EUROPE: COVID-19

Overview of European Regulatory Authority Guidance

Abstract

The following provides an overview of guidance and/or information published by European Member State Regulatory Authorities concerning the current epidemiological situation with COVID-19 and focusses on recommendations concerning the conduct of clinical trials.

Edition 1.0, 17 March 2020

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Belgium

https://www.afmps.be/fr/news/directive_sur_la_delivrance_directe_de_medicaments_aux_patients_dans_le_cadre_dessais_cliniques

Directive on the direct delivery of drugs to patients in clinical trials

FAMHP have issued a clarification concerning delivery of investigational product directly to patients. In those cases where a subject cannot access the hospital site or is not desirable in the current context IMP, where feasible, can be shipped directly to patients but must be under the sole responsibility of the principal investigator. It is not permissible for sponsors to intervene in this process. If adopted the process for shipping directly to subjects must be fully documented and traceable.

https://www.afmps.be/fr/news/covid_19_soumission_des_dossiers_par_voie_electronique

COVID-19: submission of files electronically

FAMHP have issued a clarification advising that based on the recommendations of the Belgian National Security Council regarding Covid-19 that agency staff are working from home and for this reason all submissions should be performed electronically. It stresses that Agency staff are making every effort to maintain continuity of service.

Czech Republic:

http://www.sukl.cz/leciva/doplnujici-stanovisko-odboru-klinickych-hodnoceni-lecivych

Opinion of the Department of Clinical Trials of Medicinal Products, SUKL, on ongoing clinical trials in relation to the current epidemiological situation with COVID-19.

SUKL presently strongly advises against the initiation of any newly approved clinical trials and the inclusion of new patients to any ongoing clinical trials.

Advises that subjects should be contacted by telephone to check the following:

- Whether the subject is quarantined as a result of visiting identified risk areas (listed here, https://koronavirus.mzcr.cz/staty-sveta-s-vysokym-rizikem-prenosu-nakazy/) or has been in contact with an individual confirmed with coronavirus infection
- Whether subject has confirmed coronavirus infection
- Whether subject resides in a household with an individual whom is quarantined
- Whether subject agrees with any proposed procedures as a result of the current epidemiological situation (e.g. assessment by telephone, sending study medication by courier, controlled laboratory collections

Should subjects need to visit a site:

- Site must arrange visit by telephone in advance to avoid accumulation of patients. Only necessary visits should be scheduled
- Protective equipment should be provided for both medical personnel and subjects.

Administration of any investigational product which affects the immune system is not possible/is in contraindication in subjects with confirmed coronavirus infection.

For IMP (all formulations except parenteral administration (IV) products) where subject administration is permissible provision is made for courier of IMP supply from site to subjects home address.

For IMP with parenteral administration (IV) SUKL recommends that upcoming scheduled administrations be postponed for up to 14 days. Where administration of the product cannot be postponed, the following considerations are given:

- In emergency cases, administration of IMP at the subjects home may be permissible if administration is performed by qualified medical personnel.
- Use of a specialised company licensed to carry out healthcare in the Czech Republic through qualified and properly trained CAP (medium medical staff), is possible but must be in full agreement with the principal investigators at each site. Any procedures applied should be agreed by the principal investigators also. If adopting such an approach consideration must be given to how existing clinical trial insurance will cover this. IN this scenario IMP must be issued by the principal investigator/site staff. Where infusions must be prepared by the pharmacy, requisitions should be appropriately managed prior to issuing to homecare worker for administration purposes.
- Injections that must be diluted before administration must follow the manufacturer's instructions and dilute, if permitted, directly before administration in the patient, subject to all procedures given in the pharmacy manual.
- Infusions prepared by the pharmacy should be transported under strict compliance with the conditions for the storage of the diluted product – i.e. continuous temperature measurement during transport and possibly other conditions specified by the Protocol or pharmacy manual.
- In the case of IMP administration, where there is a risk of anaphylactic reaction, these IMP should only be administered at the site, where intensive and resuscitation care is possible.

Where assessment are required prior to IMP administration e.g. blood counts, biochemistry, urine tests, and administration of IMP cannot be postponed the following should be considered:

- Arrange the exact date of the visit (and time) in the centre and perform the above highlighted assessments in advance
- Provide household assessments of the subject either by qualified staff of contracted laboratories or contractually secured healthcare providers whom employ appropriate safety measures and excludes patients whom are quarantined or living with or have been quarantined with a confirmed coronavirus case.

Denmark

https://laegemiddelstyrelsen.dk/en/news/2020/extraordinary-measures-for-clinical-trials-due-to-covid-19/~/media/46203FAB86DE42F2B735D7A13CADA1FE.ashx

Extraordinary measures for clinical trials due to COVID-19

The Danish Medicines Agency has published guidance concerning measures to adopt as a result of the current epidemiological situation with COVID-19. DKMA acknowledging that the current pandemic will likely result in more protocol deviations than normal however the expectation is that sponsors continue to escalate and manage deviations as appropriate. DKMA further highlight that where necessary changes results from COVID-19 should be handled as urgent safety measures and can therefore be implemented without delay however must still be notified within the appropriate timeframes (any such notification should include an appropriate risk assessment for the study in question).

Further areas addressed within the DKMA guidance include changes in monitoring, changes to shipment/handling of IMP, changes in visits or trial participant's affiliation to an investigator site, and changes in documentation practice.

Finland

https://www.fimea.fi/-/kliiniset-laaketutkimukset-koronavirusepidemian-covid-19-aikana

Clinical trials in the Corona virus epidemic (COVID-19)

FIMEA have published clarifying remarks with regards to changes in trial monitoring plans and supply of investigational products to patients in clinical trials.

Due to the corona virus situation, it may be justifiable to reduce the on-site monitoring of trial sites. The need for monitoring visits should be evaluated and should limit spread of the disease. Sponsors should take advantage of other monitoring tools (e.g. centralized monitoring) in order to prevent a possible on-site reduction of monitoring impacting the quality of the study and the safety of the subjects. The reasoned deviations from the original monitoring plan shall be documented and, if necessary, be subject to an appropriate relevant notification of the change of design.

In the event of an outbreak, it may be necessary to resort to exceptional arrangements for the delivery of IMP to the patient (e.g. by supplying the home address instead of the donation to the study location). In this case, the derogation must be necessary to ensure continuity of the investigation and the safety of the subjects and the reliability of the research results. The Sponsor shall notify FIMEA as soon as possible of the derogations and make an appropriate material statement of changes to the plan. FIMEA will prioritise assessment of these change declarations.

Germany

Paul Ehrlich Institute distributed email information on 16th March to existing applicants/sponsors stating the following:

"German legislation often requires the submission of paper documents and a CD-ROM when submitting documents for clinical trials. In the current Covid-19 situation, this often causes technical problems for applicants/sponsors and their employees when working from home offices. For this reason, the Paul-Ehrlich-Institut now accepts all clinical trial documents such as initial clinical trial applications and their follow-up documents such as responses to formal deficiency letters or deficiency letters with regard to grounds for non-acceptance also via CESP submission. Substantial amendments requiring approval according to §10 GCP-V; Urgent Safety Measures, change of the coordinating investigator in Germany of the clinical trial or DSURs can also be submitted via CESP. Please note that in the CESP submission under Comments the procedural step (e.g. iCTA, Resp GNA, etc.), the Vorlage-No.: and the EudraCT number MUST be in first place and in this order. Further explanations on electronic submission of clinical trials can be found at https://www.pei.de/EN/regulation/clinical-trials/electronic-submission/el-sub-applications-node.html

Substantial amendments that do not require approval according to §10 GCP-V, such as the notification of the end of clinical trials, the closure/opening of trial centres or the change of principal investigators, should still not be submitted via CESP. A later submission as paper submission plus CD-ROM is preferable."

Greece

http://www.eof.gr/web/guest/home?p_p_id=62_INSTANCE_0eNL&p_p_lifecycle=0&p_p_state=maximized&p_p_mode=view&_62_INSTANCE_0eNL_struts_action=%2Fjournal_articles%2Fview&_62_INSTANCE_0eNL_groupId=12225&_62_INSTANCE_0eNL_articleId=4783142&_62_INSTANCE_0eNL_version=1.0

Working hours of operation of EOF services

Under the provisions of Article 5(2) of the Treaty on European Communities of the Legislative Act (Government Gazed 55/A/11- 3-2020), the Department of the General Secretariat, for the period up to 10th April 2020, in the framework of measures to prevent and protect public health against the crown will operate from 10:00 to 14:00, during working days.

For the other Directorates, it is recommended to limit visits to those strictly necessary, i.e. those who cannot be processed by telephone or electronic communication, and only by appointment with the competent Service.

http://www.eof.gr/web/guest/home?p_p_id=62_INSTANCE_0eNL&p_p_lifecycle=0&p_p_state=maximized&p_p_mode=view&_62_INSTANCE_0eNL_struts_action=%2Fjournal_articles%2Fview&_62_INSTANCE_0eNL_groupId=12225&_62_INSTANCE_0eNL_articleId=4782869&_62_INSTANCE_0eNL_version=1.0

Operation of the National Medicines Agency

Under the provisions of Article 5(1) of the Treaty on European Communities of the Legislative Act (Government Gazed 55/A/11- 3-2020), the number of employees who will attend the Central Office building of the National Medicines Agency on a daily basis will not exceed 100 per day, with

distribution defined by each Directorate. Other employees are to work remotely. Attendees and distance workers will alternate on a four-day basis depending on business requirements.

Hungary

https://www.ogyei.gov.hu/tajekoztatas_klinikai_vizsgalatok_folytonossagarol

Information on the continuity of clinical trials under COVID-19 (coronavirus) - 16.03.2020

Restrictions already applied (quarantine, visitation ban in healthcare institutions, increased burden of the healthcare system, possible supply problems for medicines — IMP and non-IMP, etc.) a thorough risk assessment of ongoing investigations should be carried out and measures should be put in place to prioritise patient safety and data validation. In the event of conflict between these two objectives, patient safety should be prioritised. All decision must follow ICH GCP and EU and Hungarian legislation, inclusive of GDPR.

Patient safety is the top priority and that, consequently, any changes should be proportionate and subject to a thorough risk assessment (benefit-risk assessment, impact on the health and safety of the impacts). The risk assessment shall be repeated and properly documented, depending on the evolution of the situation. Any deviation from current practice should be proportionate, verifiable and clearly documented (see ICH GCP 5.0.4).

During the transition period, the number of protocol deviations may increase. It is important that these deviations are clearly documented (see ICH GCP 4.5.3). The authorities will take a fair approach when reviewing deviations if they are in the interests of participants and do not expose them to undue risk.

For risk groups (immunosuppressant treatment, over 60 years of age, chronic diseases) particularly at risk of coronavirus, special consideration should be given to continuing the study.

In general, it is considered prudent to stop the enrolment of patients during this period.

If a temporary relocation of a testing site takes place, notification shall be sufficient to continue the investigation at a new site. When substantial modifications to the study are required in order to ensure the patient's continued participation, sponsor may do so as an "urgent safety measure" (USM). The change will take effect immediately. The urgent safety measure should be sent to the authority and the amendment should be subsequently, officially, authorised in accordance with the usual procedure.

Sponsor, in agreement with the investigator-in-charge, shall consider converting or deferring on-site visits to telephone visits or terminating them on the basis of the risk assessment, in order to ensure that it is strictly necessary visits to the test sites. If the epidemiological situation subsequently so requires, consideration should be given to the transfer of subjects to existing or new test sites. Such relocation may only be carried out with the agreement of the subjects and the principal investigators (transfer and host), by appropriately transferring the eCRF to ensure that the new test site has access to all information and previously collected data, and to record new data. The relocation agreement should be documented in the TMF (e.g. by e-mail). If it is not possible to continue the study at a test site, it shall be suspended and everything is followed to ensure patient safety and data adequacy.

In order to reduce on-site monitoring, appropriate alternative methods should be selected. Alternative methods shall be decided on the basis of a risk analysis taking into account patient and data security in agreement with the study sites and amended Monitoring Plan on the basis of accepted changes. The choice of alternative methods shall take into account that they do not place a disproportionate burden on the test site and staff. Remote and central is monitoring through an EDC system may be an appropriate alternative, focusing on data that is most important for the safety of subjects and the quality of the data.

The sharing of patient data and the remote access of the Sponsor's representative to the electronic database of healthcare institutions is not acceptable due to the protection of particularly sensitive data and ethical considerations.

It is important to stress that proper follow-up of these transitional measures after the normalisation of the situation is essential and includes, for example, an increase in the frequency and/or time of on-the-spot monitoring in order to identify and address the possible adverse effects of the transitional measures.

Measures to address problems with access to investigational medicinal products and other medicinal products used in the clinical trial (non-IMP) shall be taken in accordance with the procedure laid down in Article 13 of The GMP. It shall be established in accordance with the procedure referred to in Article 10(2) of the processes may be carried out by a qualified and delegated person on the basis of written regulations. The transfer of test preparations between test sites, the care of patients on the spot for longer than originally planned, or the dispatch of imp from the test site to the patient's home may arise. Any transitional measure shall be designed in such a way as to ensure that

- the prescribed conditions for transport/storage of the product in question during transport and storage in the patient's home, especially in special circumstances (e.g. 2-8 °C),
- safe custody of preparations,
- and the relevant documentation of the accounts.

https://www.ogyei.gov.hu/felhivas_gyogyszerismertetoket_klinikai_vizsgalati_monitorokat_foglalkoztatoknak

Ban on Visits to Impatient Facilities

OGYEI advises of a ban implemented on visits to inpatients facilities directed towards sponsors and clinical trial monitors.

Ireland

https://www.hpra.ie/homepage/medicines/regulatory-information/clinical-trials/covid-19-(coronavirus)-and-cts

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

The safety of the subject is of primary importance, and risks of involvement in the trial, in particular with added challenges due to COVID-19, should be weighed up against anticipated benefit for the subject and society (ref: principle 2.2 of ICH GCP).

HPRA working with Department of Health, who are the responsible body for ethics committees, and HSE to the possibility of amendments relating to e.g. changes to a trial and/or sites, introduction of alternative site locations, and the possible need to suspend trials.

Priority review will be given to any new clinical trial applications relating to COVID-19, and/or amendments to existing clinical trials necessary as a result of COVID-19, priority reviews can be expedited where necessary. Substantial amendments should be submitted to the HPRA as required, and marked as "COVID-19 relevant". This will ensure appropriate prioritisation of assessment. Urgent safety measures can be used, where appropriate.

Investigator and site staff considerations

The impact of COVID-19 on the commencement of new trials, ongoing recruitment and continued subject participation needs to be considered. The ability to confirm eligibility, and to conduct key safety assessments and study evaluations, is of particular importance. Where required, recruitment should be temporarily halted, or suspended and subjects discontinued. Such decisions should be proportionate and based on benefit-risk considerations and impact on the health and safety of the subject. Where a subject is unable to attend the site, other measures, such as contact via phone or home nursing visit may be required to identify adverse events and ensure continuous medical care and oversight. However, the limitations of such methods should be taken into account, including the ability for investigator oversight. The addition of a new location to an existing trial site or the use of another trial site for subject visits may also be considered. Addition of a new trial site to the clinical trial would require amendment to the clinical trial application form and approval from the recognised ethics committee, notwithstanding the potential to use an urgent safety measure where appropriate.

Subjects enrolled in certain clinical trials may be determined as at risk groups. In particular subjects who are immunosuppressed, over 60 years of age or have long term medical conditions (this list is not considered exhaustive, and medical judgement is required). Trials involving immunosuppressant therapies may also increase the risk of COVID-19 to subjects. The impact of COVID-19 on these patient groups should be carefully considered when deciding to start or continue such trials.

An increase in protocol deviations may arise during this time. It is important that such deviations are clearly documented (ref: ICH GCP E6 4.5.3). A proportionate approach will be taken by the HPRA when such deviations are reviewed during inspections, in particular where the best interest of the subject is maintained, and the subject is not put at undue risk. This does not allow for the use of prospective "protocol waivers".

The impact of IMP provision to subjects should be considered, including what changes to existing practice may be required, should the need arise.

Alternatives may include delivering the IMP directly from the investigator site to the subject's home. Such measures raise various practical considerations, including whether the IMP is appropriate for home administration and general storage in the home, how stability of product will be maintained during transit (especially for cold chain product), how safe custody of product will be ensured and how IMP accountability will be managed. Such measures should be coupled with infection control considerations as the situation develops.

Whilst specific guidance on this topic is limited, guidance from the Pharmaceutical Society of Ireland on the home delivery of medicines may be considered during decision making (version 1, July 2014, available here. It should be noted that the guidance applies to retail pharmacy businesses and is specific to authorised products, and does not encompass all aspects relevant to the delivery of IMP, however, the principles may be of benefit in decision making. The HPRA Guide to Control and Monitoring of Storage and Transportation Temperature Conditions for Medicinal Products and Active Substances should also be considered (IA-G0011-2, dated 17 June 2017, available here.

Changes to existing practice should be proportionate and based on benefit-risk principles, and the provision of IMP to patient directly in a healthcare facility is generally regarded as best practice, notwithstanding the potential impact of COVID-19.

Sponsor and contract research organisation (CRO) considerations

The HPRA is aware that there may be an impact on the ability to accommodate on-site sponsor activities, such as monitoring visits or audits. Therefore, the necessity of on-site activities and/or appropriate alternatives may need to be considered. Centralised monitoring may be suitable alternatives in the interim, and their focus should be on core aspects of trial conduct. It should be noted that the sharing of subject data off site has data protection and ethical considerations, and is generally not acceptable.

The burden of the introduction of such measures on the site staff and facilities should also be considered, and a proportionate approach should be taken, balancing appropriate oversight with the capacity of the site.

Other on-site activities, such as sponsor support in the maintenance of essential documents at the site (the investigator site file), needs to be considered, and alternatives may be appropriate during this period. Such activities form an important aspect of sponsor oversight and support, and any deviations from current practices should be proportionate, justifiable and clearly documented (ref: ICH GCP 5.0.4).

The impact of IMP supply to sites and IMP management should be considered, including any restrictions and challenges on manufacturing, transport/delivery to sites and/or to subjects.

Amendments to register alternative sources of comparator or background therapies/ non-IMPs will be expedited.

Italy

https://www.aifa.gov.it/documents/20142/871583/Comunicato_gestione_studi_clinici_in_emergenza_COVID-19_EN_12.03.2020.pdf/ee1f33e3-bb3e-9ce9-2a93-b33e88eea94d

Clinical trials' management in Italy during the COVID-19 (coronavirus disease 19) emergency

As regards authorization requests of clinical trials and substantial amendments submitted by the OsSC, the postponement of paper documentation and CD sending referred to in the AIFA communication of 1st August 2019 (https://www.aifa.gov.it/-/aggiornamento-lettere-per-lautorizzazione-di-sperimentazioni-cliniche-e-relativi-emendamenti-sostanziali) is allowed. Paper documentation and CD will however have to be sent to the Clinical Trial Office as soon as feasible.

Submission letters should apply the stamp duty on the transmission letter by virtual payment (except in the cases provided for in article 17 of the legislative decree n° 460/1997 and in article 82, par. 5 of the legislative decree n° 117/2017) and to digitally sign the letter uploaded in the OsSC.

In case the submission via OsSC is not possible and paper transmission is needed as provided for in the AIFA communication of 2nd October 2018 (https://www.aifa.gov.it/-/attivazione-nuovapiattaforma-ossc-aggiornamento-02-10-2018), transmission by e-mail will not be accepted. Exception is made only for the submission of clinical trials regarding treatment of COVID-19 (coronavirus disease 19): authorization requests are allowed to be submitted by mail to apa@pec.aifa.gov.it and related documentation can be sent via Eudralink or similar ways within the same e-mail.

Ethics Committees evaluations of clinical trials/substantial amendments

Without prejudice to the current legislation and internal procedures of each single Ethics Committee, their meetings may also be held by web-conferences or other telematic ways, with the appropriate frequency to manage urgencies due to the current emergency.

Management of clinical trial activities outside investigational sites

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

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

Investigational medicinal product (IMP) management

If possible, when the patient goes to the study site for a visit, it may be useful to provide an amount of medicinal product covering a longer period of time than is normally estimated. According to current legislation (article 7 of the Ministerial Decree 21st December 2007), the Sponsors must send investigational drugs needed for the trial to the pharmacy of the investigational site, that is in charge for their registration, appropriate storage and delivery to the investigator. Therefore, considering the COVID-19 serious emergency, even if the priority mode remains the delivery to the hospital pharmacy that then proceeds to the subsequent delivery to the investigational centre, direct deliveries from the hospital pharmacy to the trial subjects also through dedicated couriers can be arranged, upon indications of both the hospital pharmacy Director and the Principal Investigator (PI). It is intended that the hospital pharmacy is responsible for the process supervision; the pharmacy and the PI must be constantly informed on the delivery, according to procedures established for the correct conduction of the trial and by the above-said risk plan, that must take into account the IMP typology, administration methods, conservation and transport. Adequate remote communication ways with involved subjects must be implemented to replace the information that will no longer be provided in person. Depending on the case, telephone and/or video call can be used to inform the patient, where deemed necessary. Adequate tracking of what is being implemented in this emergency situation is recommended.

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

Clinical examinations

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

Sites Closures

If a site is closed to the public for COVID-19 containment measures, it should be carefully assessed if the clinical trial staff is able to guarantee the continuity of the trial itself. In case the site is unable to follow the patients undergoing the trial, the study should be temporarily halted or, where possible, enrolled patients should be transferred to the nearest active trial site. Information exchange between PIs must be assured, as well as the transmission of clinical documentation and other trial material (e.g. IMPs) between sites. Contacts between Sponsor and health structures involved must be updated according to new agreements. A site not authorized to participate in the specific clinical trial is not considered as suitable as back-up, since it is not active, it does not know the trial and could not ensure a proper therapeutic continuity for the patient.

Clinical trial monitoring

Sponsors are invited to draw up a risk evaluation plan and implement an action plan taking into account the need to reduce unnecessary contacts in this period of COVID-19 epidemiological emergency. First of all, it should be assessed whether in-situ monitoring visits can be replaced by an enhanced centralised monitoring or whether such local visits can be postponed. Exceptional methods such as telephone contacts or, even better, videoconferences with the trial site staff can be implemented for the purpose of source data verification. These methods must be described in a specific SOP by the Sponsor/CRO and must be evaluated and approved by the Personal Data Protection Officer of the trial site. Other unusual monitoring methods involving more risky ways of accessing sensitive data, such as video recording of source document or making available to monitors original documents in shared electronic areas, must always be agreed with the Personal Data Protection Officer of the hospital, but it is considered appropriate that a specific opinion by the Italian Data Protection Authority be obtained.

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

In reiterating that such measures should be intended as extraordinary and limited to the coronavirus emergency period, by way of derogation from the FAQ 11 of the EMA document "Q&A: Good clinicalpractice (GCP)"–GCP Matters (https://www.ema.europa.eu/en/human-regulatory/researchdevelopment/compliance/good-clinical-practice/qa-good-clinical-practice-gcp), the Sponsor is allowed to sign contracts directly with such specialized agencies/companies. All other indications in the afore-mentioned FAQ remain applicable, such as for example: − the need that the PI remains responsible for the supervision; that efficient communication contacts are established between the staff in charge and the PI; that the staff in charge is suitably trained and that duties and responsibilities are stated in the contract and/or delegation log; that the protection of data confidentiality is assured.

Possibility of exceptional expenses reimbursement

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

Latvia

https://www.zva.gov.lv/lv/jaunumi-un-publikacijas/jaunumi/iespejamas-izmainas-klinisko-petijumu-veiksana-saistiba-ar-covid-19

Possible Changes in Clinical Trials Related to Covid-19

When deciding on changes in the conduct of clinical trials, the research centres and sponsors must take into account the safety of subjects and the capacity of the medical staff where an emergency situation due to COVID-19 has been declared. When evaluating the situation, account should be taken of the fact that the safety of subjects is the main concern, especially for patients at risk (e.g. immunocompromised patients and elderly patients).

It is also necessary to assess which aspects are critical to the conduct and continuation of the study. These conditions should be assessed by the study sponsor in conjunction with the study operators, taking into account the current situation in the country. The National Agency for Medicinal Products (ZVA) shall be informed of any changes to the studies relating to COVID-19. Deviations from normal practice must be well documented.

If the necessary amendments are assessed as urgent safety measures, they may be introduced without the authorisation of the ZVA by submitting information on them to the ZVA. The ZVA undertakes to examine all applications for the COVID-19 in an accelerated procedure.

The sponsor is responsible for assessing the materiality of the changes in determining whether they should be submitted as a substantial amendment. The following are general recommendations of the ZVA on possible solutions for continuing clinical trials in an emergency situation, but it should be noted that these recommendations are not definitive and that each particular situation should be assessed individually, depending on the type of study and the current situation in a country which can change rapidly in a global pandemic environment.

1. Permissible changes in the progress of patients ' visits, taking into account that the risk of infection WITH THE Sars-CoV-2 virus, which causes covid-19, should be limited as much aspossible.

- Conducting patient visits to patient homes;
- Reduction in the number of patient visits (changes to the schedule of the study), including longer duration of the medicinal product;
- If there is a risk of infection with the SARS-CoV-2 virus, which causes COVID-19 (e.g. patients with COVID-19 treatment), it may be possible to provide patient visits to another study centre or to open a new centre;
- Remotely carried out by means of communication solutions (telephone or video visit), if the tests provided for in the visit permit. Such a solution is possible even if the subject is quarantined.

2. If a patient is not able to undergo laboratory, instrumental, imaging or other tests for reasons related to COVID-19, the patient's safety should be considered .

3. The sponsor may decide to discontinue the study or stop the inclusion of patients.

4. Exceptionally, the delivery of study medicinal products to the patient's home provided by the Centre's staff taking into account the national distribution conditions of the medicinal product and the conditions of transport and storage of the investigational medicinal product. In the case of appropriate documentation it is also possible to transfer the study drug among the study centres if they could be missing in any of the centres.

In extreme circumstances, the direct delivery by courier of Medicinal products to which the ZVA should be reported as a substantial amendment may be considered when the epidemiological situation critically deteriorates.

5. Verification of remote data on on-the- spot monitoring visits based on the risk assessment of the particular study should be allowed, but it should be noted that the electronic transmission of patient-identifiable confidential information for monitoring purposes is not permissible

Netherlands

https://english.ccmo.nl/latest/news/2020/03/13/accessibility-ccmo-due-to-coronavirus-outbreak

Accessibility CCMO due to coronavirus outbreak

As a result of the Cabinet's call to work from home as much as possible for the time being (valild until 6th April 2020), CCMO is now less accessible. Despite the situation that has arisen, CCMO strives to safeguard the continuity of work processes as much as possible. For the time being, however, a large proportion of the office staff will be working from home, which means that CCMO is less accessible than you are used to. We will do our utmost to deal with questions via e-mail and telephone as quickly as possible.

https://english.ccmo.nl/latest/news/2020/03/16/recommendations-for-the-conduct-of-clinical-research-at-the-time-of-restrictive-measures-due-to-the-coronavirus

Recommendations for the conduct of clinical research at the time of restrictive measures due to the coronavirus

CCMO emphasises that in all cases the safety of research subjects and the health of healthcare professionals is paramount. As a sponsor or investigator, you should consider whether the clinical research, or parts of the clinical research, can be temporarily halted or not. CCMO realises that in many cases this is not possible with ongoing research. For example, because the subjects have to be given the study medication or because tests have to be carried out to ensure the safety of the subject. This may lead to protocol deviations, substantial modifications, urgent safety measures, temporary halt of the research or otherwise.

Recommendations given include:

- Set up a risk analysis on the consequences of the coronavirus on the conduct of the clinical research, whereby the safety of the participants is paramount;
- Record all deviations from the protocol and the standard procedure in writing; unless the subject's safety is at stake, these protocol deviations need not be submitted to the review committee;
- A deviation from the protocol or a protocol modification due to urgent safety measures to eliminate immediate hazards to the subject can take place without prior approval by the review committee. However, this must be reported immediately to the review committee;
- Study medication can be sent directly to the research subject by courier from the (hospital) pharmacy for reasons of subject safety; you need not inform the review committee about this, but do record this temporary procedure in writing;
- If the trial is (partially) suspended, this must be reported immediately to the review committee;

- 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;
- The procedure for submitting a substantial amendment to the review committee has not been changed. If it concerns an amendment which has an impact on the safety of research subjects and requires a fast-track assessment procedure given the emergency of the situation, you are advised to contact the review committee about the procedure to be followed.

Norway

https://legemiddelverket.no/nyheter/driftssituasjonen-ved-legemiddelverket

The operating situation at the Norwegian Medicines Agency

Both the Norwegian Medicines Agency and other authorities have introduced measures to reduce the risk of infection of coronaviruses. This means that we have lower staffing than usual. Tasks that are important for ensuring public and animal health are given priority. For lower priority tasks, it may take longer than normal to get answers to inquiries.

https://legemiddelverket.no/godkjenning/klinisk-utproving/endringer-som-folge-av-covid-19-

Changes as a result of covid-19

The Norwegian Medicines Agency has reduced staffing due to the general measures taken in society. Therefore, extended processing time must be assumed for applications for clinical trial and change applications in clinical trial.

Given measures that are now being implemented in society and in the health service due to Covid-19, it is likely that many clinical trials will not be possible to conduct as planned. The Norwegian Medicines Agency will encourage anyone conducting studies to pay attention to infection protection first. We ask that sponsors and affected research units make the necessary priorities and measures with regard to this early so that the changes can be implemented in the safest possible way.

We have defined all changes that must be made in clinical trials as a result of Covid-19 preparedness as safety measures. This means that changes and measures can be implemented before these are approved by us. Implement first, then submit notification of the security measure, then the change message with any changes to protocol, EudraCT etc. can be submitted later.

We ask that all submissions related to covid-19 are clearly marked with this, preferably in the subject field of the email. We will prioritize the treatment of such cases.

Can study medicine for ongoing clinical trials be sent home to the patient?

Yes, the Norwegian Medicines Agency considers the repatriation of the drug to the patient as acceptable with the measures taken. As usual, requisitioning of study drugs must be done by the main investigator or another study doctor who has been given the task delegated. In this case, the study drugs must be delivered at the patient's home directly. They can't be sent, for example, the with mail or placed in a mailbox. Shipment of study drugs from sponsor to patient is not accepted.

The following changes must be made 1) A general description of procedures around home sending, this can be defined as protocol add-ons/appendix. 2) All individual shipments must be documented.

Can study participants come to another study site/other study-related site?

The Norwegian Medicines Agency considers this a necessary change in ongoing clinical trials, given the measures now being implemented. If this is accepted by all involved, i.e. involved main investigators and other study staff, as well as the patient, it is okay to do so. All extraordinary appointments must be documented at both centers, in patient records etc. It must be agreed how study data should be communicated between the two centres.

Significant medical decisions under the control of the second center must be communicated immediately to the main investigator at the centre where the patient belongs.

Can telemedicine be used in ongoing clinical trials?

The Norwegian Medicines Agency considers this a necessary change in ongoing clinical trials, given the measures now being implemented. Sponsor must decide whether this will be medically justifiable with regard to further treatment of patients. See the other answer to the question of research at other campuses.

Can it be used remote information/recruitment, or electronic ICF?

Procedures for recruitment and informed consent shall be considered by the ethics committee. Please contact the ethics committee that has approved the relevant study.

Can study change method of study-specific studies? Can, for example, nurse do the examinations in the patient home, or by other methods without visiting the patient?

The Norwegian Medicines Agency considers this a necessary change in ongoing clinical trials, given the measures now being implemented. Sponsor must decide whether this will be medically justifiable with regard to further treatment of patients. Persons who will perform study-related tasks should be trained in the surveys to be conducted. Such training should be documented. Change in procedures must be documented. See also answers to the question of research at other campuses as well as information about submission to changes in clinical trials.

Is it possible to implement Source Data Verification (SDV = source verification) remote

Remote SDV is not accepted because it puts test participants' rights at risk. Sponsor can make centralized monitoring based on data documented in eCRFs, even if it does not replace SDV. Sponsor must document what changes are introduced and for what time period. SDV resumes when the situation will eventually normalize.

Poland

http://www.urpl.gov.pl/pl/informacja-z-dnia-13-marca-2020-roku-w-sprawie-działań-zmierzających-do-zahamowania

Information of 13 March 2020 on measures to stop the spread of SARS-CoV-2019 virus

In view of the exceptional situation, especially when the World Organisation for Migration (II) has been able to take a view to preparing the Committee's work on the subject. The Directorate of Health declares that we are dealing with a pandemic, most of the forces and resources of the Office have been concentrated in this area. At the same time, the URPL management, implementing the government's recommendations, decided to send as many employees as possible (under the so-called special law) to remote work. Such work organisation requires serious logistical activities and technical solutions. We try, despite all these challenges, to conduct timely proceedings. Knowing that the epidemiological situation will not normalise in the coming days, I would like to call on all stakeholders of the Office to consider the appropriateness of submitting applications for initiation proceedings. The priority for our proceedings will be those that concern medicines, products and biocidal products that can be used in the fight against the pandemic and those saving lives and human health.

We remind you of the possibility of submitting applications in electronic form, by means of an electronic delivery box, signed with a qualified electronic signature or a trusted signature. Indeed, we encourage you to choose this form. We would also like to limit as much as possible visits to the Office building, so any decisions, including decisions and other correspondence, will be served through a designated operator, i.e. through a designated operator. Polish Post or in electronic form.

Romania

https://www.anm.ro/anunt-important-13-03-2020/

Important Announcement to the attention of companies conducting clinical trials in Romania

In view of the current epidemiological context, it is necessary to take measures to protect the population, including patients/subjects enrolled in clinical trials.

In this respect, ANMDMR requires companies conducting clinical trials in Romania:

- to identify the potential impact of general protection measures against the COVID-19 pandemic on the current activities carried out in each clinical trial;
- notify the ANMDMR of the necessary plan of specific measures; they can be considered, on a case-by-case basis, as urgent safety measures with immediate implementation.

https://www.anm.ro/anunt-important-12-03-2020/

Important Announcement to the attention of persons concerned

In view of the current epidemiological context, in order to avoid movements with documents as far as possible, ANMDMR took the decision to restrict, from 13 March to 15 April 2020 (with the possibility of extension, if necessary), of the public activity of the Registrar service. The documents can be transmitted as follows:

Medicinal products for human use:

- by post at Str. Av. Sănătescu nr. 48, sector 1, 011478 Bucharest,
- by fax at no.: +4021-316.34.97
- electronic: to registratura@anm.ro through CESP – through the single point of electronic contact (PCU-e).

Slovakia

https://www.sukl.sk/hlavna-stranka/slovenska-verzia/klinicke-skusanie-liekov/pokyny/mimoriadne-opatrenia-pre-klinicke-skusania-v-dosledku-covid-19?page_id=5303

Emergency Measures for Clinical Trials Due to Covid-19

The State Institute for Drug Control recognises that the exceptional situation in relation to the spread of COVID-19 affects the conduct of clinical trials in Slovakia. The ŠÚKL has therefore issued guidance on how to proceed in this particular situation.

Several factors can play a role in this situation, such as the quarantine of patients enrolled in the clinical trial, limited access to public places (including hospitals) due to the risk of spreading infection, etc. We assume that, as a result of this situation, there will probably be a greater number of deviations from the approved protocol than normal. We expect that the sponsors of the clinical trials will escalate and manage such deviations from the Protocol in accordance with their standard procedures and GCP inspectors shall take this situation into account in future inspections. We also consider that there may be a shortage of personnel in the clinical trial centres. It is important that the clinical trial sponsors give priority to critical tasks in the clinical trial.

The ŠÚKL will prioritise all requests for COVID-19 and, in the case of questions relating to clinical trials.

ŠÚKL recommend that changes due to COVID-19 should be dealt with as "Urgent Safety measures". Consequently, they may be implemented without consent, however should be informed in a timely fashion. Together with the notification, the sponsor of the clinical trial must provide a detailed risk assessment. It should be stressed that patient safety is our main priority and therefore all changes should be based on a thorough risk assessment by the sponsor of the clinical trial.

https://www.sukl.sk/buxus/docs/Klinicke_skusanie_liekov/Extraordinary_measures_for_clinical_trials_due_to_COVID.pdf

The guidance concerning extraordinary measures for clinical trials die to Covid-19 has been published in English and addresses changes in monitoring, changes to shipment/handling of IMP, changes to visits or trial participants affiliation to an investigator site and changes in document practice.

Slovenia

https://www.jazmp.si/obvestilo/news/detail/News/koronavirus-covid-19-obvestilo-glede-poslovanja-jazmp/

Covid-19 – Notification of the Business of JAZMP

All interested stakeholders and the public are informed that JAZMP's business is running smoothly for the time being. The JAZMP, due to unforeseen situations and harsh conditions, is closely monitored for the occurrence of the virus and will take appropriate and necessary organisational measures in the event of deterioration of the situation. We will keep you informed of any changes you make to our website.

In accordance with the instructions of the competent institutions for the restriction and the possible occurrence and spread of the disease, the JAZMP shall carry out the preventive measures provided for it. Therefore, we ask you to carry out procedures to prevent infection and to consistently follow the disinfecting protocol when entering the JAZMP business premises. The necessary provisions are located for this purpose at the entrance to the building.

Spain

https://www.aemps.gob.es/informa/notasinformativas/medicamentosusohumano-3/2020-medicamentosusohumano-3/medidas-excepcionales-aplicables-a-los-ensayos-clinicos-para-gestionar-los-problemas-derivados-de-la-emergencia-por-covid-19/

Exceptional measures applicable to clinical trials to manage problems arising from the COVID-19 emergency

The Spanish agency of medicines and medicinal products (AEMPS), as national competent authority in the authorization of clinical trials, proposes a list of recommendations as exceptional measures during the COVID-19 emergency in Spain. These measures are intended to preserve the activities of the trial as far as possible, guaranteeing the health care of the patients, protecting their safety and well-being and preserving the traceability of the actions implemented in this health emergency.

It is essential to maintain the maximum capacity of the health-care system reducing the risk of infection for the population. In addition, it is necessary to take into account the measures applied in the different autonomous communities after the declaration of the state of alert by the Government.

In this context, scheduled follow-up visits, access by external staff to the sites and monitoring of the trial on site may be affected. In some cases, it may be necessary to transfer a patient from one center to another to facilitate their healthcare. On the other hand, there may be a decrease in the staff of the sponsor in charge of monitoring the trial.

It is important that the Sponsor together with the investigator make a risk analysis and prioritize the activities that are critical and the way in which they should be carried out. Both should evaluate the application of these measures in a balanced way for each clinical trial considering their particularities, the organization of each center and the epidemiological characteristics of COVID-19 in it. These measures may be updated to adapt to epidemiological developments as determined by the Ministry of Health.

Any such exceptional measures taken must be duly documented in the trial file. However, its application does not require prior approval on a case-by-case basis as a substantial modification by

the AEMPS or by the Ethics Committee for Drug Research (EC), nor the individual notification of serious breaches of the protocol, except when expressly required in the point 2. Within four months following the date in which it is considered that the COVID-19 crisis has ended in Spain, the sponsor must communicate for each trial a report on the exceptional measures adopted that will be sent to the Agency and the Ethics Committee of Research with medicines (CEIm).

- These measures are intended to guaranty the clinical trial activity, patient safety and wellbeing and the traceability of the implemented measures.
- The application of these measures do not require Ethics Committee (EC) or Spanish Agency for Medicine and medicinal Products (AEMPS) approval, but they will be notified once the sanitary emergency situation has been finalized.
-

Scheduled treatment visits of patients in a clinical trial

The sponsor together with the investigator should consider the advisability of postponing these visits, or transforming them into telephone visits, rescheduling them in the visit schedule of the clinical trial. Every effort should be made for any critical scheduled on-site visits to take place. In the case of rescheduling visits, these deviations from the protocol will not be considered serious breaches unless they put the safety of the patient at risk.

New patients recruitment

Prospectively anticipated protocol deviations are not acceptable and it is expected that all subjects included in a clinical trial meet all the eligibility criteria. The sponsor, together with the investigator, based on a benefit / risk assessment that considers the characteristics of the trial and the circumstances of the participating sites, may interrupt the recruitment and even interrupt the treatment of the trial patients in order to avoid unnecessary risks and guarantee the best possible healthcare for patients. This analysis is especially pertinent in clinical trials involving immunosuppressant treatment and therefore an increased risk of infection, with no expectation of benefit for participants.

In the event of an interruption of the trial that leads to the cessation of treatment in part of the patients, the sponsor would have to notify these measures as "urgent security measures" explaining the measures adopted to guarantee the alternative treatment of the patients by sending an Ad-hoc report to both the AEMPS and the Ethics Committee of Research with medicines. (CEIm) within 15 days following the interruption or termination.

Access to trial treatment

Patient access to trial medication should be guaranteed under the same conditions in which it was being given. It is recommended that the researcher evaluate the possibility and convenience that, when the patient attends a scheduled visit, he receives an amount of medication that will cover a longer period of treatment.

The Pharmacy Services of the hospitals may take the measures they deemed necessary, for example, the dispensing of a treatment to be taken at home to a person authorized by the patient or the delivery from the Pharmacy Service of the treatment to the domicile of the patient when the patient circumstances make it advisable. In relation to the latter, it must be assured the proper conditions of the drug during transport and communication with the patient that allows the reception and proper

administration of the product. Section 10 of the document “Q&A: Good clinical practice (GCP)” - GCP Matters ”will be taken into account. The situation in each particular case must be assessed by the sponsor, the main researcher and the Pharmacy Service.

Monitoring Visits

We recommend the Sponsor to update the trial monitoring plans for the next four months, prioritizing centralized monitoring and remote monitoring of the participating centers, which does not entail overloading the site staff with tasks or the source data verification and postponing as far as possible the verification of source data until you can access the medical history in person. The sponsor will agree with the participating sites and teams the conditions for such monitoring.

Transfer of patients from one site to another

If the transfer of a patient from one trial center to another is necessary, this may be carried out provided that: a) a transfer agreement is signed between centers, b) the new center has access to the data collection notebook and history patient's clinic (or failing that the original center will send you a copy of it); c) the original center sends a transfer report summarizing the most relevant medical data of the patient in relation to the trial to facilitate its follow-up to the new center; d) the transfer of the patient is documented in the trial file of the two centers.

Clinical trials aimed at investigating new drugs against coronavirus

The AEMPS is prioritizing, together with the EC, the evaluation of clinical trials aimed at treating or preventing coronavirus disease. Sponsors or investigators who have a research project of this type should send a message to the Clinical Trials Area indicating in the subject: URGENT new EC COVID19. An answer will be given the same day.

Sweden

https://www.lakemedelsverket.se/sv/behandling-och-forskrivning/coronavirus

The work of the Swedish Medical Products Agency in connection with the outbreak of coronavirus/covid-19 – Impact on Clinical Trials

The Swedish Medical Products Agency is aware that there are challenges in the conduct of clinical trials in connection with the coronavirus outbreak.

Document deviations carefully

We believe that protocol deviations may occur as a result of subjects being unable to conduct scheduled study visits and sponsor staff are unable to visit the relevant clinics under the circumstances.

However, we do not consider that any protocol abnormalities that may occur as a result of the coronavirus in themselves constitute a serious breach. However, we urge sponsors to carefully document deviations and consider whether these need to be reported as a serious violation to the Swedish Medical Products Agency in accordance with LVFS 2011:19, Chapter 8. 11 §.

Changes to the trial

The safety of the subjects is our top priority. If the sponsor deems that changes need to be made in relation to the approved protocol, it shall be submitted in the form of an application for a material change in accordance with LVFS 2011:19, Chapter 7. Changes to the trial.

The changes to be made shall be clearly justified, the consequences for the subjects and the scientific value of the trial shall be clearly described in the application.

Clearly indicate in the cover letter to the application for substantial modification that it is being implemented as a result of the current situation with the coronavirus outbreak. The Swedish Medical Products Agency can then handle the matter promptly.

United Kingdom

https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/covid-19-guidance-sponsors-sites-and-researchers/

COVID-19: Guidance for sponsors, sites and researchers (v1.1 13 March 2020)

Amendments to existing studies to address COVID-19 elements

There are a number of possible scenarios where there may be a need to rapidly amend an existing study.

All amendments requiring submission should be submitted by email through the usual email route, clearly marking them with the subject header: IRAS ref# Amendment - COVID-19, so that they can be expedited.

All amendments should be sent to participating sites in accordance with existing guidance. To support site implementation it is important that:

- The changes and local implications are made clear
- Any changes to documentation are provided in tracked changes
- For multi-centre studies in Scotland or Northern Ireland, amendments should be provided to R&D offices through the national coordinating functions as usual.
- In England and Wales All correspondence to sites should be copied to R&D/I department and the PI/ delivery teams
- Where indicated below, the sponsor should include the category and confirm that no assessment is required.

Studies where the sponsor wants to add in testing for SARS-CoV-2 for safety purposes

This may be implemented for example where studies include taking samples, and safety checks need to be implemented so that the appropriate protection is put in place for sample handling. Such arrangements should be treated as an urgent safety measure with subsequent notification in the usual way. Consider using a separate specific information sheet to provide information about additional tests rather than modifying an existing Participant Information Sheet.

Studies adding new COVID-19 related elements

This could include amendments to add sub-studies or components, e.g to enable epidemiological analysis of COVID-19, or to add patients with COVID to an existing trial of a treatment.

Submit the amendment in the usual way making clear that the amendment relates to COVID-19, so that the review can be expedited.

Amendments to existing studies impacted by wider COVID-19 response

There are a number of possible scenarios where there may be a need to rapidly amend an existing study with no COVID-19 related aspects, but due to the wider impact of COVID-19 on NHS staffing, restrictions on movement of people or in response to Government advice. Guidance is given for each scenario below. All amendments that need to be submitted to a review body should be sent by email through the usual email route. All amendments should be sent to sites in accordance with the guidance above.

Safety of patients of course remains a priority. If the safety of a participant is at risk because they cannot complete key safety checks, then consideration to discontinuing that participant must be considered. Where necessary, urgent safety measures may be implemented first and notified subsequently.

Changes instigated by sponsors across the study

Studies where sponsors need to change their site monitoring arrangements, or make changes to administrative arrangements to reduce burden or physical contact with sites

Any such changes should not increase the burden on NHS sites. These should be handled as a non-substantial amendment that does not require HRA/HCRW Approval or R&D agreement. For studies involving the NHS/HSC, these should be marked by the sponsor as category C and not requiring assessment and sent directly to sites following the instructions above. These should be implemented at sites on the date specified by the sponsor.

Any change to remote monitoring must not result in confidential patient information being sent to the sponsor if this has not already been addressed in the participant information sheet. Source data verification may be done remotely by electronic means if the necessary security arrangements can be put in place, if the arrangements are in line with the information.

Studies making changes to how or when patients are seen to avoid exposing patients or to reduce burden on clinical services

In some cases changes will be deemed by the sponsor to reduce risk of potential exposure to COVID-19 by participants, for example changing participant site visits to phone calls or postal questionnaires. Sponsors must not make any such changes that would create additional burden to NHS staff or resources. These should be handled as a non-substantial amendment that does not require HRA/HCRW Approval or R&D agreement. For studies involving the NHS/HSC, these should be marked by the sponsor as category C and not requiring assessment and sent directly to sites following the instructions above. These should be implemented at sites on the date specified by the sponsor.

In some cases changes will be deemed by the sponsor to potentially increase risk to participants, eg less frequent participant checks. Sponsors must not make any such changes that would create additional burden to NHS staff or resources. These should be handled as a substantial amendment. Such amendments will be categorised and assessed according to existing guidance, but the process

will be expedited. They should be sent to sites following the instructions above. These should be implemented at sites on the date specified by the sponsor.

Studies where treatment or investigational medicinal product need to be sent by courier direct to participants or other alternative mechanisms of provision

Sponsors must assess the risks relating to the product and consider any shipping and storage arrangements. Participants must consent verbally to providing contact details for shipping purposes. Where participants are self-isolating or in quarantine, arrangements for a nominated person to collect product may be implemented with the participant's verbal consent. Any such temporary arrangements should be handled as a non-substantial amendment that does not require HRA/HCRW Approval or R&D agreement. For studies involving the NHS/HSC, these should be marked by the sponsor as category C and not requiring assessment and sent directly to sites following the instructions above. These should be implemented at sites on the date specified by the sponsor.

Studies where sponsors need to implement a temporary halt to all or some of the study or extend the duration of a study due to COVID-19.

For CTIMPs this is a substantial amendment. Such amendments will be categorised and assessed according to existing guidance, but the process will be expedited. They should be sent to sites following the instructions above. These should be implemented at sites on the date specified by the sponsor.

For non CTIMPs, these should be handled as a non-substantial amendment that does not require HRA/HCRW Approval or R&D agreement. For studies involving the NHS/HSC, these should be marked by the sponsor as category C and not requiring assessment and sent directly to sites following the instructions above. These should be implemented at sites on the date specified by the sponsor.

Studies that need to be closed

For any studies not involving provision of treatment to participants, a notification to the REC or study-wide review (for non-REC studies) should be provided, and an end of study report should subsequently be provided.

For any studies involving provision of treatment to participants, careful consideration should be given to post-study care. If this cannot be in line with the information provided in the participant-information sheet, a substantial amendment should be submitted. Such amendments will be categorised and assessed according to existing guidance, but the process will be expedited. They should be sent to sites following the instructions above. These should be implemented at sites on the date specified by the sponsor.

Changes instigated by individual sites due to clinical requirements

Studies where sites need to suspend recruitment

Sites must raise such issues with the sponsor as early as possible if this is likely to occur.

Where such arrangements will affect the whole study the sponsor should follow the instructions above.

Studies where sites need to move participant visits due to re-allocation of staff and resources to clinical care or limiting participant contact

Sites must raise such issues with the sponsor as early as possible if this is likely to occur.

Where possible such arrangements should be handled prospectively as an amendment. In cases where there is no time to arrange for such review, changes should be implemented as urgent safety measures and reported retrospectively. In any such situation the impact on participants should be considered and arrangements made to cover this, for example additional transport.

The options are to set up as a sub-contracted site of the existing site if oversight can be maintained by the existing site, or to set up new sites, or to implement direct home care arrangements by the sponsor. For study types where addition of new sites is a substantial amendment, existing guidance for submitting a substantial amendment for new sites should be followed. In all other cases, existing guidance for non-substantial amendments and addition of new sites should be followed.

Establishing subsidiary sites is a non-substantial amendment. These should be handled as a non-substantial amendment that does not require HRA/HCRW Approval or R&D agreement. For studies involving the NHS/HSC, these should be marked by the sponsor as category C and not requiring assessment and sent directly to sites following the instructions above. These should be implemented at sites on the date specified by the sponsor.

Studies where sites need to withdraw participants

Sites must raise such issues with the sponsor as early as possible if this is likely to occur.

For any studies involving provision of treatment to participants, careful consideration should be given to post-study care. If this cannot be in line with the information provided in the participant-information sheet, a substantial amendment should be submitted. Such amendments will be categorised and assessed according to existing guidance, but the process will be expedited. They should be sent to sites following the instructions above.

Studies where Principal Investigator(s) are taken off a study

If the absence will be greater than one month the REC should be notified. If the Principal Investigator will be absent for greater than three months alternative arrangements should be put in place.