DZHK
DEUTSCHES ZENTRUM FÜR
HERZ-KREISLAUF-FORSCHUNG E.V.

DZHK-SOP-P-01

Data review

Version: V3.0 Effective Date: 14.07.2023

Replaces Version: 2.0 Dated: 01.03.2019

Change note: Title: Renaming

1. addition of biospecimen data and image data
2. adjustments
3. new section DZHK-LIMS
4. new section BDMS

This SOP is a translation from the original German SOP and valid without signatures. Printouts are not updated!

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1 INTRODUCTION

This SOP describes the means by which the acquisition systems currently used for DZHK studies, secuTrial® for clinical data, CentraXX for biospecimen data, and TrialComplete for imaging and biosignal data, provide support for the quality assurance processes of these three entities. Adherence to the timeframes and quality processes recommended here is, first, significant to the management of a study, as it controls both data quality and patient fee reimbursements. On the other hand, these processes are relevant beyond the individual study for the subsequent use of the procedures described in the DZHK Use and Access Policy.

1.1 LIST OF ABBREVIATIONS

Abbreviation	Explanation
DZHK	German Centre for Cardiovascular Research
SOP	Standard operating procedure
LIMS	laboratory information and management system
IBDMS	Imaging and biosignal data management system
TTP	Trusted Third Party

1.2 OBJECTIVE

This SOP describes the procedure for performing quality assurance of clinical data in SecuTrial®, biospecimen data in CentraXX and biosignal and image data in TrialComplete. The focus is on which functions have to be used at which point in the documentation process in order to correctly document the progress of the acquisition.

However, descriptions of the way in which quality assurance is to be performed are not the subject of this SOP. In particular, this SOP does not specify how clinical monitoring should be performed in a study-specific manner.

1.3 TARGET GROUP

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

In particular, the SOP addresses principal investigators of DZHK studies, as they are responsible for the data quality of their study.

1.4 APPLICATION AND TASKS

The quality assurance process serves to increase the completeness and correctness of the recorded clinical data, biospecimen data, and biosignal and image data. In particular, by correctly using the secuTrial® functions provided for this process, the status of individual

data records can be viewed or queried in the system at any time. This is a basic requirement for the billing process, as well as for making data available through the transfer office of the DZHK.

1.5 TERMS AND DEFINITIONS

This SOP describes the use of the following functions or components of the various IT acquisition systems:

- **Study Nurse:** A person to whom the secuTrial® role Study Nurse is assigned. The role is assigned based on the associated user application.
- **Clinical Investigator:** A person to whom the secuTrial® Clinical Investigator role is assigned. The role is assigned based on the associated user application. Usually, at least the local study coordinator are holders of this role. Several persons per site can also have the Clinical Investigator role.
- **Form:** In the context of this SOP, the term form always describes an electronic data entry form implemented in secuTrial®. Forms with related content are usually combined into a form family.
- **Item:** A single question or 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, if necessary depending on the existing study arms.
- **Visit plan:** The patient-specific visit plan is the collection of all visits (including already performed and future planned visits) of a patient. The specific structure of the visit plan depends on the respective study protocol and the assignment to the study arm.
- **Complete data capture:** A function that marks the data capture in a form as completed. This function is triggered by the "save + finish capture" button.
- **Ask/answer/close query:** Functions that are used to ask/answer/close queries about patients, visits or individual items within a form.
- **Set Review A status:** A function that sets Review A status to a form/visit. This locks all affected forms for further entries or changes. The query functionality remains unaffected. The Review A status can only be removed by persons with special authorizations.
- **Set Review B Status:** A function that sets Review B status to a form/visit. This permanently locks all affected forms for further data entry. The query functionality remains unaffected. The Review B status cannot be removed, not even by the data handling staff.

2 CLINICAL DATA (SECUTRIAL®)

2.1 PREREQUISITE

2.1.1 Devices/Hardware

PC with access to the internet for the use of secuTrial®, as well as a user access for secuTrial®. Access is requested digitally by the main study center during initiation.

2.1.2 Staff

The initial documentation of clinical data in secuTrial® is usually performed by a person in the role of study nurse or clinical investigator. The person carrying out the documentation must have participated in one of the regularly offered training courses on the use of the software by the data handling Göttingen.

The person in charge of the respective enrolling study center (role: clinical investigator) releases the clinical data after completion of data entry for quality control and study-specific monitoring by setting the Review A status. Several persons per site can also have the role of clinical investigator.

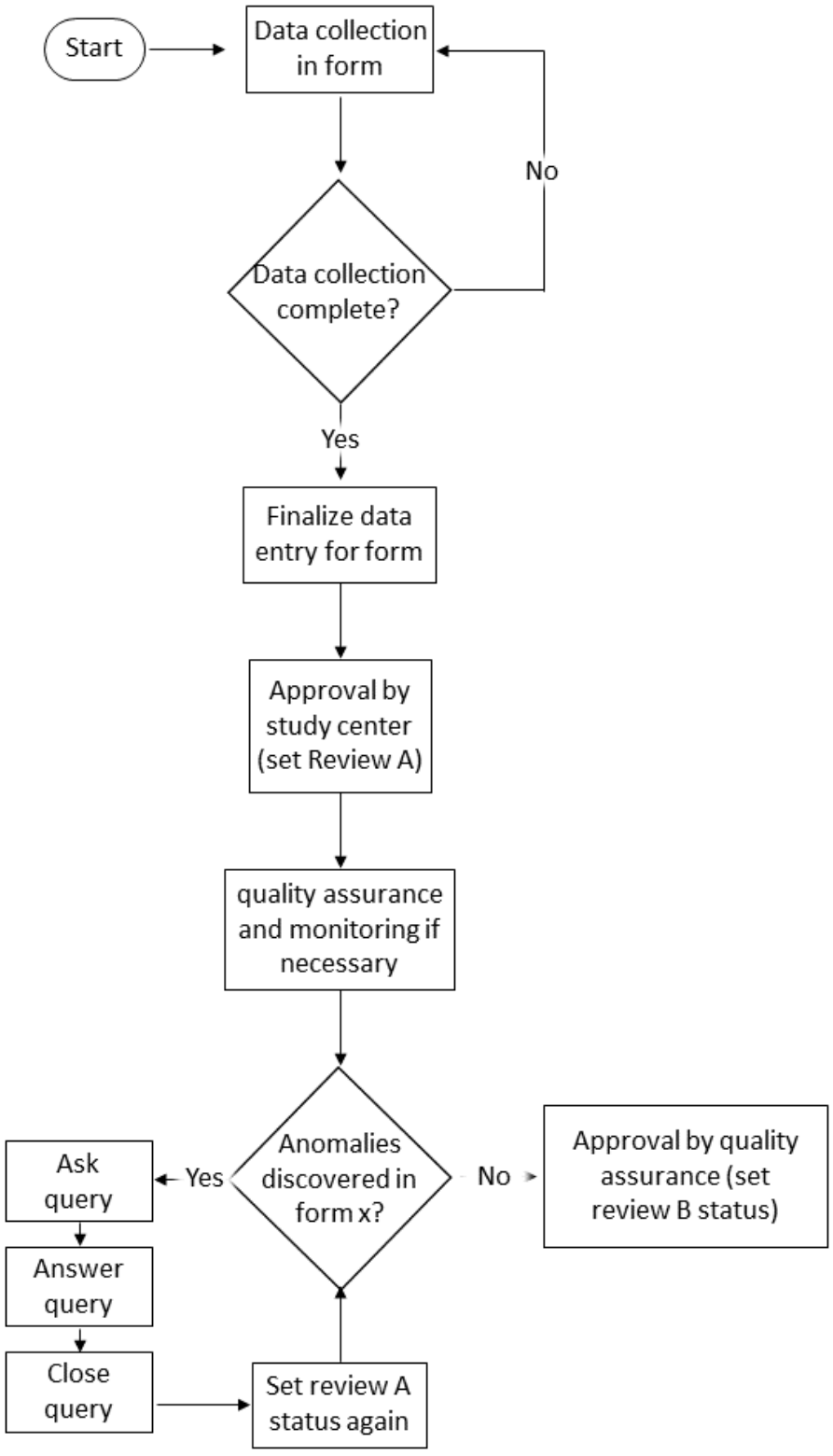
The review of clinical data takes place in two stages. On the one hand, a check of the clinical data is performed by the study-specific quality assurance of the sponsor or its delegates; for example, by clinical monitors. In addition, the data handling performs a study-wide quality assurance procedure on behalf of the DZHK. The personnel performing the quality assurance ask so-called queries.

Queries are answered by the persons initially documenting, i.e., the study nurse or clinical investigator roles, in the enrolling study center. Queries are closed after their complete resolution by the study-specific quality assurance.

The responsible persons in the study center or in quality assurance (monitors) issue the Review B status after all queries of a form or a visit have been processed.

2.2 PROCESS OF IMPLEMENTATION/WORK PROCESS/WORK STEPS

2.2.1 Flow Chart of the process procedure



2.2.2 Implementation

The following quality assurance procedure must be performed for each visit. The rights required to perform the respective steps (e.g., setting Review A) are only available to persons who have the required role (e.g., Clinical Investigator) in secuTrial®. The roles are assigned on a study-specific basis and assigned when the user application is submitted.

Data collection:

The clinical data collected during the patient visit are entered into the associated form in secuTrial®. Data entry can take place in one or several sessions, whereby the form must be saved at the end of a session at the latest. As soon as a form has been completely filled out, the documentation must be finally completed 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 responsible person of the study center (Clinical Investigator) is informed about the status change of the form by an automatic notification (via e-mail). The Clinical Investigator is obliged to check the entries.

Approval by study center ("Review A Status“):

After the entries have been checked, the form is released for quality assurance by the responsible clinical investigator in the enrolling study center by setting the Review A status. This step should usually be done within two weeks after the completion of the data entry or at the latest 6 weeks of all examinations belonging to the patient visit. Timely data entry has been shown to be a quality criterion in clinical trials.

After the Review A status is set, the study-specific quality assurance or the responsible clinical monitor is informed about the approval for quality assurance by an automatic notification (via e-mail).

Implementation of quality assurance:

All harmonized items are subjected to DZHK quality assurance, which is identical across studies. This includes, for example, automated quality control through data handling. In addition, separate quality assurance measures can be specified for each study, including clinical monitoring. These are carried out by the main study center or third parties, for example an external CRO, on the visits or forms released by means of Review A status. If abnormalities are detected during these processes, queries are raised, which in turn must be answered promptly by the study nurse or clinical investigator at the study center collecting the data. After all queries have been answered, the Clinical Investigator must again approve the affected forms for quality assurance (by setting the Review A status). If the response is sufficient, the queries are closed by quality assurance. Otherwise, new queries will be submitted. The message function of secuTrial® can be used for communication between quality assurance and the study center.

DZHK quality assurance is performed within two months after release of all forms of a visit. Internal study quality assurance and - if applicable - clinical monitoring should take place within four months after release of a visit.

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

After completion of all quality assurance measures, the Review B status is set by the study center or quality assurance. Setting the Review B status is technically only possible if no more queries are open.

At the latest six months after the patient visit, all forms of the visit should reach Review B status. This is a prerequisite for the payment of patient fees. After the Review B status is set, the local study coordination in the data collecting study center is informed about the status change by an automatic notification (via e-mail).

2.2.3 Dealing with deviations

Premature completion of data entry can be cancelled by users.

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

The premature setting of Review B status, e.g. before completion of quality assurance, 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 Service4Studies website of the DZHK.

3 BIOBANKING (DZHK-LIMS, CENTRAXX)

3.1 PREREQUISITE

3.1.1 Devices/ Hardware

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

3.1.2 Staff

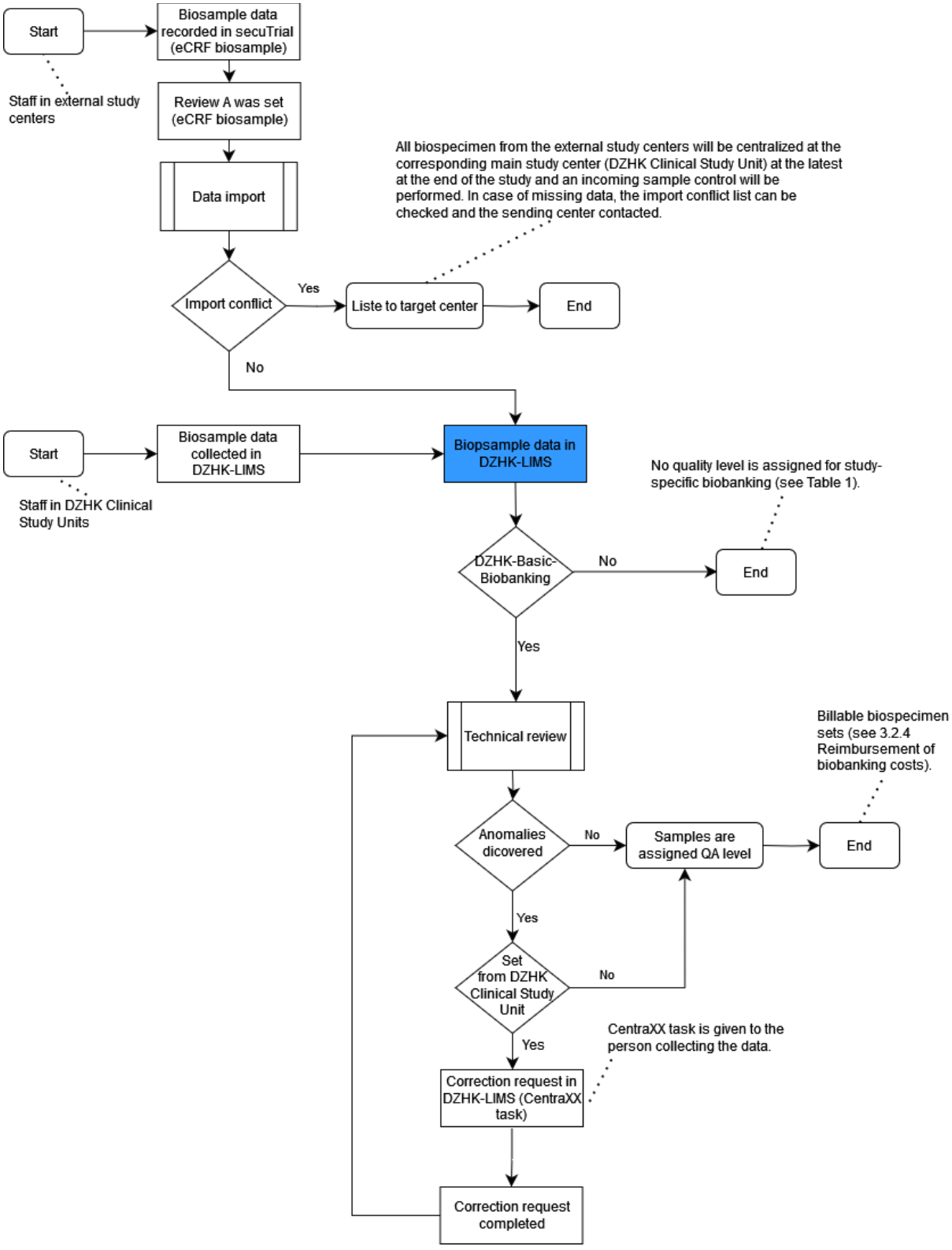
The initial documentation of biosample data in the DZHK-LIMS (for DZHK Clinical Study Units) or in secuTrial® (for study centers that have never had and still have a DZHK Clinical Study Unit) as well as necessary corrections after a data review are usually performed by a person in the roles of "study nurse" and/or "MTLA". The person must be trained internally and should ideally have participated in a training on the use of the DZHK LIMS, if it is a DZHK Clinical Study Unit. These trainings are offered by the biobanking team upon proactive request.

3.2 PROCESS OF IMPLEMENTATION/WORK PROCESS/WORK STEPS

Only biospecimen with completely and plausibly recorded data sets can be fully included in the regular re-use processes. Since the DZHK basic biobanking is owned by the DZHK e.V. and is transferred directly to the DZHK Heart Bank for subsequent use, these data are technically reviewed according to the specifications in the DZHK biobanking SOPs. In case of identified discrepancies, the capturing persons are requested to review the data, provided that the data were originally captured in the central DZHK LIMS. For biospecimen data that were 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. In the DZHK-LIMS, the biospecimen are assigned the quality level 1-3 achieved after testing and review as the sample status.

For biospecimen from study-specific biobanking, the study is responsible and can use reports to control data from all study centers.

3.2.1 Flow chart of the process procedure



3.2.2 Implementation

The conduct of the data validation and the data review differ slightly depending on the type of biobanking involved and the study center at which the biosample data were collected.

	DZHK Basic Biobanking	**Study specific Biobanking**
External study center	1. Data acquisition 2. Review A (manual data validation 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 acquisition 2. Review A (manual data validation and data review) 3. Data transfer to the central DZHK-LIMS at Review A Status 4. Manual review by "central principal investigator" via report from the central DZHK-LIMS (Excel file)** 5. For data review contact staff external study center by the study
DZHK Clinical Study Unit	1. Data acquisition in 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 acquisition in the central DZHK-LIMS 2. Manual review by „central principal investigator“ via report from the central DZHK-LIMS (Excel file)** 3. For data review contact staff DZHK Clinical Study Unit by the study

Table 1: Overview of data validation and data review depending on biobanking and study center.

* For quality assurance purposes, a technical review of the biosample data for completeness (all data points requested in the collection workflows) and plausibility (e.g., the time stamp) is performed daily between 01:00 and 06:00 at night for each DZHK basic biobanking set.

** Quality assurance is performed by the sponsor itself using the biobanking report (→ Registration IT user application with the LIMS user role "central principal investigator"). In case of incomplete datasets or implausible values, the study gets into direct contact with the respective enrolling study centers.

3.2.3 Dealing with deviations

Deviations are summarized in correction tasks in the DZHK LIMS. The CentraXX tasks must be processed according to the data review guideline (LF-B-13). The deviation is to be reviewed, confirmed or corrected. The deadline of the corrections is 7 working days.

3.2.4 Reimbursement of biobanking costs

Each sponsor is obliged to reconcile the invoicing of the enrolling centers with the biobanking reporting (user role "Central Study Management"). DZHK basic biobanking sets

that have been finally checked and approved for billing are marked with quality levels 1-3 (QA1, QA2, QA3) (column AliQualiCode). Biospecimen that do not contain an indication there have not yet been tested. Biospecimen containing the Quest indication have been flagged as conspicuous, but the correction request has not yet been completed. Biosamples containing the indication QA0 could not be assigned an assured quality level even after the correction process and are thus of very limited use for further research purposes. For more detailed guidance, please refer to the biobanking reimbursement factsheet.

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

Terms regarding IBDMS:

- IBDMS: Imaging and Biosignal Data Management System
- DICOM: Digital Imaging and Communications in Medicine
- „Signed“-eCRF-status: equals secuTrial®-status Review A
- „Monitored“-eCRF-status: equals secuTrial®-status Review B
- „Approved” -eCRF-status: equals closed eCRF status
- TrialComplete: The clinical data management system of Telekom Healthcare Solutions

4.1 PREREQUISITE

4.1.1 Devices/Hardware

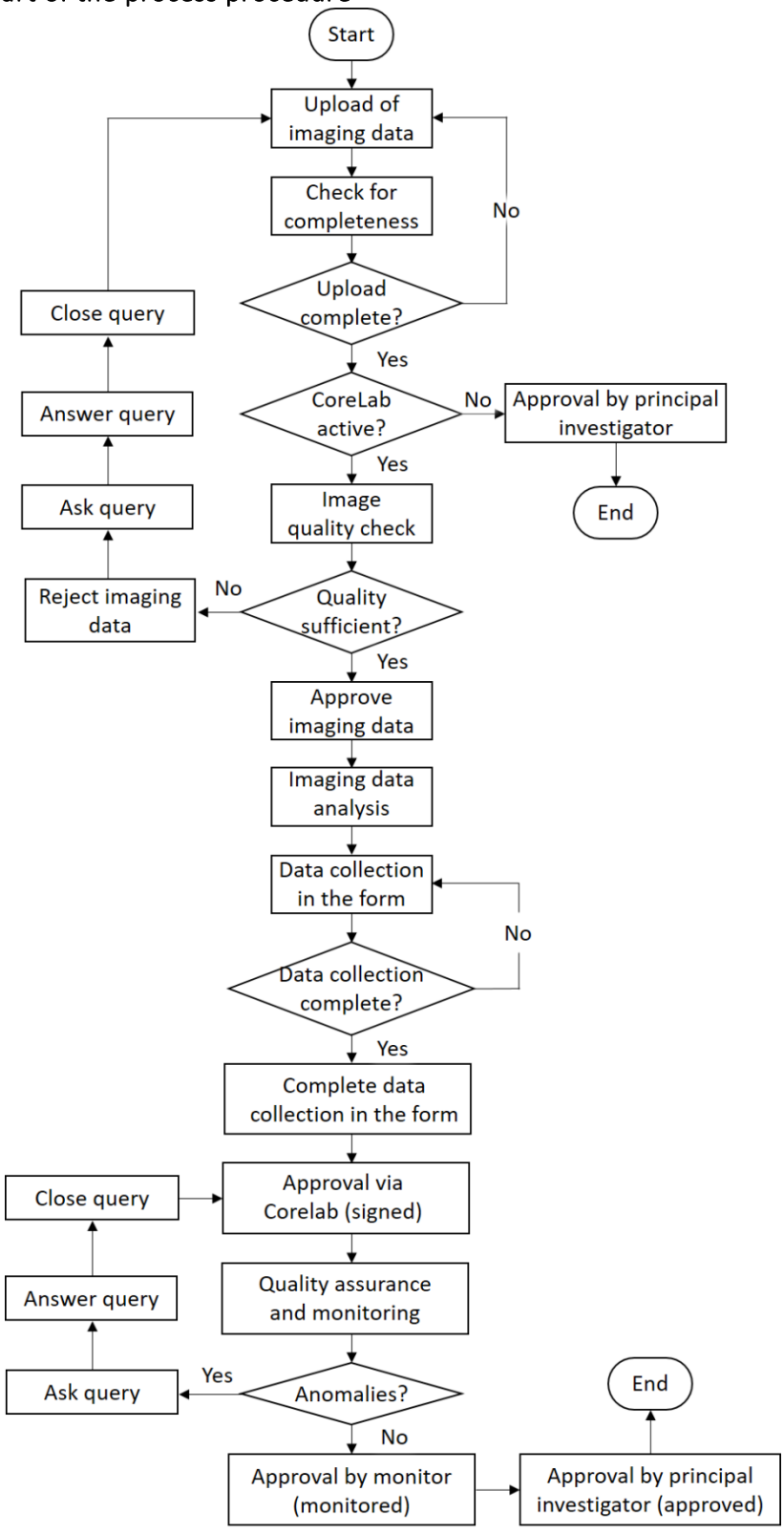
- PC with internet access (port:http/443) for using TrialComplete (DZHK-IBDMS)
- IBDMS user access
- visit for which documentation is to be made has been created/activated in secuTrial®
- valid consent has been given to TTP

4.1.2 Staff

Study staff at the study center who exclusively upload DICOM data to IBDMS are assigned the role "Document Uploader". For Imaging CoreLab staff, the roles "Imaging Analyst", "Imaging CRA" and "Imaging Reader" are assigned for quality input control and image data evaluation. Monitoring can be performed with the "Monitor" role. Additional roles are available to center staff for study-specific tasks ("Data Accountant" role, "Data Enterer" role). The study management has the role "Coordinating Investigator".

4.2 PROCESS OF IMPLEMENTATION/WORK PROCESS/WORK STEPS

4.2.1 Flow chart of the process procedure



4.2.2 Implementation

4.2.2.1 Documentation of imaging and biosignal data

The DICOM image data of a visit are 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 time of the visit is recommended and defined for each study. The upload MUST be completed after 8 weeks at the latest, shorter study-specific requirements are possible and will be communicated by the study.

After the upload, the person as well as persons with the monitor role 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 about matching the requested and uploaded DICOM data and about the time window for timely upload.

4.2.2.2 Documentation of the data of the central analysis

If a central office in the study analyzes the data, the data will be documented in TrialComplete's eCRF. Individuals in the roles of Imaging CRA, Imaging Analyst will be designated for this office.

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

If the quality is insufficient, the imaging or biosignal data should be rejected ("Reject"). In parallel, a notification with the reason is created in TrialComplete and sent to the uploader by email. If possible and available, imaging and biosignal data with a better quality will be uploaded afterwards. The reject-notification should also lead to the improvement of the collection and processing processes for subsequent studies in the study center.

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

Once data is set "Approve", a workorder "Process documents" is created for specific persons (role "Imaging Analyst") with the task to perform the data analysis. The result data is captured in the TrialComplete eCRFs by the Imaging Analyst. Once the data collection is complete, it is finalized and signed ("Signed") by the Imaging Analyst (Status Review A). Documentation MUST be completed within 6 weeks of evaluability.

4.2.2.3 Completion of data quality assurance (Monitored)

For monitoring clarifications, the query management system MAY be used for data quality. The person with the role "Monitor" or "Coordination Investigator" MAY check the documentation and issue queries for image data documents, eCRFs or items in eCRF and direct them to documenting persons or roles. The respective queries are listed in the task

management under "Study Queries" and are to be processed by the data collectors. Only after all queries have been resolved the form WILL be set to "Monitored" status by the person with the monitor role. The study management can also monitor the forms and additionally set the status "Approved".

4.2.2.4 Ensuring process quality

The roles Document Uploader, Data Accountant, Data Enterer or Coordination Investigator can also download a daily updated report in the TrialComplete system, which lists all visits with required DICOM data collection with and without upload for each center. The monthly report on the completeness overview with corresponding statistics on data quality (purpose DZHK Heart Bank) is generated by the IBDMS quality manager at the end of the month and sent to principal investigator, coordinators and monitors. These then have the opportunity to point out to centers insufficient completeness of DICOM data and to promote a higher upload performance.

In the case with participation of a CoreLab, the monthly QA report additionally shows parameters on the form entries, such as the proportion of processed forms, the distribution of quality scores and the completeness of key outcomes. Further information on the outcome data in the forms can be obtained on a daily basis from another TrialComplete Report.

4.2.3 Dealing with deviations

The eCRF status "Signed" can be cancelled by the roles Imaging Analyst, Monitor and Coordinating Investigator.

The eCRF status "Monitored" can be canceled by the roles Monitor and Coordinating Investigator.

The eCRF status "Approved" can be canceled by the Coordinating Investigator role.

5 APPENDIX

5.1 MODIFICATIONS

Modifications compared to the previous version.

Section	Description of the modifications compared to the previous version
Title	Renaming of the SOP title
1.	Addition of biospecimen and image data
2.	Adjustments
3.	New section on DZHK-LIMS
4.	New section on IDMS

5.2 PERSONS INVOLVED

Name	Role	Contribution
Mahsa Lee	First author	Drafted the SOP
Ivonne Wallrabenstein	First author	Drafted the SOP
Roberto Lorbeer	First author	Drafted the SOP
Alexandra Klatt	Review	Scientific Review
Sabine Hanß	Project lead Data handling	Scientific Review
Christian Schäfer	DZHK-LIMS	Scientific Review
Jens Schaller	IBDMS	Scientific Review
Julia Hoffmann Ilka Wilhelmi	DZHK main office	Coordination

5.3 LITERATURE AND REFERENCES

1. User manual for secuTrial® version 1.0
2. Flowchart for study preparation/implementation (German)
3. LF-B-07 guideline data review in DZHK-LIMS (German)