FindMeCure TrialHub

Guidance on the Management of **Clinical Trials during the COVID-19 (Coronavirus) Pandemic**

Country Report

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Overview

2020 began with a surprise for many people, industries and governments. The coronavirus outbreak turned the world upside down and became a global threat the likes of which we hadn't experienced for ages. Unfortunately, the clinical research industry was also impacted severely mostly due to the social distancing measures recommended by national and global organisations and the risk of people getting infected when visiting a hospital, interacting with study teams and other patients or travelling in public transport. This resulted in halting many recruitment activities in the countries until further notice and cancelling patient visits while clinical trials are on hold.

It didn't take much time until the regulatory agencies issued guidance with regards to the conduct of clinical trials during the COVID-19 pandemic. This prompt action taken by both the European Medicines' Agency (EMA) and the U.S. Food and Drug Administration (FDA) was in direct response to global concerns around assuring the safety of clinical trial participants, maintaining compliance with good clinical practice (GCP) and minimizing risks to trial integrity during this unprecedented time.

These latest regulatory guidelines permit sites, sponsors and CROs to adjust their study operations to navigate the crisis during the pandemic, however, there are conditions that must be met in order for new solutions to be considered.

Following are the key recommendations from EMA and FDA, and how countries adapt to these and the situation in their local guidelines.

European Medicines Agency (EMA)

For ONGOING TRIALS, the commission suggests:

- Replacement of physical visits should be replaced with phone or video sessions where possible.
- Suspension of further recruitment.
- Closing of sites and possible postponing of trials in affected locations.
- Transfering of participants to investigational sites that are away from risk zones or closer to the patient's home.
- Using local laboratories, outside of the trial facility, to complete critical laboratory tests, imaging, and other diagnostic tests if the patient is unable to get to / unsafe at the facility hosting the trial.
- Considering changes in the distribution of investigational medicinal products (IMPs) to protect the safety and well-being of trial participants and the integrity of the clinical trials. The recommendation takes into account social distancing measures and possible limitations in trial site/hospital resources, all in order to avoid treatment interruptions.
- Remote source data verification (SDV) will only be considered for clinical trials involving products to treat or prevent COVID-19 or, in the final data cleaning steps, for pivotal trials of products for serious or life-threatening conditions that lack sufficient treatment options.
- How to communicate to the authorities urgent actions to protect trial participants against any immediate hazard or other changes with an effect on patient safety or data robustness. Additionally, a set of examples is given to clarify how to classify mitigating measures.

All measures will be used exclusively during the coronavirus pandemic, and will be revoked once the current health crisis in the EU/EEA has been surpassed.

The Guidance has been agreed by:

The Clinical Trials Expert Group (CTEG) of the EC, the Clinical Trials Facilitation and Coordination Group (CTFG), and the Good Clinical Practice Inspectors' Working Group.

The entire text of the Guidance can be found here.

US Food and Drug Administration (FDA)

The FDA has also released guidance on what sponsors should be considering in order to maintain compliance with Good Clinical Practice while ensuring COVID-19 exposure and safety risks for trial participants are minimised.

The **FDA Deputy Commissioner for Medical and Scientific Affairs**, Dr Anand Shah said: "*The FDA is helping industry and investigators navigate the COVID-19 pandemic and assess how to move forward with critical clinical trials. The FDA released this guidance to emphasise that at all times, patients' safety should continue to be at the forefront of considerations. We want to support the continuance of these clinical trials in compliance with good clinical practice and minimising risks to trial integrity, while also safeguarding the health and well-being of study participants.*"

FDA considerations for ONGOING TRIALS:

- Sponsors, in consultation with clinical investigators and Institutional Review Boards (IRBs) / Independent Ethics Committees (IECs), should determine whether the participant's welfare is best served by continuing in the trial as per the protocol or by discontinuing the use of the IMP or participation in the trial. This will be dependent on circumstances, such as the ability to conduct appropriate safety monitoring, the potential impact of COVID-19 on the IMP supply chain and the nature of the disease under study in the trial.
- Alternative methods for safety assessments should be evaluated as patients may not be able to get to the investigational site; however, they must be sufficient to assure the safety of trial participants. Sponsors should determine if in-person visits are necessary to fully assure the safety of trial participants.
- COVID-19 screening procedures required by the healthcare system do not need to be reported as a change of clinical protocol.

- Changes in protocol that typically require review and approval by the IRB/IEC or FDA may be implemented without if they minimise or eliminate immediate hazards or protect the life and well-being of participants but must be reported afterwards.
- Home delivery of certain IMPs by secure delivery methods is allowed, if scheduled visits at clinical sites will be significantly impacted by COVID-19.
- The guidance also provides considerations for situations where patients are unable to travel to a trial site to receive investigational products that need to be administered via infusion, providing recommendations for documenting changes in trial protocol and shipping investigational products to health care providers.
- The FDA recommends reviewing the protocol for the collection of data regarding efficacy endpoints, such as use of virtual assessments, delays in assessments, and alternative collection of research-specific specimens, if feasible. If the efficacy endpoint data is not collected, the reasons for failing to obtain the efficacy assessment should be documented.
- **When investigators do not have electronic informed consent capabilities**, they may use other methods "*if those methods allow for an adequate exchange of information and documentation, and a method to ensure that the signer of the consent form is the person who plans to enroll as a subject in the clinical investigation or is the legally authorized representative of the subject*." FDA says this could be achieved via fax or email, with consent interviews taking place by phone.

FDA considerations for COVID-19 IMPACTED TRIALS:

- Clinical Study Reports (CSRs) must include any contingency measures that are implemented, as well as analyses and discussion of the impact of the implemented measures on safety and efficacy reporting.
- CSRs must also provide a list of all participants affected by COVID-19, including a description of how they have been influenced.

The entire text of the Guidance can be found here.

How do countries respond to the COVID-19 pandemic in their national regulatory guidelines?

Key highlights on the national regulatory guidelines of popular for clinical trials countries.

*** Note:** *We have only listed those countries from a region where information is available.*

North America

United States. Canada

USA

Authority:
US Food and Drug Administration (FDA)
Reference:
FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic

- **Ensuring the safety of trial participants is paramount**.
- Sponsors should consider each circumstance, focusing on the potential impact on the safety of trial participants, and modify study conduct accordingly. Study decisions may include those regarding continuing trial recruitment, continuing use of the investigational product for patients already participating in the trial, and the need to change patient monitoring during the trial. **In all cases, it is critical that trial participants are kept informed of changes to the study and monitoring plans that could impact them.**

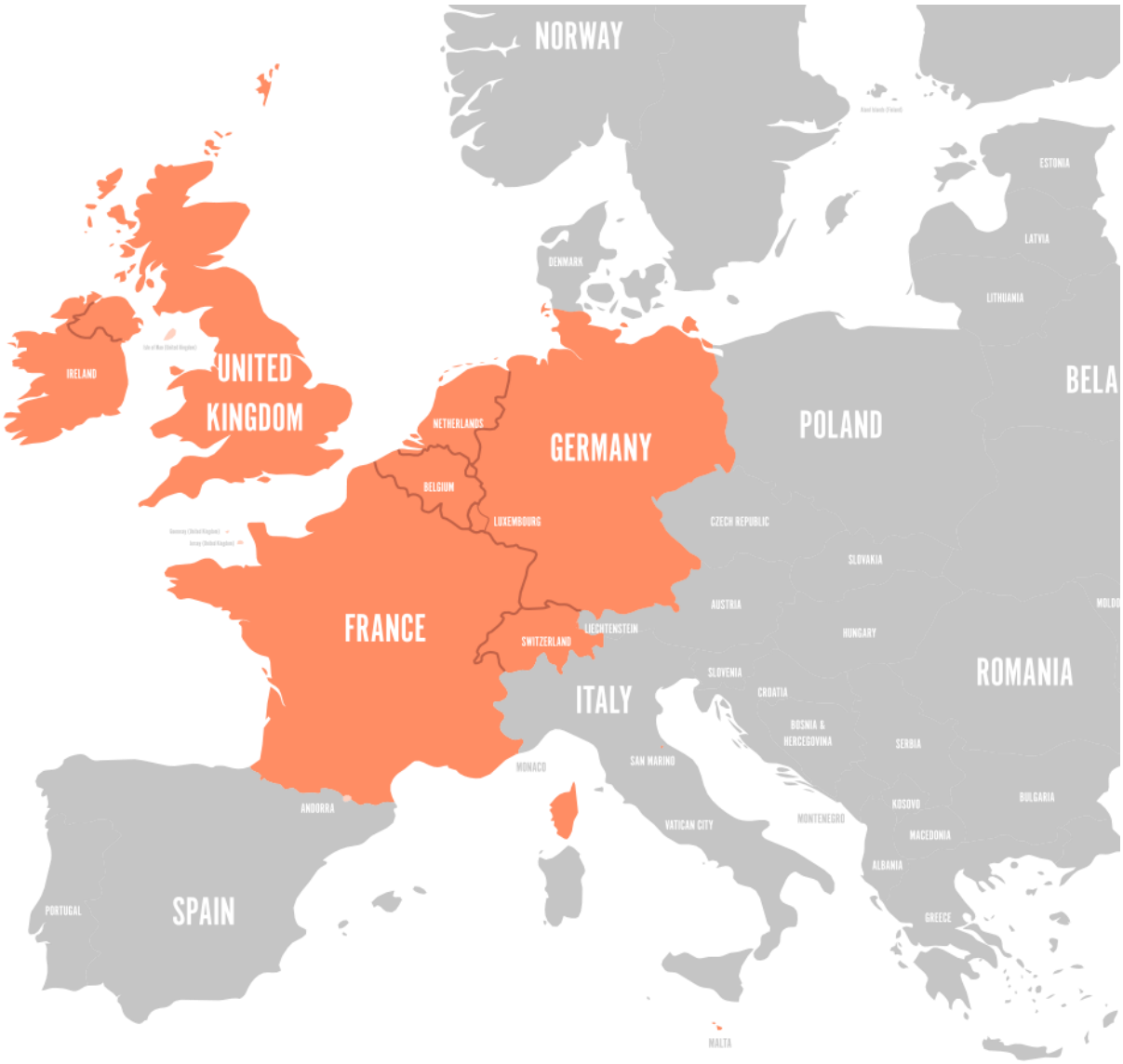
Canada

Authority:
Health Canada
Reference:
Management of clinical trials during the COVID-19 pandemic: Notice to clinical trial sponsors

- As per paragraph C.05.010(b) of the Food and Drug Regulations (FDR), the sponsor must ensure that the clinical trial is conducted in accordance with the requirements of the protocol, which has been authorized by Health Canada and approved by REB(s). **Health Canada recognizes that there may be an increase in protocol deviations during the COVID-19 pandemic**.
- **Halting recruitment or temporarily halting the trial may be required in some circumstances**. If this happens, sponsors are to inform Health Canada using a clinical trial application notification (CTA-N).

Western Europe

Austria. Belgium. France. Germany. Ireland. Luxembourg. Netherlands. UK



Austria

Authority:
Agency for Health and Food Safety (AGES)
Reference:
Update: COVID-19 - Changes for clinical trials

- **All measures taken to protect the participants due to the urgent need for action by the COVID-19 pandemic are to be documented by the sponsor together with a justification and benefit / risk evaluation**.
- These changes should be communicated to the Federal Office as an urgently required security measure (Section 37a (4) AMG) simultaneously with the implementation ("notification"). A substantial amendment is not necessary.
- The notification should be made via e-mail to clinicaltrials@basg.gv.at. "COVID-19" and "urgent safety notification" should be mentioned in the subject. A joint notification for several studies is permitted as long as they are referenced with the EudraCT number in the cover letter.
- After the end of the pandemic situation or at the request of the Federal Office, a summary report on all measures taken in this way must be submitted as a one-off substantial amendment.

Belgium

Authority:
Federal Agency for Medicines and Health Products
Reference:
Addendum to the Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic

A national directive is available to supplement the European guidelines for the management of clinical trials during the coronavirus pandemic. It is the result of collaboration between the FAMHP, the Clinical Trial College, the BAREC (Belgian Association of Research Ethics Committees, Belgian Association of Research Ethics Committees), and several research centers. The national directive is applicable from its publication and supplements the European guidelines.
The national directive will be regularly updated according to the evolution of the pandemic.

These new guidelines should help sponsors of clinical trials manage:

- clinical trials for the prevention or treatment of COVID-19
- ongoing clinical trials in Belgium

Communication with authorities - priority is given to any (new) clinical trial applications for the treatment or prevention of COVID-19 infection, and/or substantial amendment applications and notifications to existing clinical trials necessary as a result of COVID-19.

France

Authority:
Agence Nationale de Sécurité du Medicament et des Produits de Santé (ANSM)
Reference:
Covid 19 - Ongoing clinical trials

NEW TRIALS

- The relevance of initiating new trials must be weighed and priority must be given to trials related to the management of patients infected with SARS-CoV-2. As requested by the World Health Organization, the sponsor must ensure that the title COVID-19 is included in the research title.

ONGOING TRIALS

- For ongoing trials, the situation is unprecedented and should lead all stakeholders to put in place all the necessary measures to ensure the safety of patients participating in research. Adaptation of follow-up conditions could be considered but also an appropriate measure to guarantee, if necessary, the continuation of treatment when the clinical situation justifies it.
- The continuation of inclusions may accordingly be considered in situations of unmet medical need, provided potential risks associated with the risk of concomitant SARS-CoV-2 infection are taken into account.
- For patients already included in a clinical trial with active ongoing treatments, risk evaluation should consider the risk associated with interrupting treatment on one hand, and the risk associated with continuing treatment in an epidemic context, as well as the

strain on research teams on the other hand. Priority must also be given to patients with progressive, life-threatening pathologies.

Communication with authorities - Priority is given to any (new) clinical trial applications for the treatment or prevention of COVID-19 infection, and/or substantial amendment applications and notifications to existing clinical trials necessary as a result of COVID-19.

Germany

Authority:
Federal Institute for Drugs and Medical Devices (BfArM)
Reference:
Approval procedure (COVID-19 clinical trials)

- The European harmonized recommendations will be followed.
- Changes that are necessary due to the pandemic will be given priority. Therefore, a corresponding brief reference to "COVID-19" in the subject line of the cover letter is necessary. If possible, an electronic submission via the European CESP portal is to be performed.
- A separate e-mail address CT-COVID@bfarm.de has been set up for inquiries about clinical trials in the context of COVID-19. It is to be used only for inquiries, not for submitting changes or approval requests.

Ireland

Authority:
Health Products Regulatory Authority (HPRA)
Reference:
COVID-19 Related Human Research – Expedited Regulatory and Ethical Review

- **Expedited Review** - The HPRA, in conjunction with the Department of Health, the National Office for Research Ethics Committees, and the Health Research Declaration Committee (HRCDC), have agreed an expedited review process for human health research related to COVID-19 (SARS-CoV-2, coronavirus). **A key development is the establishment of a dedicated COVID-19 national research ethics committee (NREC-COV19) by the Minister for Health. In the interests of time and resource efficiency, applications for ethical**

review of all human health research studies related to COVID-19 should be submitted to the NREC-COV19. Applications for clinical trials of human medicines, or clinical investigations of medical devices, will be given a priority and expedited review by the HPRA. The NREC-COV19 will review applications concurrently with regulatory review processes and will endeavour to facilitate an expedited ethical review.

- **Submitting Applications** - Applications for clinical trials or clinical investigations should be marked 'COVID-19', and this should be included in the research title. Applications can be sent in parallel to HPRA and the COV19-REC to obtain an expedited national decision. Copy either the HPRA clinical trials (clinicaltrials@hpra.ie) or medical devices (devices@hpra.ie) mailbox when making an application. Also, contact HPRA as early as possible in advance of the submission, to ensure that they can prioritise the application.

HPRA Contacts:

➔ Clinical trials should be submitted through the usual CESP route and copied to submissions@hpra.ie.

➔ For further information, see the *HPRA Guide to Clinical Trial Applications* or contact clinicaltrials@hpra.ie.

➔ Information on clinical investigations of medical devices is available here.

➔ For further information on the HPRA response to COVID-19, visit hse.ie and gov.ie/health-covid-19.

NREC-COV19 Contacts:

➔ All applications for ethical review should be submitted to nationaloffice@nrec.ie. This will be **the central contact point for both the NREC-COV19 and HRCDC**.

UK

Authority:
Medicines and Healthcare Regulatory Agency (MHRA)
Reference:
Managing clinical trials during Coronavirus (COVID-19)

- If **a trial has been halted due to COVID-19**, it does not need to be reported directly to the agency but must be noted on the trial master file, unless there is a direct participant safety issue or a medicines supply issue.
- **Patients can be provided with investigational medicinal products (IMPs) at home** if they cannot get to the trial site. However, verbal consent to giving shipping information, a risk assessment, and all necessary posting/storage requirements must be completed. If the patient is unable to sign for the package, a follow up phone call is required to ensure the IMPs were successfully delivered.
- **Remote monitoring is encouraged**: replacing in-person visits with phone or video calls and reducing the number of monitoring visits, but consent must be given for trial operators to remove sensitive information from the trial site or access it remotely.
- **Reporting of serious adverse events and submission of annual safety reports and end of trial notifications** should be made as promptly as possible, especially if participant safety is at risk or the event has the potential to impact participants of other trials.
- **Protocol deviations are expected** as patients may need to self-isolate or be unable to travel to trial sites. However, they must be well documented in order not to constitute a serious breach.
- **Protocol waivers are still unacceptable**.

Southern Europe

Greece. Italy. Spain. Portugal

Greece

Authority:
National Organisation for Medicines
Reference:
Announcement

- As part of precautionary measures to prevent the transmission of COVID-19, the National Organisation for Medicines recommends **limiting visits to the absolutely necessary**, i.e., those that cannot be processed by telephone or e-mail.

Italy

Authority:
National Institute of Health
Reference:
COVID-19 emergency: instructions for requesting pre-submission hearings for Phase 1 clinical trials in the attachments on this page

- In order to provide users with technical-scientific support for the submission of Phase I and I / II Clinical Trials Applications, the Technical-Scientific Secretariat and the experts of the Commission in charge are available to grant pre-submission hearings in a videoconference mode.
- Hearing requests must be sent to the Secretariat of the Commission (by e-mail to mariafrancesca.cometa@iss.it and for information to segreteria.commac@iss.it), using the facsimile of the application.
- **Requests must be accompanied by a summary report (of maximum 30 pages) and the list of questions that are intended to be addressed to the experts of the Commission**.
- The report, contained in a maximum of 30 pages, must contain information on:
- The requests received will be examined by the Technical-Scientific Secretariat, which will assess the admissibility of the request. In the event of a positive response, the Secretariat will establish the methods and timing of the hearing and convene the experts who will be present at the hearing.

Portugal

Authority:
National Authority of Medicines and Health Products (INFARMED)
Reference:
COVID-19: Exceptional measures in the scope of testing Clinicians during the period of risk to public health (Version 2 dated 04/15/2020)

ONGOING TRIALS

In this context of a public health emergency, the set of measures presented below can be implemented immediately, without requiring notification or approval prior to substantial changes, with the exception to "*Treatment Discontinuation*", which must be notified as an urgent safety measure. These recommendations are also applicable to clinical studies with medical devices or cosmetic products:

- **Treatment Discontinuation** - There may be a need for immediate interruption of study treatment, whenever that the safety of the participants is at stake. In such cases, an "urgent safety measure" notification is to be submitted as soon as possible with a detailed explanation of the context and of the precautions taken to ensure alternative treatment of participants.
- **Suspension of Recruitment** - Each sponsor should analyse the feasibility of starting a new clinical study under current conditions. Further, a risk analysis for each ongoing clinical trial against the characteristics of the tests, the population to recruit, the research centre, and the risk epidemiological data. In this sense, the suspension of the recruitment is allowed whenever the same justifiably carries an additional risk of SARS-CoV-2 infection for patients.
- **Scheduled Visits** - The sponsor should assess the need to review the visit plan adopted in the protocol of the study. **Conducting remote visits, using telephone calls or other means (telematic) technologies, is possible**, and the collection and registration of all information planned for the visit in question (including the method of conduct and the identification of the research team member responsible for carrying it out). **It must be ensured that the use of telematic means is permitted 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 testing centre by the team member who collects that consent, or, for example, by e-mail (video or sound registration is also

accepted). **Must be subject to confirmation by signature of the participant, once the current situation is normalized.**

- **Centralized Monitoring** - Conducting centralized monitoring visits, based on a risk assessment, is allowed and encouraged. Reducing monitoring activities to what is possible remotely, even if this implies delaying the review of source data, for when it is possible to have access in person and in agreement with the test centre and principal investigator. **Centralized monitoring cannot imply the retention of source documents or access to personal data by unauthorized persons. Likewise, remote access to patients' clinical data, recorded in computer systems belonging to the trial centre, can only be accessed if they guarantee compliance with Good Clinical Practices in this matter, and the General Data Protection Regulation.**
- **Breakdown of Supply of IP** - A reserve stock for participants, for a minimum of 3 months is to be guaranteed. In cases where this is not possible, evaluation on the possibility of suspending the recruitment of participants is to be done.

NEW TRIALS

- 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).
- Applicants must submit the study through RNEC, clearly identifying the scope of COVID-19, and send an e-mail to INFARMED (trials.clinicos@infarmed.pt) and CEIC (ceic@ceic.pt), in order to streamline the process with a view to expeditious approval.

Communication with INFARMED - The preferred means of contact is the e-mail: Ensa.clinicos@infarmed.pt All submissions related to processes prior to the implementation of RNEC, must at this stage be submitted by e-mail.

Spain

Authority:
Spanish Agency for Medicines and Health Products (AEMPS)
Reference:
Exceptional measures applicable to clinical trials to manage problems arising from the emergency by COVID-19

ONGOING TRIALS

- Measures are intended to guarantee the safety and well-being of patients and the traceability of the implemented actions.
- Their application does not require approval by the AEMPS or the CEIm, but they must be communicated once the health crisis of COVID-19 is terminated.

NEW TRIALS

- The AEMPS is prioritizing, together with the CEIm, the evaluation of clinical trials aimed at treating or preventing coronavirus disease. Sponsors or researchers who have a research project of this type should send a message to the Clinical Trials Area indicating in the subject: URGENT NEW COVID-19 CT. An answer will be given on the same day.

Contacts for queries related to AEMPS recommendations:

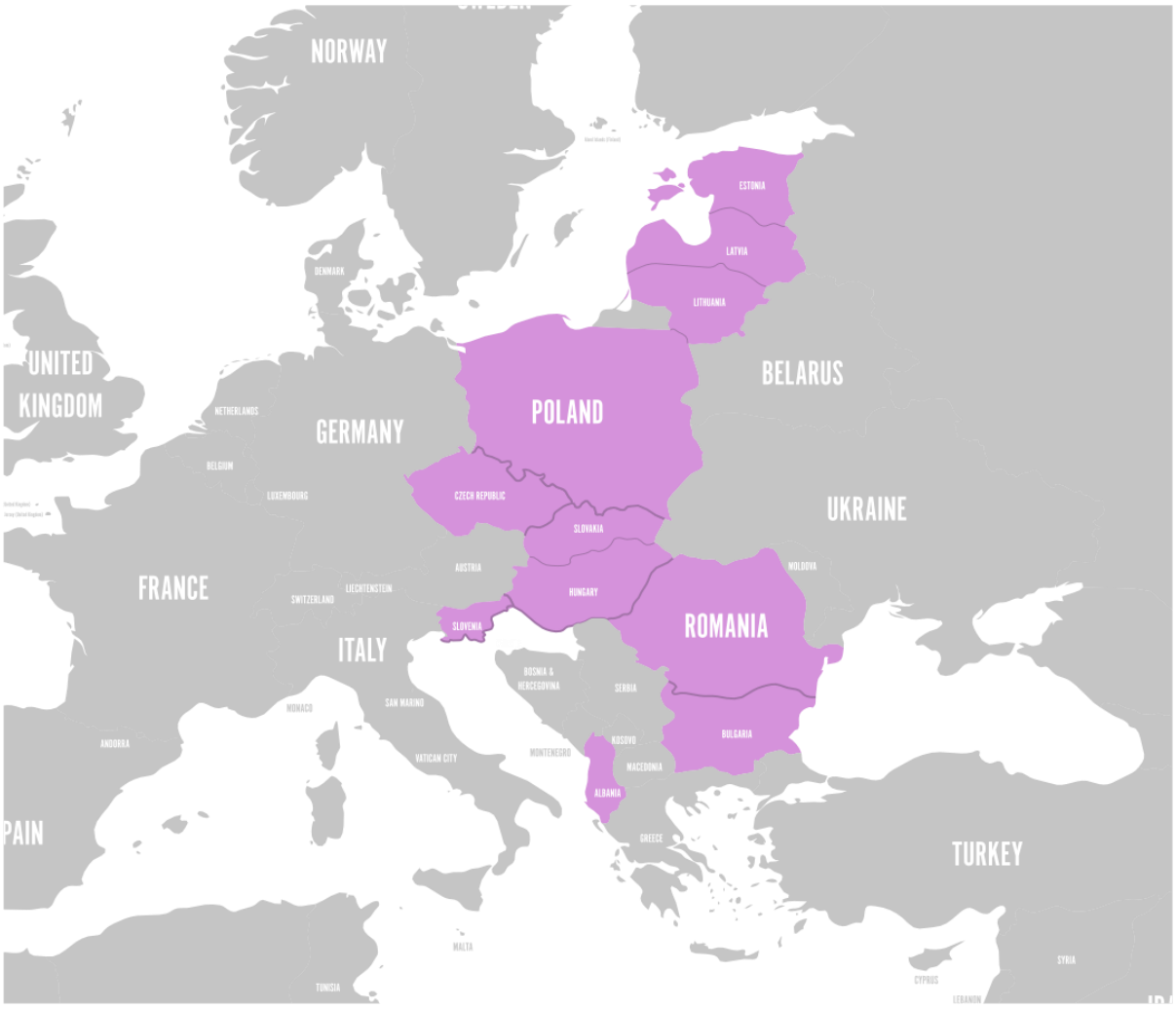
➔ Department of Medicines for Human Use: Clinical Trials Area - aecaem@aemps.es

➔ Department of Inspection and Control of Medicines: Area of BPC and BPFV - area_bpc_bpfv@aemps.es

In all coronavirus related cases, URGENT COVID-19 should be indicated and priority will be given to these answers.

Central And Eastern Europe

Albania. Bulgaria. Croatia. Czech Republic. Hungary. Poland. Romania. Slovak Republic. Slovenia. Estonia. Lithuania. Latvia



Bulgaria

Authority:
Bulgarian Drug Agency (BDA)
Reference:
Guidance for sponsors conducting clinical trials (related to COVID-19 pandemic)

- Allows for electronic submissions (for the duration of the crisis) of certain documentation:
  - ➔ Notification of change of an Investigator (not PI)
  - ➔ Notification of an updated insurance certificate
  - ➔ Notification of recommendations from an independent data evaluation committee
  - ➔ CT Progress Report
  - ➔ Annual Safety Report

Czech Republic

Authority:
State Institute For Drug Control (SÚKL)
Reference:
Supplementary opinion of the SÚKL Clinical Trials Department on ongoing clinical trials in connection with the current epidemiological situation with COVID-19 of 16 March 2020, updated 18 March 2020

With regard to the conduct of ongoing clinical trials or to-be-commenced clinical trials in view of the current coronavirus epidemiological situation, SÚKL provides its general recommendations for those cases when the sponsors propose and plan their own measures aimed at patient/trial subject safety in relation to the globally serious situation - **always ascertain the trial subject's situation in advance by phone**.

- **Applications for authorisation/notification of clinical trials on COVID-19 shall be assessed as a priority in abbreviated timelines**. SÚKL have resumed their involvement in VHP procedures. Acceptance of involvement as a Reference Member State will be addressed with regard to current capacities and workload of all of SÚKL's concerned assessors. Any other applications for clinical trial authorisation/notification will be assessed as usual.
- Recommendations for **ongoing or authorised clinical trials**:

- ➔ **Initiation visits for trial subjects newly enrolled in ongoing clinical trials** - Where the sponsor evaluates the risk/benefit ratio for newly enrolled patients as favourable for enrolment in the study, the initiation visit has to be organised at the trial site, taking into account all of the conditions (COVID-19 medical history, phone arrangements for the time of the visit, provision of protective equipment to the patient and healthcare staff). During the initiation visit to the trial site, the investigator, in an interview with the patient, shall explain everything regarding the clinical trial and shall obtain a signed informed consent from the patient.
- ➔ The initiation of COVID-19 clinical trials and the enrolment of new trial subjects to such clinical trials shall be conducted in compliance with the approved documentation without further limitations.
- ➔ If **a trial subject's participation in a clinical trial is terminated** (early termination or regular completion) and the patient is not to come to the trial site any more, it is possible to organise the collection of unused study medication from the trial subject by a courier service. Everything has to be properly recorded in the clinical trial documentation.

- **Informed Consent Form** / Patient Information Sheet
  - ➔ In case that the trial subject should be informed, SÚKL does not recommend delivering the information through ways other than “personal contact”.
  - ➔ In case an amendment to the Patient Information Sheet (PIS) / Informed Consent Form (ICF) or an updated version of the Patient Information Sheet/Informed Consent Form is issued, it is necessary to submit this PIS/ICF amendment or updated version of the PIS/ICF to SÚKL and to the ethics committee for approval prior to its use in the clinical trial. An exception to this rule shall be PIS/ICF amendments or PIS/ICF updated versions containing safety information that need to be communicated to trial subjects as soon as practicable. In such a case, PIS/ICF amendments or PIS/ICF updated versions shall be presented to trial subjects as soon as possible and thereafter shall be notified to SÚKL and to the ethics committee. A PIS/ICF amendment or updated version may be sent to the trial subject by e-mail or post, but it is not possible to require that a document delivered in this manner be signed and the signed document be returned by post or a scan of

the signed document be returned by e-mail. In case e-mail is used, the investigator/study team member shall ask the trial subject to acknowledge the receipt of the document and shall enter this fact to the CRF, and shall add the e-mail to source documentation. If the document is sent by post, the investigator/study team member shall check the receipt of the document by phone and shall enter this fact into the CRF and source documentation. During the next visit, the trial subject shall sign the PIS/ICF amendment or updated version, date it with the study visit date, and confirm that he/she was familiarised with this document.

- Initiation of **newly authorised clinical trials / recruitment of new trial subjects (patients) -** The commencement of newly authorised clinical trials and the enrolment of new trial subjects (patients) in ongoing clinical trials must be considered by the sponsor very carefully, always reviewing the risk/benefit ratio. To protect the safety of the trial subjects, SÚKL recommends not to:

  ➔ Commence new clinical trials or enrol new patients/trial subjects in ongoing clinical trials wherever that pose a risk to trial subjects and in clinical trials the initiation of which is not currently necessary with a view to the current epidemiological situation.

  ➔ Where the enrolment of new patients to clinical trials is resumed, the sponsor shall be obliged to send this information to SÚKL and to the ethics committee together with an evaluation of the risk/benefit ratio for the newly enrolled patients in light of the current situation in the concerned trial site and the concerned location. The notification is not subject to reimbursement for expert activities. SÚKL shall confirm (take note of) the receipt of this information.

  ➔ Conduct clinical trials involving healthy volunteers or “healthy patients”, i.e., such clinical trials that do not provide therapeutic benefit to the enrolled trial subjects, such as bioequivalence or pharmacokinetic studies.

- Sponsors are notified to check the **validity of SÚKL's authorisation/approval for to-date not initiated clinical trials**:

  ➔ In case the expiry of the authorisation/approval of a notified clinical trial is approaching (i.e. 1 year of the date of issue of the authorisation/approval of the clinical trial), it is necessary to reapply for the issue of the authorisation/approval of

a notified clinical trial with SÚKL prior to the expiry date of the application. The handling of such application shall be considered a substantial amendment and is subject to fee.

➔ In case an authorisation/approval of notified clinical trial expires, SÚKL shall not re-issue a backdated authorisation/approval of notified clinical trial and the sponsor will have to submit an application for the issue of a new authorisation/approval of notified clinical trial (resubmission) and cover the full fee for expert activities.

Estonia

Authority:
State Agency of Medicines
Reference:
Guidance on Clinical Trial Management in the Context of COVID-19 Pandemic

- All decisions to adjust clinical trial conduct should be based on risk assessment by the sponsor in cooperation with principal investigators. It is expected that the sponsor performs a risk assessment of each individual ongoing trial and implements measures that prioritise patient safety and data validity. In case these two conflict, patient safety should take priority. The sponsor should reassess risk as the situation develops. This reassessment should also be documented and included in any amendments to the trial.
- The sponsors are recommended to consider temporary halt of recruitment to ongoing clinical trials. Trials that have been approved but have not yet started recruitment should be postponed. Opening additional sites to existing studies should also be postponed. Temporary halt of ongoing trials or withdrawal of individual trial subjects may be appropriate methods of risk mitigation in certain cases.
- All protocol deviations must be carefully documented.
- Where a substantial amendment to the study plan is required due to temporary measures, the amendment should be in the form of a local or global sub-protocol or annex to the existing protocol. There is no need to update the entire protocol. This will hopefully add flexibility to the planning of the trial and help speed up the evaluation process.

- The State Agency of Medicines and the national ethics committees are prepared to evaluate amendments to the study plans in an expedited manner.
- All notifications to the State Agency of Medicines should be sent to trials@ravimiamet.ee and „COVID-19“ should clearly be written in the subject line.
- **Electronic Signatures** - The informed consent document may be signed by an electronic signature as long as it meets the requirements for a qualified electronic signature set out in Article 3 (12) of Regulation (EU) No. 910/2014 of the European Parliament and of the Council.

Hungary

Authority:
National Institute of Pharmacy and Nutrition (OGYÉI)
Reference:
Information on the continuity of clinical trials under COVID-19 (coronavirus) - 25.03.2020

- **General Considerations** - A thorough risk assessment of ongoing investigations should be carried out considering restrictions already applied and expected (quarantine, visitation ban in healthcare institutions, increased burden of the healthcare system, possible supply problems for medicines — IMP and non-IMP, etc.) and measures should be put in place to **prioritise patient safety and data validation. In the event of conflict between these two objectives, patient safety should be prioritised**:
  - ➔ The risk assessment shall be repeated and properly documented, depending on the evolution of the situation.
  - ➔ Changes to trial conduct should be agreed with and communicated clearly to investigational sites.
  - ➔ In cases when obtaining wet ink signature is difficult, agreements may be documented with alternative methods e.g. e-mail exchange.
  - ➔ In case of ongoing studies with populations particularly at risk of coronavirus (immunosuppressant treatment, over 60 years of age, chronic diseases), special considerations should be made regarding the continuation of the study.

➔ **In general, it is considered prudent to stop the enrolment of patients during this period**. In case of temporary halt of recruitment due to COVID-19 notification shall be sufficient and the restart of recruitment is not considered as a substantial amendment either. Notifications can be made within one letter even in case of more clinical studies.

- **Urgent Safety Measures -** When substantial amendments of the study are required in order to ensure the patient's continued participation, the sponsor may do so as an "urgent safety measure" (USM). The change will take effect immediately. The urgent safety measure should be sent to the authority and the amendment should be subsequently, officially authorised in accordance with the usual procedure.
- **Patient Information** - Considering the current situation with its restrictions, in case of ongoing trials, a new informed consent form may be necessary and patients may have to be re-informed. Alternative opportunities for this re-information should be considered, e.g. contacting enrolled subjects via telephone or video-call, and obtaining oral consent followed by confirmation via e-mail. Every consent obtained this way must be documented, and confirmed by the participants with wet-ink signatures as soon as possible, when attending the study site again. **In Hungary, electronic patient information sheets and informed consent forms are not permitted according to the law and that must be followed in the current extraordinary situation as well**.
- **Monitoring Visits** - Sponsor, in agreement with the Investigator, shall consider converting or deferring on-site visits to telephone visits or terminating them on the basis of the risk assessment, in order to ensure that it is strictly necessary visits to the test sites. Currently, OGYÉI does not support visits carried out at the patient's home, because of its limited availability, its negative effect on the spread of the virus, and the disproportionate burden of the investigational staff.
- If any site moves to another settlement of the institution or to another healthcare facility due to the crisis and there the study is continued, OGYÉI only needs to be informed subsequently giving the exact dates of the address change. There is also an opportunity for the investigator to move the patient care to a private practice that has not been marked as a satellite-site before, but the Institute and the Ethics Committee needs to be informed, and subsequently, this needs to be submitted as an amendment.

- **Monitoring** - In order to reduce on-site monitoring, appropriate alternative methods should be selected. Alternative methods shall be decided on the basis of a risk analysis taking into account patient and data security in agreement with the study sites and amended Monitoring Plan on the basis of accepted changes. The choice of alternative methods shall take into account that they do not place a disproportionate burden on the test site and staff. Remote and central monitoring through an EDC system may be an appropriate alternative. It is important to stress out that proper follow-up of these transitional measures after the normalisation of the situation is essential and includes, for example, an increase in the frequency and/or time of on-the-spot monitoring in order to identify and address the possible negative effects of the transitional measures.
- **IMP Management** - The transfer of IMPs between sites, the patient's increased supply with IMPs during on-site visits, or the dispatch of IMP from the site to the patient's home may arise. In case of trials where the patient self-administers the medication at home, transport of IMP and non-IMP (rescue-medication) to patients' home can be considered. In cases like this the responsibility remains with PI. Transportation of IMPs from the site/institution pharmacy is preferred.
- **Hungarian National Competent Authority agrees to make accelerated assessment in case of submissions of COVID-19 clinical trial applications**.

Latvia

Authority:
State Agency of Medicines of Latvia (SAMLV)
Reference:
Possible Changes in the Conduct of Clinical Trials with COVID-19

- When deciding on changes in the conduct of clinical trials, study centers and sponsors should take into account the safety of subjects and the workload of medical personnel. It is also necessary to consider which aspects are critical for conducting and continuing the research. If the necessary amendments are assessed as **urgent safety measures**, they can be implemented without permission by submitting information about them to the SAMLV. **The Agency undertakes to process all applications related to COVID-19**

under an expedited procedure. The sponsor is responsible for assessing the significance of the change, determining whether it should be submitted as a substantial amendment. Any changes in the course of studies related to COVID-19 should be reported to the State Agency of Medicines. Deviations must be well documented.

- The following are general recommendations from the SAMLV on possible solutions for continuing clinical trials in an emergency, but it should be noted that these recommendations are not definitive and should be assessed on a case-by-case basis depending on the type of study and the current situation in a global pandemic:
  - ➔ Changes in the frequency of patient visits should be allowed, taking into account the need to minimize the risk of infection with SARS-CoV-2 virus, which causes COVID-19;
  - ➔ Reduction of the number of patient visits (changes are made to the study schedule), including the dispensing of medicines for a longer period of time;
  - ➔ If there is a risk of infection with the SARS-CoV-2 virus that causes COVID-19 at the study center (e.g., the center treats patients with COVID-19), patients may be visited at another existing study center or a new center may be opened.
  - ➔ Remote visits using communication solutions (telephone or video visit) if permitted by the examinations specified in the visit. This solution is also possible if the subject is quarantined.
- If, for reasons related to COVID-19, a patient is unable to perform laboratory, instrumental, imaging, or other examinations and this would compromise patient safety, exclusion of the patient from the study should be considered.
- The sponsor may decide to discontinue the study or suspend the inclusion of patients.
- Exceptionally, the delivery of an investigational medicinal product to the patient's home , which is provided by the staff of the center in compliance with the conditions for the distribution of medicinal products and the conditions for the transport and storage of investigational medicinal products, shall be permitted. By providing appropriate documentation, it is also possible to redistribute study drugs between study centers if they may be missing at one of the centers. In extreme circumstances, in the event of a critical deterioration of the epidemiological situation, direct delivery of the medicinal

product by courier may be considered, which should be notified to the SAMLV as a major change.

- Remote data checks instead of on-site monitoring visits based on the risk assessment of the specific study are allowed, but it should be noted that **electronic transmission of confidential patient identification information for monitoring purposes is not allowed**.

Lithuania

Authority:
State Medicines Control Agency
Reference:
Ensuring the Conduct of Clinical Trials During the COVID-19 Pandemic

ONGOING TRIALS

- In special circumstances and when subjects are unable to attend study centers for scheduled study visits (e.g. due to self-isolation, impaired access to personal health care facilities, etc.), c**linical trial sponsors and study centers must ensure the safety and continuity of treatment in all cases**. Clients should regularly conduct risk assessments and document decisions made. All measures should be coordinated with research centers.
- **Dispensing of investigational medicinal products (IMPs) to patients outside the study center**:
  - ➔ In order to ensure the uninterrupted provision of IMP to subjects and in the absence of other options, the sponsor may consider with researchers the possibility of delivering IMP directly to patients' homes. In all cases, confidential patient personal data cannot be disclosed, i.e., patients may be provided with IMP only from study centers according to randomisation or other protocol procedures. The sponsor cannot supply IMP to patients directly.
  - ➔ The IMP can be delivered to the patient by the staff of the research center or by the services of a contracted courier company. The sponsor and the center must take all necessary measures to ensure proper transport and storage conditions and traceability of the IMP. Prior to sending or delivering the IMP, the study center staff must inform and obtain the consent of the subject, and the patient must be given

precise instructions on the continued use of the IMP. The procedure for administering the IMP to the patient should be documented in the relevant study documents.

- ➔ Following an assessment of the potential risk, the possibility of delivering IMPs directly to patients should not be considered in early-phase clinical trials where it is necessary to ensure that patients are monitored, including when taking the IMPs. This option should not be considered until the patient has gained sufficient experience with IMP.
- ➔ If necessary and without violating the requirements of the research protocol, the IMP may be transferred from one research center to another in the territory of the Republic of Lithuania. In this case, the sponsor must ensure proper transport conditions and traceability of the IMP.
- ➔ All these measures should be applied only if it is not possible for the subject to perform the procedures specified in the study protocol and to administer the IMP at the study center itself. If the sponsor decides to take these measures, they should inform the Agency of the measures taken at the specific study centers. The information is to be sent at least once a week by e-mail: vvkt@vvkt.lt and Ilonalvanoviene@vvkt.lt.

- If necessary, the sponsor may consider transferring the subject to another study center to ensure the patient's continued participation in the clinical trial. All decisions and actions taken must be documented to ensure traceability and reliability of study data.
- **Monitoring** - It is recommended visits to research centers to be replaced by other means of supervision - telephone calls, central monitoring, etc. **It should be noted that remote verification of source documents where the research center submits the source documents of the subjects electronically or in another way is not acceptable**.

NEW TRIALS

- Lithuanian State Medicines Control Agency will urgently evaluate applications for new clinical trials on investigational medicinal products for the treatment of COVID-19 infection.

Romania

Authority:
National Agency for Medicines and Medical Devices (NAMMD)
Reference:
COVID-19 Information Clinical studies

- In view of the current epidemiological context, it is necessary to take measures for the protection of the population, including patients/subjects enrolled in clinical studies. In this regard, NAMMD requests companies conducting clinical studies in Romania:
  - ➔ to identify the potential impact of the general protection measures against the COVID-19 pandemic on the current activities carried out within each clinical study;
  - ➔ to notify NAMMD regarding the plan of specific measures that are required; these can be considered, on a case-by-case basis, emergency safety measures with immediate implementation.
- In the context of the COVID-19 pandemic, NAMMD informs that they are considering prioritizing the evaluation of clinical studies with drugs for the treatment of COVID-19 infection; depending on the number of requests and the phase of the study (priority has phase III), a term of completion of the evaluation of maximum 7 days is expected. It should be mentioned that NAMMD also supports, for this type of studies, the coordinated evaluation at EU level through the VHP procedure; in this case, the timing of the procedure will be established in agreement with the other Member States.
- In the context of the COVID-19 pandemic, scheduled visits of the subjects enrolled in the clinical studies will not be possible, except in the cases where, on a case-by-case basis, the doctor (the main investigator) will consider it an emergency and any postponement in that case may affect the safety of the subject/patient. In all other situations that are not urgent, NAMMD strongly recommends:
  - ➔ rescheduling visits or replacing them with telephone visits;
  - ➔ identifying solutions for delivering medication at the patient's home;
  - ➔ remote monitoring;
  - ➔ delaying the initiation of new clinical studies or new research centers.

Slovakia

Authority:
State Institute for Drug Control (ŠÚKL)
Reference:
Emergency Measures For Clinical Trials Due to Covid-19

- ŠÚKL assumes that this situation is likely to result in a larger number of deviations from the approved protocol than normal. Hence, clinical investigators are expected to escalate and manage such deviations from the protocol in accordance with their standard procedures; and GCP inspectors will take this into account in future inspections.
- ŠÚKL also considers that there may be a shortage of staff at clinical trial centers. It is important that clinical trial sponsors prioritize critical roles in clinical trials.
- ŠÚKL prioritises all COVID-19 applications and for questions regarding clinical trials.
- It is recommended that changes as a result of COVID-19, which will have a major impact on the benefit-risk ratio of the clinical trial, be treated as '**Urgent Safety Measures**'. In order to protect the participants in the clinical trial, these may be implemented without the approval of ŠÚKL; however, the Agency has to be informed about them at trial-sukl@sukl.sk**.** Together with the notification, the sponsor of the clinical trial should provide a detailed risk assessment. **It should be stressed that patient safety is a top priority and therefore all changes should be based on a thorough risk assessment by the sponsor**.

ŠÚKL Contacts:

➔ E-mail at trial-sukl@sukl.sk

➔ Call at **+421 2 507 01 208**

In all coronavirus related cases, e-mails should be clearly labelled with COVID-19 in the subject line.

Central And South America

Argentina. Bolivia. Brazil. Chile. Colombia. Ecuador. Guyana. Mexico. Paraguay. Peru. Suriname. Uruguay. Venezuela

Brasil

Authority:
Agencia Nacional de Vigilancia Sanitaria (ANVISA)
Reference:
New Coronavirus: Technical Note and Specific Guidelines for Ongoing Clinical Research

ONGOING TRIALS

- The National Health Surveillance Agency (ANVISA) issued a Technical Note providing guidance to sponsors, centers, and researchers on the conduct of clinical research and bioequivalence studies that may be impacted by COVID-19:
  - ➔ **The safety of the participants and the conduct of the clinical trial must be guaranteed with Good Clinical Practice (GCP)**.
  - ➔ It is essential that clinical research participants are informed about changes in the protocol that may affect them.
  - ➔ Due to the travel restrictions of clinical research participants, sponsors should consider whether there are alternate methods for assessment (e.g. telephone contact, virtual visit, alternative site for evaluation, including laboratories or image centers) that can be implemented.
  - ➔ Screening procedures for COVID-19 in clinical research participants need not be reported to the Agency as an amendment of the protocol. This provision applies even if the screening procedures are during scheduled visits, except in cases where the sponsor intends to incorporate data collected on COVID-19 as part of a new research objective.
  - ➔ Amendments to the protocol performed exclusively due to the COVID-19 require authorization from ANVISA. These amendments must also be added in the annual study report.
  - ➔ All measures must be taken in order to protect research subjects, in particular those who are at higher risk. In that sense, there is no impediment from the health point of view to carry out direct delivery of the medication to the patient's home, provided that the participant is properly guided as to the use of the drug. All the necessary records, including proof of receipt, should be made, in order to guarantee the

traceability of all information and the maintenance of adequate transport and storage conditions. All these measures must be reported in the annual study report.

- ➔ If scheduled monitoring visits at the clinical research site are discontinued, sponsors should consider opting for the use of central and remote monitoring to maintain supervision of sites.
- ➔ All the inevitable deviations from the clinical protocol in the face of coping with COVID-19 should be documented.
- ➔ **Efforts to minimize impact on the integrity of clinical research study and to record deviations from the protocol are important**.

- **All COVID-19 research protocols will undergo an expedited review**. This requirement will continue as long as the World Health Organization (WHO) designates COVID-19 as a global public health emergency.

Peru

Authority:
Ministerio de Salud
Reference:
COVID-19: Guidance for Ongoing Clinical Trials

- **Clinical trial initiation, maintenance, and conclusion may continue under the responsibility of the sponsor who may implement strategies to protect research participants**. Any strategies implemented must be communicated to INS by e-mailing (consultaensayos@ins.gob.pe).
- **Scheduled face-to-face visits of clinical trial participants** - The sponsor or his representative, together with the Principal Investigator, shall consider the feasibility of postponing or rescheduling such visits, or transforming them into telephone visits, or rescheduling them into virtual visits. For those cases when this is not possible, the sponsors or their representatives must supply the personal protection elements to minimize the risk of infection and guarantee a means of transport to the patient so that they have minimal contact with other people. **In all cases, access of research subjects to their own medication and procedures must be guaranteed**.
- **Recruitment** - Recruitment may continue based on a benefit / risk assessment that considers the characteristics of the trial and circumstances of participating centers. If

the sponsor decides to interrupt recruitment of new participants in order to avoid unnecessary risks, this should be reported.

- **Access to Trial Treatment** - Patient access to trial medication should be guaranteed under the same conditions stipulated in the approved study protocol. It is recommended that the researcher evaluate the possibility and convenience for a patient to receive an amount of medication to cover a longer treatment period during scheduled visit.
- Any of these exceptional safety measures or others that the sponsor wants to adopt must be duly documented and immediately communicated to the OGITT.

Oceania

Australia. New Zealand

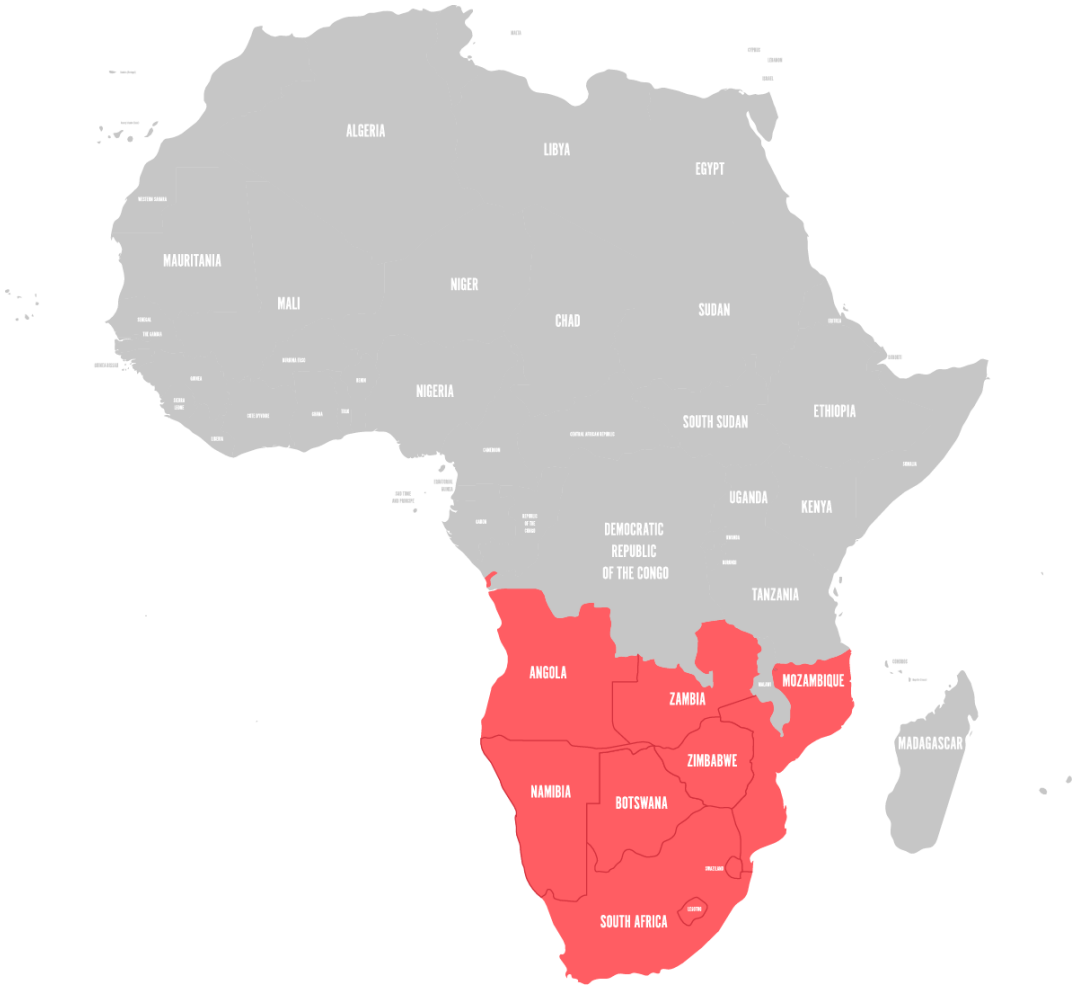
Australia

Authority:
Therapeutic Goods Administration (TGA)
Reference:
Clinical Trial Processes Information relating to COVID-19

- The TGA is giving activities relating to the COVID-19 pandemic the highest priority.
- The purpose of this guidance is twofold:
  - ➔ to assist those overseeing, conducting and reviewing clinical trial research;
  - ➔ to maximise the safety of research participants and to minimise risks to participants and the community, to researchers and other institutional staff, and to trial integrity, and to address prioritisation of clinical trial research.

South Africa

Angola. Botswana. Lesotho. Malawi. Mozambique. Namibia. South Africa. Swaziland, Zambia. Zimbabwe



South Africa

Authority:
Medicines Control Council (MCC)
Reference:
Conduct of Clinical Trials of Health Products during the Current COVID-19 Pandemic

- The South African Health Products Regulatory Authority issued SAHPRA Policy on Conduct of Clinical Trials of Health Products during the Current COVID-19 Pandemic. The guidance covers items such as participant safety, maintaining compliance with good clinical practice (GCP), and minimizing risks to trial integrity.

Supplementary References

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- European Pharmaceutical Review, 2020. COVID-19 update: running clinical trials during the coronavirus pandemic. Available from: <https://www.europeanpharmaceuticalreview.com/article/116456/covid-19-update-running-clinical-trials-during-the-coronavirus-pandemic/>. [7 April 2020].

- GOV.UK, 2020. MHRA guidance on coronavirus (COVID-19). Available from: <https://www.gov.uk/government/collections/mhra-guidance-on-coronavirus-covid-19>. [23 April 2020].

About FindMeCure and TrialHub

The Bridge Between Patients and Clinical Trials

FindMeCure is a TA-agnostic platform allowing patients and caregivers to volunteer for clinical trials and engage with sites. This allows sponsors to provide excellent support to volunteers for their clinical trial while boosting patient recruitment. So far 620,000 patients have searched for clinical trials through the FindMeCure infrastructure.

We understand the **industry's need for fast, accurate and condition-specific data**, therefore we created **TrialHub**

TrialHub provides real-time Intelligence on country feasibility and patient recruitment:

- over 335 000 clinical trials analysed for competition, enrollment, and country capacity
- database of more than 1 million investigators in 70 countries
- country-specific patient pathway mapping
- direct-to-patient channels assessment

For more information:

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