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ANNEX VII_No.2

GUIDANCES TO MANAGE CLINICAL TRIAL DURING COVID-19

From EMA- Versión 2, 27/03/2020

The European Commission, the European Medicines Agency (EMA) and national Head of Medicines Agencies (HMA) have updated the measures for sponsors 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 2 (27/03/2020).***

Key changes from v1 (20-03-2020): additional clarification on obtaining informed consent; link to methodological guidance on statistical considerations in relation to COVID-19 pandemic; advice on IMP stocks, safety reporting, conduct of audits; temporary halts

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. Therefore, EMA, EC and HMA strongly support the efforts of the GCP Inspectors' Working Group for developing a harmonised EU/EEA-level guidance to mitigate the negative effects of the COVID-19 pandemic on the conduct of clinical trials.

The situation is evolving, and pragmatic actions may be required to deal with the challenges of conducting research, and in ensuring the rights, safety and wellbeing of participants. The points mentioned below are intended to provide guidance for all parties involved in clinical trials during this time.

Due to the urgency, this guidance is issued without prior public consultation. The sponsors should note that due to the rapidly evolving situation further updates to this guidance are possible and likely.

Sponsors and investigators need to take into account that there might be specific national legislation and guidance in place, which they should consult and which can be used to complement this guidance, or, with respect to particular matters may take priority over these recommendations. This document is however seeking to include most of the current guidance across Member States with the aim to serve as an EU-level harmonised set of recommendations.

It is attached the ***Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic Version 2 (27/03/2020)***

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 in ongoing trialsSafety Reporting**
- **Risk assessment**
- **Communication with authorities**
- **Agreement with and communication to sites and participants**
- **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**
- **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.

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SPAIN

The Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) [Spanish Agency for Medicines and Medical Devices], as competent national authority in the authorisation of clinical trials, proposes a series of exceptional application recommendations during the period the COVID-19 crisis lasts in Spain.

"Exceptional measures applicable to clinical trials to manage problems arising from the COVID-19 emergency" Date of publication: 16 March 2020

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.

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. 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.

Any one of these exceptional measures adopted must be duly **documented in the trial archive**. However, their application **does not require prior approval** on a case-by-case level as a substantial amendment by the AEMPS or the Drug Research Ethics Committee (CEIm) and neither the individual notification of serious non-compliance with the protocol, except when it is expressly required as in the point 2.

In the four months following the date on which it is considered that the COVID-19 crisis has finished in Spain, the sponsor must provide for each trial a report about the exceptional measures adopted which will be sent to the AEMPS and the CEIm

1. Scheduled in-person visits for clinical trial patients

The sponsor, together with the investigator, must consider the advisability of **postponing said visits**, or **turning them into telephone visits, re-scheduling them on the clinical trial schedule of visits**. It

must be guaranteed that the critical scheduled in situ visits are carried out. In the case of rescheduling visits, these protocol deviations will not be considered serious non-compliance unless they put the patient's safety at risk.

2. Recruitment of new patients

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

In the case of a **discontinuation of the trial that involves the stopping of the treatment on some patients,** the sponsor will have to **notify said measures as "urgent safety measures"** explaining the measures adopted to guarantee the alternative treatment of the patients by sending **an ad hoc report** to the **AEMPS and Ethics Committee (CEIm)** in the **15 days following the discontinuation or finalisation**.

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, preservation of the treatment must be ensured during transport, and communication with the patient, allowing treatment reception and appropriate administration of the same must be maintained. Section 10 of the document "Q&A: Good Clinical Practice (GCP)" – GCP Matters" will be taken into account. The situation must be assessed in each particular case, by the sponsor, the principal investigator and the Pharmacy Department.

4. Monitoring visits

It is advisable for the sponsor to **update monitoring plans for the trial for the next four months, giving priority to centralised monitoring and remote monitoring of the participating** sites that do not **involve the overloading of tasks on the site staff nor the review of source data and postponing as far**

as possible the verification of source data until able to access medical records in person. The sponsor will agree conditions for said monitoring with the participating sites and teams.

5. 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.

6. Clinical trials aimed at researching new drugs against coronavirus

The AEMPS, together with CEIms, **is prioritising the assessment of clinical trials aimed at treating or preventing disease due to coronavirus**. Sponsors or investigators who have a research project of this type must send a message to Clinical Trials Area indicating in the subject line: URGENT new CT COVID19. A response will be given on the same day.

ITALY

The Italian Medicines Agency (AIFA) provides indications regarding the management of clinical trials in Italy during the COVID-19 (coronavirus disease 19) emergency, valid until further notice.

"Clinical trials' management in Italy during the COVID-19 (coronavirus disease 19) emergency",
12 March 2020

1. Submission of clinical trials and substantial amendments

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

- As regards authorization requests of clinical trials and substantial amendments submitted by the OsSC, the postponement of paper documentation and CD-rom sending referred to in the AIFA communication of 1st August 2019 (https://www.aifa.gov.it/-/aggiornamento-lettere-per-l-autorizzazione-di-sperimentazioni-cliniche-e-relativi-emendamenti-sostanziali) is allowed.
- It is anyway recommended, whenever possible, to apply the stamp duty on the transmission letter by virtual payment (except in the cases provided for in article 17 of the legislative decree n° 460/1997 and in article 82, par. 5 of the legislative decree n° 117/2017) and to digitally sign the letter uploaded in the OsSC.
- Paper documentation and CD-rom will have to be sent to the Clinical Trial Office as soon as possible.
- In case the submission via OsSC is not possible and paper transmission is needed as provided for in the AIFA communication of 2nd October 2018 (https://www.aifa.gov.it/-/attivazione-nuova-piattaforma-ossc-aggiornamento-02-10-2018-), transmission by e-mail will not be accepted.
- Exception is made only for the submission of clinical trials regarding treatment of COVID-19 (coronavirus disease 19): authorization requests are allowed to be submitted by mail to apa@pec.aifa.gov.it and related documentation can be sent via Eudralink or similar ways within the same e-mail.
  Please note that, in this case, the whole authorization process of such requests will continue by e-mail and the Applicant is requested to return in the OsSC as soon as possible, as provided for the temporary paper management (AIFA communication of 6th August 2018: https://www.aifa.gov.it/documents/20142/871583/comunicazione_OsSC_06.08.18.pdf/20bdd0c0-d754-817c-93ac-ca7b0476f1e5).

2. 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.

3. Management of clinical trial activities outside investigational sites

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

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

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

- **Investigational medicinal product (IMP) management**

If possible, when the patient goes to the study site for a visit, it may be useful to provide an amount of medicinal product covering a longer period of time than is normally estimated.

According to current legislation (article 7 of the Ministerial Decree 21st December 2007), the Sponsors must send investigational drugs needed for the trial to the pharmacy of the investigational site, that is in charge for their registration, appropriate storage and delivery to the investigator. Therefore, considering the COVID-19 serious emergency, even if the priority mode remains the delivery to the hospital pharmacy that then proceeds to the subsequent delivery to the investigational centre, direct deliveries from the hospital pharmacy to the trial subjects also through dedicated couriers can be arranged, upon indications of both the hospital pharmacy Director and the Principal Investigator (PI). It is intended that the hospital pharmacy is responsible for the process supervision; the pharmacy and the PI must be constantly informed on the delivery, according to procedures established for the correct conduction of the trial and by the above-said risk plan, that must take into account the IMP typology, administration methods, conservation and transport. Adequate remote communication ways with

involved subjects must be implemented to replace the information that will no longer be provided in person. Depending on the case, telephone and/or video call can be used to inform the patient, where deemed necessary. Adequate tracking of what is being implemented in this emergency situation is recommended. All this without prejudice, if possible, to conditions set out in FAQ 10 of the EMA Document "Q&A: Good clinicalpractice (GCP)" – GCP Matters (https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-clinical-practice/qa-good-clinical-practice-gcp).

If the CRA of the study is not able to carry out the control on the final accounting of the investigational medicinal product for the purpose of reconciliation, and this operation is considered as impossible to be postponed, it can be carried out by a pharmacist of the hospital pharmacy or by the study coordinator/data manager, appropriately trained. The IMP can be returned to the Sponsor directly by the hospital pharmacy.

- **Clinical examinations**

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

- **Sites closing**

If a site is closed to the public for COVID-19 containment measures, it **should be carefully assessed if the clinical trial staff is able to guarantee the continuity of the trial itself**. **In case the site is unable to follow the patients undergoing the trial**, **the study should be temporarily halted or, where possible, enrolled patients should be transferred to the nearest active trial site**. Information exchange between PIs must be assured, as well as the transmission of clinical documentation and other trial material (e.g. IMPs) between sites. Contacts between Sponsor and health structures involved must be updated according to new agreements.

A **site not authorized to participate** in the specific clinical trial **is not considered as suitable as back-up**, since it is not active, it does not know the trial and could not ensure a proper therapeutic continuity for the patient.

- **Clinical trial monitoring**

By analogy with what stated in the previous paragraph, Sponsors are invited to draw up a risk evalutation plan and **implement an action plan** taking into account the need to reduce unnecessary contacts in this period of COVID-19 epidemiological emergency. First of all, it should be assessed **whether in-situ monitoring visits can be replaced by an enhanced centralised monitoring or whether such local visits can be postponed.**

Exceptional methods such as telephone contacts or, even better, **videoconferences with the trial site staff can be implemented for the purpose of source data verification.** These methods must be **described in a specific SOP by the Sponsor/CRO and must be evaluated and approved by the Personal Data Protection Officer of the trial site.**

Other unusual monitoring methods involving more **risky ways of accessing sensitive data,** such as **video recording of source document or making available to monitors original documents in shared electronic areas, must always be agreed with the Personal Data Protection Officer of the hospital, but it is considered appropriate that a specific opinion by the Italian Data Protection Authority be obtained.**

- **Possibility for the Sponsor to sign contracts directly with specialized service agencies/companies (e.g. home nursing services) to carry out activities related to clinical management of patients falling under the Principal Investigator's (PI) responsibility**

In reiterating that such **measures should be intended as extraordinary and limited to the coronavirus emergency period,** by way of derogation from the FAQ 11 of the EMA document "Q&A: Good clinicalpractice (GCP)"–GCP Matters (https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-clinical-practice/qa-good-clinical-practice-gcp), the Sponsor is allowed to sign contracts directly with such specialized agencies/companies. All other indications in the afore-mentioned FAQ remain applicable, such as for example:

− the need that the PI remains responsible for the supervision

− that efficient communication contacts are established between the staff in charge and the PI

− that the staff in charge is suitably trained and that duties and responsibilities are stated in the contract and/or delegation log

− that the protection of data confidentiality is assured.

- **Possibility of exceptional expenses reimbursement**

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

PORTUGAL

INFARMED

INFARMED, I.P. has provided 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", *26 March 2020.*

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 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

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.

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 recruitment

In the current context, it is recommended to suspend the recruitment activity, whenever it justifiably carries an additional risk of SARS-CoV-2 infection for the patients to be recruited.

In addition, there may be a need for immediate interruption of study treatment, whenever the safety of the participants is at stake.

In such cases, of which we highlight particularly clinical trials involving populations undergoing immunosuppression due to the treatment instituted, as well as other therapies that may constitute an intolerable risk, whenever treatment interruption is performed, in part or in all of the participants, it is up to the Sponsor to notify Infarmed, with an "urgent safety measure", to be submitted as soon as possible, with detailed explanation of the context, and of the measures.

B. 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.

C. 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, and compliance with Good Clinical Practices in this matter, and the General Data Protection Regulation, must be guaranteed.

D. Direct dispensing at home of experimental drugs

Given the exceptional circumstances, the home dispense may be accepted, based on the following premises:

- 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 trial center must be closed, 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 research 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".

E. 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)

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.

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.

- Notification (NSA) to CEIC is not required, but must be obtained the participant's consent by normal means as soon as the participant returns to the test center.

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 the safety and well-being of participants must 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

LeonResearch

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