



Supplementary recommendations to the document *European 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. This guidance provides sponsors with recommendations for actions regarding clinical trials and the people involved in them. The guideline can be found on the homepage of the European Medicines Agency (EMA)¹ as well as in the European Commission's legal collection (Eudralex, Volume 10)².

Although the guideline consists of harmonised recommendations at EU level, which is co-developed and fully supported by Germany, there are specific national laws and guidelines in many EU member states, including Germany, regarding certain topics in clinical trials that must be taken into account and may take precedence over the European recommendations. Therefore, such areas require closer consideration and interpretation. These topics include, in particular, temporarily applicable measures for source data verification, if on-site monitoring at trial sites is not indicated owing to the COVID-19 (coronavirus) pandemic, and the shipment of investigational medicinal product (IMP) to the trial subject, in case IMP distribution to the trial subject at the trial site is not possible.

1. Recommendations for conducting remote monitoring

It must first be determined through a risk analysis 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 form of telephone and/or video visits will be limited to essential core data and processes 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 IMP(s) used and the complete recording of (serious) adverse events (pharmacovigilance) and key outcome parameters.

The possibility of remote access to source data may exceptionally be considered as a temporary solution during the COVID 19 pandemic. A possibility to provide such direct access would be camera access to prepared study documents and records. However, the essential requirements of data protection must be guaranteed. Documents or recordings containing personal data of trial subjects must not leave the trial site, not even as copies; thus, such data must not be permanently stored outside the trial site. Transmission of data and/or documents of any kind that goes beyond the mere

¹ <https://www.ema.europa.eu/en/news/guidance-sponsors-how-manage-clinical-trials-during-covid-19-pandemic>

² https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf

transmission of a camera image content as well as the use of cloud solutions remain fundamentally inadmissible. The same applies to the transfer of such camera image content to third countries. The information and communication technology must be designed to ensure DSGVO (German name for General Data Protection Regulation)-compliant transmission. As a general rule, the established messenger services are not suitable for this purpose. In this context, please be referred 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 2019³.

It must also be ensured that monitoring by video camera is performed exclusively by the sponsor's authorized personnel (i.e. the clinical monitor) in accordance with the written consent of trial subjects.

The specific procedure must be included in the list of processing activities as a defined exception with start and end dates; however, it is not known whether the responsible data protection authorities will assess this.

Before implementing monitoring by video camera, it is necessary to extend and/or adapt the monitoring plan and/or the monitoring manual accordingly. The instructions provided in these documents should ensure a structured approach and adequate documentation. The amended monitoring plan and/or monitoring manual, as well as the documentation on the implementation of video monitoring or other adapted monitoring measures, should be stored in the Trial Master File. The necessity, suitability of and compliance with the specified changes shall be reviewed periodically.

The monitoring adaptations 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 an amendment to the responsible higher federal authority and ethics committee according to § 10 GCP-V (Ordinance on the implementation of GCP in the conduct of clinical trials on medicinal products for use in humans), as these documents are usually not subject of the clinical trial authorisation and opinion, respectively.

2. Shipment of investigational medicinal products to trial subjects

Owing to the impact of the COVID 19 pandemic, it may become necessary to send IMP directly to trial subjects in individual clinical trials, either to ensure the safety and well-being of trial subjects and/or to maintain the continuation of clinical trials in accordance with the protocol and thus to ensure the evaluability of clinical trial data.

The shipment of IMP to trial subjects requires that adequate medical supervision of the subject by the investigator, in accordance with the protocol, is ensured.

The following recommendations refer exclusively to IMP used autonomously by trial subjects.

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

³ https://www.baden-wuerttemberg.datenschutz.de/wp-content/uploads/2019/11/20191106_whitepaper_messenger_krankenhaus_dsk.pdf

In case adequate shipment by the trial site is not possible (for example, owing to capacity limitations, logistics or special transport conditions for the IMP), direct transport by the sponsor may be accepted in justified exceptional cases, provided that the sponsor appoints a suitably qualified service provider as a trustee. The sponsor must contractually oblige this service provider to maintain the pseudonymisation and, if necessary, blinding of the trial subjects towards the sponsor by means of appropriate measures. Both the transport and handover conditions for the IMP should be part of the contractual arrangements, so that pharmaceutical drug safety of the IMP as well as protection of the privacy and personal data of the trial subjects are adequately safeguarded. IMP must be delivered to the trial subject directly or to a person authorized by the subject and must not be given to neighbours or deposited at a storage location. Written confirmation of dose and dose regimens 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.

As personal data are transferred to the service provider, this requires a contract of assignment with the sponsor or his legal representative.

For direct shipment of IMP to trial subjects, written instructions on storage and return of used and unused IMP should be provided to trial subjects.

When IMP is shipped by trial sites or by contracted service providers, their receipt, consumption and return must be documented in a form that allows the trial site to meet its documentation requirements (drug accountability), as defined in ICH GCP 4.6.3.

Usually, the dispensing of IMP at the trial site is associated with other trial-related activities (e.g. diagnostic investigations and/or clinical evaluations). A change in the trial protocol in this regard, for example by the introduction of a previously unplanned remote treatment or the discontinuation of previously planned trial-related measures (e.g. laboratory tests, medical consultation, etc.), requires in all cases approval by the higher federal authority and a favourable opinion by the ethics committee. Therefore, the intended trial protocol amendments must be submitted together with the intended amendments regarding IMP 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. home-care services, assume trial-related tasks, it must be ensured that the source data collected by them are transmitted to the investigator and that the persons employed are subject to the investigator's instructions and reporting obligations towards the investigator. The descriptions of trial sites (which are part of the submission to the ethics committees) must be adapted accordingly. In justified individual cases, these measures can be taken to protect against immediate hazards in accordance with § 11 GCP-V. The obligation to immediately provide post-hoc information on these measures in accordance with § 13, paragraph 5 GCP-V remains unchanged.

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