Supplementary recommendations of BfArM and PEI to the European Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic, version 4

In view of the impact of the pandemic on European healthcare systems, the European authorities published a guidance document on 20 March 2020 that provides sponsors with recommendations regarding clinical trials and the persons involved in them.

This guidance document was revised again, adopted on 4 February 2021 and published as version 4 both in the collection of laws of the European Commission (Eudralex, Volume 10)[1] and on the homepage of the European Medicines Agency (EMA)[2].

The guideline is a harmonised package of recommendations at EU level, which was co-developed and co-adopted by Germany. Some recommendations require closer consideration and interpretation, also with regard to the German legal area. These include, in particular, temporarily applicable measures for source data verification, if on-site monitoring at the trial sites is not indicated due to the coronavirus pandemic.

Additional notes and recommendations for the implementation of Remote Source Data Verification (rSDV)

This document does not repeat the recommendations of the European guideline in a comprehensive manner. Instead, only those recommendations that require interpretation and supplementation or for which the sponsor is expected to provide detailed information in an initial application in accordance with § 7ff GCP-V (Ordinance on the implementation of GCP in the conduct of clinical trials on medicinal products for use in humans) or an application for a subsequent amendment in accordance with § 10 GCP-V ('substantial amendment'), which prove that the planned procedure corresponds to the state of science and technology, are taken up in the following.

Regardless of the method chosen for rSDV, the sponsor shall first obtain the written agreement of the investigator and, if applicable, of the institution where the trial site is located.

As described in detail in the European guideline, remote access to source documents/source data for monitoring purposes should only take place **in justified exceptional cases** and **only to the extent strictly necessary**. For details, see the European guideline. Remote SDV should also only take place if suitable data protection - including data security and the protection of personal data – is ensured. This is also to be borne in mind with regard to pseudonymised data.

In justified exceptional cases, the guideline provides the following three options for source data reconciliation without the monitor being physically present at the trial site:

- The trial site provides the monitor, under the responsibility of the investigator, with copies of the source documents/source data in which personal identifying information of the trial subjects and information pertaining to their privacy has been obscured or redacted (hereinafter referred to simply as "redacted copies").
- Under the responsibility of the investigator, the trial site grants the monitor direct, controlled remote access to the systems with which the source documents/source data are managed.

[1] https://ec.europa.eu/health/documents/eudralex/vol-10_en

[2] https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/goodclinical-practice#guidance-on-clinical-trial-management-during-the-covid-19-pandemic-section

- The trial site grants the monitor, under the responsibility of the investigator, passive access to the source documents/source data via live image transmission (e.g. sharing of the screen or image/sound transmission).

Implementation requires the authorisation of the responsible higher federal authority as well as the favourable opinion of the responsible ethics committee. For this purpose, an application according to § 7ff GCP-V or for subsequent amendment according to § 10 GCP-V ('substantial amendment') shall be submitted. In this application, the planned procedure should be described in sufficient detail, beginning with a summary of the underlying, study specific risk assessment. This can be done either in the Quality Control and Quality Assurance section of the protocol (ICH-GCP, Section 6) or as an appendix to the protocol. In the latter case, the appendix to the trial protocol must be submitted with the application.

Irrespective of this, the standard operating procedures and study specific documents (including those on risk-based quality management [ICH-GCP, Section 5.0] and monitoring [ICH-GCP, Section 5.18]) used in the clinical trial should be adapted accordingly.

The method chosen for the rSDV depends very much on the infrastructure of the trial site. In the application for approval according to § 7ff or § 10 GCP-V, the sponsor shall list **all** methods that may be used for rSDV, as only the alternatives described therein are considered approved.

For each method applied for, at least the following information should be provided:

- Identification of the source documents/source data to be made available under the rSDV (e.g. those related to the primary endpoint, serious adverse events, important medical events, or the reasons for exclusion of a subject from the trial);
- Presentation of the precautions taken for data security to ensure the confidentiality of data and the privacy of the trial subjects.

Depending on the method applied for, the following additional information is required:

a. Passing on of redacted copies of original documents and documents with original data

The sponsor shall provide the following details in the protocol or in an annex to the protocol:

- Minimum copy quality requirements to be met by investigator/institution (e.g. format, resolution, colour);
- Method for ensuring that the copies are complete;
- Method for ensuring that all information that could reveal the identity of subjects is obscured or redacted, and a description of actions to be taken by the monitor and the investigator/institution if this has failed;
- Requirements to prevent loss of or unauthorized access to source documents/data during the document/data sharing process;
- Documentation requirements for the traceability of documents forwarded by the investigator/institution as well as received and processed by the monitor.

b. Direct, controlled remote access to the systems used by the trial site to manage the source documents/source data

The sponsor shall clarify the following in the application for approval:

- Name of the document management system(s) to be accessed (name of the software, version);
- Name of the system used for remote access (name of the software, version, end-to-end encryption requirement);
- Monitor access rights (two-factor identification, access limited to the trial subjects and the parts of the documentation provided for under the rSDV, right to navigate, read-only access);
- Measures to prevent permanent storage of file contents by the monitor or to ensure short term, permanent deletion of automatically generated, temporary contents;

The sponsor shall provide a written statement in the application for approval:

- Confirmation that the rSDV is conducted exclusively by the authorized person(s) (i.e. monitor) in accordance with the written informed consent of the trial subjects.
- Confirmation that remote access is provided via secured systems/environments and systems/servers within the EEA/EU and/or confirmation that the conditions set out in the European guideline for data transferred or processed outside the EEA/EU, are applied.

Note:

When establishing remote access or adding such access to an existing system, it should be ensured that the establishment or modification of such an access is validated according to the risk. Changes in running systems without sufficient validation (e.g. *quick-fix engineering updates* (QFE)) should be avoided.

c. Passive access to original documents/original data via live image transmission

The sponsor shall clarify the following in the application for approval:

- Brief description of the method used and the parties involved in the process;
- Identification of the devices and/or software used for live image transmission;
- Security measures applied (e.g. for authentication, prevention of unauthorised recordings or transmission security).

The sponsor shall make a written statement in the application for approval:

- Confirmation that the rSDV will be conducted exclusively by the authorised person(s) (i.e. monitor(s)) in accordance with the written informed consent of the trial subjects;
- Confirmation that live image transmission takes place via secured systems/environments and systems/servers within the EEA/EU and/or confirmation that the conditions set out in the European guideline for data transferred or processed outside the EEA/EU, are applied;
- Confirmation that there is a written statement from the monitor and the sponsor that
  a) the rSDV takes place in a protected environment (i.e. providing protection from unauthorised access in any form, including the use of privacy screens to prevent unauthorised viewing of source documents/source data);
  b) the viewed source documents/source data are not permanently stored and
  c) if necessary, temporarily saved files (including ones automatically generated by the system) are permanently deleted at short notice;

- Confirmation that appropriate corrective measures will be implemented in the event of technical difficulties or if the security of the transmission is no longer guaranteed.

Note:
The information and communication technology used by the sponsor and the trial site for rSDV shall be designed in such a way that secure and GDPR-compliant transmission 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[3].

Service providers for telemedicine who have the certificates, expert opinions and quality seals required according to § 5 para. 2 of Annex 31b to the Federal Master Treaty for Medical Practitioners [4] could be suitable for this purpose, provided that GCP-relevant aspects are guaranteed by the sponsor through the qualification and monitoring of these service providers.

In accordance with their legal mandate, the ethics committee and the responsible competent higher federal authority examine the information provided in the context of the evaluation or approval of an application, respectively, in accordance with § 7ff or § 10 GCP-V only cursory in relation to compliance with data protection regulations (see also “Coming into effect of the GDPR — Handbook for Ethics Committees for the Consultation or Evaluation of Studies”). The activities undertaken should be included by all parties involved in rSDV in their list of data-processing activities, which is anchored in data protection law, and might be subject to an independent assessment by the responsible data protection supervisory authorities.[5]

[3] https://www.datenschutzkonferenz-online.de/media/oh/20191106_whitepaper_messenger_krankenhaus_dsk.pdf
[4] https://www.gkv-spitzenverband.de/krankenversicherung/digitalisierung_und_innovation/videosprechstunde/kv_videosprechstunde.jsp
[5] https://www.ak-med-ethik-komm.de/docs/intern-2018/DSGVO_Empfehlungen.pdf