



GCP-Audits im Datenmanagement

- aus der Sicht des Auditors und Subject Matter Experts -

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GCP

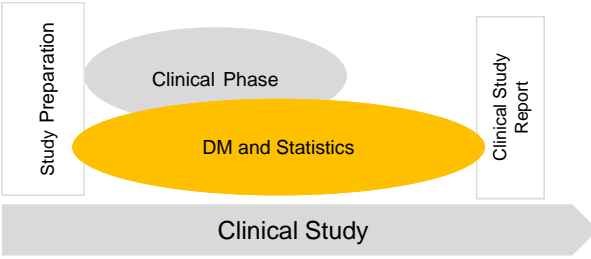
Protection / safety and well-being of human subjects

Data Credibility


- ⇒ Data must be in compliance with the clinical study protocol
- ⇒ Data must be consistent between source data, CRF and the clinical study report
- ⇒ Data must be reported completely in the clinical study report

- ⇒ Processes must be described in SOPs
- ⇒ Processes must be followed and documented properly

- ✓ Say what you're going to do
- ✓ Do what you said you were going to do
- ✓ Document what you did



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DM Audit Types

System Audit:

- Pre-contract / CRO Qualification Audits
- DM System Audit (internal / external)
- Database Audits

Clinical Study Audit:

- TMF Audits
- Site Audits

DM Document audits

- e.g. Data Management Plan, Data Validation Plan

DM Process audits

- Selected DM processes

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DM Auditor's Challenge



- **Who performs DM-audits?**
 - QA Auditors of the Sponsor
 - CRO Auditors
 - Independent Auditors

- **Do GCP-Auditors have enough background in Data Management, Biostatistics and Statistical Programming to assess the processes?**
 - Subject Matter Experts from DM and/or Biostatistics as Co-Auditors or Audit-Observer

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DM Audit Objectives



- To evaluate the DM system
- To assess compliance of DM related activities with GCP aspects, the clinical study protocol / study-specific instructions, applicable regulatory requirements and contractual agreements.
- To understand DM processes and how clinical study data are managed
- To evaluate the interactions between the audited party and other parties involved in the clinical study
- To determine that adequate resources are in place to meet the DM obligations

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DM Audit Areas



- **Organization and Facilities**
- **QA System and Written Procedures** for DM
- **Training and Qualification** of DM-staff
- **DM Processes and Quality Control**
- **Database, IT Systems**
- **Validation of IT Systems**
- **Contracts and Agreements**

- **Interaction** between DM department and other departments involved in clinical studies e.g. Biostatistics, Clinical Research

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Audit Process



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Audit Preparation



- Determine purpose and scope of the audit (⇒ Audit Plan)
- Review SOPs, Contracts and applicable guidelines/regulations
- Review previous audit reports (if available)
- Define expectations for Data Management and Statistics
 - reconcile with other Data Manager, Statisticians, Statistical Programmer
 - what is important to check for the company /special project (checklist)
 - how much time is granted for DM and STATS-Sessions
 - ⇒ liaise with Lead-Auditor and discuss/prepare agenda
- Preparation meeting with Lead-Auditor / Audit-Team
- Define role and tasks during the audit (e.g. Co-Auditor/Subject Matter Expert (SME)/Observer)

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Audit Conduct



- Interviews with selected staff to assess their understanding of their role and DM related responsibilities
- Document review (DM Documents / DM-related SOPs)
- Observe how the system works
- Demonstration of DM Systems (e.g. Databases)
- Compare information obtained in interviews with documentation
- Facility tour (e.g. office facilities, server room)

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Audit Conduct – General Questions



- Development and maintenance of Standard Processes
- SOPs for Data Management, Statistics (and Medical Writing)
- Interfaces between these functions available
- Willingness to provide SOPs to Auditors/Sponsor
- Provision of current projects (i.e. number of projects currently active , in the last year)
- Indicating which activities are outsourced /subcontracted to third parties and their audit plan
- Quality control system implemented
- Willingness to provide number and qualification of employees (CVs and job description)
- Training logs and certificates
- Organization chart and fluctuation information by department



Audit Conduct – Data Management Questions



- Hardware and Software used in DM
- Architecture of servers and workstations
- Specification of Systems for Database and collection of data (EDC) (Vendor, contract status, version, validation status , certificates) / "Software as a Service " (SaaS) / Audit trail
- Randomization Tools – interface to database system (Process, Validation)
- IVRS/IWRS - Interactive Voice /Web Response Systems (Vendor, contract status, version, validation status, certificates)
- Coding Tools (Manually or system based)
- Statistical Analysis System (SAS, SPSS, other)
- Backup and Disaster Recovery (Frequency, where and how long are back-ups stored)

Audit Areas & Audit Questions & Findings

Audit Conduct – Questions Data Management

- ? **Are procedural documents available and adequate for all DM related activities?**
- ? **Procedures for DB testing available**
 - Study-specific test plan
 - UAT Procedures available
- ? **Procedures for release of DB available –Checklist?**
 - Check of implementation of all protocol items into the eCRF -> Approval?
 - eCRF development should be performed by a cross-disciplinary team of qualified individuals (e.g. trial manager, statistician, data manager, medical)
- ? **Procedures for Functional specification should exist identifying each data item (incl. field names, types, units, validation logic and conditional skipping)**
- ? **Change Management for update and re-distribution of Clinical Database /eCRF should exist**
- ? **Access control and management**
 - Which roles have which access – defined (read only for sponsor)?
 - Training documented?
 - Unique access for each user with individual accounts
- ? **Query resolution strategy should be in place**
 - omitted /sent/closed/deleted query

Audit Conduct – Questions Data Management



- ? **Lab Data**
 - Procedures available for standardizing units across sites?
 - Reference ranges (collected and maintained?)
 - When / how are external lab data transmitted – flexible, defined format required?
 - Validated transfer in general– if not, validation on study level?
- ? **DB lock**
 - Checklist: All required database lock and closure documents present
 - Will this list shared with the sponsor ?
 - Written procedure should be in place (incl. Checklist) for revoking access to EDC and providing data to investigators
 - SOP for unlock and re-lock of DB in place?
- ? **How are post-final database updates handled and documented?**
 - information of the Sponsor /approval by the Sponsor?
- ? **Procedures for (blind) data review meetings available ?**
 - How are blind data review meetings planned, conducted , documented and approved?
- ? **How is Coding of AE/CM and MH organized**
 - Documented procedures for data coding should be in place detailing the procedures to be used
 - Data coding should be performed only by personnel trained (on the system, - in the relevant coding dictionaries (⇒ CV))
 - Coding conventions or Coding guidelines available?
- ? **How is the database prepared for archiving (XML and SAS datasets) and sent to the Sponsor?**
 - Process for export of data
- ? **Written handover procedures from data management to statistics available?**

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Audit Trail



"Documentation that allows reconstruction of the course of events."

Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95)

"The use of audit trails or other security measures helps to ensure that only authorized additions, deletions, or alterations of information in the electronic record have occurred and allows a means to reconstruct significant details about study conduct and source data collection necessary to verify the quality and integrity of data."
Guidance for Industry , Computerized Systems Used in Clinical Investigations

"A process that captures details such as addition, deletions or alterations of information in an electronic record without obliterating the original record. An audit trail facilitates the reconstruction of the history of such actions relating to the electronic record."

Reflection paper on expectations for electronic source data and data transcribed to electronic data collection tools in clinical trials

"Audit trails need to be readable and changes to audit trail data should be prevented by the system. The responsible investigators, sponsors and inspectors should be able to review the audit trail."

Reflection paper on expectations for electronic source data and data transcribed to electronic data collection tools in clinical trials

"An audit trail should be maintained as part of the source documents for the original creation and subsequent modification of all source data."

Requirement 3, ICH GCP 4.9.3 and 5.5.4

"12.4 Management systems for data and for documents should be designed to record the identity of operators entering, changing, confirming or deleting data including date and time. "
EudraLex The Rules Governing Medicinal Products in the European Union Volume 4, Annex 11: Computerized Systems

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Audit Trail



- **Automated - Automatisiert**
The entries in the audit trail must be automatically recorded by the system whenever an electronic record is created, modified or deleted
- **Secure - Sicher**
Audit trail data must be stored in a secure manner and must not be editable by any user
- **Contemporaneous - Zeitgleich**
Audit trail entries must be time stamped according to a controlled clock which cannot be manipulated.
- **Traceable - Rückverfolgbar**
Each audit trail entry must be attributable to the individual who collected it. Updates made to data records must not delete or alter previous values and the reason for changing the data must also be recorded.
- **Archived - Archivierbar**
The audit trail must be retained as long as the electronic record is required to be stored
- **Available - Verfügbar**
The audit trail must be available for agency/auditor review

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External Electronic Data



Electronic data from external providers (e.g. Central Lab, Special Lab, PK etc.)

SOPs for import data should be available

- into Database
- into EDC

Recommendation: Data Transfer Agreement /Plan



To be defined:

- Contact details (sender and recipient of data)
- Frequency and method of transfer Variable/element specifications
- Type of assessments collected based on the protocol schedule of events and the variables to be transferred
- Format of transfer (CSV files, Excel, ASCII, SAS®, etc.)
- Frequency of transfer
- Quality control/validation steps performed to maintain data integrity
- Reconciliation of data transfers against the clinical database and sends the DTP to the recipient for review.

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Audit Conduct – Questions Statistics and Statistical Programming



- ? **Procedural documents available and adequate for all statistics related activities?**
 - SAP
 - Programming and validation of SDTM /ADaM/TLFs
 - Preparation of Reviewer Guides
 - QC and Validation process and documentation
- ? **Statistical Analysis Plan**
 - Preparation and Approval mandatory (Approval by sponsor)
 - Template available (incl. Definition of Analysis Sets, Algorithms for derived variables)
- ? **Programming Guidelines**
 - Good Programming Practice for SAS/other programming language available and followed
 - Is this checked
- ? **Validation of SAS programs?**
 - Procedures available and documentation
 - Implementation of validation strategies (source code review; double programming)
 - LOG Window check ; How are Errors , Warnings and suspicious Notes handled ?
- ? **Macro Library available and used for programming**
 - Procedures available (SAS Macros used must be validated and not be editable by the users and
- ? **Directory structure defined**
 - Protection of raw datasets
 - Clear definition of macros (global /study specific)
 - Different status of SAS programs can be maintained

SDTM=Standard Data Tabulation Model
ADaM=Analysis Data Model
TLF=Tables, Listing and Figures

Randomization



ICH GCP 1.48 *Randomization*

Process of assigning trial subjects to treatment or control groups, using an element of chance to determine the assignments in order to reduce bias.

ICH GCP 1.48 *Randomization*

Das Verfahren der Zuordnung von Prüfungsteilnehmern zu Behandlungs- oder Kontrollgruppen, wobei die Zuordnung nach einem Zufallsmechanismus vorgenommen wird, um Verzerrungen zu vermindern.

- ? Where are randomization plans stored
 - ? Who How is double blindness of a clinical trial secured
 - ? generate the randomization plan
 - ? Software ? Vendor, Specification/Validation of Software used to generate plan/sealed envelopes
 - ? Interface – how is it organized to get the list into the database
 - ? Step must be validated and corresponding documentation must be available !!!!
 - ? Dummy randomization: Specification and signature
 - ? How is it ensured that the correct randomization is used when creating the final run
- ! QC documentation of randomization should be filed in the TMF

Validation of SAS Programs



Quality Control / Validation of SAS Programs

Validation: Confirmation by examination and provision of objective evidence that software specifications conform to user needs and intended uses, and that the particular requirements implemented through software can be consistently fulfilled.

✓ **Doing the right thing, doing it right, consistent repeatable**

Transformation of data must be documented and method must be validated

"1995: WHO Guidelines for Good Clinical Practice (GCP) for Trials on Pharmaceutical Products"

How ? Procedure available to decide which validation is used (Sponsor decision?)

- Independent double programming
- Source code review
- Check of outputs /Check of LOG for Errors, Warnings and Suspicious Notes

! Documentation of QC and Validation to be filed in the TMF



SAS Programs

Deliverable to Sponsor of each step as (executable) program

References



- ICH E3 "Structure and Content of Clinical Study Reports"
- ICH E6 "Guideline for Good Clinical Practice"
- ICH E9 "Statistical Principles for Clinical Trials"
- ICH Q9 "Quality Risk Management "

- FDA Guidance for Industry and FDA Staff, *General Principles of Software Validation*; January 2002
- FDA Guidance for Industry, *Computerized Systems used in Clinical Investigations*, May 2007
- FDA Guidance for Industry; *Electronic Source Data in Clinical Investigations*, September 2013
- FDA, "21 CFR Part 11, Electronic Records; Electronic Signatures; Final Rule"

- EMA Reflection paper on expectations for electronic source data and data transcribed to electronic data collection tools in clinical trials , GCP Inspectors Working Group (GCP IWG) , June 2010
- EMA Reflection Paper on the Use of Interactive Response Technologies (Interactive Voice/Web Response Systems) in Clinical Trials, with Particular Emphasis on the Handling of Expiry Dates , December 2013
- EMA Guideline on Missing Data in Confirmatory Clinical Trials, January 2011
- PIC/S Guidance: Good Practices for Computerized Systems in Regulated "GxP" Environments (www.picscheme.org)

- GAMP®5 "A Risk-Based Approach to Compliant GxP Computerized Systems " (www.ispe.org)

Audit Follow-up / Audit Report / CAPA



- Urgent issues / serious concerns are to be communicated in an expedited manner
- Audit Report will be issued
- CAPA Plan needs to be implemented
 - Respond on time
 - Clearly state what action(s) is/are intended to take (or has already taken) to address the finding
 - Clearly state the timeline for the action(s)
 - Provide relevant documentary evidence if any finding is disputed
 - Do what you say

Guidance for Responding to Audit Findings



Responses should be **SMART**:

- **S**pecific
- **M**easurable
- **A**chievable
- **R**ealistic
- **T**ime driven

SMART



Specific

- Perform the necessary further assessments to identify the full extent of the finding.
- Consider not only how to correct the identified deficiency but also the root cause of the problem.

Measurable

- Clearly state what corrective and preventative actions are intended to take to address the finding.
- State the specific deliverables from the proposed corrective and preventative actions, e.g. updated work instruction, training record, etc.

Achievable / Realistic

- Do not make promises which cannot be delivered, as corrective and preventative actions will be followed up by an inspector at re-inspection.
- Comply with the appropriate legislation and consider the best way to do so in the context of the business model.

Time driven

- Clearly state the timeline for the corrective / preventative action(s) for each finding.

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z.B.:

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- *GVP: Basic und Refresher Kurse*
- *Monitoring Kurse*
- *Audit- und Inspektion Vorbereitungskurse*



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