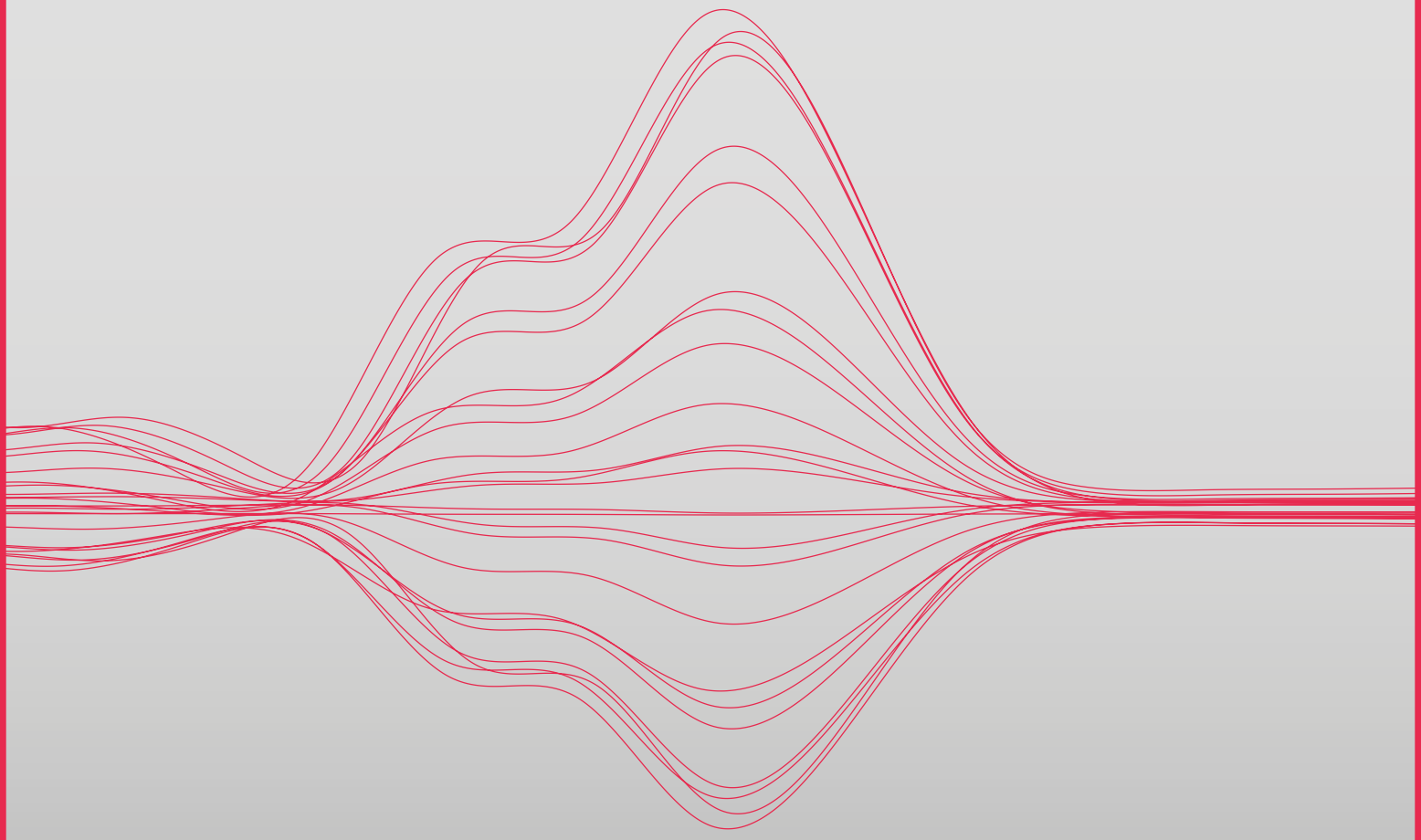
A GLOBAL GUIDE TO

Managing clinical trials during the COVID-19 pandemic

SECOND EDITION



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Introduction

Many countries are starting to emerge from the COVID-19 pandemic lockdown, whilst other have been retaining or even imposing new restrictions. The consequences of these restrictions continue to affect the conduct of clinical trials globally. Pharmaceutical companies are now facing even more challenges in order to adapt and ensure continuity of clinical trials on human medicines: from continuing difficulties in accessing trial sites, to limited trial staff availability, all the way to disruptions in the global supply chain causing constraints in the provision of investigational medicinal products (IMPs) to trial subjects. These challenges not only lead to difficulties in meeting the strict clinical trial protocol requirements, but also delay the conduct of clinical trials and the market entry of innovative therapeutics, affecting the financials of companies undergoing the lengthy, costly and risky process of R&D.

Regulators across the world have introduced temporary derogatory regimes and issued guidance to assist sponsors, investigators and other stakeholders in ensuring continuity of clinical trials, safety of trial subjects, and integrity of trial data during the COVID-19 pandemic. Some medicines agencies have also lowered the requirements for protocol amendments and facilitated e-communication. While the appropriate measures to be taken in a specific trial may vary depending on many factors, sponsors should generally consider the following measures when appropriate: (i) transfer of trial subjects away from risk zones to trial sites that are closer to their homes; (ii) conversion of on-site visits into telephone or video visits; (iii) direct supply of IMPs to trial subjects' homes (including the provision of larger amounts of IMPs than normally foreseen); and/or (iv) conversion of on-site monitoring into remote monitoring.

Moreover, although the measures taken by medicines agencies across the globe vary, they all aim at ensuring the rights, safety and wellbeing of trial subjects. Therefore, any actions taken by sponsors to manage clinical trials during the COVID-19 pandemic require continuous critical risk assessment and, where appropriate, pragmatic actions in the best interest of trial subjects.

This global guide aims at assisting trial sponsors and other interested readers to navigate through the patchwork of measures adopted by governments and regulators globally. While the situation remains highly dynamic, in this second edition we present the regulatory environment in more than 50 countries worldwide, with additions in Africa and the Asia-Pacific region.

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Egypt

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Which measures should be taken to ensure the supply of investigational medicinal products (IMPs)?	N/A
How should clinical trials be monitored?	N/A
How should protocol amendments be managed and communicated to competent authorities?	N/A
When should the initiation, continuation, halt, suspension or extension of clinical trials be considered, and which criteria apply?	N/A

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Ghana

Have competent authorities issued any guidance?	To date, no specific guidance regarding the management of clinical trials during the COVID-19 pandemic has been issued. However, the Food and Drug Authority Ghana (FDA) put in place guidelines for the conduct of clinical trials during emergencies. The guidelines are accessible here.
How should the closure/new opening of trial sites, the transfer of patients to other trials sites and/or diagnostic tests be handled?	N/A
How should investigational visits be managed?	FDA recommends alternative methods of investigational visits by observing all the social distancing rules. Sponsors and investigators may consider virtual and telephone conversations to minimize physical contact.
Which measures should be taken to ensure the supply of investigational medicinal products (IMPs)?	N/A
How should clinical trials be monitored?	N/A
How should protocol amendments be managed and communicated to competent authorities?	N/A
When should the initiation, continuation, halt, suspension or extension of clinical trials be considered, and which criteria apply?	Sponsors may suspend clinical trials for reasons relating to COVID-19. Sponsors must inform the FDA of such a decision.

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Nigeria

Have competent authorities issued any guidance?	The National Agency for Food and Drug Administration and Control (NAFDAC) issued a "Guidance to sponsors of clinical trials in Nigeria including COVID-19 related trials" (Guidance). The Guidance is accessible here. On March 29, 2020, NAFDAC also published on its website notes to serve as an additional guide to all parties involved in clinical trials in Nigeria during the COVID-19 pandemic (Notes). The Notes are accessible here. The Notes apply in addition to the other documentation/regulations on clinical trials, which include Guidelines for Conduct of Clinical Trials during Emergencies.
How should the closure/new opening of trial sites, the transfer of patients to other trials sites and/or diagnostic tests be handled?	N/A
How should investigational visits be managed?	As trial subjects may be unable to attend scheduled visits, the Notes recommend considering other measures to ensure continuous medical care oversight, e.g. through home nursing and telephone contact.
Which measures should be taken to ensure the supply of investigational medicinal products (IMPs)?	Sponsors should assess the risks relating to IMPs and consider any alternative shipping and storage arrangements to ensure that IMPs are provided to trial subjects without compromising the treatment blinding.
How should clinical trials be monitored?	N/A
How should protocol amendments be managed and communicated to competent authorities?	NAFDAC acknowledges that COVID-19 is likely to introduce more protocol deviations than normal. It is expected that sponsors escalate and manage such protocol deviations in accordance with their standard procedures. Sponsors must report all protocol deviations to the relevant regulatory bodies. In all cases, sponsors must ensure the safety and well-being of trial subjects who are already participating in trials.
When should the initiation, continuation, halt, suspension or extension of clinical trials be considered, and which criteria apply?	According to the Notes, sponsors should critically assess the need to initiate new trials or include new trial subjects in an ongoing trial. Furthermore, sponsors and investigators should evaluate possible changes to ongoing trials during the COVID-19 pandemic based on a risk assessment. Possible changes may include: • a temporary halt of the trial; • suspension or slowing down of recruitment of new trial subjects; and/or • site closure. In all cases, sponsors must ensure the safety and well-being of trial subjects already participating.

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South Africa

Have competent authorities issued any guidance?	The South African Health Products Regulatory Authority (SAHPRA) issued the "Policy on conduct of clinical trials of health products during the current COVID-19 pandemic" (Policy) on March 25, 2020. The policy is accessible here. This policy is an adaptation of the Guidance on Conduct of Clinical Trials of Medicinal Products During the COVID-19 Pandemic published by the US Food and Drug Administration (FDA) on March 18, 2020, (please see the US section below). SAHPRA issued a communication regarding "Good Clinical Practice (GCP) training and expeditated review of clinical trial applications during COVID-19 pandemic," on April 13, 2020, (Communication). The Communication is accessible here. The Communication provides that SAHPRA has amended the requirements for face-to-face GCP training to permit comprehensive online GCP training for the duration of the COVID-19 pandemic in line with social distancing recommendations.
How should the closure/new opening of trial sites, the transfer of patients to other trials sites and/or diagnostic tests be handled?	SAHPRA recognizes that the COVID-19 pandemic may affect the conduct of clinical trials and that challenges may arise, for example, from site closures. In such cases, it should be assessed whether investigators can provide required in-person assessments at an acceptable alternate location.
How should investigational visits be managed?	SAHPRA recommends alternative methods where necessary and feasible for safety assessments such as telephone contact, virtual visits, and alternative locations for assessment (including local laboratories or imaging facilities).
Which measures should be taken to ensure the supply of investigational medicinal products (IMPs)?	SAHPRA encourages IMPs to be delivered to trial subjects directly where appropriate. This would specifically include IMPs distributed for self-administration. For IMPs that are normally administered in a healthcare setting, consulting SAHPRA on plans for alternative administration (e.g. home nursing or alternative sites by trained but non-study personnel) is recommended.
How should clinical trials be monitored?	If planned on-site monitoring visits are no longer possible, sponsors should consider altered monitoring approaches, e.g. optimizing use of central and remote monitoring programs to oversee trial sites. Additional monitoring may be necessary in certain circumstances. Specifically, when trial subjects who no longer have access to IMPs may be subject to withdrawals.

How should protocol amendments be managed and communicated to competent authorities?	SAHPRA recognizes that protocol amendments may be required, and that there may be unavoidable protocol deviations due to COVID-19 illness and/or COVID-19 control measures. SAHPRA encourages sponsors and principal investigators to consider alternative approaches or changes to the protocol or investigational plan to limit exposure to COVID-19. However, typically such protocol amendments should not be implemented before review and approval by SAHPRA and relevant ethics committees. Changes to the protocol that will have minimal impact on trial subjects should be simply notified to SAHPRA. Where protocol amendments have potential to affect the safety of trial subjects and trial integrity, the protocol amendments should be submitted to SAHPRA for approval before proceeding. Sponsors and principal investigators should document how restrictions relating to COVID-19 led to the changes in the study conduct and the duration of those changes. It should also be indicated which trial subjects were affected and how they were affected. Furthermore, if changes in the protocol will lead to amending data management and/or statistical analysis plans, the sponsors should consider such changes in consultation with the Clinical Trials Unit (CTU) of the SAHPRA. Apart from that, any COVID-19 screening procedures that are mandated by the healthcare system, in which a clinical trial is being conducted, are not required to be notified as an amendment to the protocol, unless the sponsor is incorporating the data collected as part of a new research objective.
When should the initiation, continuation, halt, suspension or extension of clinical trials be considered, and which criteria apply?	Sponsors should consider each circumstance, focusing on the potential impact on the safety of trial subjects, and modify study conduct accordingly where appropriate. Sponsors, in consultation with principal investigators, including national principal investigators and Research Ethics Committees (RECs), may determine that the protection of a trial subject's safety, welfare and rights is best served by continuing a trial subject in the trial as per the protocol, or by discontinuing the administration or use of IMPs or other products, or even by discontinuing participation in the trial. Such decisions will depend on specific circumstances, including the nature of the IMPs and other products, the ability to conduct appropriate safety monitoring, the potential impact on the IMPs and other products supply chains, and the nature of the disease under study in the trial.

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Tunisia

Have competent authorities issued any guidance?	To date, no guidance has been issued.
How should the closure/new opening of trial sites, the transfer of patients to other trials sites and/or diagnostic tests be handled?	N/A
How should investigational visits be managed?	N/A
Which measures should be taken to ensure the supply of investigational medicinal products (IMPs)?	N/A
How should clinical trials be monitored?	N/A
How should protocol amendments be managed and communicated to competent authorities?	N/A
When should the initiation, continuation, halt, suspension or extension of clinical trials be considered, and which criteria apply?	N/A

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Uganda

Have competent authorities issued any guidance?	To date, no guidance has been issued.
How should the closure/new opening of trial sites, the transfer of patients to other trials sites and/or diagnostic tests be handled?	N/A
How should investigational visits be managed?	N/A
Which measures should be taken to ensure the supply of investigational medicinal products (IMPs)?	N/A
How should clinical trials be monitored?	N/A
How should protocol amendments be managed and communicated to competent authorities?	N/A
When should the initiation, continuation, halt, suspension or extension of clinical trials be considered, and which criteria apply?	N/A

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Zimbabwe

Have competent authorities issued any guidance?	On April 9, 2020, the Medicines Control Authority of Zimbabwe (MCAZ) issued a circular concerning the conduct of clinical trials during COVID-19 pandemic (Circular). The Circular is accessible here.
How should the closure/new opening of trial sites, the transfer of patients to other trials sites and/or diagnostic tests be handled?	Investigators must take all necessary and reasonable steps to ensure that trial subjects face minimal challenges in travelling to trial sites.
How should investigational visits be managed?	The Circular recommends exploring alternative methods of investigational visits (e.g. telephone calls).
Which measures should be taken to ensure the supply of investigational medicinal products (IMPs)?	Investigators should ensure access to IMPs in case discontinuation of their supply could be detrimental to trial subjects' health and safety. The Circular recommends exploring alternative methods of supply, such as home delivery for self-administered IMPs. In any case, the Circular requires compliance with: • Ministry of Health and Child Care recommendations; • social distancing; and • the need to ensure minimal exposure to COVID-19.
How should clinical trials be monitored?	N/A
How should protocol amendments be managed and communicated to competent authorities?	Protocol amendments should not be implemented before review and approval by either the MCAZ or the Medical Research Council of Zimbabwe. For urgent protocol amendments and deviations, principal investigators should submit a request to the Director General of the MCAZ. Clinical trial submissions should be submitted electronically.
When should the initiation, continuation, halt, suspension or extension of clinical trials be considered, and which criteria apply?	Decisions on initiation, continuation, halt, suspension, or extension of clinical trials should be evaluated based on the protocol in place and the local situations.

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Australia

Have competent authorities issued any guidance?	All Australian state and territory Departments of Health, the Therapeutic Goods Administration (TGA), National Health and Medical Research Council and the Clinical Trials Project Reference Group (together the Australian Medicines Agencies) released guidance on clinical trials for institutions, Human Research Ethics Committees (HRECs), researchers and sponsors (Combined Statement). The Combined Statement is representative of current thinking and best practice in Australia on the conduct of clinical trials during the pandemic but is not a new statement of law and may be subject to change in light of the unprecedented circumstances. The Combined Statement is accessible here, the New South Wales Health Department statement is accessible here, and the Queensland Clinical Trials Coordination Unit statement is accessible here.
How should the closure/new opening of trial sites, the transfer of patients to other trials sites and/or diagnostic tests be handled?	The Australian Medicines Agencies have not provided extensive comment on this issue. While a change in trial site address does not trigger a requirement to notify the TGA, whether this change is considered to be the addition of a new site will be for the trial sponsor and approving HREC to determine.
How should investigational visits be managed?	The Australian Medicines Agencies recommend alternative models to conduct trials where appropriate, for example, decentralized and teletrials, hybrid models, and remote monitoring visits and investigator meetings.
Which measures should be taken to ensure the supply of investigational medicinal products (IMPs)?	The Australian Medicines Agencies recommend the delivery of clinically essential medication to trial subjects in self-isolation quarantines, or who are positive for COVID-19. The New South Wales Health Department provided for the possibility to dispense IMPs via third parties, dispense extended supplies, and deliver IMPs to trial subjects' homes. The Queensland Clinical Trials Coordination Unit guidance contemplates delivery of IMPs to trial subjects.
How should clinical trials be monitored?	The Australian Medicines Agencies consider changes to trials that enable remote data verification to be in the public interest. The Australian Medicines Agencies recommend alternative models to conduct trials where appropriate, for example, decentralized and teletrials, hybrid models, and remote monitoring visits and investigator meetings. The Queensland Clinical Trials Coordination Unit and the New South Wales Department of Health similarly advise that site monitoring may be amended to reduce physical contact. The collection and storage of biospecimens should be done in accordance with biosafety containment protocols. The Australian Medicines Agencies recommend: • applying Universal/Standard precautions; • including clinical annotations where biospecimens have been collected from donors known to be actively infected with COVID-19 or other transmissible microorganisms or vectors; and • all human-derived biospecimens should be processed, managed and used in approved facilities.

How should protocol amendments be managed and communicated to competent authorities?	The Australian Medicines Agencies accept protocol amendments that include the addition of new COVID-19 related elements where appropriate procedures for handling samples are in place, but subsequent notification must still be made in line with usual processes. Deviations from the trial protocol, including changes to existing therapeutic goods, addition of therapeutic goods or sites, and variations that are not responsive to COVID-19 under the clinical trial notification (CTN) scheme, must still be reported to the TGA. Changes in relation to remote data verification will not warrant amendment to individual trial subject information or consent forms, and in this regard trial subject consent may be presumed.
When should the initiation, continuation, halt, suspension or extension of clinical trials be considered, and which criteria apply?	Sponsors and investigators should undertake ongoing contingency planning to assess the ability for continued participation and capacity of resources, and while potential modifications and/or suspensions are a possibility, ultimately, safety of trial subjects remains the paramount concern. Where a trial continues unamended, trial subjects should have the option to suspend or withdraw from that trial. In case of suspensions, trial subjects' post-trial care is essential. In terms of recruiting new trial subjects or proposing new clinical trials which are unrelated to COVID-19, these proposals should consider protocols to limit physical contact and alternative models for conducting trials, as well as the impact on trial subjects' well-being and institutional and health-system resources. Institutions and sponsors should deal with any suspension of trials. However, in the case of IMPs, an unregistered device, a diagnostic or a biological this constitutes a substantial amendment that will require HREC review. In respect of Aboriginal and Torres Strait Islander trial subjects, the Queensland Clinical Trials Coordination Unit advises that approvals for trials involving face-to-face contact with trial subjects be suspended for "the foreseeable future" and that ongoing trials should be amended to avoid this type of contact; for example, through teletrials and other alternative data collection methods. Recruitment of new trial subjects should also be suspended.

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China

Have competent authorities issued any guidance?	On April 30, 2020, the center for drug evaluation of the National Medical Products Administration (NMPA) published a draft Guiding Principles for Managing Drug Clinical Trials during the COVID-19 Pandemic for soliciting public opinion. The draft NMPA Guiding Principles are accessible here. It is unclear when and if the draft Guiding Principles will be enacted. Besides the NMPA's draft Guiding Principles, Tianjin Medical Products Administration (TJ MPA) is one of the few government authorities that issued official guidance on the management of clinical trials during the pandemic. The guidance is accessible here. In addition, where there is no official guidance, many clinical trial sites and industry associations issued their own detailed Good Clinical Practice (GCP) guidance, including Guangdong Pharmaceutical Associations, Sichuan Pharmaceutical Association, Shanghai Public Health Clinical Centre and Southwest Medical University Affiliated Hospital. These GCP guidance are generally consistent with the key points of TJ MPA.
How should the closure/new opening of trial sites, the transfer of patients to other trials sites and/or diagnostic tests be handled?	According to the TJ MPA's official guidance, each medical institute shall take epidemic prevention and control as the most important task. Specifically, each medical institute should establish an emergency plan for clinical trial management and establish and improve a rapid link between clinical trial management and epidemic management. According to NMPA's draft Guiding Principles, if a trial site has to be closed, trial subjects need to be transferred to trial sites far from risk regions or close to home, other trial sites or potentially new trial sites. It is normally not recommended to open new trial sites. Any opening of new trial sites should be approved by the NMPA as a significant amendment. The transfer of trial subjects to other trial sites should be agreed by the trial subjects, the investigators of the dispatching trial site and the receiving trial site. The receiving trial site should be allowed to obtain patient information and data from the dispatching trial site.
How should investigational visits be managed?	According to NMPA's draft Guiding Principles, the sponsor should consider whether on-site investigational visits are necessary to ensure safety protection of trial subjects. Where an alternative safety evaluation method is feasible after the relevant risk assessment, on-site investigational visits could be replaced by phone interview or video interview, or be postponed or cancelled. Investigators should adopt alternative methods to collect adverse events or conduct routine checks in local laboratories or imaging centers.
Which measures should be taken to ensure the supply of investigational medicinal products (IMPs)?	According to GCP guidance issued by some clinical trial institutions, where IMPs can be delivered to patients' homes, such methods should be preferred. According to the NMPA's draft Guiding Principles, where IMPs can be used at home without incurring any new safety risk, the IMPs can be delivered to trial subjects' homes.

How should clinical trials be monitored?	According to the NMPA's draft Guiding Principles, where on-site monitoring can be implemented, the scope of the monitoring should take into account the legal restrictions, urgency of the monitoring and feasibility of the working staff on-site. Further, the conduct of the monitoring should be approved by the trial site. Temporarily, alternative measures, including cancellation or postponement of on-site monitoring, extension of monitoring duration, conducting phone or video interviews, central or remote monitoring may be adopted.
How should protocol amendments be managed and communicated to competent authorities?	According to TJ MPA, during the epidemic, serious adverse events (SAE) in Tianjin city may be reported via a special IT system for administering clinical trials. According to the draft NMPA Guiding Principles, any amendment to protocol should be communicated to competent authorities as soon as possible. Under some emergency circumstance, sponsors and investigators may need to adopt immediate safety measures without notifying the relevant authority in advance. However, they are required to submit the relevant information to the authority as soon as possible. Where no immediate action is required, the sponsor should submit application for significant amendment where amendment has impact on patient safety and/or scientific value of trial.
When should the initiation, continuation, halt, suspension or extension of clinical trials be considered, and which criteria apply?	According to TJ MPA, medical institutions may suspend clinical trials that have a direct impact on epidemic prevention and control and clinical trials that require collective screening and group enrolment and delay the screening of trial subjects. Clinical trials on subjects who have already participated in the trial shall continue unless the individual circumstances require cessation. The NMPA's draft Guiding Principles suggests re-evaluating the initiation and the conduct of clinical trials during the pandemic. Specifically, the sponsor should strictly evaluate the feasibility of initiating new clinical trials or recruiting new trial subjects by paying special attention to patient safety, the characteristics of the IMP and the intended indication, capability to conduct safety surveillance, the supply chain of drugs as well as the local prevention and control measures for the pandemic. It encourages sponsors to establish Data Safety and Monitoring Boards and to enhance the protection of patient safety. The clinical use of IMPs may be halted due to lack of drug supply, inability to manage or ensure safe use of IMPs. Even if there is temporary suspension of the clinical trial, sponsors should adopt measures to minimize and manage the risks to patient safety.

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Hong Kong

Have competent authorities issued any guidance?	To date, no Hong Kong competent authority (such as the Hong Kong Department of Health, the Hospital Authority, the Centre for Health Protection and the Food and Health Bureau) has issued any guidance direction in relation to the management of clinical trials in the context of the COVID-19 pandemic.
How should the closure/new opening of trial sites, the transfer of patients to other trials sites and/or diagnostic tests be handled?	N/A
How should investigational visits be managed?	N/A
Which measures should be taken to ensure the supply of investigational medicinal products (IMPs)?	N/A
How should clinical trials be monitored?	N/A
How should protocol amendments be managed and communicated to competent authorities?	N/A
When should the initiation, continuation, halt, suspension or extension of clinical trials be considered, and which criteria apply?	N/A

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Japan

Have competent authorities issued any guidance?	The Japanese Pharmaceutical and Medical Device Agency (PMDA) recently issued guidance related to the management of clinical trials in the context of the COVID-19 pandemic. The guidance is accessible here (only Japanese version).
How should the closure/new opening of trial sites, the transfer of patients to other trials sites and/or diagnostic tests be handled?	When trial subjects need to be transferred to other trial sites due to COVID-19, the following requirements need to be followed: • the two trial sites need to enter into an entrustment agreement; • both trial sites need to obtain written consent from trial subjects; • the medical records and other documents related to trial subjects need to be handed over to the current trial site; • the relative responsibilities related to the reports of trial subjects between the two trial sites need to be specified in advance; and • the records of the transfer process need to be retained.
How should investigational visits be managed?	N/A
Which measures should be taken to ensure the supply of investigational medicinal products (IMPs)?	If medical institutions need to deliver IMPs to trial subjects who cannot go to medical institutions due to concerns over COVID-19, the medical institution needs to follow the following requirements: • concluding an entrustment agreement that conforms to the ordinance of Good Clinical Practice (GCP) with the delivery company; • preparing the protocol of quality control of the delivery process; • assuming the responsibilities related to the shipment; and • retaining the records of the delivery process. However, in an emergency, a sponsor may consign the transport of IMPs to the delivery company on behalf of the medical institution by complying with the following requirements: • preparing appropriate protocol of quality control of the delivery process; • ensuring that the medical institution will enter into an entrustment agreement with the delivery company as soon as practicable after the shipment; • ensuring that the medical institution will assume the responsibilities related to the shipment; and • retaining the records of the delivery process.
How should clinical trials be monitored?	Where sponsors are restricted from visiting medical institutions due to the COVID-19 pandemic, sponsors should consider alternative methods of monitoring other than on-site monitoring. The trial protocol shall be evaluated considering the effect of the new monitoring method. The change of the monitoring method and the rationale shall be recorded, and the record shall be retained.

How should protocol amendments be managed and communicated to competent authorities?	When medical institutions and sponsors need to consult with the PMDA or submit applications of clinical trials to the PMDA, the inquires or applications should be submitted by email or by mail, in principle.
When should the initiation, continuation, halt, suspension or extension of clinical trials be considered, and which criteria apply?	Any postponement or cancellation of trials caused by COVID-19 shall be recorded under normal procedure. A medical institution needs to obtain approval from the Institutional Review Board (IRB) regarding the initiation and conduct of each clinical trial. The IRB provides its approval to the medical institutions after internal meetings usually held at relevant medical institutions. Since the IRB cannot currently meet at the relevant medical institution due to the COVID-19 pandemic, it is acceptable that discussion of all cases will be postponed to the next IRB meeting that can be held, except for urgent cases. When there are urgent issues that need to be discussed by the IRB, the IRB members may deliberate through exchanging emails following required procedures. Additionally, measures related to the safety of the participants (e.g. providing information the participants and the amendment of consent forms from participants) can be implemented without the IRB's review, but need to be reported to and discussed at an IRB meeting afterwards. These arrangements shall be recorded, and the record shall be retained.

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New Zealand

Have competent authorities issued any guidance?	The relevant regulatory body, the Health and Disability Ethics Committee Secretariat (HDECS), issued guidance which is accessible here. The relevant industry body, the New Zealand Association of Clinical Research (NZACR), also published guidance which is accessible here.
How should the closure/new opening of trial sites, the transfer of patients to other trials sites and/or diagnostic tests be handled?	New Zealand is progressively easing its lockdown measures, with most business able to reopen from Thursday, May 14, 2020. This means trial subjects will be able to come to the trial site for protocol specified visits (subject to applicable social distancing measures and health and safety requirements being met).
How should investigational visits be managed?	Sponsors, investigators and sites should evaluate the possibility to implement alternative methods for the care of trial subjects (e.g. telephone contact, virtual visit, alternative location).
Which measures should be taken to ensure the supply of investigational medicinal products (IMPs)?	Neither HDECS nor NZACR have explicitly commented on this issue.
How should clinical trials be monitored?	All trials related to COVID-19 continue to be assigned to HDECS for ongoing monitoring.
How should protocol amendments be managed and communicated to competent authorities?	Principle investigators should consider each circumstance, focusing on the potential impact on the safety of trial subjects and staff, and modify the trial accordingly. If the investigator fails to submit a substantial amendment prior to implementation, this will be treated as a substantial protocol amendment or violation and will require submission as soon as practicable.
When should the initiation, continuation, halt, suspension or extension of clinical trials be considered, and which criteria apply?	It may be the case that trial subjects' safety, welfare, and rights are best served by continuing their participation in the trial as per the protocol or by discontinuing the administration or use of IMPs or even their participation in the trial. Such decisions will depend on specific circumstances, including the nature of IMPs, the ability to conduct appropriate safety monitoring, the potential impact on the IMPs supply chain, and the nature of the disease under study in the trial.

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Singapore

Have competent authorities issued any guidance?	The Health Sciences Authority (HSA) has issued guidance on the conduct of clinical trials in relation to the COVID-19 pandemic (Guidance). The Guidance is accessible here.
How should the closure/new opening of trial sites, the transfer of patients to other trials sites and/or diagnostic tests be handled?	N/A
How should investigational visits be managed?	If on-site visits are not possible, sponsors may consider alternative methods for efficacy and safety assessment and whether such methods can reasonably assure the safety of trial subjects. The HSA suggests the use of alternative locations for laboratory tests or scans and virtual follow-up through telephone calls or video conferences.
Which measures should be taken to ensure the supply of investigational medicinal products (IMPs)?	It is possible to deliver IMPs from the trial site directly to trial subjects' homes (Direct-to-Patient, DTP) provided that sponsors and investigators have determined that IMPs can be safely and duly self-administered by trial subjects without supervision. If IMPs are supplied from an alternative location (such as from the manufacturer's premises), sponsors must provide relevant details on how trial subjects' privacy and data confidentiality will be protected before implementation. The HSA does not recommend sending more than one cycle/visit of IMPs to trial subjects by DTP if the clinical trial is in its early stages. In such case, sponsors should consult with the HSA. Sponsors should notify the HSA before the use of the DTP service, via email.
How should clinical trials be monitored?	If on-site monitoring is not possible, sponsors may consider implementing alternative options like centralized or remote monitoring. Written consent should be obtained from trial sites for remote monitoring Sponsors should notify the HSA if they intend to conduct remote monitoring.
How should protocol amendments be managed and communicated to competent authorities?	Contingency measures due to the COVID-19 pandemic should be implemented in consultation with the sponsor, investigator and/or trial sites, institutional review boards and the HSA. Sponsors should document reasons for any contingency measures implemented and perform an impact assessment of the measures taken on the safety of the trial subjects and on data credibility and trial integrity. Sponsors should notify the HSA if any of the contingency measures constitute an urgent safety measure (such as remote study visits) or if it constitutes a substantial amendment. A substantial amendment would require HSA approval.
When should the initiation, continuation, halt, suspension or extension of clinical trials be considered, and which criteria apply?	Sponsors should notify the HSA if they intend to suspend or halt the screening and recruitment of trial subjects

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Thailand

Have competent authorities issued any guidance?	To date, no guidance has been issued.
How should the closure/new opening of trial sites, the transfer of patients to other trials sites and/or diagnostic tests be handled?	N/A
How should investigational visits be managed?	N/A
Which measures should be taken to ensure the supply of investigational medicinal products (IMPs)?	N/A
How should clinical trials be monitored?	N/A
How should protocol amendments be managed and communicated to competent authorities?	N/A
When should the initiation, continuation, halt, suspension or extension of clinical trials be considered, and which criteria apply?	N/A

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Europe


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Slovakia
Austria
Hungary
France
Slovenia
Romania
Croatia
Italy
Spain
Portugal
Greece

European Union/EEA

Have competent authorities issued any guidance?	On March 20, 2020, the European Commission, the European Medicines Agency (EMA) and the national Head of Medicines Agencies published new guidance for sponsors on how to manage the conduct of clinical trials during the COVID–19 pandemic (EU Guidance). For further details please see here. The updated Version 3.0 of the EU Guidance published on April 28, 2020, is accessible here. In addition, on March 25, 2020, EMA published guidance on the actions that sponsors of ongoing clinical trials affected by the COVID-19 pandemic should take to ensure the integrity of their studies and the interpretation of study results while safeguarding the safety of trial subjects as a first priority. This complements the Good Clinical Practice (GCP) guidance on how sponsors should adjust the management of clinical trials and trial subjects during the pandemic. Please note that this guidance is under a four-week public consultation until April 25, 2020. The current draft is accessible here. Note that clinical trials in the EU are authorized and supervised at national level. Therefore, sponsors and investigators should consider that there may be specific national legislation and guidance in place, which they should consult in addition, and which can be used to complement the EU Guidance, or, with respect to specific matters, may prevail over the EU Guidance.
How should the closure/new opening of trial sites, the transfer of patients to other trials sites and/or diagnostic tests be handled?	**Site closure:** If it is not feasible for a site to continue participation at all, sponsors should consider if the trial site should be closed and how this can be done without compromising trial subjects' safety and well-being and data validity. **Transfer of trial subjects:** If unavoidable, sponsors may consider the transfer of trial subjects to trial sites away from risk zones, or closer to their home, to sites already participating in the trial, or new ones. **Opening of new trial sites:** If there is an urgent need to open a new trial site for critical trial visits; for example, outside the hospital, sponsors may implement such measure as an urgent safety measure (USM) first and submit a substantial amendment notification later for the approval and initiation of an additional site. The exceptional situation could involve e.g. trial subjects who urgently need to stay in the trial and for whom no other sites are available. In such cases, it is important that trial subjects as well as investigators (both receiving and sending) agree about the transfer and that the receiving site has the possibility to access previously collected information/data for the trial subjects and that any electronic Case Report Forms (eCRFs) can be adjusted accordingly to allow the receiving site to enter new data.

	Critical laboratory tests, imaging and other diagnostic tests: For trial subjects' safety, it is acceptable to perform laboratory, imaging or other diagnostic tests at a local laboratory (or relevant clinical facility for other tests) authorized/certified to perform such tests routinely (e.g. blood cell count, liver function test, X-ray, ECG) if this can be done within local restrictions on social distancing. Sites should inform sponsors about such cases. Please note that the changes above may also be initiated by the investigator site informing sponsors. **Reimbursement of exceptional expenses:** Sponsors may reimburse, typically via investigators, expenses relating to the implementation of urgent measures for the protection of trial subjects and initially borne by them. If sponsors provide additional financial compensation to sites/investigators (e.g. to cover courier costs for IMPs delivery), this needs to be documented and performed according to national legislation. Sponsors should handle the reimbursement of such expenses in compliance with national legislation and/or guidance.
How should investigational visits be managed?	Sponsors and the investigators should consider the conversion of physical visits into telephone or video visits.
Which measures should be taken to ensure the supply of investigational medicinal products (IMPs)?	In principle, where appropriate, the direct supply of IMPs to trial subjects' homes and/or re-distribution of IMPs between trial sites should be considered. Sponsors should determine whether further education or training of trial subjects will be necessary for the receipt, handling and self-administration of IMPs. Written information on the dose regimen needs to be provided to trial subjects along with contact information for the trial site for any questions they may have. Sponsors should contract dedicated couriers for IMPs shipment with procedures in place. These procedures should ensure timely delivery directly to trial subjects or their designated caregivers to avoid, for example, IMPs being handed over to neighbors. Procedures for the accountability of the IMPs must be in place. **Delivery of IMPs directly from trial sites to trial subjects:** Sponsors may consider the possibility to deliver IMPs directly to trial subjects to avoid any risk of contagion. The delivery is generally expected to happen from trial sites (e.g. via hospital pharmacies as applicable) to trial subjects. Sponsors should bear the cost of the shipment and should provide logistical assistance to trial sites if needed; for instance, for the selection of an appropriate courier or transporter.

	Delivery of IMPs directly from sponsors to trial subjects: If, due to the COVID-19 pandemic, a trial site is not able to handle the additional burden of IMPs shipment to trial subjects, IMPs may, as an exception, be shipped to trial subjects by a distributor independent from and acting on behalf of the sponsor in line with national law or temporary national emergency measures. The following then applies: • sponsors and distributors should enter into a contract. The contract should identify all involved investigators/trial sites; • IMPs may only be dispatched to trial subjects after agreement with investigators and on the basis of the investigators' prescriptions; • investigators should explain the process to trial subjects or carers verbally and should obtain their verbal consent before agreeing with sponsors, including for the investigators to provide trial subjects' names, addresses and contact details to distributors; • distributors should not store the personal data of trial subjects for a longer period than required for the purpose of dispatching IMPs and should only use this information for the purpose of making IMPs deliveries during the period of the pandemic; and • trial subjects' names, addresses and contact details should never be provided to sponsors, and distributors should not have access to trial subjects' health information. **Re-distribution of IMPs between sites:** Any re-distribution of IMPs between sites should comply with applicable Good Manufacturing Practice (GMP) requirements and be considered only in exceptional cases where a direct distribution of IMPs to a trial site by the usual distributor is not possible or, in exceptional circumstances, where a trial subject is transferred from one site to another. Re-distribution should follow a written procedure established in cooperation with the Qualified Person (QP) or the person responsible for the distribution of IMPs. Sites should be provided with the relevant information to ensure that the process can be performed securely. Associated records should be included in the transfer. **Treatment blinding:** Alternative shipping and storage arrangements should not compromise the treatment blinding.
How should clinical trials be monitored?	**Possible temporary, alternative monitoring measures may include where appropriate:** • cancelling of on-site monitoring visits and extending of the period between monitoring visit; • implementing telephone and video monitoring; and/or • adapting the on-site monitoring plan if it is impossible to follow, supplementing it with (additional/increased) centralized monitoring and central review of data, if possible and meaningful.

	Remote source data verification (rSDV) will currently only be considered necessary for very few trials when in line with national law. Investigators should report results of adjusted monitoring/review measures to sponsors in monitoring reports and in the clinical study report. Sponsors should plan follow-up measures to be implemented when the situation is normalized. This should include increased on-site monitoring for a period that is sufficient to ensure that the impact of the reduced monitoring can be rectified, and problems resolved or properly documented. **Special restrictions:** So-called remote source data verification (e.g. providing sponsors with copies of medical records or remote access to electronic medical records) is currently not allowed in most Member States as it may infringe trial subjects' rights. In addition, provision of redacted/de-identified pdf files is not acceptable as they may put disproportionate burden on trial site staff.
How should protocol amendments be managed and communicated to competent authorities?	Sponsors should escalate and manage protocol deviations in accordance with standard procedures. Good Clinical Practice (GCP) inspectors should take a proportionate approach when reviewing such deviations, in particular when they do not put trial subjects at risk. An increase in protocol deviations in relation to the COVID-19 pandemic does in itself not trigger the actions required by Good Clinical Practice (GCP) § 5.20. Protocol deviations will, however, need to be assessed and reported in the clinical study report, following ICH E3. Sponsors should base all decisions to adjust clinical trial conduct on a risk assessment. If trial subjects' safety and data validity conflict, trial subjects' safety always prevails. Changes should be well balanced, considering, in particular, the legitimate interests of trial sites in avoiding further burden in terms of time and staffing. Sponsors should assess whether an amendment is to be regarded as "substantial." A change is substantial when it has a potential impact on the safety or physical or mental integrity of trial subjects, or on the scientific value of the trial. Submission of information is only obligatory if the amendment is a substantial amendment. Directive 2001/20/EC does not require notification, or immediate submission of information on non-substantial amendments. If the risk assessment leads to the following actions, sponsors must inform the relevant national competent authority and/or ethics committees: • urgent actions to protect trial subjects against immediate hazard. These urgent safety measures do not need prior notification; • substantial amendments that do not require immediate action from sponsors or investigators. Sponsors should submit these changes as substantial amendment applications; or • procedural or other changes to address global or local consequences of the pandemic (e.g. related to social distancing). If these changes are justifiable due to the COVID-19 pandemic, they can be notified as soon as possible, provided that they are not related to trial subjects' safety and that they do not have a serious effect on the benefit-risk balance for trial subjects and the scientific value of the trial.

	Prospective protocol waivers remain unacceptable and trial subjects should not be included in trials without proper eligibility assessment, including performance of planned tests, and written informed consent according to national laws and regulations. Compliance with the trial protocol should be ensured to such an extent that an ongoing benefit/risk assessment for the clinical trial and its subjects is still possible. Sponsors should properly assess the impact of protocol deviations on clinical data interpretability and the overall evidence generation package could be subsequently discussed within scientific advice with regulatory authorities. Sponsors should consider EU Guidance (see above) on methodological considerations. **Changes to informed consent:** There may be a need to re-consent already included trial subjects. Unless linked to the implementation of urgent safety measures, changes in informed consent procedures will need to be reviewed and approved by the relevant ethics committee in advance. If re-consents are necessary for the implementation of new urgent changes in trial conduct, alternative ways of obtaining such re-consents should be considered (e.g. via telephone or video-calls). Any consent obtained this way should be documented and confirmed by way of normal consent procedures at the earliest opportunity when the trial subjects will be back at the regular sites. When a new event is likely to have a serious effect on the benefit/risk balance of the trial, sponsors and investigators may need to take immediate actions to protect trial subjects. These urgent safety measures (USM) may be taken without prior notification, but the information needs to be provided ex post to the national competent authority and the ethics committee as soon as possible. If protocol deviations are likely to affect trial subjects' safety or well-being and/or the scientific value of the trial, but do not require immediate action from sponsors or investigators, they should be submitted as substantial amendment notifications. Changes to trial conduct should be agreed with and communicated clearly to investigators sites by sponsors. Vice versa, investigators may initiate changes to trial conduct as urgent safety measures. Investigators should report such changes to sponsors as soon as possible as well as by the latter to the competent authorities and ethics committees.
When should the initiation, continuation, halt, suspension or extension of clinical trials be considered, and which criteria apply?	The feasibility of starting a new clinical trial or including new trial subjects in an ongoing trial should be critically assessed. As regards ongoing trials, the following measures may be taken into account in the context of a risk assessment: • temporary halt of the trial at some or all trial sites; • suspension or slowing down of recruitment of new trial subjects; • extension of the duration of the trial; or • postponement of trials or activation of sites that have not yet been initiated. If a trial halt, even if only temporary, may potentially compromise the overall well-being and best interest of trial subjects, all measures need to be considered and taken to avoid this.

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Austria

Have competent authorities issued any guidance?	The Austrian Federal Office for Safety in Health Care (BASG) primarily refers to the EU Guidance (please see the EU section above). BASG recently published a FAQ to this topic which is updated regularly and accessible here (there might be regular updates). In addition, sponsors, investigators and trial sites should consider the EU Guidance (please see the EU section above).
How should the closure/new opening of trial sites, the transfer of patients to other trials sites and/or diagnostic tests be handled?	BASG has not explicitly commented on this issue, but only recommends changing trial sites that are not (or less) affected by the pandemic, unless these are triggered audits. Please see also the EU section above.
How should investigational visits be managed?	BASG has not commented on this issue. Please see also the EU section above.
Which measures should be taken to ensure the supply of investigational medicinal products (IMPs)?	BASG recommends, where appropriate, sending IMPs directly to trial subjects' homes if a continued supply of IMPs must be maintained and IMPs cannot be dispatched via pharmacies. Training on administration at home must have been provided. Should a trial site not be able to cope with the additional workload, it could be considered to provide additional staff resources to the trial sites (in line with Art. 4.2.5 and 4.2.6 ICH Good Clinical Practice (GCP)).
How should clinical trials be monitored?	BASG recommends temporary changes to the monitoring strategies if on-site monitoring visits can no longer be carried out as usual. Planned on-site monitoring visits should be cancelled and/or postponed and the visit intervals should be extended. In addition, telephone and/or video calls instead of on-site monitoring visits should be considered. Investigators must document and communicate conducted monitoring activities to sponsors. Once the situation has normalized, more on-site monitoring should be conducted to deal with backlogs, the postponed source data verification (SDV) and to address any quality problems. As regards trial site audits, sponsors should re-evaluate audit programs if on-site audits are temporarily not possible or cannot be conducted at the planned scale.
How should protocol amendments be managed and communicated to competent authorities?	Sponsors should document all measures taken to protect trial subjects due to the COVID-19 pandemic together with a justification and benefit/risk evaluation. Sponsors should also notify BASG at the same time as the implementation of the measures (by email clinicaltrials@basg.gv.at). Changes affecting trial subjects or trial integrity (substantial) should be notified to the BASG as an urgent safety notification together with their implementation. A substantial amendment is not required. For a notification only the receipt by the BASG is confirmed. There is no authorization and no publication on the BASG website.

	After the end of the pandemic or at the request of BASG, sponsors must submit a final summary report on all measures taken as a single substantial amendment (this amendment also serves to formally conclude all changes made as an urgently required safety measure and to restore the study to its initial state, if possible).
When should the initiation, continuation, halt, suspension or extension of clinical trials be considered, and which criteria apply?	BASG has not commented on this issue. However, all measures taken to protect trial subjects due to urgent action required by the COVID-19 pandemic must be documented by the sponsor together with a justification and benefit/risk assessment and should be notified to the BASG. In addition, please see also the EU section above.

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Belgium

Have competent authorities issued any guidance?	On March 16, 2020, the Belgian medicines agency (FAMHP) issued guidance on the direct dispensing of medicinal products to trial subjects in the context of clinical trials. The guidance is accessible here. On April 29, 2020, FAMHP published an addendum to this guidance (available here). Moreover, on April 30, 2020, FAMHP published a guidance on the management of clinical trials during the COVID-19 pandemic, which provides further guidance on new clinical trials (COVID-19 and non-COVID-19 related) and ongoing clinical trials (available here). In addition, sponsors, investigators and trial sites should consider the EU Guidance (please see the EU section above).
How should the closure/new opening of trial sites, the transfer of patients to other trials sites and/or diagnostic tests be handled?	Further to the EU Guidance (see above), FAMHP addresses, among other things, the following scenario as regards the continuance of existing and start of new trials: • A Belgian trial subject is enrolled in a trial in another EU Member State and due to the COVID-19 situation the foreign site closes. • The Belgian trial subject returns to Belgium where the same trial is not conducted. • The trial subject wants to continue the experimental treatment in Belgium due to its benefits. According to FAMHP, in this situation, sponsors and principal investigators have the following possibilities: • a new trial may be launched in Belgium (an initial CTA dossier to be submitted to both the ethics committee and FAMHP which is, however, under the current circumstances not recommended); or • the trial subject drops out of the clinical trial and is provided with IMPs based on compassionate use.
How should investigational visits be managed?	FAMHP recommends investigational visits outside the trial site; for example, at trial subjects' homes or alternative locations where appropriate. This should be requested by the trial site by submitting a substantial amendment notification to FAMHP and the Ethics Committee (EC). Protocol deviation (e.g. control visits) should be considered as an urgent safety measures (USM) if the change has to be immediately implemented for the trial subjects' safety and if it is considered a substantial amendment. Sponsors may consider, where appropriate, changing physical visits for telephone or video visits, postponement or complete cancellation of visits to ensure that only strictly necessary visits are performed at trial sites.
Which measures should be taken to ensure the supply of investigational medicinal products (IMPs)?	The principle investigator may send IMPs directly to trial subjects if it is difficult or undesirable for trial subjects to obtain IMPs at the trial site. Sponsors may not intervene in this process for reasons of confidentiality and integrity of trial subjects' data. The applicable shipment requirements must be fulfilled, and IMPs must be suitable for transport, storage and administration at trial subjects' homes. This process must be documented by the principle investigator and entirely traceable. All costs due to the deviations in the supply of IMPs should be reimbursed by sponsors if they are necessary to ensure the continuity of the trials.

How should clinical trials be monitored?	Certain sponsor oversight responsibilities, such as monitoring and quality assurance activities need to be re-assessed and temporary, alternative proportionate mechanisms of oversight may be required. The extent of on-site monitoring, if it remains feasible, should take into account national and local restrictions, the urgency (e.g. source data verification can often be postponed) and the availability of site staff, and should only be performed as agreed with trial sites. Possible temporary, alternative measures (to strike an acceptable balance between appropriate oversight and the capacity of and possibilities at trial sites) may include: • cancelling on-site monitoring visits and extending the period between monitoring visit; • implementing telephone and video visits (without unnecessarily increasing the burden on the trial site and taking into account trial subjects' integrity); and/or • adapting the on-site monitoring plan and supplementing with (additional/ increased) centralized monitoring and central review of data if possible and meaningful. Remote monitoring is recommended where appropriate. However, remote source data verification (e.g. providing sponsors with copies of medical records or remote access to electronic medical records) is currently not allowed in Belgium. In this context, source data refers to medical dossiers, charts of the trial subject.
How should protocol amendments be managed and communicated to competent authorities?	Sponsors must document all measures taken for ongoing trials relating to the COVID-19 pandemic. This should include justification and benefit/risk evaluation. A summary report of all measures should be available in the site master file of the trial and provided to FAMHP and EC at the end of the trial. To avoid over-reporting, FAMHP requests sponsors to keep an overview of all measures taken due to the COVID-19 situation that constitute no permanent amendments to the protocol and no urgent safety measures (USM) including description, explanation and justification of each taken measure. Furthermore, for the time being, FAMHP requests sponsors to provide an overview of measures taken every four months via email to CT.RD@fagg-afmps.be. USM relating to COVID-19 may be taken without prior notification to FAMHP and EC, when e.g. a new event is likely to have a serious effect on the benefit/risk balance of the trial. However, sponsors must inform as soon as possible FAMHP and EC of the measures taken and the plan for further action. This should be reported to FAMHP via CESP or ct.rd@fagg-afmps.be (or CTRPilot@fagg-afmps.be for Pilot Projects). A substantial amendment notification must be submitted afterwards. Sponsors do not have to notify non-substantial amendments to FAMHP or EC. Non-substantial amendments should be documented. However, if changes are likely to affect the safety or well-being of trial subjects and/or the scientific value of the trial, but do not require immediate action from sponsor or investigator, it is generally acceptable to submit them as substantial amendment applications. Moreover, the EC accepts that the sponsor adds new sites to a COVID-19 trial via a substantial amendment/modification, even if the time period of three months – between approval and substantial amendment – has not lapsed. Sponsors should manage protocol deviations in accordance with their standard procedure. A proportionate approach will be taken by the GCP inspectors when such deviations are reviewed during inspections, in particular whether the best interest of the trial subjects is maintained and they are not put at risk.

When should the initiation, continuation, halt, suspension or extension of clinical trials be considered, and which criteria apply?	FAMHP gives priority to (new) clinical trial applications for the treatment or prevention of COVID-19, and/or substantial amendment notifications and notifications relating to existing clinical trials resulting from COVID-19. To avoid any delays, sponsors are recommended to prospectively contact FAMHP to explore the feasibility of an accelerated procedure (ct.rd@fagg-afmps.be). Sponsors must notify temporary halts and USMs to FAMHP and EC within 15 days of the decision. To restart a trial after temporary halt, a substantial amendment notification must be submitted. The trial can only restart upon approval. However, if the temporary halt of recruitment is only due to the COVID-19 pandemic, restarting recruitment after notification to FAMHP and EC is possible. Moreover, sponsors should critically assess whether to initiate new trials or include new trial subjects in a trial not related to COVID-19. With respect to ongoing trials, sponsors should consider in their risk assessment whether the following measures could be the most appropriate during COVID-19: • a temporary halt of the trial at some or all trial sites; • suspension or slowing down of recruitment of new trial subjects; • extension of the duration of the trial; • postponement of trial or activation of trial sites that have not yet started; • closing of trial sites; • if unavoidable (it should be justified that this is a truly exceptional situation based on the personal risk-benefit ratio for the individual trial subject), transfer of subjects to trial sites away from risk zones, or closer to their homes, to trial sites already participating in the trial, or new ones; and/or • there may be a need for critical laboratory tests, imaging or other diagnostic tests to be performed for patient safety. Patients should also not be included in trials without proper eligibility assessment, including performance of planned tests and written informed consent according to national laws and regulations. When trial subjects are incapable of giving their informed consent (e.g. when they are under intensive medical care), sponsors may need to obtain informed consent of these trial subjects or their representatives later (as soon as feasible). There may also be a need to re-consent trial subjects who are already included. However, alternative ways of obtaining such re-consent can be considered, e.g. through contacting the trial subjects via telephone or video-calls and obtaining verbal consent supplemented with email confirmation (this should be documented and confirmed by way of normal consent when trial subjects return to the trial sites).

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Croatia

Have competent authorities issued any guidance?	The Croatian Ministry of Health (Ministry of Health) issued guidance on the conduct of clinical trials during the COVID-19 pandemic. The guidance states that the relevant stakeholders (e.g. investigators and sponsors, as well as competent national authorities) are expected to follow the EU Guidance (please see the EU section above) as well as any national rules. The guidance is accessible here.
How should the closure/new opening of trial sites, the transfer of patients to other trials sites and/or diagnostic tests be handled?	If necessary, the competent authorities may transfer trial subjects from one trial site to another in agreement with principal investigators and only in accordance with the decisions of the Crisis Management Department. A prior consent of the directors of both trial sites as well as reporting such conduct to the Ministry of Health is required. If necessary, the transfer of trial subjects may also be implemented as an emergency measure, however, followed by subsequent notification and/or request for an approval of the amendments.
How should investigational visits be managed?	The Ministry of Health recommends conducting visits by telephone or video call where appropriate.
Which measures should be taken to ensure the supply of investigational medicinal products (IMPs)?	For IMPs for parenteral administration, the Ministry of Health recommends considering any possibility of delaying the use of IMPs (at trial subjects' homes or at the trial site). Apart from that, the Ministry of Health recommends sponsors continue delivering IMPs to trial sites from where it may be supplied to trial subjects' homes by the principle investigator. However, in this case, trial subjects must give their prior consent to sharing personal data (statement). However, it is not permitted to deliver IMPs directly by sponsors to trial subjects' homes.
How should clinical trials be monitored?	Monitoring through telephone and video calls is recommended where appropriate. However, remote access to trial data, including remote source data verification is not permitted.

How should protocol amendments be managed and communicated to competent authorities?	The Ministry of Health recommends documenting all deviations from the trial protocol due to the COVID-19 pandemic and to report deviations to the Ministry of Health only in case of a significant impact on the safety of trial subjects. Only necessary and significant documents related to the further conduct of trials and the safety of trial subjects shall be submitted to the Ministry of Health during the COVID-19 pandemic. The Ministry of Health recommends submitting documentation electronically via email to pisarnica@miz.hr including a mandatory reference to the class (i.e. reference number) of the decision of the Ministry of Health and a trial plan for the respective clinical trial. Larger documents should be sent via post or courier and on CD, if necessary. Any request/notification sent electronically should be signed by a person authorized by sponsors.
When should the initiation, continuation, halt, suspension or extension of clinical trials be considered, and which criteria apply?	Where appropriate, sponsors may suspend clinical trials for reasons relating to the COVID-19 pandemic. They must inform the Ministry of Health and the central ethics committee of such decisions.

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Czech Republic

Have competent authorities issued any guidance?	On March 20, 2020, the Czech medicines agency (SUKL), issued updated guidance, replacing the documents of March 13, 2020, and March 16, 2020. The guidance is accessible here. In addition, sponsors, investigators and trial sites should consider the EU Guidance (please see the EU section above).
How should the closure/new opening of trial sites, the transfer of patients to other trials sites and/or diagnostic tests be handled?	SUKL has not explicitly commented on this issue. Please see also the EU section above.
How should investigational visits be managed?	SUKL recommends telephone consultation of trial subjects to ensure their safety.
Which measures should be taken to ensure the supply of investigational medicinal products (IMPs)?	SUKL permits the supply of IMPs to trial subjects' homes only in emergency situations.
How should clinical trials be monitored?	SUKL has not explicitly commented on this issue. Please see also the EU section above.
How should protocol amendments be managed and communicated to competent authorities?	SUKL acknowledges that protocol deviations may become necessary in the context of the COVID-19 pandemic. Sponsors do not need to report amendments of the monitoring plan including changes of on-site visits to remote monitoring or changes of dates of monitoring to SUKL or to the ethics committee. However, every amendment should be documented and justified in the clinical trial dossier. SUKL allows information to to be provided to trial subjects as regards deviations from the trial protocol by telephone or email (an acknowledgment of email receipt is necessary) where appropriate. This should be documented.
When should the initiation, continuation, halt, suspension or extension of clinical trials be considered, and which criteria apply?	SUKL has not explicitly commented on this issue. Please see also the EU section above.

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Denmark

Have competent authorities issued any guidance?	The Danish medicines agency (DMA) issued guidance regarding extraordinary measures for clinical trials due to COVID-19 pandemic. The guidance is accessible here. In addition, sponsors, investigators and trial sites should consider the EU Guidance (please see the EU section above).
How should the closure/new opening of trial sites, the transfer of patients to other trials sites and/or diagnostic tests be handled?	DMA recommends that sponsors consider whether there could be a need (in certain cases) to transfer trial subjects from one site to another (e.g. to new sites or existing sites in less affected areas).
How should investigational visits be managed?	DMA recommends postponement of on-site visits and conduct of telephone consultations where appropriate.
Which measures should be taken to ensure the supply of investigational medicinal products (IMPs)?	DMA has also introduced a temporary option to distribute IMPs directly to trial subjects without involving the investigator or trial site pharmacies. Furthermore, DMA recommends providing trial subjects with IMPs for a longer period than normal, where appropriate. This option is valid until September 1, 2020, or until further notice.
How should clinical trials be monitored?	DMA recommends postponing on-site monitoring where appropriate. In the risk assessment, sponsors should consider whether remote audits or postponing of audits is the preferred option. On-site monitoring can be performed to the extent possible and as agreed by sponsors with trial sites. If the on-site monitoring plan cannot be followed, monitoring should be supplemented with centralized monitoring and central review of data, if possible. Monitors are not allowed to conduct remote source data verification (e.g. of patient records) in Denmark; however, provided that certain conditions are met, the following clinical trials are exempted from this prohibition until September 1, 2020: • clinical trials investigating treatment and prevention of COVID-19; and • pivotal clinical trials soon reaching Data Lock Point and thereby trial completion, analysis and reporting of trial data.
How should protocol amendments be managed and communicated to competent authorities?	DMA recommends that deviations due to COVID-19 pandemic should be handled as urgent safety measures (USM), so they can be implemented without approval from DMA. However, DMA shall be notified about the deviations unless the changes are covered by the guidance. DMA expects normal practice to be restored and notification carried out by September 1, 2020.

When should the initiation, continuation, halt, suspension or extension of clinical trials be considered, and which criteria apply?	It is DMA's general expectation that all first in human (FiH) trials will be put on hold, since they require an agreement with an intensive care unit, which DMA foresees cannot be ensured with proper contingency during the COVID-19 pandemic. Sponsors should assess whether clinical trials should be put on temporary halt in each specific case. In this case, sponsors should notify DMA. DMA continues, to any possible extent, to assess all trials within the normal deadlines so that trials can be initiated as soon as the situation has stabilized.

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Finland

Have competent authorities issued any guidance?	The guidance of the Finnish medicines agency (Fimea) is accessible here. Furthermore, Fimea follows closely the EU Guidance (please see the EU section above).
How should the closure/new opening of trial sites, the transfer of patients to other trials sites and/or diagnostic tests be handled?	Fimea has not explicitly commented on this issue. Please see also the EU section above.
How should investigational visits be managed?	Fimea has not explicitly commented on this issue. Please see also the EU section above.
Which measures should be taken to ensure the supply of investigational medicinal products (IMPs)?	Fimea recommends the delivery of IMPs to trial subjects' homes where appropriate.
How should clinical trials be monitored?	Fimea advises considering changes to monitoring plans (i.e. using other monitoring methods than on-site monitoring where appropriate).
How should protocol amendments be managed and communicated to competent authorities?	Sponsors must notify Fimea of any exceptional arrangements as soon as possible and submit the protocol amendment. Fimea will prioritize the evaluation of these amendments. For protocol amendments relating to the EU Guidance on conducting clinical trials during the COVID-19 pandemic, a single fee of EUR900 will be charged, regardless of how many amendments per trial during and after the pandemic are required.
When should the initiation, continuation, halt, suspension or extension of clinical trials be considered, and which criteria apply?	Fimea supports the prevention of the spread of COVID-19 and the minimization of such activities related to clinical trials, which may potentially contribute to the spread of the virus and which are not essential for ensuring the safety of trial subjects.

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France

Have competent authorities issued any guidance?	On March 20, 2020, the French medicines regulatory authority (ANSM) issued guidance relating to ongoing trials and opened an online FAQ section to assist sponsors (updated on April 8, 2020). The guidance of ANSM is accessible here and the FAQ on clinical trials here. In addition, sponsors, investigators and trial sites should consider the EU Guidance (please see the EU section above).
How should the closure/new opening of trial sites, the transfer of patients to other trials sites and/or diagnostic tests be handled?	ANSM recommends postponing on-site visits where appropriate. Furthermore, ANSM allows the transfer of trial subjects from one clinical trial site to another where appropriate following the procedure described in the FAQ. New clinical trial sites may be opened to unburden hospitals, to limit journeys for trial subjects or for treatment following the procedure described in the FAQ.
How should investigational visits be managed?	ANSM recommends deviations of follow-up visits and collection of information by telephone consultation where appropriate. Failure to carry out a protocol visit will not be considered a reason for leaving the trial and will not be considered a major deviation that must be notified to the ANSM.
Which measures should be taken to ensure the supply of investigational medicinal products (IMPs)?	ANSM recommends the delivery of IMPs in sufficient amounts for longer durations and to trial subjects' homes in compliance with safety instructions, patient information, and traceability requirements. Supplying of IMPs to trial subjects' homes must comply with safety instructions, patient information and traceability requirements.
How should clinical trials be monitored?	The ANSM recommends postponing monitoring visits at trial sites. Centralized monitoring remains possible. Please see also the EU section above.
How should protocol amendments be managed and communicated to competent authorities?	Measures for the management of clinical trials during the COVID-19 pandemic are exceptional and clinical trials will be conducted in the previous form at the end of the COVID-19 pandemic. Therefore, any provisional deviations that sponsors want to turn into permanent are subject to authorization by ANSM.
When should the initiation, continuation, halt, suspension or extension of clinical trials be considered, and which criteria apply?	Sponsors should consider the relevance of initiating new trials. ANSM will give priority to trials relating to the treatment of COVID-19 subjects.

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Germany

Have competent authorities issued any guidance?	The German Federal Institute for Drugs and Medical Devices (BfArM) and the Federal Institute for Vaccines and Biomedicines (PEI) explicitly refer to the updated EU Guidance (please see the EU section above). Furthermore, on March 26, 2020, BfArM and PEI published supplementary recommendations to the EU Guidance (last updated on May 19, 2020, version 3.0). The updated supplementary recommendations in English are accessible here (BfArM) and here (PEI). The topics subject to the supplementary recommendations generally take precedence over the EU Guidance.
How should the closure/new opening of trial sites, the transfer of patients to other trials sites and/or diagnostic tests be handled?	The EU Guidance as regards the closure of trials sites, the transfer of trial subjects to trial sites away from risk zones and the opening of new trials sites including critical laboratory tests, imaging and other diagnostic tests should be considered on a case-by-case basis. Furthermore, if external service providers, e.g. home-care services, assume trial related tasks, the investigator must ensure that the source data collected by them are transmitted to the investigator and that the persons employed are subject to the investigator's instructions and reporting obligations towards the investigator. Documents or recordings containing personal data of trial subjects must not leave the trial site, not even as copies. The essential requirements of data protection must be guaranteed by sponsors and investigators.
How should investigational visits be managed?	BfArM and PEI recommend changing on-site investigational visits to telephone consultations or telemedical visits where appropriate. However, if on-site investigational visits at the trial site need to be fully converted to telephone consultations or telemedical visits since on-site visits are not possible due to the COVID-19 pandemic, the sponsor must notify the BfArM or PEI and the competent ethics committee as an amendment to the clinical trial protocol requiring prior approval.
Which measures should be taken to ensure the supply of investigational medicinal products (IMPs)?	BfArM and PEI encourage the delivery of IMPs autonomously used by trial subjects directly to their homes where appropriate. In this case, investigators must ensure adequate medical supervision of the concerned trial subjects in accordance with the protocol. Furthermore, BfArM and PEI recommend that supply of IMPs to trial subjects' homes should be done by trial sites themselves. Shipment should be organized in a manner that allows tracking of both transport and delivery. Trial subjects should acknowledge the receipt of IMPs. Only in justified exceptional cases where adequate supply of IMPs by trial sites is not possible (for example, owing to capacity limitations, logistics or special transport conditions for IMPs), BfArM and PEI recommend direct supply of IMPs by sponsors to trial subjects' homes. For this, sponsors must appoint a suitably qualified service provider as a trustee. In addition, sponsors must contractually oblige this service provider to maintain the pseudonymization and, if necessary, blinding of the trial subjects towards sponsors by means of appropriate measures.

	BfArM and PEI consider amendments regarding IMPs supply to trial subjects as a substantial amendment that requires approval by BfArM or PEI and a positive opinion the competent ethics committee.
How should clinical trials be monitored?	BfArM and PEI recommend remote monitoring in the form of telephone and/or video consultation where appropriate. However, such remote monitoring should be limited to essential core data and processes to avoid an unnecessary burden on the investigator and the trial team. Furthermore, the possibility of remote access to source data, i.e. camera access to prepared study documents and records, is only a temporary solution during the COVID-19 pandemic. Particularly, remote access to source data should only take place in justified exceptional cases and only to the extent strictly necessary. The essential requirements of data protection must be guaranteed. Regardless of the method chosen for remote Source Data Verification (rSDV) (as further specified in the EU Guidance and the BfArM/PEI recommendations), sponsors must first obtain the written agreement of the investigator and, if applicable, of the trial site. Monitoring by video camera must be performed exclusively by sponsors' authorized personnel (i.e. the clinical monitor) in accordance with the written consent of trial subjects. The temporary adaptation of the monitoring plan and/or the monitoring manual does not require the submission of an amendment notification to BfArM or PEI and the competent ethics committee. Sponsors shall summarize the monitoring measures due to the COVID-19 pandemic in the trial report after completion of the trial. The amended monitoring plan and/or monitoring manual, as well as the documentation on the implementation of remote monitoring or other adapted monitoring measures should be stored in the trial master file. Sponsors should periodically review the necessity and suitability of the measures.
How should protocol amendments be managed and communicated to competent authorities?	A change in the trial protocol; for example, by the introduction of a previously unplanned remote treatment, the discontinuation of previously planned trial-related measures (e.g. laboratory tests, medical consultation) or the direct supply of IMPs to trial subjects' homes, requires approval by BfArM or PEI and a positive opinion by the competent ethics committee. Investigators must inform trial subjects about the changed procedures with a supplement to the trial subject information and the trial subjects should give their consent.
When should the initiation, continuation, halt, suspension or extension of clinical trials be considered, and which criteria apply?	Sponsors should evaluate whether continued recruitment during the pandemic is appropriate or should be suspended. If recruitment is to be halted, a notification of deviation to BfArM or PEI and the competent ethics committee is required; however, the amendment form can be omitted for reasons of simplification. A resumption of recruitment again requires a change notification, again, subject to approval by BfArM or PEI and the competent ethics committee. For COVID-19 related communication with BfArM, please include the term "COVID-19" in the subject of the email or cover letter. For inquiries in the context of new clinical trials in COVID-19, please use the email address CT-COVID@bfarm.de.

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Greece

Have competent authorities issued any guidance?	On March 17, 2020, the Greek medicines agency issued guidance on the management of clinical trials in light of the COVID-19 pandemic. The guidance is accessible here. In addition, sponsors, investigators and trial sites should consider the EU Guidance (please see the EU section above).
How should the closure/new opening of trial sites, the transfer of patients to other trials sites and/or diagnostic tests be handled?	The Greek medicines agency has not explicitly commented on this issue. Please see also the EU section above.
How should investigational visits be managed?	The Greek medicines agency has not explicitly commented on this issue. Please see also the EU section above.
Which measures should be taken to ensure the supply of investigational medicinal products (IMPs)?	The Greek medicines agency has not explicitly commented on this issue. Please see also the EU section above.
How should clinical trials be monitored?	The Greek medicines agency recommends changes in the monitoring plan, reinforcing centralized monitoring and remote monitoring where appropriate. However, trial subjects' source documents may not be remotely monitored.
How should protocol amendments be managed and communicated to competent authorities?	Sponsors should continuously assess and document deviations. Any required deviation in the procedures (temporary interruptions of trial subjects' recruitment, temporary interruptions of clinical trials, closing of the clinical trial center) may be considered as an urgent safety measure (USM) and be carried out without the authorization of the Greek medicines agency. However, sponsors must provide information to the Greek medicines agency about the measures taken and the assessment of the risk of such measures. Sponsors must inform clinical trial sites about any required deviations. It is important that the clinical trial sites agree to the deviations promoted by sponsors.
When should the initiation, continuation, halt, suspension or extension of clinical trials be considered, and which criteria apply?	The Greek medicines agency has not explicitly commented on this issue. Please see also the EU section above.

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Hungary

Have competent authorities issued any guidance?	The Hungarian medicines agency (HU Authority) launched a website with recommendations and measures taken with respect to the COVID-19 pandemic. The website is updated regularly and is accessible here. The latest update regarding the continuation of clinical trials during COVID-19 was published on May 5, 2020. In addition, sponsors, investigators and trial sites should consider the EU Guidance (please see the EU section above).
How should the closure/new opening of trial sites, the transfer of patients to other trials sites and/or diagnostic tests be handled?	Where appropriate, HU Authority recommends moving trial subjects to existing or new trial sites if necessary to cope with the COVID-19 pandemic. Such transfer of trial subjects may only be carried out with the consent of the trial subjects as well as the principle investigators (sender and recipient), ensuring that the new trial site may access all information and data collected previously and may be suitable for recording new data. The agreement on the transfer shall be documented (e.g. with emails). When critical laboratory or diagnostic tests are required when the trial subject cannot reach the trial site, it is acceptable that the tests are done at a local laboratory (or relevant clinical facility for other tests) authorized/certified (as legally required nationally) to perform such tests routinely. The sponsor must be informed thereon. In the event of a temporary relocation of a trial site, notification of HU Authority is sufficient to resume the investigation at the new site. Informed consents may be collected and information obligation towards study subjects may be performed via telecommunication. Sub-investigators may now take over the role of principle investigators without the formal approval of the HU Authority if the principle investigator is no longer available, for example, due to COVID-19.
How should investigational visits be managed?	Where appropriate, HU Authority recommends postponing on-site visits in order to ensure that only strictly necessary visits are made to trial sites. Visiting trial subjects in their home environment is not recommended by the HU Authority.
Which measures should be taken to ensure the supply of investigational medicinal products (IMPs)?	HU Authority encourages the transfer of IMPs between trial sites as well as the supply of trial subjects with IMPs for a longer period than originally planned if needed. In case of self-medication, the supply of IMPs (non-IMPs, rescue medication) to a trial subject's home may be a viable option, under the supervision of the principal investigator. Delivery from the trial site (pharmacy) should be primarily preferred. Independent distributors may also be contracted to supply IMPs in accordance with the EU Guidance.
How should clinical trials be monitored?	HU Authority encourages alternative monitoring methods (e.g. remote or central monitoring) to reduce on-site monitoring activities where appropriate. The description of the alternative monitoring measures must be submitted together with the clinical trial authorization application or it shall be treated as a substantial amendment.

	However, sharing of trial subjects' data and remote access to the electronic database of trial sites by sponsors' representatives is not permitted for data protection reasons. It is essential that robust follow-up measures are planned and ready to be implemented when the situation is normalized. This should include increased on-site monitoring for a period that is sufficient to ensure that the impact of the reduced monitoring can be rectified, and problems resolved or properly documented.
How should protocol amendments be managed and communicated to competent authorities?	If substantial protocol amendments are necessary to ensure the continued involvement of trial subjects, sponsors may implement those as urgent safety measures (USM) which become effective immediately. Any amendments shall be introduced after clear information and in agreement with the trial sites. Sponsors should assist trial sites with detailed instructions for local implementation of any change, including the clear indication of any amendments (track changes) in the documents. It is sufficient for sponsors to notify HU Authority about these amendments to be formally authorized in accordance with normal practice later. Instead of original wet ink signatures, the use of alternative documentation tools (such as printed email) is permitted by HU Authority. However, the use of electronic patient information leaflets and consent forms is not permitted. In order to prevent the spread of the infection and to prevent the delay of treatment, alternative measures (via telecommunications measures) are accepted to inform trial subjects and to obtain informed consent in COVID-19 related clinical trials and other clinical trials aiming the treatment or prevention of serious diseases without appropriate therapeutic possibilities. All proceedings before and communication with the HU Authority have now been made electronic (e.g. no need for even CD attachments to claims).
When should the initiation, continuation, halt, suspension or extension of clinical trials be considered, and which criteria apply?	Sponsors should suspend a trial if it is not possible to continue the trial at a particular site. Sponsors should also consider postponing enrollment of trial subjects. Furthermore, measures should be taken to ensure the safety of trial subjects and the adequacy of data. HU Authority recommends sponsors consider whether to continue the trial for trial subjects at particular risk from COVID-19 (e.g. subjects undergoing immunosuppressant therapy, subjects over 60, subjects with chronic diseases).

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Ireland

Have competent authorities issued any guidance?	On April 2, 2020, the Irish medicines regulatory authority (HPRA) provided updated guidance on the management of clinical trials during the COVID-19 pandemic (version 5.0). The updated guidance is accessible here. HPRA also created a webpage devoted specifically to COVID-19 updates, which can be accessed here. In addition, sponsors, investigators and trial sites should consider the EU Guidance (please see the EU section above).
How should the closure/new opening of trial sites, the transfer of patients to other trials sites and/or diagnostic tests be handled?	HPRA recommends the addition of a new location to an existing trial site or the use of another trial site for trial subject visits where appropriate. This would still require amendment to the clinical trial application form and approval from the responsible ethics committee, notwithstanding the potential to use an urgent safety measure (USM) where appropriate. All routine compliance inspections to trial sites have been postponed until further notice.
How should investigational visits be managed?	Where a trial subject is unable to attend the site, HPRA recognizes that other measures, such as contact via telephone or home nursing visit may be required to identify adverse events and ensure continuous medical care and supervision. However, limitations of such methods should be considered, including the ability of investigator oversight.
Which measures should be taken to ensure the supply of investigational medicinal products (IMPs)?	HPRA recommends the supply of IMPs directly to trial subjects' homes and/or other alternatives for the delivery of IMPs where appropriate. HPRA currently considers direct supply of IMPs from sponsor to trial subjects not acceptable. The allocation of IMPs is the responsibility of the investigator and the supply of IMPs from the trial site to the trial subjects' homes via a delivery service may be considered, and the sponsor may provide assistance and advice to the investigator in relation to this. The delivery is subject to compliance with the ICH good clinical practice (GCP).
How should clinical trials be monitored?	HPRA recommends considering remote monitoring of clinical trials where appropriate. Centralized monitoring may be a suitable alternative in the interim, with a focus on core aspects of trial conduct. It should be noted that off-site trial subject data involves data protection and ethical considerations and is generally not acceptable.

How should protocol amendments be managed and communicated to competent authorities?	Substantial amendments to ongoing clinical trials, or other urgent amends, should be submitted to HPRA as required and marked as "COVID-19 relevant."
When should the initiation, continuation, halt, suspension or extension of clinical trials be considered, and which criteria apply?	HPRA recommends re-examining the commencement of new trials, ongoing recruitment and continued trial subject participation, including halting or suspending recruitment, and discontinuing trial subjects. In this context, particular attention should be given to the continuance of trial subjects who may be determined as at-risk groups; for example, trial subjects who are immunosuppressed, over 60 years of age or have long term medical conditions. Furthermore, attention should be given to the impact on trial subjects in any trials involving immunosuppressant therapies.

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Italy

Have competent authorities issued any guidance?	On March 12, 2020, the Italian medicines agency (AIFA) introduced a temporary derogatory regime aimed at tackling some of the challenges raised by the spread of COVID-19 with respect to the management of clinical trials conducted in Italy. On April 7, 2020, AIFA updated the guidance issued on March 12, 2020, providing additional recommendations on managing clinical trials during the COVID-19 pandemic. The updated guidance is accessible here. In addition, sponsors, investigators and trial sites should consider the EU Guidance (please see the EU section above).
How should the closure/new opening of trial sites, the transfer of patients to other trials sites and/or diagnostic tests be handled?	AIFA recommends the transfer of trial subjects to other clinical trial sites, in case the measures adopted by local competent authorities lead to the closing of involved trial sites. Where appropriate, sponsors may consider: • entering into service agreements with third-party providers to carry out activities related to clinical management of trial subjects (e.g. home nursing services); and/or • reimbursing expenses borne by trial subjects if they keep appropriate supporting documentation. Where possible, such reimbursement should be indirect (i.e. through the healthcare facility).
How should investigational visits be managed?	AIFA recommends canceling or postponing non-urgent visits. Where appropriate, AIFA encourages the performance of clinical examinations in: • laboratories near trial subjects' homes; and/or • private sites (in the absence of viable alternatives).
Which measures should be taken to ensure the supply of investigational medicinal products (IMPs)?	Sponsors should consider the following options to provide trial subjects with IMPs: • directly delivering IMPs from the hospital pharmacy of the trial site to trial subjects' homes, also by means of specialized couriers, under the supervision and responsibility of the concerned hospital pharmacy and principal investigator; • delivering IMPs from the hospital pharmacy of the trial site to trial subjects through their caregivers or relatives; or • delivering IMPs from sponsors' authorized warehouses to trial subjects' homes. Furthermore, AIFA allows the provision of larger amounts of IMPs to trial subjects at the site for covering a longer period.
How should clinical trials be monitored?	AIFA encourages performing clinical trial monitoring by means of telephone calls or videoconferences where appropriate.

How should protocol amendments be managed and communicated to competent authorities?	Sponsors may immediately implement urgent measures to cope with the COVID-19 pandemic by submitting a notification to the ethics committee flagging the urgency due to the COVID-19 pandemic. Sponsors must notify such measures as substantial amendments due to the COVID-19 pandemic and not as urgent safety measures (USM). Where necessary, sponsors may obtain trial subjects' informed consent through alternative methods (e.g. telephone or email). Sponsors may also obtain the informed consent verbally, in the presence of a witness. Without prejudice to the above, sponsors must obtain trial subjects' written consents as soon as possible.
When should the initiation, continuation, halt, suspension or extension of clinical trials be considered, and which criteria apply?	If the trial site is unable to follow-up on trial subjects, the trial should be temporarily halted or, where appropriate, enrolled trial subjects should be transferred to the nearest active trial site. Sponsors must notify the ethics committee of any suspension or halt of the clinical trial as well as any enrollment as a substantial amendment.

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Luxembourg

Have competent authorities issued any guidance?	To date, no official guidance has been issued by Luxembourg authorities regarding the management of ongoing clinical trials during the COVID-19 pandemic. Sponsors, investigators and trial sites should consider the EU Guidance (please see the EU section above).
How should the closure/new opening of trial sites, the transfer of patients to other trials sites and/or diagnostic tests be handled?	The Luxembourg authorities have not explicitly commented on this issue. Please see also the EU section above.
How should investigational visits be managed?	The Luxembourg authorities have not explicitly commented on this issue. Please see also the EU section above.
Which measures should be taken to ensure the supply of investigational medicinal products (IMPs)?	The Luxembourg authorities have not explicitly commented on this issue. Please see also the EU section above.
How should clinical trials be monitored?	The Luxembourg authorities have not explicitly commented on this issue. Please see also the EU section above.
How should protocol amendments be managed and communicated to competent authorities?	The Luxembourg authorities have not explicitly commented on this issue. Please see also the EU section above.
When should the initiation, continuation, halt, suspension or extension of clinical trials be considered, and which criteria apply?	The Luxembourg authorities have not explicitly commented on this issue. Please see also the EU section above.

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The Netherlands

Have competent authorities issued any guidance?	The Netherlands medicines agency (CCHR) issued guidance aiming at harmonizing the approach of local authorities during the COVID-19 pandemic. The guidance is accessible here. In addition, sponsors, investigators and trial sites should consider the EU Guidance (please see the EU section above). In case of circumstances that are not covered by the guidance, CCHR suggests taking proportional measures and making sure that deviations from the protocol are well documented.
How should the closure/new opening of trial sites, the transfer of patients to other trials sites and/or diagnostic tests be handled?	CCHR has not explicitly commented on this issue. Please see also the EU section above.
How should investigational visits be managed?	CCHR has not explicitly commented on this issue. Please see also the EU section above.
Which measures should be taken to ensure the supply of investigational medicinal products (IMPs)?	The trial site hospital pharmacy may send IMPs directly to trial subjects' homes (e.g. by means of couriers) where appropriate.
How should clinical trials be monitored?	CCHR has not explicitly commented on this issue. Please see also the EU section above.
How should protocol amendments be managed and communicated to competent authorities?	CCHR recommends documenting all deviations from the protocol and the SOP in writing. Notification of such deviations only needs to be submitted to the review committee if trial subjects' safety is at stake. Deviations due to urgent safety measures (USM) to eliminate immediate hazards to trial subjects are permitted without prior approval by the review committee. However, this must be reported immediately to the review committee. A fast track review policy with the review committee applies to substantial amendments to the protocol, which have an impact on trial subjects' safety. CCHR temporarily suspended the obligation to submit a cover letter with a wet signature for initial applications and substantial amendments to the review committee and/or the competent authority. Instead, a digital or scanned signature of the applicant is sufficient.

When should the initiation, continuation, halt, suspension or extension of clinical trials be considered, and which criteria apply?	If the trial is (partially) suspended, for reasons concerning trial subjects' safety, this must be reported immediately to the review committee. A temporary halt for other reasons should be reported within 15 days. If the study is terminated prematurely, this must be reported to the review committee as soon as possible, but at the latest within 15 days.

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Norway

Have competent authorities issued any guidance?	The Norwegian medicines agency (NoMA) issued guidance relating to the management of clinical trials. The guidance is accessible here. In addition, sponsors, investigators and trial sites should consider the EU Guidance (please see the EU section above).
How should the closure/new opening of trial sites, the transfer of patients to other trials sites and/or diagnostic tests be handled?	NoMA recommends inviting trial subjects to attend their appointments at a different trial site where appropriate.
How should investigational visits be managed?	NoMA recommends changing the method for study-specific examinations during the COVID-19 pandemic where appropriate. For example, a study nurse may carry out examinations without physically visiting trial subjects (e.g. at trial subjects' homes or by other appropriate methods).
Which measures should be taken to ensure the supply of investigational medicinal products (IMPs)?	Where appropriate, the hospital pharmacy of the trial site may send IMPs directly to trial subjects' homes.
How should clinical trials be monitored?	Sponsors may implement centralized monitoring based on data documented in electronic Case Report Forms (eCRFs). Remote source data verification is strictly prohibited.
How should protocol amendments be managed and communicated to competent authorities?	NoMA considers all changes made in clinical trials as a result of the COVID-19 pandemic as urgent safety measures (USM) that do not require prior approval.
When should the initiation, continuation, halt, suspension or extension of clinical trials be considered, and which criteria apply?	NoMA has not explicitly commented on this issue. Please see also the EU section above.

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Poland

Have competent authorities issued any guidance?	On March 19, 2020, the Polish medicines agency issued guidance on clinical trials conducted during the COVID-19 pandemic. The guidance is accessible here. In addition, sponsors, investigators and trial sites should consider the EU Guidance (please see the EU section above).
How should the closure/new opening of trial sites, the transfer of patients to other trials sites and/or diagnostic tests be handled?	The Polish medicines agency has not explicitly commented on this issue. Please see also the EU section above.
How should investigational visits be managed?	The Polish medicines agency has not explicitly commented on this issue. Please see also the EU section above.
Which measures should be taken to ensure the supply of investigational medicinal products (IMPs)?	The Polish medicines agency has not explicitly commented on this issue. Please see also the EU section above.
How should clinical trials be monitored?	The Polish medicines agency has not explicitly commented on this issue. Please see also the EU section above.
How should protocol amendments be managed and communicated to competent authorities?	Sponsors should immediately inform the Polish medicines agency and the ethics committee about any safety measures taken.
When should the initiation, continuation, halt, suspension or extension of clinical trials be considered, and which criteria apply?	The Polish medicines agency recommends sponsors to reconsider any new applications for the initiation of a clinical trial during the COVID-19 pandemic. In the case of any event potentially affecting the safety of trial subjects, sponsors and principal investigators should halt the respective clinical trial in accordance with the applicable protocol.

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Portugal

Have competent authorities issued any guidance?	On March 17, 2020, (updated on March 31, 2020, and April 3, 2020), the Ethics Committee for Clinical Research (CEIC) issued guidance on clinical trials or intervention studies in light of COVID-19 pandemic. The guidance is accessible here. On March 26, 2020, (updated on April 15, 2020, and May 11, 2020), the Portuguese medicines agency (Infarmed) issued guidance on exceptional measures in the context of clinical trials during the period of public health risk. The guidance is accessible here. In addition, sponsors, investigators and trial sites should consider the EU Guidance (please see the EU section above).
How should the closure/new opening of trial sites, the transfer of patients to other trials sites and/or diagnostic tests be handled?	It is recommended to transfer trial subjects to other clinical trial sites where appropriate. Sponsors must notify CEIC. CEIC considers such measures as urgent safety measures (USM) and, both CEIC and Infarmed, consider such measures as non-substantial amendments to the trial protocol/SOP.
How should investigational visits be managed?	It is recommended to replace face-to-face visits with telephone or video calls where appropriate. Sponsors must notify CEIC. Sponsors must obtain trial subjects' consents for the use of telematic means. Verbal consent is accepted if recorded by the trial team or sent by email (video or sound registration), subject to confirmation by the trial subjects' signature once the current situation is normalized. CEIC and Infarmed consider such measures as a non-substantial amendment to the trial protocol/SOP.
Which measures should be taken to ensure the supply of investigational medicinal products (IMPs)?	The hospital pharmacy of the trial site may supply IMPs directly to trial subjects' homes in compliance with the Good Clinical Practice (GCP) and other applicable regulations provided that: • trial subjects cannot reach the trial site due to the COVID-19 pandemic; • sponsors submit a notification to CEIC (as a non-substantial amendment); • transport of IMPs complies with GDP requirements, is tracked and recorded, and records on packaging and temperature/humidity during transport are kept (these requirements are further applicable to transfer of IMPs to other trial sites); • a nurse (or appropriately qualified individual) assists trial subjects with the correct administration of IMPs if necessary (sponsors must notify CEIC if home nursing is not foreseen in the trial protocol/SOP as a substantial amendment); • the principal investigator and the research team (including the trial site pharmacy) supervise the delivery of IMPs; • access to trial subjects' personal data (name and address) for this purpose is consented; and • trial subjects are informed about the administration and surveillance process, and have necessary means to communicate adverse events.

	• trial subjects are informed about the administration and surveillance process and have necessary means to communicate adverse events. Import/export of IMPs is allowed provided Infarmed is given notice including a description of the situation and statements on the indispensability of supplying the IMPs to a specific trial subject.
How should clinical trials be monitored?	CEIC and Infarmed encourage remote monitoring (e.g. by telephone or video calls) where appropriate. Sponsors and investigators must safeguard trial subjects' data confidentiality.
How should protocol amendments be managed and communicated to competent authorities?	Sponsors must document, classify and notify all protocol deviations to CEIC. Sponsors must notify Infarmed about implemented measures and deviations, the assessment of the implementation of these measures and, after the pandemic ends, their impact on the clinical trial. Deviations necessary to cope with the COVID-19 pandemic do not constitute substantial amendments to the trial protocol, unless risks to trial subjects' safety and well-being, requiring changes to the informed consent, result from such measures. Supply of IMPs to trial subjects' homes does not require prior formal re-consent (verbal consent by telephone or video calls, if possible confirmed by follow-up email, is sufficient).
When should the initiation, continuation, halt, suspension or extension of clinical trials be considered, and which criteria apply?	Infarmed advises sponsors to consider temporary or permanent halts of trials where appropriate. CEIC recommends the initiation of approved clinical trials to be carefully evaluated while there is no guarantee that conditions to comply with the SOP exist. New trial subjects may not be included in the trial, if full compliance with applicable inclusion and exclusion criteria, according to the protocol, cannot be ensured.

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Romania

Have competent authorities issued any guidance?	The Romanian medicines agency (ANMDMR) published two press releases addressed to sponsors. The documents are accessible here and here. In addition, sponsors, investigators and trial sites should consider the EU Guidance (please see the EU section above).
How should the closure/new opening of trial sites, the transfer of patients to other trials sites and/or diagnostic tests be handled?	Certain hospitals (including certain trial sites) were assigned to treat COVID-19 patients exclusively. Therefore, trial subjects may have to be moved to other trial sites.
How should investigational visits be managed?	ANMDMR recommends temporarily suspending scheduled visits of trial subjects, unless the principal investigator considers them necessary. Generally, ANMDMR encourages telephone consultations where appropriate.
Which measures should be taken to ensure the supply of investigational medicinal products (IMPs)?	ANMDMR recommends delivering IMPs to trial subjects' homes where appropriate.
How should clinical trials be monitored?	ANMDMR encourages remote monitoring where appropriate.
How should protocol amendments be managed and communicated to competent authorities?	Sponsors should assess the potential impacts of measures taken by local authorities, for the protection against COVID-19, on each clinical trial. They should notify ANMDMR of any measures taken to cope with the pandemic. ANMDMR will prioritize the evaluation of clinical trials related to medicines used for the treatment of COVID-19.
When should the initiation, continuation, halt, suspension or extension of clinical trials be considered, and which criteria apply?	ANMDMR recommends delaying the initiation of new trials and the opening of new trial centers.

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Russia

Have competent authorities issued any guidance?	To date, no specific guidance has been issued.
How should the closure/new opening of trial sites, the transfer of patients to other trials sites and/or diagnostic tests be handled?	N/A
How should investigational visits be managed?	N/A
Which measures should be taken to ensure the supply of investigational medicinal products (IMPs)?	N/A
How should clinical trials be monitored?	N/A
How should protocol amendments be managed and communicated to competent authorities?	N/A
When should the initiation, continuation, halt, suspension or extension of clinical trials be considered, and which criteria apply?	N/A

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Slovakia

Have competent authorities issued any guidance?	On March 16, 2020, the Slovakian medicines agency (the State Institute for Drug Control) issued guidance on clinical trial management during COVID-19 pandemic. The guidance is accessible here. On March 13, 2020, the Slovakian medicines agency also issued guidance on the supply of IMPs to trial subjects during the COVID-19 pandemic. The guidance is accessible here. In addition, sponsors, investigators and trial sites should consider the EU Guidance (please see the EU section above).
How should the closure/new opening of trial sites, the transfer of patients to other trials sites and/or diagnostic tests be handled?	The Slovakian medicines agency has not explicitly commented on this issue. Please see also the EU section above.
How should investigational visits be managed?	The Slovakian medicines agency has not explicitly commented on this issue. Please see also the EU section above.
Which measures should be taken to ensure the supply of investigational medicinal products (IMPs)?	Trial sites may dispense IMPs to trial subjects' relatives at an approved clinical trial site where appropriate. Trial sites may also supply IMPs directly to trial subjects' homes by means of couriers where appropriate.
How should clinical trials be monitored?	The Slovakian medicines agency has not explicitly commented on this issue. Please see also the EU section above.
How should protocol amendments be managed and communicated to competent authorities?	The Slovakian medicines agency recommends that investigators manage any deviations from the protocol in accordance with their SOP. The Slovakian medicines agency considers deviations resulting from COVID-19 pandemic and affecting the risk-benefit assessment of clinical trials as urgent safety measures (USM). Although USM do not require prior approval, sponsors should notify the Slovakian medicines agency including a detailed risk assessment.
When should the initiation, continuation, halt, suspension or extension of clinical trials be considered, and which criteria apply?	The Slovakian medicines agency has not explicitly commented on this issue. Please see also the EU section above.

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Slovenia

Have competent authorities issued any guidance?	On March 24, 2020, the Slovenian medicines agency (JAZMP) published a notice to sponsors and their partners, informing them of the publication of the new EU Guidance (updated on May 13, 2020). The notice is accessible here. In the absence of any specific national guidance, sponsors, investigators, trial sites and other stakeholders are thus expected to follow the EU Guidance (please see the EU section above).
How should the closure/new opening of trial sites, the transfer of patients to other trials sites and/or diagnostic tests be handled?	JAZMP has not explicitly commented on this issue. Please see also the EU section above.
How should investigational visits be managed?	JAZMP has not explicitly commented on this issue. Please see also the EU section above.
Which measures should be taken to ensure the supply of investigational medicinal products (IMPs)?	JAZMP has not explicitly commented on this issue. Please see also the EU section above.
How should clinical trials be monitored?	JAZMP has not explicitly commented on this issue. Please see also the EU section above.
How should protocol amendments be managed and communicated to competent authorities?	Sponsors should base any decision to deviate from the protocol on a risk assessment. Sponsors should inform JAZMP of all measures (taken and planned to be taken) affecting the performance of clinical trials. Sponsors may take urgent safety measures (USM) without prior notification, if they inform JAZMP as soon as possible. Measures affecting trial subjects' safety and/or the scientific value of the trial, but not requiring immediate action from sponsors or investigators, will have to be notified to JAZMP as substantial amendments. Such substantial amendment notifications should contain the label "COVID-19."
When should the initiation, continuation, halt, suspension or extension of clinical trials be considered, and which criteria apply?	JAZMP has not explicitly commented on this issue. Please see also the EU section above.

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Spain

Have competent authorities issued any guidance?	On March 16, 2020, the Spanish medicines agency (AEMPS) published guidance on measures concerning clinical trials management during the COVID-19 pandemic. The guidance is accessible here. In addition, sponsors, investigators and trial sites should consider the EU Guidance (please see the EU section above).
How should the closure/new opening of trial sites, the transfer of patients to other trials sites and/or diagnostic tests be handled?	According to AEMPS, any change of clinical trial sites requires: • a transfer agreement between sponsors and clinical trial sites; • transfer of data collection notebook and trial subjects' medical records to the new site; • sending of a transfer report summarizing trial subjects' most relevant medical data; and • filing of the documentation concerning trial subjects.
How should investigational visits be managed?	Sponsors and investigators should consider where appropriate: • postponing visits; or • using remote systems (e.g. telephone calls). However, investigators should carry out scheduled critical on-site visits. AEMPS considers rescheduling of visits as non-serious infringement, unless it puts trial subjects' safety at risk.
Which measures should be taken to ensure the supply of investigational medicinal products (IMPs)?	The trial site hospital pharmacy may dispense IMPs to an authorized person or deliver IMPs to trial subjects' treatment homes where appropriate. The investigator may evaluate the possibility (and convenience) to provide a higher quantity of IMPs to cover a longer period of treatment where appropriate.
How should clinical trials be monitored?	Where appropriate, sponsors should update monitoring plans for the next four months by prioritizing: • centralized monitoring; • remote monitoring; and/or • postponement of source data verification.

How should protocol amendments be managed and communicated to competent authorities?	The principal investigator must document, in the clinical trial file, any exceptional measures taken. However, the implementation of such measures does not require prior authorization by AEMPS for substantial amendments, unless the trial is interrupted or terminated. Within four months after the end of the COVID-19 pandemic in Spain, sponsors have to communicate, for each clinical trial, a report on the exceptional measures taken and send it to AEMPS and the ethics committee (CEIm).
When should the initiation, continuation, halt, suspension or extension of clinical trials be considered, and which criteria apply?	Sponsors and investigators may interrupt the recruitment and even stop the treatment in order to avoid unnecessary risks for trial subjects. These measures must be notified to AEMPS and CEIm within 15 days.

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Sweden

Have competent authorities issued any guidance?	The Swedish medicines agency (MPA) published guidance relating to the management of clinical trials in the context of the COVID-19 pandemic. The guidance is accessible here. In addition, sponsors, investigators and trial sites should consider the EU Guidance (please see the EU section above).
How should the closure/new opening of trial sites, the transfer of patients to other trials sites and/or diagnostic tests be handled?	Sponsors may change clinical trial sites where appropriate. In such cases, sponsors must submit a substantial amendment notification in accordance with applicable regulations. MPA will handle such applications quickly.
How should investigational visits be managed?	MPA has not explicitly commented on this issue. Please see also the EU section above.
Which measures should be taken to ensure the supply of investigational medicinal products (IMPs)?	MPA recommends delivering IMPs to trial subjects' homes where appropriate and provides some guidance on aspects to consider if home delivery of IMPs is considered.
How should clinical trials be monitored?	MPA recommends that sponsors carry out and document a renewed risk analysis and update the monitoring plan under current circumstances. In addition to postponing monitoring visits, this may result in increasing digital collection of monitoring data and to have ongoing contact with trial sites via telephone and email.
How should protocol amendments be managed and communicated to competent authorities?	Emergency situations in relation to COVID-19 are considered urgent safety measures (USM) that sponsors may implement without prior approval of MPA. However, sponsors must inform MPA without delay. In case of protocol deviations, concerning trial subjects not being able to conduct scheduled study visits and sponsor staff not being able to visit affected clinics under current circumstances, sponsors must protocol such nonconformities and decide whether these need to be reported as a serious violation to MPA in accordance with applicable regulations.
When should the initiation, continuation, halt, suspension or extension of clinical trials be considered, and which criteria apply?	MPA has not explicitly commented on this issue. Please see also the EU section above.

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UK

Have competent authorities issued any guidance?	The UK medicines regulatory authority (MHRA) issued guidance which is constantly being updated in response to the rapidly evolving COVID-19 pandemic in the UK. The latest guidance is accessible here, (dated April 22, 2020) with an additional blog post detailing the MHRA's direction which is accessible here. In addition, during the Brexit transition period, ending on December 31, 2020, sponsors, investigators and trial sites should consider the EU Guidance (please see the EU section above).
How should the closure/new opening of trial sites, the transfer of patients to other trials sites and/or diagnostic tests be handled?	While MHRA has not explicitly commented on this issue, MHRA has indicated that the trial site has a duty of care towards trial subjects in relation to any actions taken at the trial site. Please see also the EU section above.
How should investigational visits be managed?	Changes to the visiting procedure during a trial may become necessary. Generally, accurately documented telephone consultations should be preferred to in-person visits where COVID-19 renders in-person visits impossible. While MHRA allows a reduction in the number of trial subjects visits as a result of the COVID-19 pandemic, without submitting a substantial amendment notification, investigators must appropriately document the risk assessment and rationale to ensure mitigation of risks and protection of trial subjects' safety. If it is not possible to ensure adequate monitoring of the trial subjects (even with adaptions such as telephone consultations), the benefit/risk balance of the trial should be revisited, and any additional measures discussed with the MHRA prior to submission of a substantial amendment for authorization.
Which measures should be taken to ensure the supply of investigational medicinal products (IMPs)?	MHRA recommends that investigators should consider delivering IMPs to trial subjects' homes where appropriate (this can be delivered from the trial site or directly from the sponsor). A substantial amendment notification to MHRA is not required. Sponsors must carry out a risk assessment (and record it internally) and trial subjects must verbally consent (which is documented) to providing contact details for shipping purposes. Sponsors and investigators should consider: • storage requirements for IMPs and stability in transit; • delays in postal services; • IMP accountability (i.e. the mechanism to confirm that the trial subject has received the IMPs); and • if any training is required for administration of the IMPs. A risk assessment needs to be undertaken if COVID-19 related issues affect the ability of the investigator or trial site to perform IMP accountability – it all depends on whether anything needs to be returned after being used by the trial subject. Alternative methods should be considered, such as asking trial subjects to make a count, or submit a photograph or quarantining the packaging returned for a period of time.

How should clinical trials be monitored?	MHRA supports remote monitoring and the use of alternative means of oversight such as teleconferences/videoconferences, but the protection of confidential information must be addressed if there is direct access to trial subjects' Electronic Health Records away from the site – there should be strict privacy controls (including firewalls and other data security measures) around what can be accessed and from where provided by sponsor and host organization (with input from Caldicott Guardian). Please refer to the MHRA blog, the HRA blog and the MHRA GCP Forum FAQs on monitoring/remote monitoring for further guidance. Please see also the EU section above.
How should protocol amendments be managed and communicated to competent authorities?	Deviations due to COVID-19 pandemic do not constitute a serious breach of clinical trial protocol and sponsors do no need to report them to MHRA (subject to a few exceptions, including where trial subjects are being put at risk and if a trial is halted due to a medicine supply issue). Deviations may include: • halting/delaying a trial (in this case, the trial master file should note this, including the reasons why; no amendment notification would be required when the trial restarts, provided that there are no substantial amendments to the Clinical Trial Authorization or a substantial amendment was approved to halt the trial in the first place); • discontinuing a trial subject (e.g. if the safety of a trial subject is at risk); • remote monitoring; and/or • changes to the visiting procedure during a trial. Sponsors should actively participate in decision-making and also ensure support in documenting protocol deviations due to adaptations and deal with any regulatory/ethics committee notifications/submissions. Investigators can implement urgent safety measures (USM) where necessary to protect trial subjects against any immediate hazard to their health or safety (these are not pre-planned changes to trial conduct as a result of COVID-19, e.g. changes to IMP delivery methods or scheduling). Notification of USMs must be made to the MHRA and the relevant ethics committee within three days of their implementation.
When should the initiation, continuation, halt, suspension or extension of clinical trials be considered, and which criteria apply?	MHRA considers trial subjects' safety as the main focus that cannot be compromised under any circumstances. Investigators should carry out a risk/benefit assessment on a trial by trial basis regarding the continuation of the trial for both ongoing trial subjects and recruitment of new trial subjects. The risk/benefit assessment should (as a minimum) take into account: • participant population; • IMP mode of action; and • trial design.

It should consider whether to halt recruitment, continue with different approach to delivery and/or putting risk mitigation in place, or stopping or suspending the trial completely. If a trial has been halted, the sponsor will need to inform MHRA if they do not recommence the trial within 15 days of the decision.

This includes ensuring all prospective trial subjects still meet eligibility criteria to participate in a clinical trial (prospective protocol waivers remain unacceptable) and ensuring timely reporting of serious adverse events (SAE) and suspected unexpected serious adverse reactions (SUSAR).

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Ukraine

Have competent authorities issued any guidance?	The State Expert Center of Ministry of Healthcare of Ukraine (State Expert Center) published guidance (consisting of two documents) concerning clinical trials management during the COVID-19 pandemic. The guidance is accessible here and here. Moreover, State Expert Center issued non-official guidance on reporting serious adverse events (SAE). The guidance is accessible here.
How should the closure/new opening of trial sites, the transfer of patients to other trials sites and/or diagnostic tests be handled?	Sponsors and investigators may consider transferring clinical trials subjects to alternative trial sites, if current trials sites are closed due to measures adopted by local competent authorities. Transfers shall be possible provided that: • there is an alternative trial site under the trial protocol; • the alternative trial site has the possibility to introduce new data to the electronic Case Report Forms (eCRFs) and has access to prior collected data of trial subjects; • informed consent of respective trial subjects is obtained; and • proper documenting by sponsors and investigators from both trial sites is conducted.
How should investigational visits be managed?	Investigators and sponsors may consider rescheduling investigational visits. If it is impossible for clinical trials subjects to reach clinical trial sites, members of the trial team may visit trial subjects at their homes for clinical or diagnostic tests in accordance with the protocol. In addition, trial subjects may undergo testing in other laboratories than those within trial sites; however, such other laboratories shall be specified by sponsors/investigators.
Which measures should be taken to ensure the supply of investigational medicinal products (IMPs)?	Sponsors should consider the appropriateness of delivering IMPs to trial subjects' homes in compliance with applicable regulations. IMPs should be supplied to trial subjects' homes by the trial team/trial site. Alternatively, the supply may be performed by third-party service providers subject to further requirements.
How should clinical trials be monitored?	Alternative monitoring measures, including telephone calls, video calls and the use of electronic communication devices should be considered where appropriate, given they ensure trial subjects' safety, confidentiality and protection of personal data. Remote monitoring should be considered only if it does not create an extra burden on trial sites. Remote monitoring is subject to approval by sponsors and proper documenting. Remote monitoring shall not be used for monitoring trial subjects' source data. Furthermore, monitoring of source data shall be postponed as far as possible until the renewal of access to source medical records.

How should protocol amendments be managed and communicated to competent authorities?	Investigators may deviate from trial protocols to avoid risks for trial subjects. Such deviation does not require prior approval from the State Expert Center. Investigators must notify such deviations to the ethics committee and sponsors, while the latter must approve them (if necessary) and submit a notification to the State Expert Center. State Expert Center considers deviations concerning the treatment of trial subjects' personal data as substantial amendments requiring, inter alia, trial subjects' express informed consents which may be obtained during the quarantine of trial subjects; for example, via telephone and confirmed by email. All consents obtained, as described above, must be documented. When it becomes practically possible, trial subjects must sign an amended informed consent form in writing.
When should the initiation, continuation, halt, suspension or extension of clinical trials be considered, and which criteria apply?	In case of risks to trial subjects' safety due to the impossibility to complete key evaluations or adhere to risk mitigation steps, and/or in case trial sites cannot continue trials (and there is no possibility to transfer trial subjects to alternative sites), the State Expert Center recommends withdrawing trial subjects and terminating/suspending the recruitment of new trial subjects. New clinical trials subjects shall not be included in trials if there is no possibility to assess inclusion/exclusion criteria, including testing and/or obtaining written informed consent.

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Latin America

Argentina

Have competent authorities issued any guidance?	On March 20, 2020, the Argentinian medicines agency (ANMAT) published guidance for sponsors relating to the COVID-19 pandemic. The guidance is accessible here.
How should the closure/new opening of trial sites, the transfer of patients to other trials sites and/or diagnostic tests be handled?	Investigators should avoid the conglomeration of trial subjects at trial sites where appropriate. Every transportation of trial subjects should be filed in the mitigation plans documents and notified to ANMAT by sponsors.
How should investigational visits be managed?	Sponsors should restrict face-to-face contacts, for example, by establishing a remote monitoring system by telephone or videoconference.
Which measures should be taken to ensure the supply of investigational medicinal products (IMPs)?	In regards of the supply of IMPs, ANMAT recommends: • supplying IMPs directly to trial subjects' homes; and/or • providing trial subjects with a larger amount of IMPs to cover a longer period of time where appropriate.
How should clinical trials be monitored?	Sponsors should restrict face-to-face contact; for example, by establishing a remote monitoring system by telephone or videoconference.
How should protocol amendments be managed and communicated to competent authorities?	ANMAT has not explicitly commented on this issue. The general protocol amendment rules apply.
When should the initiation, continuation, halt, suspension or extension of clinical trials be considered, and which criteria apply?	Sponsors should suspend recruiting activities (for phase I, II or III trials) on healthy trial subjects, except for trials relating to the prevention or treatment of COVID-19. Sponsors and investigators should consider the suspension of all recruiting activities and trial subjects' treatments to avoid unnecessary risks. If a trial is interrupted, sponsors and the investigator must inform ANMAT accordingly.

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Brazil

Have competent authorities issued any guidance?	The Brazilian medicines agency (ANVISA) issued guidance on the conduct of clinical trials during the COVID-19 pandemic. The guidance is accessible here.
How should the closure/new opening of trial sites, the transfer of patients to other trials sites and/or diagnostic tests be handled?	ANVISA recommends taking proactive actions to cope with any COVID-19 pandemic related impact on the conduct of clinical trials.
How should investigational visits be managed?	Sponsors should evaluate whether alternative methods for safety assessments (e.g. telephone contact, virtual visit, alternative location) could be implemented when necessary and feasible.
Which measures should be taken to ensure the supply of investigational medicinal products (IMPs)?	Certain IMPs (e.g. for self-administration) may be amenable to alternative secure supply methods. For IMPs that are normally administered in a hospital setting, sponsors should consult ANVISA about plans for alternative supply (e.g. home nursing or alternative sites).
How should clinical trials be monitored?	If planned on-site monitoring visits are no longer possible, sponsors should consider the central and remote monitoring to maintain oversight of clinical trials and trial sites.
How should protocol amendments be managed and communicated to competent authorities?	COVID-19 screenings that may be mandated by the trial site do not need to be reported as an amendment to the protocol even if done during investigational visits, unless sponsors are incorporating collected data as part of a new research objective.
When should the initiation, continuation, halt, suspension or extension of clinical trials be considered, and which criteria apply?	Sponsors and investigators are encouraged to engage with Brazilian health regulators (e.g. Ministry of Health, ANVISA and the Ethics Committee) as early as possible when they need to implement urgent amendments to the protocol or informed consent to cope with the COVID-19 pandemic. Sponsors should document any actions taken.

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Chile

Have competent authorities issued any guidance?	On April 9, 2020, the Public Health Institute (PHI) issued general guidelines for sponsors of clinical trials. The guidance is accessible here. Also, on April 22, 2020, PHI issued an informative note regarding clinical trials in the context of the COVID-19 pandemic. The informative note is accessible here.
How should the closure/new opening of trial sites, the transfer of patients to other trials sites and/or diagnostic tests be handled?	To ensure the safety of trial subjects, the following measures have been adopted: • the possibility of facilitating the access of trial subjects to trial sites using a sponsor-reimbursed taxi service to avoid the use of public transport in cases where trial subjects do not have their own means of transportation; and • the possibility of referring trial subjects under treatment in trial sites located in low accessibility areas to other trial sites (already involved in the same trial) located in more accessible areas. All the above will be subject to the availability on the new trial site to provide adequate treatment of the trial subject, the new consent of the trial subject, and notification to the relevant Ethics-Scientific Committee. Other activities can be included with the aim of ensuring flexibility considering the current contingency, as well as ensuring continuity of the timely treatment of all trial subjects. The responsibility for these activities lies on sponsors and investigators.
How should investigational visits be managed?	Even when the government has ordered a mandatory quarantine in certain communes of Chile, there are exceptions to this measure, applicable both to trial subjects and to personnel working at trial sites (e.g. temporary permits limited for 12 hours to attend prearranged appointments at trial sites). Also, PHI provides for the possibility to assist trial subjects directly at home through the services of a healthcare professional duly qualified for the administration of the investigational medicinal products. Further, sponsors should evaluate whether alternative safety methods and evaluations (e.g. telephone contact, visit alternative location for evaluation, including local laboratories) could be implemented, as needed.
Which measures should be taken to ensure the supply of investigational medicinal products (IMPs)?	The following measures have been adopted by PHI regarding the supply of IMPs: • the possibility to provide trial subjects who attend to their scheduled visits with additional amounts of IMPs to cover longer periods of time, if compatible with the requirements of the specific clinical trial protocol; • delivery of IMPs by the trial site through a duly authorized health facility (e.g. medication storage facilities or pharmacies) within this trial site to trial subjects' homes through specialized couriers; • in cases where IMPs are not yet available at trial sites, supply of IMPs by drugs logistics operators directly to trial subjects' homes; • in cases where for logistical reasons the sponsor cannot guarantee the delivery of IMPs through drugs logistics operators, trial sites may coordinate other strategies to ensure access to IMPs for all trial subjects, either by direct courier from trial sites or by courier national services; and • all the above will apply only when establishing the due registration of the dispensing and temperature control of the supply chain in accordance with safeguards for guaranteeing the quality of the product under investigation.

	Additionally, on May 11, 2020, PHI published an informative note regarding the supply of IMPs during the COVID-19 pandemic, which is accessible here. In a nutshell, the document provides guidance on the delivery of IMPs directly to trial subjects' homes, the detailed information to be included about IMPs being supplied as well as specific informed consent to be provided by trial subjects including data about the delivery and its conditions, all before the delivery of IMPs is carried out (except in case of urgency).
How should clinical trials be monitored?	PHI has informed that sponsors may perform remote monitoring visits to trial sites, among other measures that can be adopted to ensure the continuity of trials.
How should protocol amendments be managed and communicated to competent authorities?	The need to establish new processes or modify existing processes will vary according to the protocol and specific situation. In all cases, it is important to communicate to trial subjects about the new procedures and to submit this information to the relevant Ethics-Scientific Committee. New protocols and protocol amendments have to be reviewed and approved by the relevant Ethics-Scientific Committee and PHI, before being implemented. However, it is not necessary to report as a protocol amendment the screening procedures for the detection of COVID-19, unless the sponsor is incorporating the data collected as part of a new research objective. Sponsors and investigators must make efforts to anticipate changes in the protocols or informed consents due to the COVID-19 pandemic. They should document how the restrictions relating to COVID-19 provoke changes in the conduct of the trial, the duration of those changes, and indicate which trial subjects are affected and in which way. Also, all the exceptional procedures and activities to be adopted shall be diligently and timely notified to the Clinical Studies Section of PHI, through the GICONA electronic system. Moreover, for any question about clinical trials being conducted during the COVID-19 pandemic, PHI has indicated the email address: estudiosclinicos@ispch.cl.
When should the initiation, continuation, halt, suspension or extension of clinical trials be considered, and which criteria apply?	Sponsors, jointly with investigators and Ethics-Scientific Committees, may determine in the best interest of trial subjects' welfare and rights whether: • a trial subject should continue according to the protocol; • the protocol should be amended; • the administration or use of the IMP product should be suspended; or • if the trial subject should no longer participate in the trial. Such decisions will depend on specific circumstances and should take into account the nature of the IMPs, the ability to perform appropriate safety monitoring, the potential impact on the trials, the product supply chain and the nature of the pathology under study, among others.

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Colombia

Have competent authorities issued any guidance?	The Colombian medicines agency (INVIMA) issued guidance to reduce risks for trial subjects during the COVID-19 pandemic.
How should the closure/new opening of trial sites, the transfer of patients to other trials sites and/or diagnostic tests be handled?	INVIMA recommends where appropriate: • limiting trial subjects' access to trial centers; and • guaranteeing transportation to reduce contact between trial subjects and other persons.
How should investigational visits be managed?	INVIMA recommends limiting visits to critical care only and scheduling remote visits where appropriate.
Which measures should be taken to ensure the supply of investigational medicinal products (IMPs)?	IMPs should be sent to trial subjects' homes where appropriate.
How should clinical trials be monitored?	INVIMA recommends remote monitoring of the clinical trial where appropriate.
How should protocol amendments be managed and communicated to competent authorities?	Sponsors and trial sites should assess the risks for trial subjects and develop protocols considering the current situation, which shall be included in the SOP of the trial site and shall be notified to the ethics committee and INVIMA. This does not require prior authorization.
When should the initiation, continuation, halt, suspension or extension of clinical trials be considered, and which criteria apply?	INVIMA recommends taking all necessary protective measures when recruiting new trial subjects and considering any local guidance and restrictions relating to visiting health institutions.

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Mexico

Have competent authorities issued any guidance?	To date, no guidance has been issued.
How should the closure/new opening of trial sites, the transfer of patients to other trials sites and/or diagnostic tests be handled?	N/A
How should investigational visits be managed?	N/A
Which measures should be taken to ensure the supply of investigational medicinal products (IMPs)?	N/A
How should clinical trials be monitored?	N/A
How should protocol amendments be managed and communicated to competent authorities?	N/A
When should the initiation, continuation, halt, suspension or extension of clinical trials be considered, and which criteria apply?	N/A

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Middle East

Bahrain

Have competent authorities issued any guidance?	To date, no guidance has been issued.
How should the closure/new opening of trial sites, the transfer of patients to other trials sites and/or diagnostic tests be handled?	N/A
How should investigational visits be managed?	N/A
Which measures should be taken to ensure the supply of investigational medicinal products (IMPs)?	N/A
How should clinical trials be monitored?	N/A
How should protocol amendments be managed and communicated to competent authorities?	N/A
When should the initiation, continuation, halt, suspension or extension of clinical trials be considered, and which criteria apply?	N/A

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Kuwait

Have competent authorities issued any guidance?	To date, no guidance has been issued.
How should the closure/new opening of trial sites, the transfer of patients to other trials sites and/or diagnostic tests be handled?	N/A
How should investigational visits be managed?	N/A
Which measures should be taken to ensure the supply of investigational medicinal products (IMPs)?	N/A
How should clinical trials be monitored?	N/A
How should protocol amendments be managed and communicated to competent authorities?	N/A
When should the initiation, continuation, halt, suspension or extension of clinical trials be considered, and which criteria apply?	N/A

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Oman

Have competent authorities issued any guidance?	To date, no guidance has been issued.
How should the closure/new opening of trial sites, the transfer of patients to other trials sites and/or diagnostic tests be handled?	N/A
How should investigational visits be managed?	N/A
Which measures should be taken to ensure the supply of investigational medicinal products (IMPs)?	N/A
How should clinical trials be monitored?	N/A
How should protocol amendments be managed and communicated to competent authorities?	N/A
When should the initiation, continuation, halt, suspension or extension of clinical trials be considered, and which criteria apply?	N/A

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Qatar

Have competent authorities issued any guidance?	To date, no guidance has been issued.
How should the closure/new opening of trial sites, the transfer of patients to other trials sites and/or diagnostic tests be handled?	N/A
How should investigational visits be managed?	N/A
Which measures should be taken to ensure the supply of investigational medicinal products (IMPs)?	N/A
How should clinical trials be monitored?	N/A
How should protocol amendments be managed and communicated to competent authorities?	N/A
When should the initiation, continuation, halt, suspension or extension of clinical trials be considered, and which criteria apply?	N/A

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UAE

Have competent authorities issued any guidance?	To date, no guidance has been issued. At emirate level, the Abu Dhabi Department of Health issued Circulars USO/46/2020 (Circular 46) and USO/41/20 (Circular 41) address the conduct of clinical trials in the context of the COVID-19 pandemic.
How should the closure/new opening of trial sites, the transfer of patients to other trials sites and/or diagnostic tests be handled?	N/A
How should investigational visits be managed?	N/A
Which measures should be taken to ensure the supply of investigational medicinal products (IMPs)?	N/A
How should clinical trials be monitored?	N/A
How should protocol amendments be managed and communicated to competent authorities?	N/A
When should the initiation, continuation, halt, suspension or extension of clinical trials be considered, and which criteria apply?	N/A

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North America

Canada

Have competent authorities issued any guidance?	The Canadian medicines authority (Health Canada) issued guidance regarding the management of clinical trials during the COVID-19 pandemic. The guidance recognizes that there may be an increase in protocol deviations during the COVID-19 pandemic. The guidance is accessible here.
How should the closure/new opening of trial sites, the transfer of patients to other trials sites and/or diagnostic tests be handled?	Investigators may evaluate alternative locations (e.g. for imaging studies and laboratory tests) in case trial subjects are not able to reach trial sites. The use of alternative sites may create issues of confidentiality related to trial subjects' medical records (Electronic Health Record). Furthermore, trial subjects must consent to any identifiers leaving the original trial site and be assured that their confidentiality will be protected.
How should investigational visits be managed?	Investigators should consider whether alternative methods for safety assessment are feasible, should trial subjects not be able to come to trial sites. Alternative methods may include telephone contact, virtual visits via telemedicine or alternative care sites. Alternative locations for imaging studies and laboratory tests should also be considered. Alternative methods of informed consent for the trial or amendments to the trial protocol should also be considered, including electronic consent or recorded telephone consent.
Which measures should be taken to ensure the supply of investigational medicinal products (IMPs)?	The delivery of IMPs for self-administration (e.g. tablets, injectables) from Canadian trial sites directly to trial subjects may be considered where appropriate. This approach can only be considered for specific trial designs and drugs that a trial subject could take on their own. IMPs must be transported, handled and stored in a manner that mitigates the risk of exposure to temperatures outside labelled storage conditions. Verification that the IMPs have been received by the trial subject and accurate documentation of the process in the trial subjects' study record is required.
How should clinical trials be monitored?	Health Canada recommends considering central monitoring of clinical trials where appropriate. Furthermore, any delayed site visits must be documented. If alternative monitoring is conducted, careful documentation is required to capture the reason why it was done, the method used to collect the information, what data was collected, who provided the information and how the source of the information was verified. Study protocol amendments will not be needed.

How should protocol amendments be managed and communicated to competent authorities?	Health Canada recognizes that there may be an increase in protocol deviations during the COVID-19 pandemic. The clinical trial sites should have a system in place to identify, document, assess and report all protocol deviations to the sponsor and research ethics boards (REBs) in accordance with sponsor and REB requirements. Sponsors should consider alternate methods to prevent protocol deviations. Deviations and reasons for deviations need to be documented. Unless the deviations may place trial subjects at risks, sponsors do not need to report these deviations to Health Canada. Sponsors may consider submitting at regular intervals a cumulative list of deviations occurring in a particular study, rather than individual notifications.
When should the initiation, continuation, halt, suspension or extension of clinical trials be considered, and which criteria apply?	Sponsors should discuss with local REBs whether it is in the best interest of the safety, welfare and rights of trial subjects to continue the trial as per the study protocol or to halt the trial. Halting recruitment or temporarily halting the trial may be required in some circumstances. If this happens, sponsors must inform Health Canada using a clinical trial application notification (CTA-N). Sponsors should consider suspending additional site activation and recruitment.

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US

Have competent authorities issued any guidance?	On March 18, 2020, the US Food and Drug Administration (FDA) issued new guidance on clinical trial management during the COVID-19 pandemic, and followed up with an update, most recently on June 3, 2020, to include updates in a Q&A appendix (which was added to the guidance on April 2, 2020) providing additional clarification to clinical trial stakeholders. The guidance is accessible here.
How should the closure/new opening of trial sites, the transfer of patients to other trials sites and/or diagnostic tests be handled?	FDA recognizes that the COVID-19 pandemic may affect the conduct of clinical trials and that challenges may arise, for example, from site closures. In such case, it should be assessed whether investigators can provide required in-person assessments at an acceptable alternate location.
How should investigational visits be managed?	Sponsors should determine if in-person visits are necessary to fully assure the safety of trial subjects. FDA recommends the use of phone contact, virtual patient visits and/or alternative locations, including local labs or imaging centers where appropriate.
Which measures should be taken to ensure the supply of investigational medicinal products (IMPs)?	IMPs that are typically distributed for self-administration may be amenable to alternative secure delivery methods. Sponsors may implement home delivery of IMPs that would not raise any new safety risks. For IMPs that are usually administered in a healthcare setting, FDA recommends consulting the appropriate FDA review divisions regarding plans for alternative sites for administration (e.g. home nursing or alternative sites by trained but non-study personnel).
How should clinical trials be monitored?	If planned on-site monitoring visits are no longer possible, sponsors should consider altered monitoring approaches, e.g. optimizing use of central and remote monitoring programs to oversee trial sites.
How should protocol amendments be managed and communicated to competent authorities?	Although, even in the COVID-19 context, FDA encourages sponsors – where possible without jeopardizing subject health and safety – to comply with the generally applicable notification and approval requirements relative to protocol changes. FDA is currently permitting sponsors flexibility to implement changes to study protocols without filing amendment notifications or obtaining advance approval, when necessary to minimize or eliminate immediate health and safety hazards, provided certain reporting criteria are met. FDA emphasizes the need for sponsors and investigators to carefully document and report all protocol changes and deviations, including making any necessary amendments to data management or statistical analysis plans, in order to ensure that the COVID-19 impact on trial data is transparent and appropriately understood.
When should the initiation, continuation, halt, suspension or extension of clinical trials be considered, and which criteria apply?	Sponsors, in consultation with investigators and Institutional Review Boards (IRBs)/ Independent Ethics Committees (IECs), should assess whether the protection of trial subjects' safety and data integrity is best served by continuing a trial subject in the trial, or by discontinuing the administration or use of IMPs, or even by discontinuing participation in the trial.

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