DZHK
Deutsches Zentrum für
Herz-Kreislauf-Forschung

DZHK-SOP-P-01

Data review

Version: V3.2 Valid as of: 15.04.2024

Replaced version: 3.1 Of: 15.12.2023

Change note:

1. adjustments under 2., 3. and 4.
2. expansion of the list of abbreviations

Note: Printouts are not subject to the update process!

	Scientific author	**Scientific review**	**Approval WGCR spokesperson**	**Approval DZHK**
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Signature	**This SOP is a translation from the original German SOP and valid without signatures.**			

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1 INTRODUCTION

This SOP describes the means provided by the secuTrial® data capture systems currently used for DZHK studies for clinical data, CentraXX for biosample data and TrialComplete for image and biosignal data to support the quality assurance processes of these three data entities. Adherence to the recommended timeframes and GCP [1] (good clinical practice)-compliant quality processes is important for the successful conduct of each study, as it ensures both high-quality data and prompt patient fee reimbursement. On the other hand, these processes are relevant beyond the individual study for the procedures described in the DZHK regulations for secondary use of the data.

1.1 LIST OF ABBREVIATIONS

Abbreviation	Full form
IDMS	Image and biosignal data management system
CRO	Clinical research organization
DICOM	Digital imaging and communications in medicine
DZHK	German centre for cardiovascular research
eCRF	electronic case report form
GCP	Good clinical practice
LIMS	Laboratory information and management system
MTLA	Medical-technical laboratory assistant
SOP	Standard operating procedure

1.2 OBJECTIVES

This SOP describes the procedure for performing GCP-compliant quality assurance of clinical data in SecuTrial®, biosample data in CentraXX and biosignal and image data in TrialComplete. The focus here is on which functions must be used at which point in the documentation process in order to correctly document the progress of data capture.

Descriptions of the way in which quality assurance is to be carried out, however, are not the subject of this SOP. In particular, this SOP does not specify how the respective clinical monitoring should be carried out. The requirements of this SOP must be included in the data management plan of the respective study.

[1] https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-clinical-practice

1.3 TARGET GROUP

This SOP is valid for persons who record clinical data for DZHK studies in secuTrial® for data management, who use CentraXX (DZHK-LIMS) to record biosamples including associated data, and who record and quality assure image and biosignal data in TrialComplete (DZHK-IDMS).

1.4 APPLICATION AND TASKS

The GCP-required quality assurance process serves to increase the completeness and correctness of the recorded clinical data, data on biosamples as well as image and biosignal data.

The correct use of the secuTrial® functions provided for this process for the status of individual data sets is a basic prerequisite for the patient fee billing process, as well as for making data available for secondary use by the DZHK transfer office.

2 CLINICAL DATA (SECUTRIAL®)

2.1 TERMS AND DEFINITIONS

This SOP describes the use of the following functions or components of the various DZHK data collection systems. The role is assigned based on the corresponding IT user application.

- **Study Nurse:** A person to whom the secuTrial® role study nurse is assigned.
- **Clinical Investigator:** A person to whom the secuTrial® Clinical Investigator role is assigned. Usually, at least the local study coordinators are assigned this role. Several people per site can also have the Clinical Investigator role.
- **Form:** In the context of this SOP, the term form always describes an electronic data collection form (eCRF) implemented in secuTrial®. Forms with related content are usually combined into a form family.
- **Item:** A single question or a single data point in a form.
- **Visit:** A visit represents a patient contact at a specified time in secuTrial®. A previously defined collection of forms is documented for a visit, depending on any existing study arms.
- **Visit plan:** The patient-specific visit plan is the collection of all visits (including those already carried out and future planned visits) of a patient. The specific structure of the visit plan depends on the respective study protocol and the allocation to the study arm.
- **Complete data entry:** A function with which the data entry in a form is marked as complete. This function is triggered by the "Save + end data entry" button.
- **Ask/answer/close query:** Functions with which queries are asked/answered/closed for patients, visits or individual items within a form.
- **Set Review A status:** A function with which a form/visit is given the Review A status. This locks all affected forms for further entries or changes. The query functionality remains unaffected by this. The Review A status can only be removed by persons with special authorizations.
- **Set Review B status:** A function with which a form/visit is assigned the Review B status. This permanently blocks all affected forms for further data entries. The query functionality remains unaffected by this. The Review B status cannot be removed, not even by the data handling staff.

2.2 REQUIREMENTS

2.2.1 Devices/Hardware

PC with access to the Internet to use secuTrial®, as well as a user account for secuTrial®. Access is requested digitally as part of the initiation by the main study centre.

2.2.2 Staff

The initial documentation of clinical data in secuTrial® is usually carried out by a person in the role of Study Nurse or Clinical Investigator. This person must have taken part in one of the regular training courses offered by Data handling Göttingen(dzhk.support@med.uni-goettingen.de) on how to use the software.

The person in charge of the respective enrolling study centre (role: Clinical Investigator) releases the clinical data for quality control and study-specific monitoring after completion of data entry by setting the Review A status.

The review of the clinical data takes place in two stages. Firstly, the clinical data is checked by the study-specific quality assurance of the sponsor or its delegates (e.g. monitoring or data management CTO/CRO). The staff who carry out the quality assurance make queries. In addition, data handling on behalf of the DZHK carries out a cross-study quality assurance procedure of the basic dataset, which is a prerequisite for secondary use (DZHK Heart Bank).

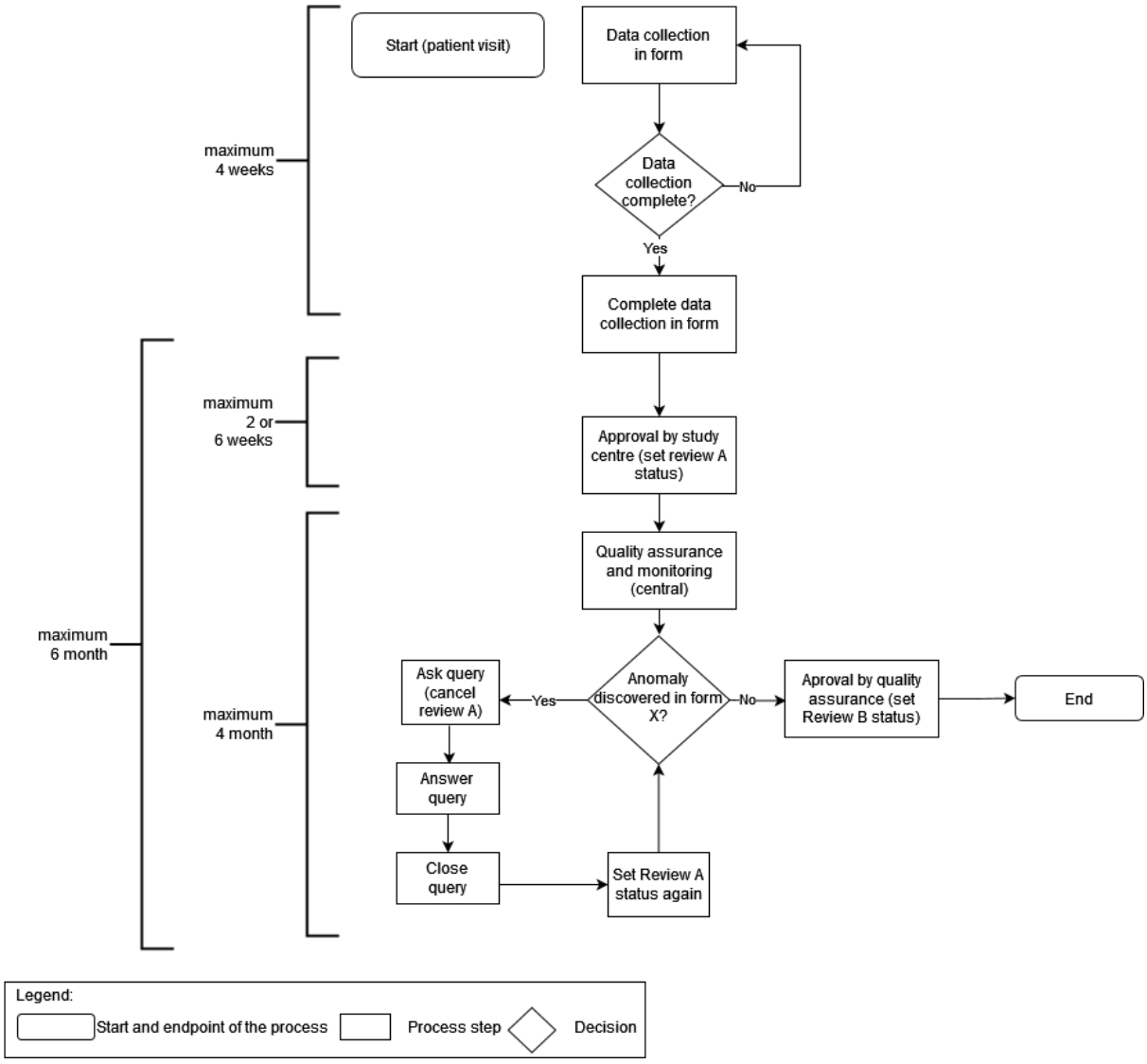
Queries are answered by the initial documenting persons, i.e. the Study Nurse or Clinical Investigator roles, in the respective enrolling study center. Queries are closed by study-specific quality assurance (monitoring or data management CTO/CRO) once they have been fully processed.

Once all queries for a form or visit have been processed, the Review B status can be set by the person responsible for study-specific quality assurance (monitoring or data management CTO/CRO).

2.3 IMPLEMENTATION PROCESS/WORK PROCESS/WORK STEPS

2.3.1 Flow-Chart of the procedure

The flow chart shows the process steps from the collection of clinical data to quality assurance through Review A and B setting.



2.3.2 Implementation

The following procedure for quality assurance must be carried out for each visit. The rights required to carry out the respective steps (e.g. setting Review A) are only available to persons who have the required role (e.g. Clinical Investigator) in secuTrial®.

Data collection:

The clinical data collected during the patient visit is entered into the corresponding form in secuTrial®. Data can be entered in one or more sessions, whereby the form must be saved at the end of a session at the latest. Once a form has been completed, the documentation must be finalized by the documenting person (Study Nurse or Clinical Investigator role) using the Data Entry function. As a rule, this process should be completed within one month of the patient visit.

After the data entry has been completed, the person responsible at the study centre (clinical investigator) is obliged to check and approve the entries.

Approval by study centre ("Review A Status"):

After the entries have been checked, the form is released for quality assurance by the responsible Clinical Investigator at the enrolling study centre by setting the Review A status. As a rule, this step should be completed within two weeks after completion of the data entry or within six weeks at the latest for all examinations included in the patient visit. Experience has shown that prompt data entry is a quality criterion in clinical trials and is a prerequisite for the payment of patient fees.

If all forms for a visit received Review A status, the study centre will invoice the main study centre for the respective visit. In order to reduce the administrative effort, it is advisable to bundle invoices several times a year. Invoices must be submitted at least twice a year by each study centre (or by the responsible department of the respective institution), namely by February 28th of the following year at the latest for patient visits completed by the end of December and by August 30th of the same year at the latest for patient visits completed by the end of June. These deadlines are binding and enable the study centre to request funds for the patient fees invoiced from the funding body by certain deadlines.

Once the Review A status has been set, the responsible clinical monitor or data management team carries out the study-specific quality assurance.

Implementation of quality assurance:

The basic dataset is subjected to an automated quality assurance of the DZHK's data handling after Review B has been set by the monitors, which runs identically across all studies.

In addition, each study must specify its own GCP-compliant quality assurance measures, including clinical monitoring. These are carried out by the study centre or contractually involved third parties, for example an external CRO, on the visits or forms approved via Review A status. If abnormalities are detected during this quality assurance, queries are raised, which in turn must be answered promptly by the Study Nurse or Clinical Investigator at the study centre collecting the data. After all queries have been answered, the Clinical Investigator of the respective study centre must release the relevant forms again for quality

assurance (by setting the Review A status). If the response is sufficient, the queries are closed by Monitoring (CTO/CRO). Otherwise, new queries will be submitted.

The quality assurance of the DZHK data handling takes place within two months after the release of all forms of a visit. The study-internal quality assurance and clinical monitoring should take place within four months of the release of a visit.

Completion of quality assurance ("Review B status"):

Once all quality assurance measures have been completed, the Review B status is set by the monitoring. Setting the Review B status is technically only possible if no more queries are open.

No later than six months after each patient visit, all forms in the visit should achieve Review B status.

Important: The setting of the quality-assured and GCP-compliant Review B status for the 42 items of the DZHK Basic Data Set must take place successively, not only at the end of recruitment, and must be defined in the data management plan of the study. This is a prerequisite for the transfer of the DZHK basic dataset and the associated biosamples of the DZHK Biobanking to the DZHK Heart Bank.

2.3.3 In case of deviations

A premature closing of the data entry can be cancelled by user.

A premature release of forms or visits for quality assurance (Review A status) can be revoked by authorized users.

The premature setting of the Review B status, for example before the quality assurance has been completed, can no longer be cancelled. All further changes to the affected form must be made using the query functionality of secuTrial®.

Further documents and training videos are available on the DZHK's Service4Studies website.

3 BIOBANKING (DZHK-LIMS, CENTRAXX)

3.1 REQUIREMENTS

3.1.1 Devices/Hardware

PC with access to the Internet to use CentraXX (DZHK-LIMS), as well as user access for CentraXX. Access can be granted at any time via an IT user application.

3.1.2 Staff

The initial documentation of the biosample data in the DZHK-LIMS (in DZHK Clinical Study Units) or in secuTrial® (in study centres that do not have a DZHK Clinical Study Unit) as well as necessary corrections after a data review are usually carried out by a person in the roles of "Study Nurse" and/or "MTLA". The person must be trained internally and should ideally have taken part in a training course on the use of the DZHK-LIMS if it is a DZHK Clinical Study Unit. These training courses are offered on request by the biobanking team (biobanking@dzhk.de). The Review A in secuTrial® does not necessarily have to be assigned by the Clinical Investigator, but can also be done by Study Nurses.

3.2 IMPLEMENTATION PROCESS/WORK PROCESS/WORK STEPS

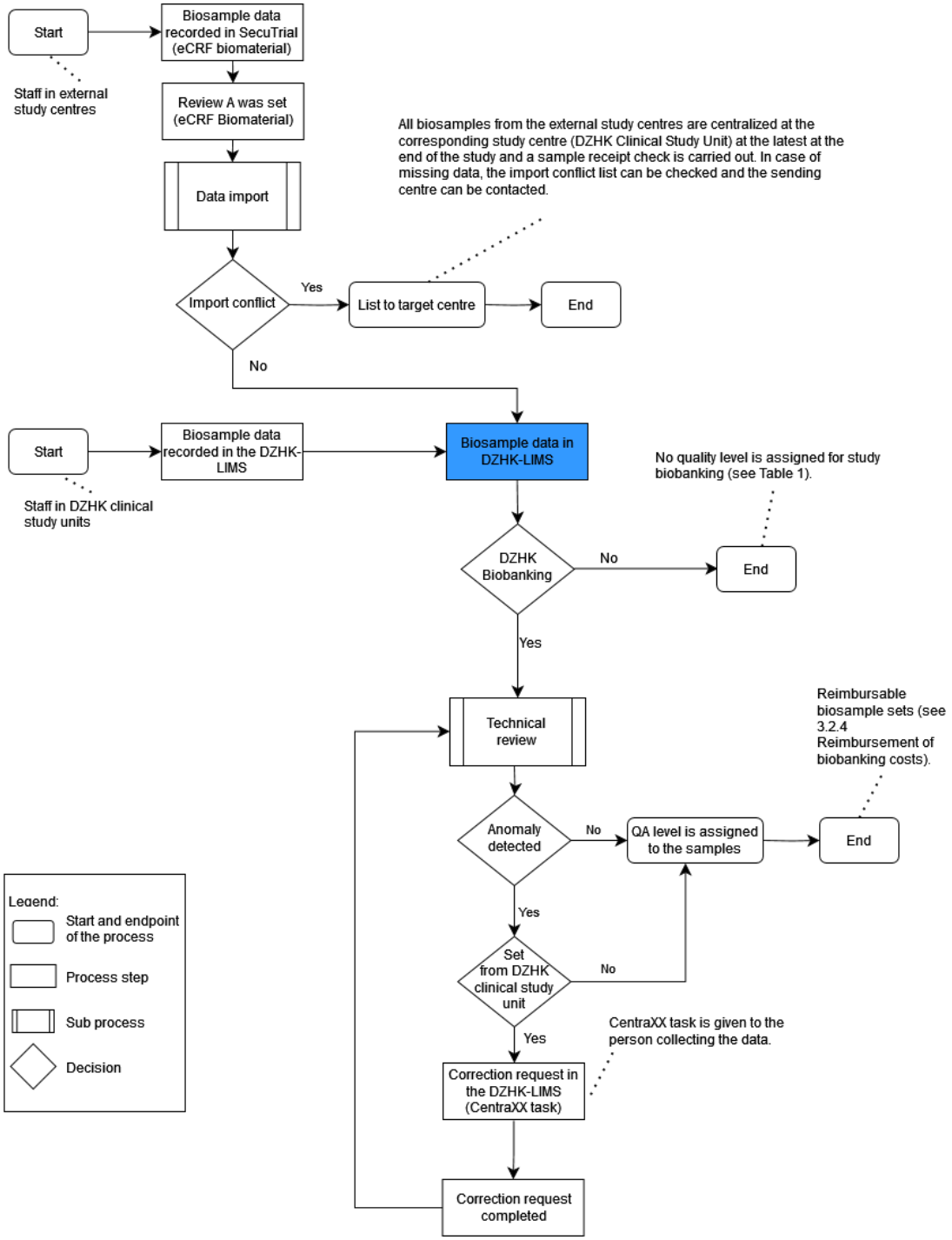
Only biosamples with complete and plausibly recorded data sets can be fully included in the regular secondary use processes. Since the DZHK biobanking[2g] is the property of the DZHK e.V. and is transferred directly to the DZHK Heart Bank for secondary use, these data are technically checked in accordance with the specifications in the DZHK biobanking SOPs. If deviations are identified, the persons recording the data are requested to review the data, provided the data was originally recorded in the central DZHK LIMS. For biosample data that was originally recorded in secuTrial®, Review A is considered a data review and trigger for the import process of the data into the central DZHK-LIMS. The biosamples receive the quality level 1-3 achieved after testing and review as sample status in the DZHK-LIMS.

The study is responsible for biosamples from study biobanking[3] and can check the data from all study centres with the help of reports.

[2] Former "DZHK basic biobanking"
[g] According to DZHK Use & Access Policy
[3] Former “study specific biobanking”

3.2.1 Flow-Chart of the procedure

The following flow chart shows the sequence of work processes from the collection of biosample data to their examination and review, in each case for external centres and DZHK Clinical Study Units.



3.2.2 Implementation

The implementation of the data check and the data review differ slightly depending on the type of biobanking and the study centre at which the biosample data were collected.

	DZHK biobanking	**Study biobanking**
External study centre	1. Data collection 2. Review A (manual data check and data review) 3. Data transfer to the central DZHK-LIMS at Review A status 4. Automated, technical review* in the central DZHK-LIMS 5. QA level assignment	1. Data collection 2. Review A (manual data check and data review) 3. Data transfer to the central DZHK-LIMS at Review A status 4. manual review by "principal investigator " via report from the central DZHK-LIMS (Excel file)** 5. For data review, contact with staff of external study centre by study
DZHK clinical study unit	1. Data collection to the central DZHK-LIMS 2. automated, technical review* in the central DZHK-LIMS 3. Data review process (see 3.2.3) 4. QA level assignment	1. Data collection in the central DZHK-LIMS 2. Manual review by "principal investigator" via report from the central DZHK-LIMS (Excel file)** 3. For data review, contact DZHK clinical study unit staff by study

Table 1: Overview of data verification and data review depending on biobanking and study centre

* For quality assurance purposes, a technical review of the biosample data for completeness (all data points requested in the acquisition workflows) and plausibility (e.g. the time stamp) is carried out daily between 01:00 and 06:00 at night for each DZHK-set[4].

** Quality assurance is the responsibility of the sponsor based on the biobanking report (→ registration IT user application with the LIMS user role "principal investigator"). In case of incomplete data sets or implausible values, the study will contact the respective study centres directly.

3.2.3 In case of deviation

Deviations are summarized in correction tasks in the DZHK-LIMS. The CentraXX tasks must be processed in accordance with the guidelines for data review (LF-B-13). The deviation must be checked, confirmed or corrected. The deadline for corrections is 7 working days.

3.2.4 Reimbursement of biobanking costs

Each sponsor is obliged to compare the invoicing of the study centres with the biobanking reporting. DZHK sets that have been finally checked and approved for billing are marked with

[4] Former „DZHK Basic Set“

the quality levels 1-3 (QA1, QA2, QA3) (AliQualiCode column). Biosamples that do not contain any information in this column have not yet been tested. Biosamples containing the information quest have been marked as conspicuous, but the correction request has not yet been completed. Biosamples containing the indication QA0 could not be assigned to a reliable quality level even after the correction process and can therefore only be used to a very limited extent for further research purposes. For further information, see the factsheet on the reimbursement of biobanking costs (in German).

4 IMAGE, BIOSIGNAL AND THEIR CENTRAL ANALYSIS DATA (DZHK-IDMS, TRIALCOMPLETE)

IDMS TERMS

- “Signed“-eCRF-status: corresponds to secuTrial®-status Review A
- “Monitored“-eCRF-status: corresponds to secuTrial®-status Review B
- “Approved”-eCRF-status: corresponds to closed eCRF status
- TrialComplete: The clinical data management system from Telekom Healthcare Solutions

4.1 REQUIREMENTS

4.1.1 Devices/hardware

- PC with internet access (port:http/443) for the use of TrialComplete (DZHK-IDMS)
- IDMS user access
- Visit to be documented has been created/activated in secuTrial®
- Valid consent has been received by the trusted third party

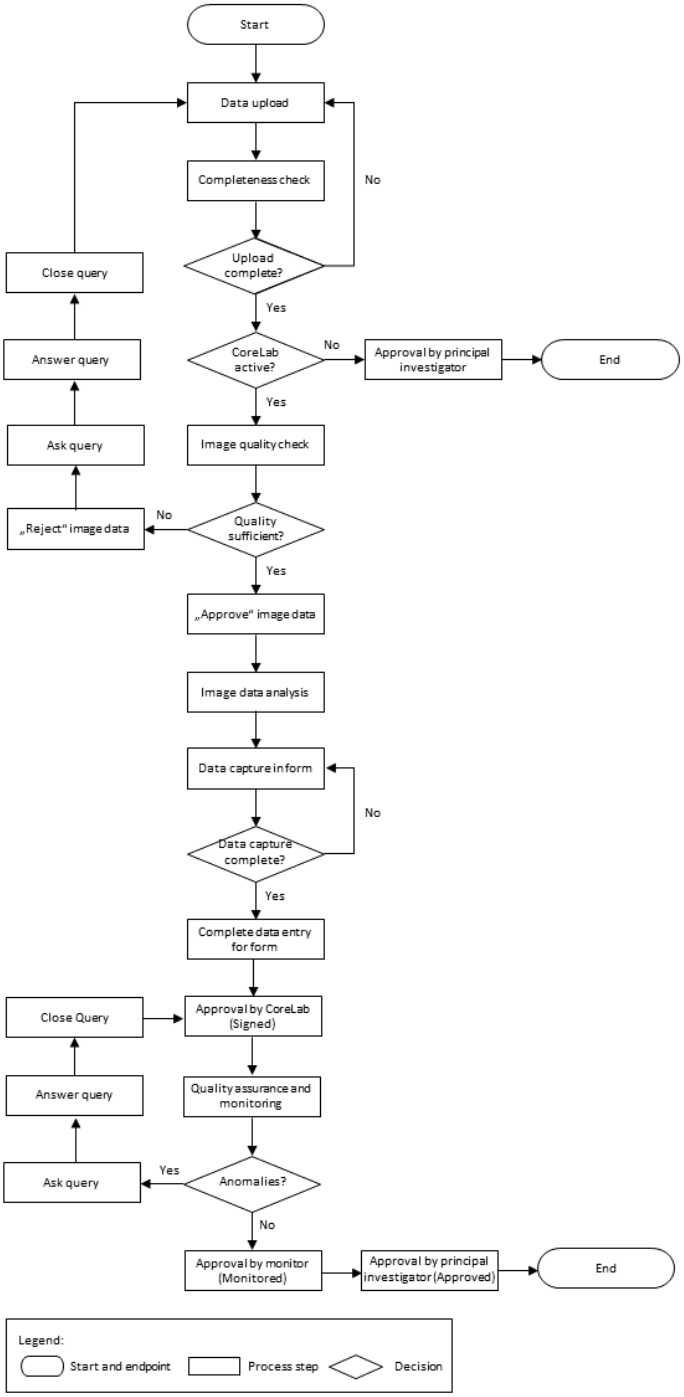
4.1.2 Staff

Staff in the study centre who only upload DICOM data to IDMS are assigned the "document uploader" role. For the Imaging CoreLab staff, there are the roles "imaging analyst", "imaging CRA" and "imaging reader" for incoming quality control and image data evaluation. Monitoring can be carried out with the "monitor" role. Further roles are available to the study centre staff for study-specific tasks ("data accountant" role, "data enterer" role). The principal investigator has the role of "coordinating investigator". Staff must be trained by the IDMS team before the roles are activated. The training courses are offered regularly and on request by the IDMS team(bdms@dzhk.de).

4.2 PROCESS OF IMPLEMENTATION/WORK OROCESS/WORK STEPS

4.2.1 Flow-Chart of the procedure

The flowchart shows the process steps from the acquisition of the image data, through the quality check of the image data and image analysis data to the release by the principal investigator depending on an existing active Imaging CoreLab.



4.2.2 Implementation

4.2.2.1 Documentation of image and biosignal data

The DICOM image data of a visit is uploaded in the TrialComplete system to the corresponding visit synchronized with the secuTrial® system. Different modalities and image series can be uploaded at different times by persons with the roles document uploader, data accountant, data enterer or coordination investigator (DZHK-SOP-P-02). An upload of DICOM data close to the visit is recommended and defined on a study-specific basis. The upload should be completed after 8 weeks at the latest; shorter study-specific requirements are possible and will be communicated by the study management.

After the upload, the person and persons with the monitor role of uploader, the monitor and the coordinating investigator receive an email about the scope of the upload and another email with the automated quality check. The automated quality check email contains information on the comparison of the requested and uploaded DICOM data and on the time window for a timely upload.

4.2.2.2 Documentation of the data from the central analysis

If a central office evaluates the data in the respective study, the data is documented in the eCRF of TrialComplete. Persons in the roles of Imaging CRA and Imaging Analyst are designated for this position.

After an image data upload, the persons (Imaging CRA and, by default, the Coordinating Investigator) receive a "Document quality check" work order. The persons (Imaging CRA role) then check the quality of the image or biosignal data.

If the quality is insufficient, the image and biosignal data should be rejected ("Reject"). At the same time, a notification with the reasons is created in TrialComplete and sent to the uploader by email. If possible and available, image and biosignal data are then uploaded in a better quality. The reject notification is also intended to improve the data collection and processing procedures for subsequent studies at the study centre.

If the quality of the image or biosignal data is sufficient (study purpose), the acceptance of the image data must be confirmed by a person (Imaging CRA role) ("Approve"). The query management system for data quality can be used for clarifications by setting a query on the primary data.

As soon as data is set to "Approve", a "Process documents" work order is created for certain persons ("Imaging analyst" role) with the task of carrying out the data analysis. The result data is recorded in the TrialComplete eCRFs by the Imaging Analyst. Once the data collection has been completed, it is finalized and signed by the Imaging Analyst ("Signed") (Status Review A). The documentation must be completed within 6 weeks of evaluability.

4.2.2.3 Completion of data quality assurance (Monitored)

The query management system for data quality can be used for clarifications in the context of monitoring. The person with the "Monitor" or "Coordination investigator" role can check the documentation and submit queries for image data documents, eCRFs or items in eCRF and address them to documenting persons or roles. The respective queries are listed in task management under "Study Queries" and must be processed by the data collectors. Only after clarification of all queries the form is set to "Monitored" status by the person with the

monitor role. The study management can also monitor the forms and additionally set the status to "Approved".

4.2.2.4 Ensuring process quality

The “Document uploader”, “Data accountant”, “Data enterer” or “Coordination investigator” roles can also download a daily updated report in the TrialComplete system, which lists all visits that have taken place with the required DICOM data collection with and without upload for each centre. The monthly report on the completeness overview with corresponding statistics on data quality (purpose DZHK Heart Bank) is created by the IDMS quality manager at the end of the month and sent to principle investigators, coordinators and monitors. They then have the opportunity to inform centres about insufficient completeness of DICOM data and to promote higher upload performance.

If a CoreLab is involved, the monthly quality assurance report also shows parameters for the form entries, such as the percentage of processed forms, the distribution of quality ratings and the completeness of key outcomes. Further information on the results data in the forms can be found in another TrialComplete report, which is updated daily.

4.2.3 In case of deviations

The eCRF status "Signed" can be cancelled by the “Imaging analyst”, “Monitor” and “Coordinating investigator” roles.

The eCRF status "Monitored" can be cancelled by the “Monitor” and “Coordinating investigator” roles.

The eCRF status "Approved" can be cancelled by the “Coordinating investigator” role.

5 APPENDIX

5.1 CHANGES

Changes compared to version 3.1.

Section	Description of the change to the previous version
Versioning	From version 3.1. to 3.2
1.	1.1. Additions List of abbreviations
2.	Terms Definitions moved here from 1.5 2.2.1 Addition of introductory sentence and legend General addition of links Clarifications to Review A and Review B
3.	3.2.1 Addition of introductory sentence and legend General addition of links
4.	4.1.2 Addition of mandatory training 4.2.1 Addition of introductory sentence and legend

5.2 PARTICIPATING PERSONS

Name	Role	Contribution
Mahsa Lee	First Author	Draft
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Christian Schäfer	DZHK-LIMS	Scientific Review
Jens Schaller	IDMS	Scientific Review
Ilka Wilhelmi	DZHK Main office	Coordination

5.3 LITERATURE AND REFERENCES

1. User guide for secuTrial® (As of 09/2923)
2. Flow chart for study preparation/implementation (German)
3. LF-B-07 Guidelines for data review in the DZHK-LIMS (German)