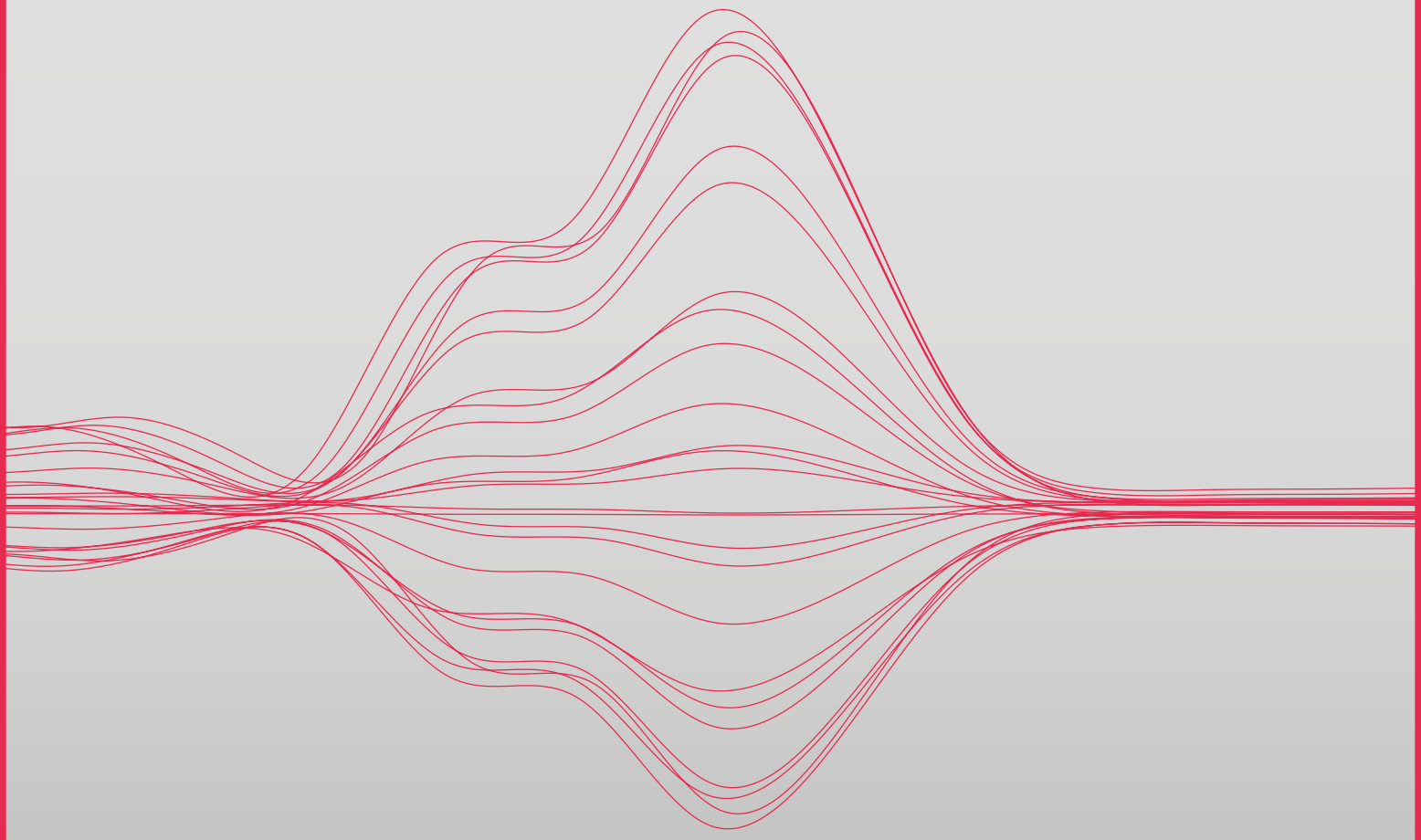
A GLOBAL GUIDE TO

Managing clinical trials during the COVID-19 pandemic



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Introduction

COVID-19 is affecting the conduct of clinical trials globally. Pharmaceutical companies are facing several challenges in ensuring continuity of clinical trials on human medicines: from trial subjects' difficulties accessing trial sites due to quarantine or local lockdown measures, across limited trial staff availability given the evolving prioritization of critical COVID-19 patient treatments, 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 significantly delay the conduct of clinical trials and the market entry of innovative therapeutics, massively 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 navigate through the patchwork of measures adopted so far in more than 30 countries worldwide. Since the situation remains highly dynamic, this document we will be updated regularly.

Main contacts

Marco de Morpurgo
Partner
Global Co-Chair, Life Sciences sector
+39 06 68 880 1
marco.demorpurgo@dlapiper.com

Nicola Landolfi
Lawyer
+39 06 68 880 1
nicola.landolfi@dlapiper.com

Dr med Kokularajah Paheenthararajah
Rechtsanwalt | Senior Associate
+49 221 277 277 307
kokularajah.paheenthararajah@dlapiper.com

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Africa

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).
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 impact 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?	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 themselves where appropriate. This would specifically include IMPs distributed for self-administration. For IMP's 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 impacted and how they were impacted. 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.

Local contact

Peter Bradshaw
Director
Location Head Corporate, South Africa
+27 11 302 0810
peter.bradshaw@dlapiper.com

Savanna Stephens
Associate
+27 (0)11 302 0830
savanna.stephens@dlapiper.com

Jeanne-Mari Butler
Candidate Attorney
+27 11 302 0855
jeannemari.mcdonald@dlapiper.com

Asia Pacific

Australia

Have competent authorities issued any guidance?	All Australian state and territory Departments of Health, the Therapeutic Goods Administration, 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 and the New South Wales Health Department 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 explicitly commented on this issue.
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.
How should clinical trials be monitored?	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.
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 Therapeutic Goods Administration (TGA).

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.

Local contacts

Melinda Upton
Partner
Global Co-Chair, Intellectual Property and Technology
+61 2 9286 8209
melinda.upton@dlapiper.com

Greg Bodulovic
Special Counsel
+61 2 9286 8218
greg.bodulovic@dlapiper.com

China

Have competent authorities issued any guidance?	To date, neither the National Medical Products Administration nor PRC Ministry of Health has issued any notice, guidance or directives regarding the management of clinical trials in the context of COVID-19 pandemic. 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, Southwest Medical University Affiliated Hospital etc. 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?	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.
How should investigational visits be managed?	The authorities have not explicitly commented on this issue.
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' home, such method should be preferred.
How should clinical trials be monitored?	The authorities have not explicitly commented on this issue.
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.
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 enrollment 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.

Local contact

Ting Xiao
Senior Associate
+86 21 3852 2111
ting.xiao@dlapiper.com

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

Local contact

Sammy Fang
Partner
+852 2103 0649
sammy.fang@dlapiper.com

Japan

Have competent authorities issued any guidance?	To date, no guidance relating to the management of clinical trials in the context of the COVID-19 pandemic 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

Local contacts

Takahiro Nonaka
Partner
+81 3 4550 2825
takahiro.nonaka@dlapiper.com

Yuya Aoki
Associate
+81 3 4550 2939
yuya.aoki@dlapiper.com

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 currently subject to a complete lockdown whereby all premises must be closed, apart from essential businesses. This means trial subjects may not be able to come to the investigational site for protocol specified visits.
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?	At the date of stand down, all trials related to COVID-19 will 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.

Local contacts

Mark Williamson
Partner
+64 9 300 3857
mark.williamson@dlapiper.com

Emma Moran
Special Counsel
+64 4 918 3070
emma.moran@dlapiper.com

Europe


Sweden
Finland
Norway
Russia
Denmark
Ireland
UK
Netherlands
Poland
Belgium
Germany
Czech Republic
Luxembourg
Ukraine
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 2.0 of the EU Guidance published on March 27, 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 etc.) 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. **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. **Delivery of IMPs directly from sponsors to trial subjects:** EU Member States have adopted different approaches with respect to the direct delivery of IMPs to trial subjects' home. Therefore, sponsors should check the relevant guidance issued on national level regarding the possibility of sending IMPs directly to trial subjects' homes. **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:** (i) cancelling of on-site monitoring visits and extending of the period between monitoring visit; (ii) implementing telephone and video monitoring; and/or (iii) 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. Investigators should report results of adjusted monitoring/review measures to sponsors in monitoring reports and in the clinical study report. **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. **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. 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.
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: (i) temporary halt of the trial at some or all trial sites; (ii) suspension or slowing down of recruitment of new trial subjects; (iii) extension of the duration of the trial; or (iv) 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.

Local contacts

Marco de Morpurgo
Partner
Global Co-Chair, Life Sciences sector
+39 06 68 880 1
marco.demorpurgo@dlapiper.com

Dr med Kokularajah Paheenthararajah
Rechtsanwalt | Senior Associate
+49 221 277 277 307
kokularajah.paheenthararajah
@dlapiper.com

Nicola Landolfi
Lawyer
+39 06 68 880 1
nicola.landolfi@dlapiper.com

Austria

Have competent authorities issued any guidance?	The Austrian medicines agency (BASG) primarily refers to the EU Guidance (please see the EU section above). BASG recently published a FAQ to this topic which is 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. 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.
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. Investigators must document and communicate changes to sponsors. 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). After the end of the pandemic or at the request of BASG, sponsors must submit a final summary report.
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. Please see also the EU section above.

Local contact

Elisabeth Stichmann
Partner
+43 1 531 78 1651
elisabeth.stichmann@dlapiper.com

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. 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: (i) 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 (ii) 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 EC.
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?	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 dossier, charts of the trial subject etc.

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. 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. However, non-substantial amendments should be documented.
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. 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.

Local contact

Bertold Bär-Bouyssière
Partner
+32 (0) 2 500 15 35
bertold.bar-bouyssiere@dlapiper.com

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 to sponsors to 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.

Local contacts

Dr. Jasna Zwitter-Tehovnik
Partner
+43 1 531 78 1042
jasna.zwitter-tehovnik@dlapiper.com

Ivan S. Maleš
Senior Associate
+43 1 531 78 1989
ivan.males@dlapiper.com

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.

Local contact

Petr Samec
Senior Associate
+420 222 817 316
petr.samec@dlapiper.com

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 June 17, 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.
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 June 17, 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 the 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.

Local contacts

Ulrik Bangsbo Hansen
Partner
+45 33 34 00 08
ulrik.bangsbo@dlapiper.com

Anna-Sophie Bager
Associate
+45 33 34 01 33
anna-sophie.bager@dlapiper.com

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 EUR 900 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.

Local contacts

Tuija Kaijalainen
Partner
+358 9 4176 0465
tuija.kaijalainen@dlapiper.com

Lauri Rantanen
Associate
+358 9 4176 0419
lauri.rantanen@dlapiper.com

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. 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.
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.
How should clinical trials be monitored?	ANSM 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?	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.

Local contacts

Jérôme Pentecoste
Partner
+33 1 40 15 25 04
jerome.pentecoste@dlapiper.com

Mathieu Da Silva
Associate
+33 (0)1 40 15 66 70
mathieu.dasilva@dlapiper.com

Théo Armbruster
Associate
+33 (0)1 40 15 25 70
theo.armbruster@dlapiper.com

Germany

Have competent authorities issued any guidance?	The German Federal medicines agencies (BfArM and PEI) explicitly refer to the EU Guidance (please see the EU section above). Furthermore, on March 26, 2020 BfArM and PEI published supplementary recommendations to the EU Guidance. The supplementary recommendations 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 the conversion of on-site investigational visits to telephone consultations or telemedical visits where appropriate. However, this must be notified to BfArM or PEI and the competent ethics commissions as a change requiring 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 is preferably 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 case 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 by the 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. The essential requirements of data protection must be guaranteed. 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 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, etc.) or the direct supply of IMPs to trial subjects' homes, require approval by BfArM or PEI and a positive opinion by the 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 to this.
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 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.

Local contacts

Dr Philipp Cepl
Rechtsanwalt | Partner
+49 221 277 277 397
philipp.cepl@dlapiper.com

Dr Thilo Streit LL.M.
Rechtsanwalt | Counsel
+49 221 277 277 351
thilo.streit@dlapiper.com

Dr med Kokularajah Paheenthararajah
Rechtsanwalt | Senior Associate
+49 221 277 277 307
kokularajah.paheenthararajah@dlapiper.com

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.

Local contact

Orestis Omran
Counsel
Head of EU-Greek Practice
+32 2500 1539
orestis.omran@dlapiper.com

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 daily and 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?	Where appropriate, HU Authority recommends moving trial subjects to existing or new trial sites if necessary to cope with the COVID-19 pandemic. 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. It should be noted that IMPs may not be delivered to trial subjects' home.
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. 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.

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. 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 e-mail) is permitted by HU Authority. However, the use of electronic patient information leaflets and consent forms is not permitted. 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 to particularly consider whether to continue the trial for trial subjects at particular risk from COVID-19 (e.g. immunosuppressant therapy, age above 60 years, chronic diseases).

Local contacts

Helga Fehér
Partner
Head of Employment, Hungary
+36 1 510 1100
helga.feher@dlapiper.com

Dr Gabor Papp
Manager
+36 30 700 4471
gabor.papp@dlapiper.com

Ireland

Have competent authorities issued any guidance?	On March 26, 2020, the Irish medicines regulatory authority (HPRA) provided updated guidance on the management of clinical trials during the COVID-19 pandemic. 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.
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. 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. 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.

Local contacts

Caoimhe Clarkin
Partner
Head of Litigation and Regulatory, Ireland
+353 1 436 5483
caoimhe.clarkin@dlapiper.com

Louise McErlean
Associate
+44 1312 425 059
louise.mcerlean@dlapiper.com

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. The guidance is accessible here. 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: (i) 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 (ii) 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: (i) laboratories near trial subjects' homes; and/or (ii) 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: (i) 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; (ii) delivering IMPs from the hospital pharmacy of the trial site to trial subjects through their caregivers or relatives; (iii) 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 consents 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?	In case 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.

Local contacts

Marco de Morpurgo
Partner
Global Co-Chair, Life Sciences sector
+39 06 68 880 1
marco.demorpurgo@dlapiper.com

Nicola Landolfi
Lawyer
+39 06 68 880 1
nicola.landolfi@dlapiper.com

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.

Local contact

Olivier Reisch
Partner
+352 26 29 04 2017
olivier.reisch@dlapiper.com

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.

Local contacts

Paul Reeskamp
Partner
+31 20 5419 309
paul.reeskamp@dlapiper.com

Marijn van der Wal
Associate
+31 20 5419 975
marijn.vanderwal@dlapiper.com

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.

Local contacts

Petter Bjerke
Partner
+47 24 13 15 00
petter.bjerke@dlapiper.com

Line Voldstad
Lead Lawyer
+47 24 15 13 00
line.voldstad@dlapiper.com

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 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.

Local contacts

Andrzej Balicki, PhD
Partner
Head of Regulatory
+48 22 540 74 01
andrzej.balicki@dlapiper.com

Jolanta Dąbrowicz
Senior Associate
+48 22 540 74 91
jolanta.dabrowicz@dlapiper.com

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, 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. 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: (i) trial subjects cannot reach the trial site due to the COVID-19 pandemic; (ii) sponsors submit a notification to CEIC (as a non-substantial amendment); (iii) transport of another IMPs complies with GDP requirements; (iv) 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); (v) the principal investigator and the research team (including the trial site pharmacy) supervise the delivery of IMPs; (vi) access to trial subjects' personal data (name and address) for this purpose is consented; and (vi) trial subjects are informed about the administration and surveillance process, and have necessary means to communicate adverse events.
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 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 (oral 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. 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.

Local contacts

Margarida Leitão Nogueira
Senior Associate
+351 21 358 36 20
margarida.nogueira@dlapiper.com

Mariana Ricardo
Senior Associate
+351 213 583 620
mariana.ricardo@dlapiper.com

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.

Local contacts

Vadim Barbu
Senior Associate
+40 372 155 842
vadim.barbu@dlapiper.com

Irina Macovei
Senior Associate
+40 372 155 800
irina.macovei@dlapiper.com

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

Local contacts

Michael Malloy
Counsel
+7 (495) 221 4175
michael.malloy@dlapiper.com

Julianna Tabastajewa, PhD
Counsel
+7 (495) 221 44 94
julianna.tabastajewa@dlapiper.com

Pavel Arievich
Legal Director
+7 (495) 221 4472
pavel.arievich@dlapiper.com

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.

Local contacts

Michaela Stessl
Partner
Country Managing Partner
+421 2 5920 2122
michaela.stessl@dlapiper.com

Jan Farbiak
Senior Associate
+421 2 5920 2112
jan.farbiak@dlapiper.com

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 EU Guidance. 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.

Local contacts

Jasna Zwitter-Tehovnik
Partner
+43 1 531 78 1042
jasna.zwitter-tehovnik@dlapiper.com

Manca Kisovec
Associate
+43 1 531 78 1037
manca.kisovec@dlapiper.com

Domen Brus
Associate
+43 1 531 78 18 48
domen.brus@dlapiper.com

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: (i) a transfer agreement between sponsors and clinical trial sites; (ii) transfer of data collection notebook and trial subjects' medical records to the new site; (iii) sending of a transfer report summarizing trial subjects' most relevant medical data; and (iv) filing of the documentation concerning trial subjects.
How should investigational visits be managed?	Sponsors and investigators should consider where appropriate: (i) postponing visits; or (ii) using remote systems (e.g. telephone calls). However, investigators should carry out critical on-site visits already scheduled. 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: (i) centralized monitoring; (ii) remote monitoring; and/or (iii) 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.

Local contacts

Paula González de Castejón
Partner
+34 91 788 7374
paula.gonzalez@dlapiper.com

Elisa Lorenzo
Senior Associate
+34 91 788 7310
elisa.lorenzo@dlapiper.com

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 case, 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.
How should clinical trials be monitored?	It should be considered whether monitoring visits can be postponed. MPA does not allow remote monitoring.
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.

Local contacts

Fredrika Allard
Special Counsel
Head of Life Sciences, Sweden
+46 8 701 78 99
fredrika.allard@dlapiper.com

Annie Johansson
Senior Associate
+46 8 701 78 77
annie.johansson@dlapiper.com

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 March 25, 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?	MHRA has not explicitly commented on this issue. 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, telephone consultations should be preferred to in-person visits where appropriate. Whilst MHRA allows a reduction in the number of trial subjects visits as a result of COVID-19 pandemic, without submitting a substantial amendment notification, investigators must appropriately document the risk assessment and rationale.
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. A substantial amendment notification to MHRA is not required if investigators have carried out risk assessment and trial subjects have provided verbal consent.
How should clinical trials be monitored?	MHRA 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?	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: (i) 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); (ii) discontinuing a trial subject (e.g. if the safety of a trial subject is at risk); (iii) remote monitoring; and/or (iv) changes to the visiting procedure during a trial.

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. 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).

Local contacts

Richard Taylor
Partner
+44 (0)114 283 3055
richard.taylor@dlapiper.com

Caroline Scott
Senior Associate
+44 (0) 8700 111 111
caroline.f.scott@dlapiper.com

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: (i) there is an alternative trial site under the trial protocol; (ii) 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; (iii) informed consent of respective trial subjects is obtained; and (iv) 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. In case 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 the 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 to withdraw trial subjects and to terminate/suspend 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.

Local contacts

Natalia Pakhomovska
Partner
Head of IPT Ukraine
+380 44 495 17 89
natalia.pakhomovska@dlapiper.com

Natalia Kirichenko
Legal Director
+380 44 490 9575
natalia.kirichenko@dlapiper.com

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: (i) supplying IMPs directly to trial subjects' homes; and/or (ii) 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 contacts, 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.

Local contacts

Martín Mittelman
Partner
+5411 411 45 500
m.mittelman@dlapiper.com.ar

Milagros Malen Gaido
Special Counsel
+1 212 335 4524
m.gaido@dlapiper.com.ar

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 impacts 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.

Local contacts

Fabio Perrone Campos Mello
Managing Partner
+55 21 3262 3027
fcamposmello@cmalaw.com

Bruna Barbosa Rocha
Associate
+55 11 3077 3525
bruna.rocha@cmalaw.com

Chile

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

Local contacts

Felipe Bahamondez
Partner
+56 2 2798 2602
fbahamondez@dlapiper.cl

Felipe Massardo
Associate
+56 2 2798 2634
fmassardo@dlapiper.cl

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: (i) limiting trial subjects' access to trial centers; and (ii) 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.

Local contact

María Claudia Martínez Beltrán
Partner
+57 1 317 4720 x112
mcmartinez@dlapipermb.com

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

Local contacts

Jorge Benejam
Partner
+52 55 5261 1892
jorge.benejam@us.dlapiper.com

Isabel Gallástegui
Associate
+52 55 5261 1885
isabel.gallastegui@us.dlapiper.com

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

Local contacts

Adam Vause
Partner
+971 4 438 6343
adam.vause@dlapiper.com

Mohamed Toorani
Legal Director
Head of Bahrain Office
+973 1755 0896
mohamed.toorani@dlapiper.com

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

Local contacts

Adam Vause
Partner
+971 4 438 6343
adam.vause@dlapiper.com

Kashif Syed
Legal Director
+965 2291 5800
kashif.syed@dlapiper.com

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

Local contacts

Adam Vause
Partner
+971 4 438 6343
adam.vause@dlapiper.com

Sarah Al-Moosa
Legal Director
+968 2464 7770
sarah.al-moosa@dlapiper.com

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

Local contacts

Brenda Hill
Legal Director
+974 4420 6126
brenda.hill@dlapiper.com

Adam Vause
Partner
+971 4 438 6343
adam.vause@dlapiper.com

UAE

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

Local contact

Adam Vause
Partner
+971 4 438 6343
adam.vause@dlapiper.com

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.
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. IMPs must be transported, handled and stored in a manner that mitigates the risk of exposure to temperatures outside labelled storage conditions.
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. 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.

When should the initiation, continuation, halt, suspension or extension of clinical trials be considered, and which criteria apply?	Sponsors should discuss with local research ethics boards (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).

Local contacts

Geoffrey D. Mowatt
Partner
+1 416 862 3375
geoff.mowatt@dlapiper.com

Sangeetha Punniyamoorthy
Partner
+1 416 862 3366
s.punn@dlapiper.com

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 on April 2, 2020 to include a Q&A appendix 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 impact 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 COVID-19 impact on trial data are 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.

Local contacts

Rebecca Jones McKnight
Partner
+1 512 457 7225
rebecca.mcknight@dlapiper.com

Christopher M. Mikson, M.D.
Partner
+1 215 656 3380
christopher.mikson@dlapiper.com