BVMA
AUDIT CERTIFICATE

The company

TRIGA-S GmbH

successfully completed the BVMA internal audit
regarding Good Clinical Practice compliance
in the conduct of clinical trials in humans in

2018, 2021 and 2024

The guidance document 'Good Laboratory Practice' was used
as an additional reference during the audit.

We herewith confirm the membership in the BVMA e.V.

Munich, 23 August 2024

Martin Krauss
President BVMA e.V.

Appendices:

- Appendix 1: Details to initial audit
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- Appendix 3: Auditors

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Appendix 1
Details to initial audit

1. Objectives and scope

The objective of the initial audit was to assess compliance of the CRO with the membership requirements of the BVMA, Good Clinical Practice (GCP), internal standards and additional applicable regulatory requirements. Potential gaps and recommendations for further improvement in line with GCP, applicable regulations and industry standards were addressed as applicable. All procedures and systems relevant to clinical development were within the scope of this audit. The individual audit plan was tailored to the services of the CRO.

The audit included interviews with staff, review of documentation and an assessment of facilities and equipment as applicable.

2. References

Guidelines/Regulations:

- ICH Guideline for Good Clinical Practice, E6 (with R2 for audits after 14 June 2017)
- European Clinical Trials Directive (2001/20/EC) of 04Apr2001
- European GCP Directive (2005/28/EC) of 08Apr2005
- National Laws and Guidelines for the conduct of clinical trials

BVMA Standards:

- List of Essential SOPs for BVMA Members (current version)
- CRO Audit Conduct for BVMA (current version)

3. Documents

Documents needed for assessment during the audit included among others the following:

- Organizational charts, documentation on training including CVs and job descriptions
- List of internal standards (SOPs), access to all internal standards, e.g. SOPs
- Study documentation (TMF)
- Internal audit plans
- Documentation on IT systems and computer systems validation

4. General audit conduct

The audit consisted of the following parts:

- Opening meeting with key staff to discuss the scope and the agenda
- Interviews with key staff members
- Review of key documentation, i.e., policies, SOPs, personnel records, examples of deliverables to assess compliance
- Tour of the facility
- Closing meeting to feedback the audit findings and its preliminary classification

5. Follow up of audit

The auditor prepared an audit report. If applicable, the audited company provided a CAPA plan addressing the observations of the auditor. Only if an auditor was fully satisfied with the audit results, a recommendation for membership of the audited company was sent to the BVMA board.

Appendix 2
Topics of Re-Audits

1. General

Each re-audit cycle has followed-up the observations from the previous audit to confirm completion of planned corrective actions. Changes in the company and the quality system were reviewed and assessed. Details to initial audits (Appendix 1) were valid for each re-audit cycle. In addition, re-audits contained special topics that were especially addressed by the auditor.

2. Topics of special interest in Re-Audits

- Training records / CVs / Job descriptions (cycle 2009-2011)
- Vendor Management (cycle 2012-2014)
- IT Systems including data back-up and computerized system validation (cycle 2015-2017)
- Implementation of ICH-GCP (R2) – focus on Risk Management (cycle 2018-2020)
- Quality Management System (cycle 2021-2026)

For the last four cycles, some more details about content of the audit are provided in the subsequent sections.

2.1. IT Systems including data back-up and archiving

The following list exemplifies topics that CROs need to address in the IT area. Depending on the scope of services provided by the CRO some of the below topics may not be relevant.

1. Facilities / server room
   - Access, physical security, environmental controls
   - Power redundancy (UPS)
2. Backup procedures for electronic data
   - Frequency, procedures, backup testing and restore
   - Scope of data backed up (system data, meta data, etc.), server virtualization
   - Media, re-cycling of media, storage of backup media, refreshing of backup media
3. Disaster recovery and business continuity
   - Procedures and frequency of testing of worst case, any pertinent plans and related communication, logs
4. Security
   - Password policy, virus protection, firewall, session timeout
   - User ID/authentication/management
   - Assignment/removal procedures of logical access rights, expiration periods

5. Privacy and confidentiality
   - Internal policies regarding privacy, confidentiality, data protection
6. Risk assessment
   - Technical vulnerability management and risk assessment/treatment
   - Breaches of confidentiality, availability and integrity
7. Incident management
   - Reporting and managing incidents
8. Mobile
   - Mobile computing and teleworking
   - Mobile device assignment and security procedures
9. Network
   - Segregation in networks (development, test, production)
10. Transmission/exchange of electronic data
    - Procedures for transmitting / exchanging electronic data with external recipients, e.g. secure pathways, encryption, portals, credentialing e.g., via SAFE, etc.
11. Data Storage
    - Data storage policy, internal documentation availability
    - Database and development source code secure storage
12. Computerized Systems Validation (CSV)
    - Inventory of systems and hardware
    - Validation records, including URS, Validation Report, CSV change control and version control

2.2. Implementation of ICH-GCP (R2) – Risk Management

The following list exemplifies topics that CROs need to address as a result of the ICH E6 Addendum. Depending on the scope of services provided by a CRO some of the below topics may not be in scope of their portfolio of systems and processes. The CRO have a strategy / process in place to address topics applicable to the services provided.

1. Adaptation of the Quality Management System
   - Systems approach, risk-based
   - Process for risk identification, risk assessment and quantification, risk communication and risk mitigation
   - Impact on audit system, audit strategy and audit planning
   - Impact on extent and strategy for QC in all operational areas
   - Scope of topics to address in SOPs for computerized systems
   - CAPA system, incl. Root Cause Analysis in case of significant non-compliance and tracking of CAPA outcomes

2. Trial Planning and Protocol development
   - Feasibility
     - Sources of information
     - Criteria to decide on site selection → list all criteria
   - Avoidance of overburdening/unnecessary complexity sponsor shares draft vs. final protocol
   - Identification of critical systems, processes and data
   - Clarity and consistency of operational documents used in the trial
3. Identification of Risks to Critical Trial Processes and Data
   - System level (SOP system, CSV, training etc.)
   - Trial level
4. Documentation, Evaluation and Control of Risks
   - Likelihood – Impact – Detectability
   - Facts and figures supporting the above assessments
   - Mitigation Plans
   - Decision-making and risk reduction plan – incorporation into protocol design, operational plans, contracts, compliance checks, training etc.
   - Definition of quality tolerance limits and trigger points/thresholds for evaluations
   - Approach when sponsor of a trial does not apply / support a risk based approach
5. Communication and Periodic Review of Risk Control Measures
   - Traceability of decision-making (based on which data, provided by whom in which accuracy, based on verifiable facts, objective evidence and clear criteria
   - Link between quality management system and risk management (continual improvement during trial execution)
   - Measures to review risk control measures to ensure QMS remains effective and relevant
6. Risk Reporting
   - Description of QMS approach followed in the trial
   - Summary of important deviations in clinical study report
7. Risk-Proportionate Approaches
   - Systems supporting centralized / risk-based monitoring
     - Availability of integrated study management systems supporting tracking of performance indicators
     - Alignment of safety and clinical operations systems and flows
     - Systems supporting generation of KPIs (Key Performance Indicator) and KRIs (Key Risk Indicator)

- Monitoring
  - Monitoring plan and study management plans
  - Onsite vs. centralized monitoring, combination of onsite/centralized
  - Scope of data and information reviewed during centralized monitoring
  - Risk assessment, mitigation, criteria/triggers for onsite visits
  - Documentation of monitoring activities
  - Computerized systems validation
- Vendor management and oversight
- IMP management and accountability
- TMF management and organization
  - Paper TMF
  - e-TMF

8. Alignment with Sponsor Oversight Activities
   - Oversight of any trial-related duties and functions
   - Oversight of vendors and their subcontractors
   - Regulatory green-light
9. Serious Breaches
   - Alignment with sponsor processes
10. Investigator Responsibilities
    - Procedures for supervision of trial team
    - Qualification and oversight of external providers contracted by investigator
    - Traceability of changes made to source data

2.3. Quality Management System

The focus of this audit cycle is going to be systems and processes related to the overall Quality Management System (QMS) required by the actual applicable ICH E6 (R2 or R3, depending on timepoint of audit, "ICH-GCP" in the following). Audits cover but may not be limited to the system of controlled documents, qualification and training, auditing including CAPA management, and vendor qualification. Activities and documents related to risk management and business continuity related to the pandemic may be included depending on both, significance for the audited CRO or on the relevance at the time point of the audit, respectively.

1. Controlled Documents (CDs)
   a) Clear and comprehensive system of CDs including index in place
   b) Relevant areas are covered by CDs including QMS, operational activities, BVMA list of topics recommended to be covered
   c) CDs are adequately detailed, specific, and clear

d) Procedures for administration of CDs are defined and comply with GCP and industry standards, e.g. with regards to:
   i. Authorization
   ii. training prior to the effectiveness
   iii. review and revision within a defined frequency
   iv. handling of uncontrolled copies
   v. handling of planned and unplanned deviations
   vi. sharing with 3rd-parties such as sub-contractors, freelancers, clients, etc.

2. Auditing
   a) A system of internal auditing is defined in writing and audits are performed as per a strategic and operational annual audit plan
   b) CDs define an adequate audit policy, e.g., risk-based, set-up of strategic (3-5 years) and annual implementation plans, etc.
   c) The extent of actual auditing reflects the size of the company and includes, as applicable, the following elements:
      i. Process audits: Risk-based approach and/or coverage of processes in defined frequency allowing flexibility
      ii. Study audits: Extent of activities, e.g., adapted to the trial complexity, regulatory relevance, number of countries/sites/subjects, etc., and this independently from a client auditing work order
      iii. Vendor audits: A system for vendor qualification is implemented and includes, e.g., categorization of vendors, risk-based qualification activities, re-qualification, and a list of qualified vendors (if applicable preferred vendors)
   d) The workflow for audit reporting including information on management and escalation is defined.
   e) A CAPA database or similar is maintained (system security/validation adapted to the size of the company).
   f) Regulatory inspections' history, CAPA management, and sharing of relevant information with clients.

3. Training
   a) A training policy is defined in writing and training records are maintained
   b) Administration of training is defined and adapted to company size, e.g., paper records vs. e-LMS
   c) Elements of training and documentation thereof include:

i. Maintenance of CVs and JDs. Sign-off and periodic review.
ii. Upon on-boarding approach to determine the adequacy of job incumbent with job description requirements.
iii. Set up and completion of individual training plans.
iv. Training of SOPs: Classroom/web-based/self-study with or without subsequent exams.
v. Initial and periodic training on external requirements, e.g., ICH-GCP, GLP, IT security, GDPR, etc.
vi. Supervision and quality control related to training and training documents.
vii. Study-specific training depending on the role is defined and performed.

d) Training files are accessible, complete, and adequately maintained.

4. Quality Management eSolutions (Training, CDs, CAPA) (if time allows)
   a) General process for CSV (computerized system validation) is described in a CD.
   b) The validation process covers change control procedures and LCM (Life Cycle Management).
   c) Implemented computerized systems are validated according to CD.

5. Miscellaneous
   a) Operational risk assessment and mitigation related a given trial with regard to applicable systems, processes, resources, etc.
   b) Review and adaptation of business continuity plans to pandemic and other business threats.
   c) Steps for implementing EMA Guidance re the structured review of audit trail data
   d) Implementation of ICH E8 (R2), i.e., approach regarding CtQFs (Critical to Quality Factor)
   e) Steps for the implementation of ICH E6 (R3)

Appendix 3
Auditors

The following auditors have performed the majority of the audits:

Alexander Both
More than 15 years of experience in quality management and GCP auditing
Held tactical and strategic positions in the pharmaceutical and CRO industry in Germany and the USA
Experience in facilitation of regulatory authority inspections, e.g. by FDA, EMA, and GLP authorities
Diploma in Bio-Engineering, certified European Quality Manager (DGQ)

Rita Hattemer-Apostel
Rita Hattemer-Apostel is CEO and co-founder of Verdandi AG.
More than 18 years work experience in pharma and two major globally operating CROs
More than 16 years in clinical quality assurance and quality management
Editor-in-Chief of the Quality Assurance Journal (John Wiley & Sons)
President of SPAQA (2003 - 2009)
Master of Science (Dipl.-Ing.) in Physics Engineering,Certified Quality Manager (RWTÜV), studies in Organizational Psychology and Coaching

Helmut Schweiger
Helmut Schweiger founded CRP - Clinical Research and Project Management as a private company in September 2000. He offers services as a Freelance Clinical Trial Manager, Clinical Research Associate and Auditor. Since 2010, Helmut Schweiger has also been working in the field of Quality Management QA/QC: Preparation, performance and follow up of GCP, GCLP, (e-)TMF audits, vendor qualification and re-qualification assessments in EU, USA and Asia. He prepares and performs mock inspections for the EMA, EMEA, FDA and PMDA authorities and participates in inspections in all regions.
Before self-employment, he has been working as CRA more than 4 years for Staticon International GmbH and more than 2 years for FRINO COMP-Arzneimittel GmbH. He holds a certified IHK degree as Data Processing Administrator and Statistician Associate and has several other certifications in different areas of medical indications.

Beat Widler, PhD
Managing Partner and co-founder of Widler & Schiemann AG
Over 25 years of work experience with Roche in Switzerland and the UK in the areas of regulatory affairs, clinical research and Quality Assurance & Risk Management. For 15 years the Global Head of Roche Clinical Quality and 5 years the Head of Roche Clinical Development UK.
Representative for more than 15 years on IFPMA, EFPIA, Interpharma working groups and delegations to Health Authorities.
Diploma & PhD in Natural Sciences from the Swiss Federal Institute of Technology in Zürich (ETH-Z)
Diploma in Pharmaceutical Medicine SwAPP