This is an unofficial, informal translation of the German text. Only the German text and its content is relevant in case of any discrepancies

Additional recommendations to the European Document Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic

In view of the impact of the pandemic on European healthcare systems, the European authorities published a guidance document on 20 March 2020, which provides sponsors with recommendations for actions to be taken with regard to clinical trials and the associated participating persons. The guideline can be found both on the homepage of the European Medicines Agency (EMA) ¹ and in the European Commission's legal collection (Eudralex, Volume 10)².

Although the guideline is a harmonised package of recommendations at EU level, which is co-developed and fully supported by the German Competent Authorities and ethics committees, there are specific national laws and guidelines in many EU member states, including Germany, regarding certain topics in clinical trials, which must be taken into account and may take precedence over the European recommendations. This therefore requires a closer look and interpretation. These topics include, in particular, temporarily applicable measures for source data verification, if on-site monitoring at the trial sites is not possible due to the COVID-19 (coronavirus) pandemic, and the shipment of investigational medicinal products to the subject if they cannot be delivered to the subject at the trial site.

1. Recommendations for conducting remote monitoring

It must first be determined through a risk assessment for what purpose, at what times and to what extent monitoring remains necessary in the clinical trial in question, despite the restrictions imposed by the COVID 19 pandemic. Where this is the case, it is strongly recommended that remote monitoring in the form of telephone and/or video visits be limited to essential core data and processes in order to avoid an unnecessary burden on the investigator and the trial team. This usually includes data required for the continuous benefit-risk assessment, such as verification of compliance with inclusion and exclusion criteria, the doses and dose regimens of the investigational product(s) used, and the complete recording of (serious) adverse events (pharmacovigilance) and key target parameters.

The possibility of remote access to source data may exceptionally be considered as a temporary solution as part of the COVID 19 pandemic. A concrete possibility would be the camera access to prepared study documents and records. However, the essential requirements of data protection law must be guaranteed.

Documents or records containing personal data of the trial subjects may not leave the trial centre, not even as copies, and thus may not be permanently stored outside the trial site. Transmission of data and/or documents of any kind, which is more than the mere transmission of a camera image content and the use of cloud solutions remain fundamentally inadmissible in this situation as well. The same applies to the transfer of such camera image content to third countries. The information and

communication technology must be designed in such a way that transmission in compliance with the DSGVO is guaranteed. As a rule, the known messenger services are not suitable for this purpose. In this context, we refer to the "Whitepaper - Technical Data Protection Requirements for Messenger Services in the Hospital Sector" published by the Conference of Independent Data Protection Supervisors of the Federal and State Governments on November 7, 2019.

In addition, it must be ensured that video monitoring is performed exclusively by the sponsor’s authorized persons (i.e. the clinical monitor) in accordance with the written consent of the trial subjects.

The specific procedure must be included in the list of processing activities as a defined exceptional case with start and end date and is subject to the reservation that it is not known whether the responsible data protection supervisory authorities will assess this.

Before implementing video monitoring visits, it is necessary to extend and/or adapt the monitoring plan and/or the monitoring manual accordingly. The instructions provided there should ensure a structured approach and proper documentation. The amended monitoring plan and/or the amended monitoring manual as well as the documentation on the implementation of video monitoring or other adapted monitoring measures should be filed in the Trial Master File. The necessity, suitability and compliance with the specified changes shall be reviewed at periodic intervals.

The monitoring adapted due to the COVID 19 pandemic shall be summarized in the trial report after completion of the clinical trial.

In Germany, the temporary adaptation of the monitoring plan and/or the monitoring manual does not require the submission of a notification of change to the responsible higher federal authority and ethics committee according to § 10 GCP Regulation (GCP-V), as these documents are usually not subject of the evaluation/approval.

2. Shipment of investigational medicinal products to the trial participants

Due to the impact of the COVID 19 pandemic, it may become necessary to send investigational medicinal products to the trial participants in individual clinical trials and/or for individual trial participants, either to ensure the safety and well-being of trial participants and/or to ensure the continuation of clinical trials in accordance with the trial protocol and thus maintain the evaluability of the clinical trial data.

A shipment of investigational medicinal products to trial participants is generally subject to the condition that their medical monitoring is maintained to the required extent in accordance with the trial protocol.

The following recommendations refer exclusively to investigational medicinal products that are used independently by the trial participants.

If it is necessary to ship investigational medicinal products to the trial participants, shipment by the trial site itself is preferred under this pandemic exception. Shipment should be made in a manner that allows tracking of both transport and delivery. The participant should acknowledge receipt of the shipment to the trial site (e.g., by returning a dated and signed receipt).

If proper shipment by the trial site is not possible, for example, due to capacity, logistics, or special transport conditions for the investigational medicinal product, direct transport by the sponsor may be accepted in justified exceptional cases, provided that the sponsor appoints a suitably qualified service provider in the sense of a trustee. The sponsor must contractually oblige this service provider to maintain the pseudonymisation and, if necessary, blinding of the trial subjects vis-à-vis the sponsor by


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means of appropriate measures. Both the transport and transfer conditions for the investigational medicinal product(s) should be part of the contractual arrangements, so that sufficient account is taken of the safety of the medicinal product on the one hand and the protection of the privacy and personal data of the trial's participants on the other. Investigational medicinal products must be delivered to the participants or a person authorized by the subject. They may not be given to neighbors or deposited at a storage location. Written confirmation of dose and dosing schedules by the investigator should also be obtained prior to shipment.

The personnel of the service provider in charge of the transport should be trained and instructed accordingly.

Since personal data is transferred to the service provider, this requires an order processing contract with the sponsor or his legal representative.

For direct shipment of investigational medicinal products, written instructions on the storage and return of used and unused investigational medicinal products should be provided to trial participants.

When investigational medicinal products are shipped by both trial sites and contracted service providers, their receipt, consumption, and return must be documented in a form that allows the trial site to comply with its documentation requirements (drug accountability) as defined in ICH-GCP 4.6.3.

A modification of the trial protocol in this respect, e.g. by introducing a previously unplanned remote treatment or the discontinuation of previously planned study-related measures (e.g. laboratory tests, medical consultation, etc.) requires approval by the competent higher federal authority in any case and a favourable evaluation by the ethics committee. Therefore, the intended trial protocol amendments must be submitted together with the intended amendments regarding the trial drug supply to the trial subjects as a substantial amendment according to § 10 GCP-V. When using telemedicine, the necessary standards, including the requirements for data protection, must be adhered to. If external service providers, e.g. nursing services, take over study-related tasks, it must be ensured that the source data collected by these services are transmitted to the examiner and that the persons employed are subject to the instructions of the examiner and are obliged to report. The examiner's descriptions must be adapted accordingly. In justified individual cases, these measures may be taken to protect against immediate risks in accordance with § 11 GCP-V. The immediate obligation to provide information pursuant to § 13 (5) GCP-V remains unchanged.

The trial participants must be informed about the changed procedures with a supplement to the patient information and should declare their consent to this.