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COVID-19 Disruptions of International Clinical Trials: Comparing Guidances Issued by FDA, EMA, MHRA and PMDA

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The COVID-19 pandemic has had a major impact on the conduct of clinical trials worldwide. Recognizing this impact, national authorities have issued guidance for sponsors, investigators and institutional review boards (IRBs)/research ethics committees (RECs) regarding the conduct of clinical trials. The chart below summarizes guidance from the U.S. Food and Drug Administration ("FDA") (updated March 27, 2020), the European Medicines Agency ("EMA") (dated March 27, 2020), the United Kingdom Medicines and Healthcare Products Regulatory Agency ("MHRA") (updated March 24, 2020), and Japan's Pharmaceuticals and Medical Devices Agency ("PMDA") (dated March 27, 2020).

Clinical Trial Considerations	United States: FDA	European Union: EMA[1]	United Kingdom: MHRA	Japan: PMDA
Continuing and/or Initiating a Protocol	Ensuring the safety of participants is paramount. Sponsors should consider whether COVID-19-imposed limitations pose new safety risks and the feasibility of mitigating the risks through amending study procedures. Sponsors should assess the availability of clinical investigators, trial support staff, trial supplies, vendor operations and information technology systems to provide trial oversight and properly assess and manage safety issues that may emerge during a study. If a Data Monitoring Committee (DMC) has been established, sponsors should consider the assessment of the DMC on the impact of	Sponsors should assess the feasibility of starting new trials or enrolling new trial participants. The protocol should address additional risks and risk mitigation measures. Sponsors should consider a temporary halt of a trial at some or all sites, a suspension or slowing of recruitment, extension of trial duration, postponement of trials or site activations, and/or closing of sites. If there is an urgent need to open a new site, the opening of the new site may be implemented as an urgent safety measure first with a substantial amendment application submitted later.	Prospective "protocol waivers" (*i.e.*, deviations from inclusion/exclusion criteria) are unacceptable. MHRA does not expect sponsors or investigators to bypass the eligibility process due to difficulties in assessing subjects and carrying out tests. Safety of patients remains a priority and patients should not be included in a trial unless they are confirmed to meet the inclusion and exclusion criteria. If a clinical trial has been halted due to issues related to COVID-19 or if it subsequently restarts without any substantial changes to the Clinical Trial Authorisation (CTA), sponsors do not generally	Not specifically addressed.

[1] EMA notes that there may be specific national legislation and guidance in place that sponsors and investigators need to take into account.

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	COVID-19 modifications on participant safety. Sponsors should consider whether continuation and/or initiation of a trial could interfere with public health measures to control COVID-19.		need to inform the MHRA. If changes do need to be made to protect participant safety moving forward, then this should be submitted as a substantial amendment notification. The trial master file should include a note that the trial was halted and the reason. Sponsors do need to inform the MHRA if a halt is due to (1) a direct participant safety issue, especially if there is the potential to impact other trials; or (2) a medicines supply issue.	
Continuing a Participant on Study	Maintaining the safety of participants is central to any decision to continue participants in the study. Sponsors should consult with investigators and IRBs to determine if a participant should continue on protocol, discontinue receipt of the investigational product, or discontinue participation in the trial. The determination depends on specific circumstances, including the nature of the investigational product, the ability to conduct appropriate safety monitoring, potential impacts on the investigational product supply chain, and the nature of the disease. Sponsors determining whether to continue administering an investigational product that	In truly exceptional situations, if unavoidable, sponsors should consider transferring participants to other sites. The potential impact of COVID-19 should be considered when deciding to start or continue trials for participants in a risk group for COVID-19 or in trials involving treatments that may increase such risk. Urgent safety measures to protect subjects against immediate hazard may be taken without prior notification to the National Competent Authority (NCA) and the Ethics Committee, but the information needs to be provided after the fact to the NCA and the Ethics	Subject safety is the MHRA's highest priority. Sponsors should consider the risk/benefit of conducting trials in medicines that act as immunosuppressants, for example, in early phase healthy volunteer trials, where there is no therapeutic benefit to the volunteer, but taking part in the trials does pose a risk of infection. If the safety of a trial subject is at risk because they cannot complete key evaluations or adhere to critical mitigation steps, then consideration to discontinuing that subject must be discussed. This may also extend to the whole trial in some cases, and a sponsor and investigator should remember they can	Not specifically addressed.

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	appears to provide benefit to participants should consider context-dependent issues, including whether the participant appears to be benefitting from the product, the availability of reasonable alternative treatments, the seriousness of the disease, and the risks of switching treatment. If discontinuation of investigational product might present a substantial risk, the sponsor should consider, after discussions with the FDA review division, amending the protocol to limit use to participants with apparent benefit. Participants should continue to be informed of study conduct modifications that affect them.	Committee as soon as possible. For changes likely to affect participant safety and/or scientific value of the trial but that do not require immediate action from the sponsor or investigator, substantial amendment applications should be submitted. Where a trial is put on hold for reasons not linked to participant safety, the sponsor should notify NCAs and Ethics Committees. Participants should be informed of changes in trial conduct that affect them.	use Urgent Safety Measures, or even temporarily halt a trial, or halt recruitment, if this is the best way forward.	
Implementation of Protocol	Changes to minimize or eliminate immediate hazards or to protect the life and well-being of participants may be implemented without IRB approval or before filing an IND/IDE amendment. These changes must be reported to the IRB after implementation. For studies under an IND, pausing enrollment to decrease potential exposure to COVID-19 does not require submission of a protocol amendment.	The overall well-being and best interests of participants should be considered when changes in ongoing trials are considered. Prospective protocol waivers remain unacceptable and patients should not be included in trials without proper eligibility assessment. Compliance with the trial protocol should be ensured to an extent that an ongoing benefit-risk assessment for the trial and participants is still possible.	Patients may become unable to undertake required clinical trial activities due to self-isolation or being advised to stay away from hospitals and general practitioner sites. MHRA states that resulting protocol deviations should be documented to enable appropriate evaluation for the trial. An increase in protocol deviations in relation to COVID-19 will not constitute a serious breach; therefore, there is no need to report this to MHRA unless	Changes from the protocol or normal procedures to ensure the safety of participants should be documented and explained. If any doubts arise, the site should consult with the sponsor. If an IRB meeting cannot be held, it is okay to hold discussions to the next IRB meeting, except for cases that need to be urgently discussed

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	Protocol amendments not required to prevent imminent safety risks can be implemented once submitted to FDA and IRB-approved. Consolidation of several protocol modifications into a single protocol amendment would be acceptable. For studies under an IDE, FDA notes its understanding of challenges to submission of 5-day Notices under 21 CFR 812.35(a)(3) due to the impact of COVID-19. Sponsors may consolidate implemented changes when submitting 5-day Notices and should update the IDE as soon as possible.	Decisions to adjust clinical trial conduct should be based on risk assessments by the sponsor and/or investigator. For trials to test new treatments for COVID-19, sponsors should seek advice on alternative procedures to obtain informed consent.	patients are being put at risk.	for subject protection purposes. If urgent discussion is required, determine the necessary procedures and consider alternative methods such as email.
Informed Consent Changes	If a patient signing informed consent is in COVID-19 isolation, electronic methods of obtaining the participant's signature should be considered consistent with FDA's 2016 guidance on electronic informed consent. If not possible, sponsors should consider having a health care worker who may enter the room provide a consent form to the patient. The investigator may then arrange a telephone or video conference with the patient and an impartial witness. If the signed informed consent document cannot be	For trials involving COVID-19 patients, if written consent by the trial participant is not possible, then oral consent can be given in the presence of an impartial witness who must sign and date the informed consent document. Having the trial participant and person obtaining consent sign and date separate informed consent forms can also be considered. In cases of acute life-threatening situations where it is not possible to obtain prior informed consent, informed consent will need to be later acquired.	If a sponsor or investigator's processes require wet-ink signatures, they should consider alternative methods of demonstrating approvals, such as email confirmation. MHRA inspectors will take a pragmatic approach to this, but sponsors or investigators may want to consider an SOP deviation to cover this in the interim.	An investigator can make changes related to subject safety, including provision of information to participants and revision of consent based on safety information, without waiting for IRB deliberation; however, the changes must undergo IRB deliberations afterwards. A record of circumstances and correspondence

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	collected, acceptable documentation includes witness and investigator attestations that the patient agreed to participate and signed the informed consent, or a photograph of the signed informed consent with an attestation of how it was obtained.	Visits to sites for the sole purpose of obtaining re-consents should be avoided. If re-consents are necessary for implementation of new urgent changes in trial conduct, alternative ways of obtaining such re-consents should be considered, including via phone or video calls and obtaining oral consents supplemented with email confirmation. Approved updated patient information and consent forms should be provided to participants by email, mail, or courier before re-consent is obtained.		should be created and stored.
Study Visits	Sponsors should consider feasible alternatives to on-site safety assessments, including telephone contacts, telemedicine contracts, or alternative locations for assessments. Since the change to telephone or video contact visits would likely result in some protocol-specific procedures not being conducted, sponsors must evaluate the potential impact on participant safety and how to mitigate the risks.	Sponsors should consider converting physical visits to phone or video visits, and postponement or cancellation of visits to ensure only strictly necessary site visits take place. If a participant cannot reach a site for safety assessments, laboratory, imaging, or other diagnostic tests may be done locally. Sites should inform sponsors of such cases. If it is a trial endpoint and samples cannot be shipped to a central lab, analysis should be performed locally and documented.	Using phone calls instead of protocol-directed in-person study visits is acceptable where possible. This will not constitute a serious breach of the protocol. A substantial amendment to update the protocol will not be required. MHRA would, however, expect that any protocol deviations are well documented internally.	Protocol deviations due to postponement or cancellation of a participant's visit should be documented and explained.
COVID-19 Screening Procedures	If health care system-mandated, COVID-19 screening procedures do not	Not specifically addressed.	Not specifically addressed.	Not specifically addressed.

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	need to be reported as a protocol amendment unless the Sponsor is using the data collected for a new research objective.			
Monitoring Activities	If on-site monitoring visits are no longer possible, sponsors should consider centralized and remote monitoring programs and document inability to access or delayed monitoring of a site.	Temporary, alternative proportionate mechanisms of oversight may be required. On-site monitoring, if feasible, should take into account national/local restrictions, urgency and availability of site staff, and should only be performed as agreed with sites. Temporary measures include cancellation/postponement of on-site monitoring visits, implementing phone and video visits, and centralized monitoring and review of data. Remote source data verification is not allowed in most Member States and provision of redacted/de-identified pdf files will not be acceptable.	If participant monitoring visits need to be reduced due to COVID-19, this will not require a substantial amendment. However, sponsors and investigators should ensure that their risk assessment and rationale is appropriately documented. MHRA supports remote monitoring where appropriate but advises consideration of the following: (1) Direct access to patients EHR (Electronic Health Record) away from the site may create confidentiality issues; (2) Trial participants will need to consent to any identifiers leaving the site and be assured that their confidentiality will be protected. The use of alternative means of oversight such as teleconferences /videoconferences is encouraged.	If on-site monitoring is not possible, alternative monitoring methods should be considered. A record shall be maintained for modifications to on-site monitoring.
Investigational Product Delivery and Accountability	Regulatory requirements for investigational product accountability remain. If sites are significantly impacted, certain investigational products may allow for alternative secure delivery methods.	Sponsors must assess risks relating to the investigation medicinal product (IMP) and consider alternative shipping and storage arrangements. Changes in distribution may include providing larger amounts of	If a trial volunteer cannot attend a trial site, then delivery of IMP to a patient's home is acceptable and no substantial amendment notification to the MHRA is required. Sponsors should do a risk-	Investigational drugs may be delivered to a participant's home if the participant is unable to come to a site. The site is responsible for the

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	For investigational product dispensed through a pharmacy for self-administration at home, home delivery of the product that would not raise new safety risks may be implemented to protect patients from coming to sites. A protocol change would be required to permit home delivery for the change from pharmacy dispensing for self-administration at home to direct-to-patient shipments. If the extent of home delivery is limited to certain participants, documentation through protocol deviation may also be acceptable. If the change is then included in a protocol amendment, such change may be part of a cumulative amendment rather than an urgent protocol change. The FDA review divisions should be consulted regarding plans for alternative administration of investigational products normally administered in a health care setting. Sponsors should consider safety risks of missing an investigational product infusion due to inability to come to a site. When suitable alternative arrangements cannot be made, discontinuing investigational product	trial medications to the participant to sustain him/her for a longer period. Re-distribution of IMP between sites should only be considered in cases where direct distribution by the usual distributor is not possible or in the exceptional circumstance where a participant is transferred between sites. Re-distribution should follow a written procedure established with the person responsible for the distribution of IMP. EMA notes it foresees direct delivery of IMP from sites to participants. Sponsors should check NCA guidance regarding direct sponsor to participant shipment. EMA recommends appropriate stock of in vitro diagnostic devices and medical devices be maintained in case of distribution failure.	assessment and record this internally. Participants must consent verbally (and this should be documented in their notes) to providing contact details for shipping purposes. If the participant does not want to sign for the delivery due to self-isolation, then a follow-up phone call could be used to confirm they have received the package. The sponsor should also consider if any training is required for administration of the IMP. The following factors need to be taken into consideration if providing an IMP to a participant at home: (1) Storage requirements; (2) Assurance about the integrity of the product during transit; (3) The stability of the product and margin of safety; (4) Potential to affect continuity of supply; (5) Mechanism for confirming that the subjects have received the IMP; (6) Whether the medicine needs to be signed for and sent by courier or recorded delivery; and (7) Whether there needs to be a follow-up call to the subject.	delivery and should consider the study design, the investigational drug properties and the participant's condition. The process for ensuring delivery to the participant should be determined in advance and documented.

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	treatment while continuing study participation with potentially delayed assessments may be an appropriate option.			
Data Capture and Study Reporting	Sponsors should consult FDA review divisions regarding COVID-19 effects on efficacy assessments and protocol changes affecting data management and/or statistical analysis plans. Sponsors should document specific protocol deviations and the reasons for such. Investigators must document as protocol deviations any modifications to protocol-specific procedures that occur prior to IRB approval and FDA submission of a protocol amendment implementing the modification.	Sponsors are expected to continue safety reporting. Audits should be avoided or postponed. Sponsors should escalate and manage protocol deviations in accordance with their standard procedures. Additional financial compensation that is provided to sites/investigators for reimbursement of exceptional expenses should be documented.	If capacity issues related to COVID-19 prevent timely reporting, sponsors and investigators should report this as soon as possible after the capacity issue is resolved. Deviation from protocol-defined timelines in this case does not require a substantial amendment to MHRA. Particular attention should be paid to timely reporting of suspected unexpected serious adverse reactions (SUSARs) that put participant safety at risk on a trial or have the potential to impact participants of other trials. Every effort should be made to notify MHRA in these cases.	Protocol deviations to ensure the safety of participants are expected and the investigator should maintain a record of the deviations and the reasons for such.

This alert is one of a series of advisories and webinars issued by Ropes & Gray on COVID-19 topics. Please check our Coronavirus Resource Center for additional information and updates.