



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

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Version 2.0
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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 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 sponsor escalates and manages 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.

Changelog, version 1.0 to 2.0:

Version 2.0 of this guidance includes the following updates:

- New bullet point (1): Whom to address inquiries that do not concern regulatory aspects of conducting clinical trials in Denmark.
- Bullet point 2 updated: Guidance to our expectations of the content in the submitted notifications.
- Bullet point 4 updated: Opportunity to distribute medicinal products directly from sponsor to trial participants added.
- Bullet point 5 updated: Specific requirements for First in Human trials added.

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).

Sponsor's risk assessment should be provided with the notification. The risk assessment should be concise and address the impact of the changes on the trial subject safety including whether some safety data is no longer collected and if this impact trial subject safety or trial data.

We expect that notifications are continually submitted to us, if substantial changes are made to below procedures.

- **Changes to visit schedule:**
In case of changes to the visit schedule, please indicate whether there are visits which, for example, switch to telephone contact. Please state whether some on-site visits are maintained. The changes must be motivated and submitted together with a risk-benefit statement for the concerned trial participants.
- **Shipment of trial medication to the trial participants:**
It is important that the procedure is documented, but we do not expect the instruction to be submitted. However, the requirements set out in this guidance must be addressed in the notification to us, including such aspects as storage conditions, participant's knowledge/training in administration, etc. (please consult bullet point 4).
- **Notifications covering multiple clinical trials:**
Notifications is allowed to cover several clinical trials if concerning non-protocol-specific changes. When normal procedures are restored, notification must be submitted individually.

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

3. Changes in 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.

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.

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/>. 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 (such as NIMP) be kept appropriately high to ensure continuity in the event of shortage.

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.

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 expect this agreement cannot be ensured during the COVID-19 pandemic with proper contingency and it is therefore our 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.

6. Changes in documentation practice

As stated above, it is expected that the sponsor performs a thorough risk assessment of each individual ongoing trial and implements 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 sponsor 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.