LÆGEMIDDELSTYRELSEN
DANISH MEDICINES AGENCY

Any discrepancies between the Danish and English version of this guidance the Danish should take precedent.

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Extraordinary measures for clinical trials due to COVID-19

We are aware that COVID-19 has consequences with regards to the conduct of clinical trials with medicinal products in Denmark. Multiple factors play a role such as trial participants in quarantine, limited access to public places (including hospitals) due to the risk of spreading infections etc. We acknowledge that the consequences are likely to be more protocol deviations than normal, but this increase of protocol deviations due to COVID-19, should not by itself trigger notifications to us. We expect that the sponsors escalate and manage such protocol deviations in accordance with their standard procedures. Our GCP inspectors will take the situation into account during future inspections with focus on processes implemented during COVID-19

We also acknowledge that lack of resources can occur such as shortage of staff at the clinical trial sites, as staff could be involved in the COVID-19 state of readiness. It is important that sponsors in their risk assessment consider prioritisation of critical tasks in the clinical trial and how these are best maintained.

We are also aware that the rapid and unpredictable development of the COVID-19 pandemic results in a need for continuous adjustments of the activity level in the ongoing clinical trials in Denmark. We support that clinical research in Denmark continue to the greatest extent possible during what seems to be an elongated pandemic. Therefore, we recommend that sponsors of clinical trials regularly reassess whether the activity level is appropriate under the current conditions of the pandemic.

We acknowledge the consequence being, among other things, that recruitment in clinical trials might be suspended and resumed depending on COVID-19 stress on the healthcare system. It is important that it is agreed with the individual investigators and that communication with the trial participants is thoroughly considered in order to mitigate any uncertainty that this extraordinary situation may cause.

We prioritise all requests regarding regulatory aspects in clinical trials with medicinal products in regards to COVID-19 and can be contacted per mail kf@dkma.dk in case of questions related to clinical trials. Please mark any contacts clearly with 'COVID-19' and the EudraCT number in the subject field. You can also contact our helpline (4488 9123). This guidance will be updated continuously.

We refer to the published European guideline in this area. This includes general procedures for clinical trials during the COVID-19 pandemic as well as academic issues. Important differences and clarifications in relation to this Danish guidance:

- We should not be notified of the implementations made during the COVID-19 pandemic to the same extent as presented in the EU guidance. Notifications must be submitted when the situation is stabilized (see section 2).
- In Denmark, we allow the dispatch of IMP from sponsor directly to the trial participants (see section 4).
- In Denmark, we allow remote data source verification under certain conditions (see section 3).

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We also refer to the responsible regional ethics committees and the National Ethics Committee website, for clarification on consent, financial compensation, etc.: http://www.nvk.dk/covid19.

Clinical trial applications investigating treatment or prevention of COVID-19
Under the stabilised conditions in Denmark the time to first response is adjusted to 10 work days for clinical trials investigating treatment or prevention of COVID-19. If our assessment raise questions this might extend the timeline but we prioritise to have any issues resolved immediately. Please use our checklist on our website ensuring that all necessary documents are submitted.

We point out that clinical trials should, as usual, comply with Good Clinical Practice (GCP) and applicable legislation, which is detailed in our guidance. In addition, non-commercial sponsors / applicants who do not have experience in conducting clinical research should consult the GCP units before submitting the application. Reference is also made to Annex 2 of the GCP Executive Order, which is recommended to be used as a template for a protocol.

Please submit clinical trial applications by mail or EudraLink to kf@dkma.dk and remember to add 'COVID-19' to the subject.

If possible, we ask that we are kept informed of planned submissions and their submission deadlines. This is a great help in our effort to quickly and efficiently assess COVID-19 trials. Furthermore, if possible we recommend to attach key references from the submitted package, such as new COVID-19 publications.

Other clinical trial applications
The impact of the current COVID-19 outbreak should be considered as it may be appropriate to postpone trial initiation and recruitment.
We continue to the possible extent to assess all trials within the normal deadlines so that trials can be initiated as soon as the situation has stabilised.

Changelog, version 5.0 to 6.0:
Version 6.0 of this guidance includes the following updates:

- Introduction: Adjusted to current conditions. The initial response time for CTAs adjusted to 10 work days.
- Section 2.3 updated: Deadline and notification requirment updated.
- Section 3.2 updated: Expectations of rSDV amendments added.
- Section 4.4 added: Precision that shipment of IMP directly from site is allowed if complying with our Q&A.
- Section 5.3 updated: Activity in FiH trials adjusted to current conditions.

1. Inquiries related to COVID-19 disease and preventive measures

Inquiries about risk of infection, measures and testing of COVID-19, which are not related to regulatory aspects of conducting clinical trials with medicinal products in Denmark. These inquiries should be addressed to the Danish Government joint hotline at: +45 70 20 02 33.
Please be informed of the questions and answers at the Danish Health Authority's webpage on COVID-19: www.sst.dk/en/English.

If you are involved in a trial as a patient or staff, please contact the trial investigator.

2. Handling of changes initiated due to COVID-19

We recommend that changes due to COVID-19 should be handled as 'Urgent Safety Measures'. Consequently, they can be implemented without approval from the Danish Medicines Agency. We should only be notified of changes implemented during the COVID-19 pandemic, that does not comply with this guidance and its terms, and have a significant impact on the benefit-risk of the trial (see section 2.1).

As part of the notification, we expect a high-level trial-specific risk assessment that briefly and accurately addresses the impact of the changes to patient safety in the trial. This includes if there are safety parameters (blood tests, vital parameters, etc.) that are not collected and what impact this will have on patient safety and trial data.

It should be considered for all trials to postpone on-site visits or if possible, transferring them to telephone consultations (in accordance with section 3 and 5).

If substantial changes to patient safety or data integrity occur without requiring immediate changes in the trial, these should be submitted in accordance with normal substantial amendment procedures e.g. implementation of remote Source Data Verification. We do not consider addition of COVID-19 testing substantial and we do not wish to be notified, if trial subjects are diagnosed with COVID-19.

2.1 Updated notification procedure

Based on the notifications received until now, we have decided that it is no longer necessary to submit changes covered by this guidance. However, changes must be continuously documented in the Trial Master File.
Specifically, this means that, for example, stopping inclusion at one or several sites (study halt), changes to the visit schedule (see section 5) and delivering medicine directly to participants will no longer be subject to notification requirements. Please note that sponsors are obliged to submit notifications when the situation has stabilised (see sub-section 2.3).

The requirement of submitting notifications within 7 days is still valid in those cases where other substantial changes are made, which significantly impact the benefit-risk or this guidance and its terms are not followed.
In addition, we must be notified if there is an acute shortage of IMP without any substitution possibilities. In the notification, sponsor must explain how safety is monitored for trial participants who are deprived of treatment. Furthermore, we always need to be informed if the trial is terminated prematurely in accordance to normal practice.

It should be emphasised that patient safety is our main priority and consequently, all changes should be based on a thorough risk assessment.

2.2 Format and content of notifications

You should not submit documentation such as SOPs or instructions for those changes implemented because of the COVID-19 pandemic. We do expect an overview of the substantial changes, which should be justified on account of the trial population and indication.
In addition, it should be clearly stated that our recommendations from this guideline have been taken into consideration, accompanied with thorough justification in the event of non-compliance.

Notifications submitted is allowed to cover multiple clinical trials. However, First in Human trials must be addressed individually (please see section 5).
The notification can be carried out by, for example, an Excel sheet (it might be appropriate using the same documentation added to the TMF with the overview of

deviations), where all clinical trials are listed and it is noted which general and specific measures have been implemented. Please note that it is up to the sponsor how these orientations are most easily prepared.

2.3 COVID-19 stabilisation and restoring normal practice

When the normal procedures are restored, a notification must be submitted describing all actions taken in the trial due to the COVID-19 pandemic. These must follow the same requirements as given above, why a risk assessment is expected for both patient safety and data integrity. Furthermore, the notification must clarify how sponsor plan to follow-up on, among other things, the lack of on-site monitoring (see section 3).

The notification can be submitted as a comprehensive list of deviations in each trial. The documentation submitted may be the same as added to the TMF.
However, if the studies are extended due to delays in handling COVID-19, it is important that the Expected Last Patient Last Visit (LPLV) is reported for each EudraCT number.

Sponsor must continuously assess whether it is possible to re-establish standard procedures and inform the Danish Medicines Agency of this by notification in accordance to above. The individual sites should be consulted on local requirements for their institution and their acceptance documented.

Notification of deviations should be done immediately after implementation of standard procedures. However, we expect that standard practice is restored and notification provided to us by December 1, 2020. We will assess the need for an extension one month prior the deadline.

Please note that substantial changes to the clinical trial that the sponsor wishes to retain must be submitted as an amendment for approval.

3. Changes in monitoring and audits

3.1 Monitoring

We acknowledge the need to adjust the monitoring of clinical trials. It is important that the overall risk assessment address any need for changes to monitoring strategies due to COVID-19. This risk assessment should take into consideration whether recruitment should be stopped temporarily. In addition, agreement with investigator sites on any changes should be obtained. Decisions should be driven based on patient safety considerations.

- On-site monitoring can be performed to the extent possible and as agreed with investigator sites. If it is not possible to follow the on-site monitoring plan, monitoring should be supplemented with centralised monitoring and central review of data, if possible.

- Remote SDV (Source Data Verification) is allowed in accordance with below section

Sponsors should be aware that these requirements might be subject to change during the evolution of the pandemic.

It is essential that robust follow-up measures are planned for when the situation is normalised, especially in regards to data collection. This should likely include increased on-site monitoring for a period that is sufficient to ensure that the impact of the reduced monitoring has been established and handled.

3.2 Remote Source Data Verification

The COVID-19 pandemic is a long-term burden for the Danish health care system. This means that there will continue to be restrictive access to some clinical trial sites. As a result, onsite monitoring might be disrupted for a long period, which can have serious consequences for data validity in some clinical trials. Therefore, in dialog with the Danish Data Protection Agency, we have decided to allow remote access to source data (remote Source Data Verification (rSDV) and prepared the following prerequisites for sponsors to establish remote access to source data.

Sponsor shall assess if ongoing trials, or soon to launch critical trials, where verification of source data is needed to ensure the quality of the final data. If this is the case, the sponsor must prepare a monitoring plan for remote SDV if on-site monitoring is not possible. Such plan should identify critical data that is going to be verified. Critical data are considered by the Danish Medicines Agency to be primary efficacy parameters, important safety data as well as any important secondary efficacy data to the extent that these can be verified in the same documents as the primary efficacy data. Only these data must be requested by the sponsor and verified.

Remote SDV should at this point only be required for a few clinical trials:

- Clinical trials investigating treatment and prevention of COVID-19
- Pivotal clinical trials soon reaching Data Lock Point and thereby trial completion, analysis and reporting of trial data.

Implementation of remote access must be carried out in close collaboration with the site investigators. The investigators should consult relevant personnel at the hospital's regarding possible solutions, practicality and security.

We also point out that sponsor is responsible for ensuring that remote SDV complies with GDPR. In this connection, a separate risk assessment must be prepared regarding data protection for the established procedures. Consideration should be made whether access is contemplated at the monitor's home or office. In case of doubt regarding data protection, the investigator and sponsor/monitor can contact the Danish Data Protection Agency.

This temporary option is valid until 1 December 2020. We will assess whether an extension is needed one month before expiry. A substantial amendment must be submitted to the Danish Medicines Agency if sponsor introduce remote access to source data.

Substantial amendment requirements introducing rSDV

The following is expected to be addressed in the application for an amendment for approval of rSDV:

- Justification for the use of rSDV in the specific trial.
- Justification for the use of rSDV under the current conditions of the COVID-19 pandemic, e.g. restrictive access to the sites concerned.
- Which method is used (see below options). Key elements of the chosen procedure must be clarified, for example, platform, IT security measures, how the rights of the trial participant are ensured.
- A statement from the sponsor that the minimum requirements stated below are met.
- Information about the agreement with respective investigators and what they have given consent to in regards to performing rSDV and how this is documented.

For non-commercial sponsors in Denmark, which are monitored by the Danish GCP units, other conditions apply regarding remote access to e.g. patient records. The GCP unit monitors is employed by the Danish health care system and their contractual conditions are expected to include appropriate safeguards.

The following general conditions must be met in addition to the specific terms mentioned by each of the three different procedures

a) Establishing remote access must be in accordance with the principles of necessity and proportionality and must always be done in a way that protects the rights of the participants and does not place unnecessary burden on site staff. The sponsor must never put pressure on the investigator to establish remote access to source data.
b) Remote access to Danish source data may only take place from a location within EU/EEA.
c) Access must be established under secure conditions. This include a secure connection on a machine protected from unauthorized access. The location must ensure that outsiders cannot overlook the process.
d) Monitor and involved site staff must be trained in the process.
e) The principal investigator and the institutions data officer must assess the necessity for monitors to sign a written confidentiality agreement committing to securely destroy any documents, whether paper or electronic, as soon as they have been used for SDV and committing not to make any additional copies (or recording in the case of video access) of any non-pseudonymised document, etc.

1. Electronic remote access to patient records and other source data

Conditions for method 1.

a) The access shall be restricted to read-only. Furthermore, monitors access should be restricted for trial subjects only to the extent possible.
b) The IT system must have an event log that shows when the monitor has accessed specific information.
c) Monitor must have personal access to the system.
d) The personal access must be provided with 2-factor authentication.
e) The system shall not, to the possible extent, allow the monitor to make local copies. Any data storage on the monitor's computer should be limited to the extent possible.
f) A log must document which data the monitor has accessed if not possible to restrict monitors access exclusively to the data of the trial subjects. This should proof that the monitor has not accessed other data than relevant for the SDV task for the specific trial subjects. This must be documented in the TMF.
g) It must be clarified that no data may be deducted/archived from the systems for monitoring purposes. This also applies to images/screenshots of source data.
h) Monitors remote access shall be terminated immediately when the need for remote access is no longer present.

2. Video conference where source data is reviewed with help of site staff

Conditions for method 2.

a) The video connection must be capable to provide high quality video to ensure readability. Screen sharing functionality can be used.
b) It must be clarified that no data may be deducted/archived from the systems for monitoring purposes. This also applies to images/screenshots of source data.

3. **Transfer of pseudo-anonymised copies of source documents**

Conditions for method 3.

a) Monitor must prepare a written request to investigator site about the source data needed for specific study participants to conduct SDV.
b) The site staff must pseudo-anonymise the requested documentation, do a quality check that anonymised areas cannot be read, and then deliver the documentation to the monitor in an encrypted form of communication.
c) A statement must be signed by the monitor that all documents has been destroyed or returned to the site. This statement must be submitted to the site as documentation.
d) At the earliest opportunity, when the possibility of on-site monitoring is re-established, the pseudo-anonymised documentation must be checked to relate to the subjects concerned.

3.3 Audits

Onsite audits should currently be avoided/postponed in order not to visit investigator sites unnecessarily. The sponsors should consider in their risk assessment whether remote audits or postponing of audits is the preferred option. On-site as well as remote audits should only be conducted after agreement with the investigator and if the audits are assessed as critical, e.g. triggered audits with the purpose of investigating serious non-compliance.

Audit of the areas under sponsor responsibility, including audits of contracted parties should only be conducted with appropriate consideration for the sponsor's, contracted party's and authorities' implemented restrictions and in accordance with the sponsor's assessment of criticality.

4. Changes to shipment/handling/stock of IMP

In case of urgent shortage of IMP at some sites, we acknowledge the need to potentially re-distribute IMP between sites in accordance with GMP annex 13 (section 47). Sponsors should assess whether sites can handle and control such a redistribution process, especially in case of restricted conditions for storage, such as the need for specific conditions out of room temperature (e.g. 2-8° C).
Redistribution should follow a written procedure established in cooperation with the Qualified Person or the person responsible for distribution of IMP, and sites should be provided with sufficient information to ensure that the process can be performed securely.

4.1 Hand-out of IMP at on-site visits:

If on-site visits are required, but the frequency of visits is limited, it should be considered whether the trial participant can be given IMP for a longer period than normal. It should be considered for all trials whether the trial participants should have IMP handed out for a longer period than usual in the event of a deterioration of the current situation. However, it should be taken into account that certain marketed drugs are used in the treatment of COVID-19. The primary concern is that no deficiencies arise, so that COVID-19 treatment is prevented.

4.2 Hand-out of IMP at pharmacies:

In open trials (it is not appropriate if IMP is blinded), it may be an advantage to supply IMP through the Danish pharmacies. Such procedure is subject to the following terms:

a) This only applies to clinical trials on Danish sites during the COVID-19 pandemic and a risk assessment must be carried out with priority to patient safety.
b) The trial drug must be marketed and used within the approved indication (according to the SmPC).
c) A simple process for reimbursement of the expense should be implemented.
d) It must be ensured that the name of the sponsor or investor is printed on the label together with a reference code, that ensure identification of the site, investigator and trial subject.
e) There must be procedures in place at the investigator site to ensure that the IMP is accounted for (for compliance monitoring).

4.3 Shipment of IMP directly to trial subjects from investigator site

The Danish Medicines Agency Q&A guideline on supplying trial medicine directly to trial subjects (within the section 'virtual/telemedicine trials') must be followed with patient safety as utmost priority. Among other things, this entails that procedures are in place ensuring that the trial medicine is delivered to the trial subject or their relatives only, and that it is possible for the trial subject to store the medicine in a suitable way. In other words, the trial medicine must be delivered personally and not delivered to neighbours or placed outside the door. In addition, sponsor must make sure that the trial subject has the required training to self-administrate trial medicine or otherwise assess if assistance from a nurse may be required (see section 5).

4.4 Temporary option to distribute directly to clinical trial subjects from sponsors (temporary exemption from § 23 (2), of the GDP executive order because of COVID-19):

We acknowledge that clinical trials may experience acute IMP shortages caused by COVID-19 related quarantines and cancellations of on-site visits. Considering these highly unusual circumstances, we have decided upon a temporary possibility for sponsors to distribute trial medicine directly to the trial subjects without involving the investigator or hospital pharmacies.

This temporary option is valid until 1 December 2020. We will assess whether an extension is needed one month before expiry.

Sponsors may avail themselves of this option on the following terms:

a) Sponsor has a MIA (manufacturing authorisation) or a WDA (wholesale authorisation) that covers distribution of investigational medicinal products.
b) Sponsor may only distribute investigational medicinal products for clinical trials on Danish sites and should be on the basis of a risk assessment with patient safety as utmost priority.
c) Prior to the direct distribution, the viability of distribution via investigator/hospital pharmacy should have been investigated.
d) A courier needs to ensure that the shortest possible route of transportation is used and that the terms of storage are met in all parts of the supply chain. This must be documented.
e) The requirements as set in section 4.3 of this guidance must be followed in the widest possible extent with patient safety as utmost priority.
f) Direct distribution to trial subjects is implemented as an urgent safety measure. Notification to us on this procedure must comply with the general requirements set in this guidance (see section 2).
g) The trial medicine may only be dispatched to trial subjects after agreement with the investigator and on the basis of the investigator's prescription. Furthermore, procedures for the accountability of the trial medicine must be in place (among other for compliance monitoring).
h) Sponsor may not store the personal data of the trial subject for a longer period than is required for the purpose of dispatching the medicine to the

subject. Sponsor may only authorise a limited number of employees to process the personal data in order to dispatch the medicine.

i) Sponsor must ensure that trial subjects is informed that the trial medicine will be delivered directly to their homes.

4.5 Trial subjects assigned to a Danish site but living abroad

We do not limit the delivery of IMPs to trial subjects, who are assigned to a Danish site, but who are staying abroad. However, it is important that the sponsor in these cases consult the authorities of the country concerned, whether they impose requirements or restrictions.

4.6 Stock of trial related medicinal products and medical devices

We recommend that stocks of IMP and other necessary medicinal products (NIMP) be kept appropriately high to ensure continuity in the event of shortage. It is important, as stated above, that it is taken into account that certain marketed drugs are used in the treatment of COVID-19 and other critical illnesses. The same applies for medical devices, including IVDs, which are used for safety/efficacy monitoring and other data collection.

5. Changes in visits or trial participants' affiliation to an investigator site

We recommend the sponsor to 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. In such cases, it is important that both trial subjects and both investigators (receiving and providing) agree about the transfer and that the receiving site has the possibility to access previously information/collected data for the trial subject and that any eCRF can be adjusted accordingly to allow the receiving site to enter new data. Such agreement can be documented e.g. in email correspondence filed in the TMF.

The sponsor (in cooperation with the principal investigator) should also consider whether physical visits can be converted to phone visits, postponed or cancelled completely to ensure that only strictly necessary visits are performed at sites. It may be considered to use electronic systems, such as video/telecommunications or e.g. electronic diaries if considered to relief burden from the trial staff. This is, of course, provided that the IT systems used are secure and valid.

This consideration should also be part of the sponsor's risk assessment in relation to the COVID-19 pandemic.

Consideration should be given to whether inclusion should be halted. In addition, it might be necessary to terminate studies if, for example, the primary effect parameters of the study cannot be monitored on site or using a local laboratory.
Furthermore, in case it is not feasible for a site to continue participation at all, the sponsor should consider if the trial site should be terminated and how this can be done to best ensure patient safety and data validity.

5.1 Use of qualified and trained personnel to administer trial medications and conducting other diagnostic tests at the trial subject's residence

We recognise the increased need to collect blood tests, side effects, etc. at the trial subject's residence. Furthermore, it might be appropriate to administer IMP at the trial subject's residence with assistance from qualified and trained personnel

This is acceptable if carried out under the terms set in the EMA GCP Q&A (question 10), with the following changes under COVID-19:

a) The justification for using such procedures may be based on the exceptional circumstances of the COVID-19 pandemic (in relation to question 10 of the Q&A).
b) The qualified and trained personnel must comply with the strict requirements for containment of COVID-19.
c) Consent is not expected, but the subjects need to be informed of the procedural change (in relation to question 10 of the Q&A).

If an external supplier of the above mentioned service is used, the contractual conditions must comply with questions 11 and 12 in the same Q&A. Sponsor should facilitate this to the greatest extent possible during the COVID-19 pandemic.

5.2 Blood sampling and other diagnostics tests can be transferred to a local laboratory

There may be a need for blood sampling and other diagnostics tests to be performed locally because of the changes to the visit schedule. It is acceptable that blood sampling and other diagnostic tests are done at a local laboratory if authorised/certified to perform such tests routinely and the local facility have the necessary precautions in place to ensure COVID-19 containment.

If the protocol uses a central lab for analysis but it is not feasible for the sample to be shipped, then this should be clearly stated in the clinical study report in accordance with ICH E3 (Structure and content of clinical study reports).

5.3 Special precautions for First in Human trials

It is a requirement in First in Human (FiH) trials that an agreement has been made with the intensive care unit in the event that serious side effects should occur.

We support that FiH activities is carried on in the widest possible extent. It is essential that sponsors take the current conditions of the pandemic into consideration of their risk-assesment and assess if relevant to obtain updated acceptance from the intensive care unit that that they have the resources to receive and treat trial participants. This can be documented by, for example, mail correspondence.

It might be relevant for the intensive care unit to be advised and accept that a new trial participant is dosed, or dose-escalated, one day in advance if the conditions worsens in regards to the pandemic. In addition, recruited trial participants under the COVID-19 pandemic are still expected to be properly informed of the risk that they will not receive IMP administration, due to a lack of resources at the intensive care unit.

5.4 Communication should be strengthened to the trial during the COVID-19 pandemic

During the COVID-19 pandemic we might experience increased levels of anxiety and concern among some trial subjects. This is expected due to, among other things, the procedural changes that might affect the trial subject's participation in the trial and the associated uncertainty as to whether treatment is discontinued or how/when the treatment is continued. We therefore encourage sponsors to develop a specific COVID-19 communication plan, that clarifies whom is responsible for the needed strengthened communication together with how and when information should be given to the trial subjects. This will also allow trial subjects to ask questions and share their concerns.

6. Changes in documentation practice

As stated above, it is expected that the sponsors perform a thorough risk assessment of each individual ongoing trial and implement measures which priorities patient safety and data validity. In case these two conflicts, patient safety should take priority.

These risk assessments should be based on relevant parties' input and should be documented on an ongoing basis. In case this risk assessment affects trial conduct, the Danish Medicines Agency should be notified.

The sponsors should reassess risk as the situation develops. This reassessment should also be documented.

With regards to the need for wet ink signatures e.g. from investigator sites, alternative means of documentation (e.g. emails) should be considered.