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. We expect that the sponsors escalate and manage such protocol deviations in accordance with their standard procedures, and our GCP inspectors will take the situation into account during future inspections.

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 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.

Clinical trial applications investigating treatment or prevention of COVID-19

We have reduced the time to first response to three 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: https://laegemiddelstyrelsen.dk/en/licensing/clinical-trials/trials-in-humans/guideline-for-applications-for-authorisation-of-clinical-trials-of-medicinal-products-in-humans/~/media/F1B0966F3509446A94FCC9D27976DA3E.ashx

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.

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 2.0 to 3.0:
Version 2.0 of this guidance includes the following updates:

- Introduction updated: General information regarding submission and timelines for clinical trial applications.
- Bullet point 2 updated: Changed requirements for notifications and further clarification of format.
- Bullet point 3 updated: Sections regarding audits added.
- Bullet point 4 updated: Hand-out of IMP at on-site visits and clarification that stockpiles of medicines should take the needs of COVID-19 treatment into account.
- Bullet point 5 updated: Clarification regarding use of local laboratories for blood sampling and diagnostics tests as well as clarification for FiH trials treating critically ill patients without other treatment options.

1. Inquiries related to COVID-19 disease and preventive measures
We receive many 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; however, we should be notified about the changes (kf@dkma.dk) without delay (within 7 days) if the benefit-risk is significantly impacted (please see sub-section 2.1).

It should be considered for all trials to postpone on-site visits or if possible transferring them to telephone consultations.

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. We do not consider addition of COVID-19 testing substantial.

2.1 Updated notification procedures
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, changing the visit schedule 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 notification requirement mentioned in the introduction is still valid in those cases other substantial changes is made 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.

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 bullet point 5).
The notification can be carried out by, for example, an Excel sheet, 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.
These notifications can also cover multiple clinical trials as stated in section 2.2. 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.

We expect that normal practice is restored and notification is carried out by June 17, 2020. We will assess the need for an extension two weeks prior the deadline.

We also refer to the published European guideline in this area. This includes general and procedures for clinical trials during the COVID-19 pandemic as well as academic issues: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf.

We refer to the responsible regional ethics committees and the National Ethics Committee website, for clarification on, among other things, consent and financial compensation: http://www.nvk.dk/covid19.
3. Changes in monitoring and audits

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.

- The sponsor should assess whether clinical trials should be put on temporary halt, in which case authorities should be notified (please be referred to bullet point 2 about notifications covering multiple clinical trials).

It is essential that robust follow-up measures are planned for when the situation is normalised. 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.

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.

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.

Temporary option to distribute directly to clinical trial subjects (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 17 June 2020. We will assess whether an extension is needed two weeks 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 Danish Medicines Agency Q&A guidelines on supplying trial medicine directly to trial subjects (within the section 'virtual/telemedicine trials') must be followed to the greatest extent possible with patient safety as utmost priority: [https://laegemiddelstyrelsen.dk/en/licensing/clinical-trials/clinical-trials-questions-and-answers/](https://laegemiddelstyrelsen.dk/en/licensing/clinical-trials/clinical-trials-questions-and-answers/). 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 neighbors 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.

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.

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.

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 understand and accept that the trial medicine will be delivered directly to their homes.

**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.
Stock of trial related medicinal products: 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.

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

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.

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)

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 foresee that this agreement cannot be ensured during the COVID-19 pandemic with proper contingency and it is therefore our general expectation that all FiH trials will be put on hold.

Specifically, this means that recruitment for FiH trials should be halted. Thus, new trials should not be initiated and, for ongoing trials, higher dose levels than already initiated should not be started. This means that ongoing treatment can continue if it is in the interest of the trial participant.

We are aware that some FiH trials involve treatment of critically ill patients without other treatment options. In those cases, the trial may continue recruitment and dose escalation. This is conditioned that acceptance must be obtained from the intensive care unit that also state how it is ensured that the intensive care unit have the resources to receive and treat trial participants under COVID-19.

This can be documented by, for example, mail correspondence.
The intensive care unit must be advised and accept that a new trial participant is
dosed or dose-escalated one day in advance. In addition, recruited trial participants
under the COVID-19 pandemic are 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.

6. Changes in documentation practice
As stated above, it is expected that the sponsors perform a thorough risk assess-
ment of each individual ongoing trial and implement measures which priorities pa-
tient 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, alterna-
tive means of documentation (e.g. emails) should be considered.