to being duly registered in the study documentation, **must be notified to CEIC, as NSA**

ii. Temporary and/or permanent discontinuation can be considered, if clinically appropriate/necessary

iii. The redistribution of the ME between centers is allowed, as long as transport measures are properly tracked and taken care of;

iv. ME transport services must comply with good distribution practices issued by Infarmed, I.P., now applicable to the context of medicines experimental.

v. The return of the ME by the patient to the trial center, for as long as requested by the center, can be made by mail or a transport company, and the participant must be reimbursed for the associated costs;

vi. Whenever the study medication, provided at home, requires administration by a nurse or other qualified person, this person must be included as a member of the study team.

- Whenever the protocol already provides for "home nursing" services, including the collection of biological products, these may be extended to the availability and/or administration of the ME, once the safety of the intervention is safeguarded, requiring **notifying the CEIC as NSA.**
- Whenever not provided in the protocol, or has not been approved by the CEIC, this possibility **should be submitted to CEIC as PAS**, despite the possibility of direct implementation, and subsequent notification, provided that justified by the Principal Investigator (PI) and safeguarded the security and the confidentiality of the participants.

4. About Informed Consent

Alternative procedures for obtaining consent may be required for participants already included in clinical trials or for the inclusion of new participants. Like this:

i. For ongoing studies, obtaining re-consent for the implementation of urgent changes to the conduct of the study related to the situation in Covid-19, can be done by oral consent by phone or video calls, if possible confirmed by email, after the participant has received the new amended consent.

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- Not all changes to procedures resulting from Covid-19 require prior formal re-consent, such as ME delivery at the participant's home.
- Changes to informed consent to accommodate changes in procedures resulting from Covid-19, provided that they are not considered as major changes to the protocol (see paragraph 7.v), do not require immediate notification (NSA) to CEIC.
- With the current situation normalized, consent from the participant should be obtained by normal means as soon as the participant returns to the center and CEIC previously informed (ANS) of this latest version of consent Informed.

ii. When the sponsor plans to start a study in Covid-19, alternative procedures for obtaining consent from participants can be considered.

- When written consent cannot be obtained, due to the patient's physical isolation, consent can be obtained orally, in the presence of an impartial witness.
- In addition, consent can be obtained by signing the participant and the doctor who obtained the consent in independent documents.

- CEIC is responsible for evaluating and authorizing alternative procedures proposed when submitting the study

5. About materials for participants and / or patients

i. The provision of an **explanatory leaflet** (s) to the patient for the administration of medication, the **CEIC (NSA) must be notified**

ii. **Explanatory leaflets or other information dissemination materials for participants regarding infection with the new coronavirus**, should be given, preferably to the patient, by the investigator physician and **notified to CEIC as NSA.**

6. About deviations from the protocol

i. In order to allow an appropriate and expeditious assessment (if applicable) each sponsor must ensure that **deviations from the protocol are adequately documented,** since an increase in these deviations is expected;

ii. Protocol deviations, justified by Covid-19, do not initially constitute a serious violation, unless participants have been put at risk;

iii. Deviations from the protocol, such as in relation to the eligibility of participants for the studies, justified by the difficulties in the evaluation of the subjects and in testing are not acceptable.

iv. It will be up to the sponsor to classify deviations from the protocol, and in this context, notify CEIC, depending on the impact on the safety and well-being of participants.

- The notification of major deviations must be made in an aggregated form, per study, with discrimination of centers and patient and/or altered visit, within a maximum period of 30 days between identification of the deviation and the information to CEIC (despite a possible change to these notification deadlines).

7. About activating centers, recruiting new participants and/or continuing the study

The suspension and/or postponement of procedures for activating trial centers and/or new approved trial centers must be considered, as well as the temporary suspension of recruitment in active centers. Like this:

i. No participant can be included in a study if it is not possible to verify the procedures necessary to fully comply with the inclusion criteria and exclusion rules provided for in the protocol;

ii. New participants should also not be included if there is no guarantee that there are conditions to comply with the study protocol;

iii. Whenever the safety of a participant is at risk, because he cannot conclude key assessments or follow critical mitigation steps, should be discussed the possibility of discontinuing the study;

iv. Urgent measures remain at the disposal of any investigator and/or sponsor to mitigate participants' risk, as well as temporary interruption of study and/or recruitment;

v. If it is necessary to transfer a patient from one trial center to another, based on the individual risk-benefit assessment, it must be notified to CEIC as an urgent security measure (NSA);

- Any temporary interruption of the study, including for logistical reasons, as the unavailability of the study team, should be considered as urgent security measure, and then notified to CEIC (NSA)
- Most of the observed deviations aim to guarantee the safety and well-being of the participants, not constituting changes to the protocol.
- The waiver of compliance with the protocol remains unacceptable.
- Major changes to the protocol with an impact on safety and well-being of the participants, which imply changes to the consent and therefore re-consent, should be submitted as PAS, which will be evaluated expeditiously.

8. On the risk / benefit of conducting certain clinical trials

Clinical trials that may have an additional risk of infection without possible benefit to the participant, must be carefully reassessed about its beginning and/or continuation, such as clinical trials with drugs that act as immunosuppressant in healthy volunteers, where there is no therapeutic benefit for the voluntary.

- **CEIC should be notified (NSA**) of these decisions.

9. On contingency plans of the Sponsors

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

- These contingency plans - Sponsors' guidelines -, when applicable to two or more clinical trials, can be notified together, clearly indicating the EudraCT numbers to which they apply in the Request letter.

10. About EC participants infected with the new coronavirus

i. Infection of clinical trial participants by the new coronavirus should be considered as an adverse effect and notified 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 procedures of the study, all records must be kept, and the risk-benefit assessment patient care should remain a priority.

- **CEIC should be notified (NSA) of the decision to keep the patient in the study as soon as possible.**

11. On extraordinary expenses

i. All additional expenses resulting from the procedures implemented in view of the situation in Covid-19, must be covered by the sponsor, preferably in advance.

ii. Any additional expenses, due to the Covid-19 situation, paid by the participants must be reimbursed through the trial sites, as usual.

12. On the validity and signature of CEIC documents

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

i. The Sponsors/Applicants must consider the alternative methods of communication as valid, 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, can be sent later, through the usual channels, when requested by interested parties.

13. On Evaluation of Clinical Trials of New Drugs for Covid-19

CEIC has developed expeditious procedures for evaluating new clinical trials designed to treat or prevent disease by the new coronavirus (SARS-CoV-2).

- Applicants must submit the study through RNEC, clearly identifying the scope of Covid-19, and sending email to CEIC (ceic@ceic.pt), in order to streamline the process with a view to expeditious approval.
- Depending on the nature of the study in question and whether additional clarifications are requested, CEIC foresees a response time (between submission and final decision) between 48 to 72 hours (on working days).

All requests for substantial amendments resulting from changes in procedures in the face of Covid-19, will be evaluated expeditiously by CEIC, being necessary for this, when the submission by usual means, communication via e-mail to ceic@ceic.pt.

All amendments to previously approved clinical trial procedures, whenever they do not require submission to CEIC as PAS, according to this information, must be documented, and notified to CEIC, for clinical trial monitoring by the this Commission.

The Applicant can make a single submission, via RNEC, relating to more than one study (for several EudraCT), whenever applicable for equal procedures.

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

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

Original document of March 17, 2020, updated March 31, 2020 is included in the annex VII No.1 of 26 March, 2020.

IT IS ADDED TO THIS INFORMATION ABROVE MENTIONED THAT CEIC HAS TAKEN OUT AN ADDITIONAL NOTIFICATION:

NOTICES / INFORMATION of new CEIC procedures related to Covid19, *25 March 2020*

1. Suspension of reception in person and by mail

All documentation that would be delivered in person or sent by mail, should be sent by email to the following address: ceic@ceic.pt.

We warn that the subject of the email must clearly mention the reason for the notification / submission and the identification of the trial or study (EudraCT / Protocol number / CEIC code).

2. Communication of CEIC deliberations to the Ethics Committees of the centers where the study will take place

CEIC informs that, temporarily and exceptionally, it will not be possible to send the deliberative letters of requests for opinions to the Ethics Commissions of the centers where the study will take place.

Aware of the importance of this articulation, we propose that, in relation to the processes submitted via RNEC, the Ethics Commissions can consult CEIC deliberations through this platform.

For studies that were not submitted by RNEC, we request that, whenever possible, applicants / sponsors inform the Ethics Committee of the CEIC's decision.

CONTINGENCY PLANs FOR CONDUCTING OF CLINICAL TRIAL

To carry out a specific contingency plan in each project, the impact of the COVID-19 must be evaluated in the following terms:

- RISKs; The COVID-19 disease creates risks for clinical trial in:
  - Subject safety:
    Subject can´t have study visit at site or on time, Staff can´t get there or Site is closed
  - Data integrity and quality
    Maintaining GCP compliance and trial integrity

- Situation in each country (SP- IT- PT) where the project is ongoing or will be performed:
  - Government stance; recommendation, duration, site with high risks
  - Outside travel allowed
  - Local travel allowed
  - Activities

- Situation at sites:
  - Contact
  - Open site
  - Measures implemented in the sites: Information about the site and location, and contact from sites
  - Study Staff may not be available to conduct study visit
  - Back up in the study staff.

- Measures implemented by CRO / Sponsor / Sites
  - Implementation
  - Communication to third parties, to EC/CA
  - Follow up
  - Assessment

Overview of important topics to be considered for creating of Contingency plan or Action Plan, for the mitigation of potential risk on the projects, associated to the COVID-19, in the different possible scenarios and taking into account the guidelines to manage the clinical trial during COVID-19 that have been emitted by the different Competent Authorities :

- ***Sites in start-up phase***
  - Submission new projects; check if the EC/CA
  - Submission of clinical trials and substantial amendments

- Ethics Committees evaluations of clinical trials/substantial amendments
- Evaluation of Clinical Trials of New Drugs for Covid-19

- ***Sites in recruitment phase***
  - Recruitment of new patients
  - Scheduled in-person visits for clinical trial patients
  - Patient visits at sites
  - Clinical examination

- **Sites with patients ongoing, recruitment closed**
  - Schedule monitoring visit
  - Monitoring visit and reports
  - Protocol deviation notification
  - Communication with site staff and EC
  - Management of clinical trial activities outside investigational sites
  - IMP and shipments
  - Materials for participants and / or patients
  - Site closing: Transfer of patients from one site to another
  - Exceptional expenses reimbursement
  - Study´s Patient infected with COVID-19

- **Sites in database cleaning/close out phase**
  - CRF /EDC
  - Queries

This format could be used by monitor and could be adapted and updated for each project.

Study title				Study code			

Sites in starting-up phase

Site name and location	Regulatory status: EC/CA delays expected?	Contract status?	Site staff availability	SIV planned /postponed?	Impact expected on milestones	Other	Monitor comments

Sites in recuitment phase

Site name and location	Recruiting expected? Paralised?	Travel restrictions?	Site staff availability	Patient availability	PDs expected?	IMP availability, dispensing	Monitor comments

Sites with patients ongoing, recruitment closed

Site name and location	Travel restrictions	Site staff availability	Number of patients ongoing	Patient availability	PD expected (visits missed, labs ass. Missed…)	IMP availability, dispensing	Monitor comments

Sites in database cleaning/close out phase

Site name and location	Travel restrictions	Site staff availability	Number of patients	SDV expected SDV done	Remote monitoring availability	Impact on database closure	Monitor comments