LÆGEMIDDELSTYRELSEN
DANISH MEDICINES AGENCY

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Version 1.0
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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 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' in the subject field. You can also contact our helpline (4488 9123). This guidance will be updated continuously.

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 without delay (kf@dkma.dk). Sponsor's detailed risk assessment should be provided with the notification.
It should be emphasised that patient safety is our main priority and consequently all changes should be based on a thorough risk assessment.

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 and meaningful.
- The sponsor should assess whether clinical trials should be put on temporary halt, in which case authorities should be notified.

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.

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Changes to shipment/handling 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. Please also refer to our Q&A regarding virtual/decentralized trials where the expectations regarding IMP and the trial subject's knowledge/training is described: https://laegemiddelstyrelsen.dk/da/godkendelse/kliniske-forsoeg/spoergsmaal-og-svar/.

We foresee that there will be the need for delivery of IMP directly to trial subjects during the COVID-19 pandemic to avoid that the trial subject has to go to the site with consequent risk of spreading infection. If possible, it should be the sponsor's first priority to perform this task in agreement with investigator site pharmacies.

We are investigating possibilities that sponsors could deliver IMP directly to the trial participants. We will update this document accordingly as soon as possible once determined.

Stock of IMP: It is recommended for all IMP and non-IMP in clinical trials that appropriate stock is maintained to ensure treatment in case of distribution failure.

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) are in agreement 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 scan be done to best ensure patient safety and data validity.

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.