EVERSHEDS SUTHERLAND

Clinical trials

Impacts of Covid-19

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Implications of Covid-19 on the conducting of clinical trials

The current Covid-19 pandemic's impact on European healthcare systems, such as limited or no patient contact; restricted site access; shortage of investigational medicinal products; the quarantining of healthcare professionals and changes to the trial protocol are having a knock-on effect for both ongoing and planned clinical trials in Europe, and subsequently, the treatment of patients.

In light of the current circumstances, sponsors and investigators need to adapt the way they manage trials, which are critical to the development of medicines and vaccines. We've outlined some of the points to be aware of in this briefing.

Latest guidelines from the EMA, EC and HMA

On 20 March 2020 and updated as version 2 on 27 March 2020, the EMA (the European Medicines Agency) together with the European Commission and the Heads of Medicines Agencies (HMA) published the Guidance on the Management of Clinical Trials during the Covid-19 (Coronavirus) pandemic. In brief, according to the guideline, there are a number of considerations to be had, including the effects of Covid-19 on ongoing studies; on adding a new site to an existing trial; ongoing recruitment and inclusion of new trial participants, or on the start of a new trial.

Although this guide is seeking to serve as an EU-level harmonized set of recommendations, there might be specific national legislation and guidance in place. Thus, further to the European guidance documents by EMA, in Germany, the higher federal authorities, Federal Institute for Medicines and Medical Devices (BfArM) and the Paul-Ehrlich-Institute (PEI), issued supplemental national guidance 26 March 2020 on required changes to clinical trial protocols, the supply of investigational medicinal products (IMP), and the conduct of site monitoring during the Covid-19 pandemic. The dynamic developments in this pandemic may lead to rapid changes in any guidance recommendations. Sponsors and investigators are requested to monitor for revisions of relevant documents.

Although the EMA and BfArM emphasize that research and development of therapeutics for the treatment or prevention of Covid-19 infection is of outstanding importance and that such clinical trial applications will receive preferential treatment, the regulations for clinical trials must nevertheless be observed. How clinical trials are to be conducted in the light of Covid-19 related obstacles is outlined below.

FAQs on conduct of clinical trials in times of Covid-19

How do we conduct risk assessments under Covid-19 circumstances?

In light of the increased risks due to Covid-19, the health and safety of trial subjects is of particular importance. This must be carefully considered against the anticipated benefits for the participant and data validity. The sponsor must carry out a risk assessment for each ongoing trial and the investigator must carry out a risk assessment for each individual participant.

In case of a conflict, the trial subject's safety prevails. Any risk assessment must be kept up to date depending on changes in the given circumstances.

Is it possible to initiate new trials?

In general, yes. However, starting a new clinical trial or including new trial participants in an ongoing trial should be critically assessed by sponsors. Additional risks to trial participants should be addressed in the risk benefit section of the trial protocol along with risk mitigation measures. In any case, the safety of trial participants is paramount, especially when additional challenges arise due to Covid-19.

According to the EMA guidance and national supplementary documents, priority should be given to clinical trials for the treatment of Covid-19 and diseases related to it as well as trials on serious diseases with no satisfactory treatment alternatives.

How to initiate trials for the treatment of Covid-19

Submission of large, multi-national trial protocols for the investigation of new treatments for Covid-19 are explicitly welcome. EMA provides a full fee waiver and a fast-track procedure for scientific advice. Developers of medicines or vaccines are invited to contact EMA as soon as possible by emailing to 2019-ncov@ema.europa.eu.

The German federal authority BfArM treats all applications and requests for advice in connection with clinical trials and drug development related to Covid-19 "with utmost priority and flexibility". These should be sent to BfArM via the e-mail address CT-COVID@bfarm.de (not for submission of variation notifications or applications for authorization). Applications for scientific advice as well as clinical trials on diagnosis, prophylaxis or therapy of Covid-19 are processed free of charge during the Covid-19 pandemic.

How to proceed with ongoing trials

With regard to ongoing trials, sponsors must conduct a risk assessment as to whether and to what extent measures such as temporary interruptions to a trial or on the basis of individual sites are necessary, or whether postponement of the trial or extending the duration of the trial may be recommended. Also, sponsors should consider modifying a trial where health issues of trial participants require so. According to the guidelines such modifications may by for example:

- transferring trial subjects to other trials
- suspension or slowing down recruitment of new trial subjects
- postponement or complete desist of visits to ensure that essential visits are made to the inspection sites only
- establishing or replacing on site visits by video or telephone conferences
- closure of trial sites
- including study sites that have not yet been part of the trial
- other measures to ensure patient safety

Should recruitment processes continue?

Sponsors of clinical trials need to evaluate whether continued recruitment during the pandemic is appropriate or should be suspended.

If recruitment is to be suspended, an amendment notification is required by the relevant higher federal authority, but relaxations on the formal procedure are possible, for example, the applicable form does not have to be used for simplification reasons, instead an email approach is possible (such approach at least is possible with the German BfArM using ct@bfarm.de). The resumption of recruitment again requires a change notification, subject to approval, to the responsible higher federal authority and the responsible Ethics Committee.

How to manage deviations in trial protocols

Covid-19 also causes considerable delays in the conduct of clinical trials. This may result in deviations from the protocol. Sponsors are advised to evaluate the pandemic's impacts on existing trial designs of ongoing or planned clinical trials.

The EMA acknowledges that the pandemic situation is likely to result in more protocol deviations than are considered under normal circumstances and expects a sponsor to escalate and manage such protocol deviations in accordance with its standard procedures. GCP inspectors shall take a reasonable approach when such deviations are reviewed during inspections, in particular where the best interest of the participant is maintained and trial participants are not put at risk.

If need be, contacting the relevant authorities (Federal Institute for Medicines and Medical Devices (BfArM) in Germany, EMA on EU level) at an early stage may be of help, for example in cases when change notifications are required to the protocol.

Based on the supplemental national guidelines issued by the German authorities BfArM and PEI due to Covid-19, any change notifications currently are processed by the BfArM with priority, if there is a corresponding reference to "Covid-19" in the subject line of the request. BfArM requests electronic submission of a change notification via the European portal CESP (Common European Submission Portal) as far as possible.

Are there changes concerning safety reporting?

Safety reporting obligations for clinical trials continue to apply during this pandemic. This concerns both the immediate reporting of serious adverse events (SAE) by the investigator to the sponsor unless the trial protocol says otherwise, as well as the sponsor's reporting obligations towards authorities and Ethics Committees.

If, in connection with SAE reporting, a trial participant is unable to visit the site in person, initial communication with the investigator may take place by phone to decide whether the participant's appearance in person, for example, for further testing, is necessary based on safety considerations.

Should audits still take place?

EMA outlines in its document that in the current situation, in general, audits should be avoided or postponed. Still, if permitted and happening, audits must be conducted in accordance to applicable local and/or social distancing restrictions. Exceptions may be justified, for example, with critical trials or audits in order to investigate serious non-compliance.

How to conduct a clinical trial under increased protection measures for trial subjects (according to the guidance document by German authority, BfArM)

Conducting clinical trials even in times of Covid-19 while ensuring a high level of protection of the trial subjects may be possible by introducing respective measures, such as, for example:

Remote monitoring

The sponsor's responsibilities to monitoring and quality assurance need to be reassessed. On-site monitoring should take into account national and local restrictions, and the urgency and availability of site staff. Alternatives should be considered.

Remote access to source data may be an exceptional temporary solution in the context of the pandemic. Review of trial documents and recordings is possible by camera and video transfer. In any case, essential data protection requirements must be ensured. Documents or recordings containing personal data of trial subjects must not leave the trial site. Given this, the common and known messenger services are not deemed suitable for this purpose.

With phone and video visits, it must be ensured that such are carried out in accordance with the trial subjects' consent. Before implementing monitoring by video camera, it is necessary to extend and/or adapt the monitoring plan and/or the monitoring manual accordingly. The amended monitoring plan and/or monitoring manual and the documentation on the implementation of adapted monitoring measures should be stored in the Trial Master File.

In Germany, the temporary adaptation of the monitoring plan and/or manual does not require the submission of an amendment to the responsible higher federal authority and Ethics Committee according to the German GCP-Regulation (GCP-Verordnung, Ordinance on the implementation of GCP in the conduct of clinical trials on medicinal products for use in humans).

Shipment of investigational medicinal products (IMPs) to trial subject

In order to avoid on-site visits by trial participants, it may be necessary to send IMPs directly to individuals. With such approach, the required level of medical monitoring must be maintained in accordance with the trial protocol. Sufficient attention must be paid to both the safety of the medicinal product, and the protection of the privacy and personal data of the trial subject.

Strict documentation of transport, delivery, consumption and return is crucial. Written instructions for storage and return of IMPs must be provided to the trial subject. If the investigator itself is unable to send IMPs, a transport service commissioned by the sponsor and carried out by a suitably qualified service provider may be accepted in exceptional cases. Still, this is to be conducted on an anonymized basis and trial subjects must remain unknown to the sponsor. IMPs must be delivered directly to the trial subject or an authorized representative and must not be left with a neighbour or deposited at a storage location.

If a change in the protocol is necessary in this context (for example, due to remote treatment or the omission of laboratory tests or medical consultations), the approval of the responsible higher federal authority and a consenting evaluation by the ethics committee is required. The trial subjects must also be informed and must give their consent.

How to obtain informed consent from trial subjects

In cases where obtaining written informed consent from a trial participant is not possible (for example, due to physical isolation), consent could be given orally in the presence of an impartial witness. Also, the trial participant and the person obtaining consent may sign and date separate informed consent forms.

Potential Covid-19 trial participants could lack ability to consent due to the severity of their medical condition. In this case or when minors are included, consent has to be obtained from the legal representative(s). In case of acute life-threatening situations, where it is not possible within the therapeutic window to obtain prior informed consent, informed consent will need to be acquired later, if allowed by national legislation.

Consents to be obtained once again in ongoing clinical trials should not be a reason for on-site visits by trial subjects. Instead, consent may be obtained by phone or video call followed by e-mail confirmation. However, an updated information consent form must be sent to the trial participant in advance and everything must be documented properly.

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