

Comprehensive and effective system of standard operating procedures for investigator-initiated trials

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According to GCP, sponsors and organizations that take over sponsor responsibilities, are responsible for implementing a quality management system with written standard operating procedures (SOPs). Changes in the German Drug Law and Medical Device Act made these principles mandatory also for investigator-initiated trials, in which SOPs had been rarely used until 2000. This changed with the introduction of the (Coordinating) Centers for Clinical Trials as central service units for clinical trials at university hospitals all over Germany since 1999. They constituted a quality management working group which developed concerted SOPs for clinical trials with medicinal products and medical devices as well as SOP templates for trial sites considering the characteristics of academic structures. The SOPs described in this publication have become major instruments to enhance the quality of investigator-initiated trials and to ease the cooperation of (Coordinating) Centers for Clinical Trials.

**Heike Moenkemann^{*1}, Rita Pilger²,
Sylvia Reinecker³, Peggy Houben⁴ &
Ursula Paulus¹**

¹Clinical Trial Center Cologne, University of Cologne, Gleueler Str. 269, 50935 Köln, Germany

²Coordination Center for Clinical Studies Charité–KKS Charité, Berlin, Germany

³Clinical Trial Center, Philipps University of Marburg, Marburg, Germany

⁴Clinical Trial Center Leipzig, University of Leipzig, Leipzig, Germany

^{*}Author for correspondence:

E-mail: heike.moenkemann@uk-koeln.de

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Background

The principles of the GCP guideline (ICH-GCP E6) [1] became binding for clinical trials in EU member states by the council directive 2001/20/EC [2], which had to be implemented into national legislation within 3 years. In Germany this was accomplished with the 12th amendment of the German Drug Law [3] and the German GCP Ordinance in 2004 [4] thereby leveling the requirements for industrial and academic clinical trials. For clinical trials with medical devices comparable standards were determined with the 4th amendment of the German Act on Medical Devices [5], the Ordinance on Clinical Trials with Medical Devices [6] and the Medical Device Safety Plan Ordinance in 2010 [7]. This legal framework includes the obligation to apply the international standard ISO 14155 [8] while conducting clinical trials with medical devices.

The compliance with the standards of GCP (ICH-GCP [1], ISO 14155 [8]) when conducting clinical trials provide public assurance that the rights, safety and well-being of trial subjects are protected, and that the clinical data obtained are credible. Among others these standards request sponsors of clinical trials to implement written standard operating procedures (SOPs; ICH-GCP [5.1.1] [1] and ISO 14155:2011 [8.1] [8]), which are defined as detailed, written instructions to achieve uniformity of the performance of a specific function (ICH-GCP [1.55] [1]). SOPs ensure the quality of products and services as well as the compliance with regulatory requirements and internationally accepted ethical standards in clinical trials. Further advantages are that valuable knowledge can be retained, work effort as well as the susceptibility

to process errors can be reduced, and that they can be used as part of a personnel training program minimizing effects of staff fluctuation [9].

In German investigator-initiated trials (IITs), SOPs were rarely used until 2000. This began to change fundamentally with the foundation of (coordinating) centers for clinical trials (ZKS/KKS) as central structures at university hospitals. Today the ZKS/KKS constitute a network of 18 members (KKS-Network), of which 13 have been initially funded by the Federal Ministry of Education and Research (BMBF). The objective of the KKS-Network was and is to support clinical trials and foster quality which was achieved through establishing quality management (QM) systems by each member thereby implementing national quality standards with international acceptance. The QM working group of the KKS-Network has been developing, finalizing and revising a collection of 64 concerted SOPs since 2003. Additionally, most of the ZKS/KKS established departments focusing on qualifying trial site teams for conducting clinical trials and central quality assurance units of academic sponsors [10].

This work provides a comprehensive overview of the set-up, implementation and resulting structure of the QM systems for IITs implemented by the members of the KKS-Network based in German university hospitals.

Methods

■ History & basic features of the QM working group

The concept of ZKS/KKS was launched with the assignment to improve IITs all over Germany. Today the ZKS/KKS are central service units with a QM system available which complies with the regulatory requirements for conducting national and multinational clinical trials. In general, the ZKS/KKS offer comprehensive advisory support covering all aspects of clinical trial planning and conduct; they are partners of the (principal) investigators and take over central services as project management, monitoring, data management, (pharmaco)vigilance, and biometry the range of which depends on the individual structure; they qualify trial (site) teams for conducting clinical trials; and most of the ZKS/KKS also developed central quality assurance units of academic sponsors. To exchange their experience within the KKS-Network and to avoid redundant activities, the ZKS/KKS launched a QM working group in 2000, consisting of quality managers of each member. This group has been driving the development of concerted SOPs for most aspects of clinical trials with the first documents finalized in 2003. These SOPs cover central topics of project management, monitoring, (pharmaco)vigilance, biometry and quality management, all of which are essential for the conduct of national and multinational clinical trials.

The QM working group updated current SOPs due to changes in regulatory requirements, extended the field of (pharmaco)vigilance SOPs to reflect acquired knowledge, developed SOPs for clinical trials with medical devices due to regulatory changes and SOP templates for trial sites, and translated all SOPs relevant for the conduct of multinational clinical trials into English (see ‘The SOP system in the context of multinational trials’) [11,12] within a project funded by the BMBF from 2008 to 2011.

■ *Modus operandi* of the QM working group

The members of the QM working group meet on a regular basis and agreed on principles of their *modus operandi*, which are documented in a general SOP and a policy.

The SOPs developed by the members are operating procedures applying to all clinical trials conducted by the ZKS/KKS. The general SOP describes the work processes and the quality requirements taken into account when writing or revising concerted SOPs.

For each SOP a responsible author is nominated considering the individual expertise, who can involve experts of the ZKS/KKS as appropriate. The development/revision of procedures include critical reviews within the QM working group. A challenge associated with the development/revision procedure is the variable structures of the ZKS/KKS. These must be taken into account in order to adopt the SOPs by all members in consensus as required by policy. Yet processes remain which cannot be harmonized. These are reflected in paragraphs for local specification visualized by gray-ing them out. The SOPs are finalized and declared valid by the author and then are approved by the QM working group spokesman and the board of the KKS-Network. A triennial revisions cycle is scheduled, unless amended regulatory requirements or other significant reasons demand a preterm revision. At the end of each revisions cycle the SOP author evaluates if the SOP can remain valid for the next revisions cycle or not, thereby clarifying relevance of contents. In addition, new relevant regulations are taken into account. The Head Office of the KKS-Network takes over to update QM working group members on the development of the EU regulatory network. It is noteworthy that the Head Office continuously comments on draft regulations and directives of both the EU and German governments.

Results

■ Structure of concerted SOPs for IITs

All valid SOPs consist of a disclaimer page, a cover page, the SOP itself which is subdivided into six defined chapters, and defined types of appendices for both standard formats have to be used (Figure 1).

The SOP-chapters cover the 'objective' describing the regulated processes within one or two sentences. The 'scope' highlights the regulatory framework (e.g., medicinal products, medical devices), the type of clinical trial for which the SOP is applicable (e.g., multinational with participation of at least one trial site in Germany), and the departments and functions concerned. In the 'background' the regulatory framework is stated in adequate detail. The principle part is dealing with the 'process sequences' presented in a two-columned tabular structure: one column presents a description of the process steps, and the other the function they are bound to. 'References' are listed next and all amendments to the previous version are documented chronologically in a tabular form at the end of the SOP in the 'history of amendments'. Definitions, diverse kinds of forms, checklists, manual templates and hints for investigators are some of the associated appendices of the SOPs.

■ Modular design of the SOP system

The system of concerted SOPs includes a total of 64 main documents and is designed in a modular structure combining related subjects within the same module (Figure 2). The nine modules are standard procedures, clinical trial preparation, adverse events, monitoring, investigational medicinal product, ethical and regulatory topics, quality assurance and biometry (Box 1). The SOP templates for trial sites (PZ) have a special status compared to the other modules (see 'Extension of the SOP system in specialized fields').

Extension of the SOP System in specialized fields Pharmacovigilance

As a result of increased experience and the implementation of pharmacovigilance database solutions in a number of ZKS/KKS, the amendment of the CT-3 [13], and the release of the ICH-E2F in 2011 [14], this SOP module underwent an extensive review and extension from six to ten main documents which are compartmentalized hierarchically (Figure 3). A comprehensive SOP describing general responsibilities and procedures constitute the framework of this module. Subordinate SOPs deal with the implementation of these responsibilities and procedures which have to be taken into account while designing and conducting a clinical trial.

Clinical trials with medical devices

As a result of fundamental changes of German regulatory requirements in 2010 and the release of the amended ISO 14155:2011 [8] new SOPs describing the changed procedures in the fields of ethical and regulatory topics before and after a clinical trial, patient/device safety [15], and preparation of clinical trial reports (Figure 4).

Four types of clinical trials with various regulatory requirements were identified and the procedures specified in five SOPs accordingly (Box 1).

SOP templates for trial sites & site management organizations

The regulatory obligation to implement a QM system with written operating procedures applies to sponsors



Figure 1. Example of a valid concerted standard operating procedure. Shown are the first three pages displaying the disclaimer, cover page and index of the MO03-H Monitoring Visit During a Clinical Trial.

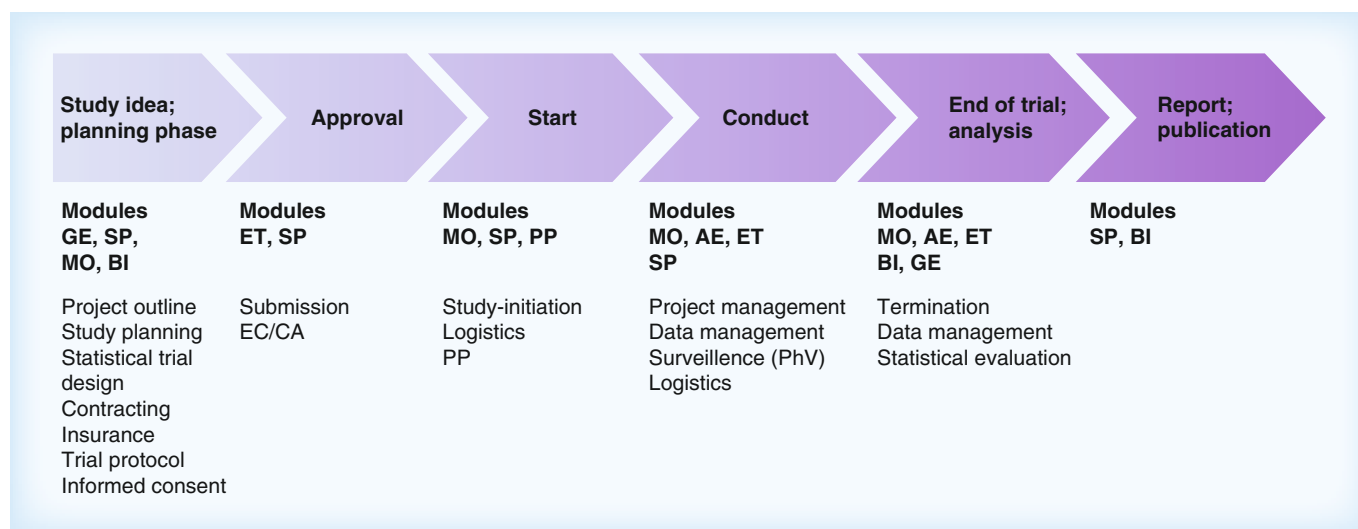


Figure 2. Modular system of the system concerted standard operating procedures.

AE: Adverse events; BI: Biometrics; CA: Competent authority; EC: Ethical committee; ET: Ethical and regulatory topics; GE: Standard procedures; MO: Monitoring; PhV: Pharmacovigilance; PP: Investigational medicinal products; SP: Clinical trial preparation.

and those ZKS/KKS that take over sponsor responsibilities. Meanwhile, SOPs are also expected at trial sites by regulatory authorities and auditors. Due to the varying workflows in different fields of indication at trial sites SOPs can hardly or not at all be harmonized in a comparable way as was described for the other modules. Therefore, the thirteen PZ-SOPs developed

constitute templates that were allotted to four distinct PZ-modules (Box 2). By implementing these SOP templates, the procedures at a trial site are both standardized on a high quality level and meeting all applicable ethical and regulatory requirements. However, based on the heterogeneity of trial site structures, these SOP templates are adapted to local conditions

by trial site teams. In particular, the approach of site specific elaborations draws special attention to small populations or vulnerable study cohorts. For example, these issues are addressed in pediatric trial sites or emergency units treating unconscious patients.

Implementation of concerted SOPs within a federal structure
All members of the KKS-Network committed themselves to implement the concerted SOPs into each QM system. All SOPs developed and finalized by the QM working group were to be implemented unchanged as agreed in a self-commitment statement in their policy. This agreement ensures high and comparable quality standards and to facilitate the cooperation between ZKS/KKS, thus bringing about competitive advantages. To accomplish these purposes the challenges of the harmonization

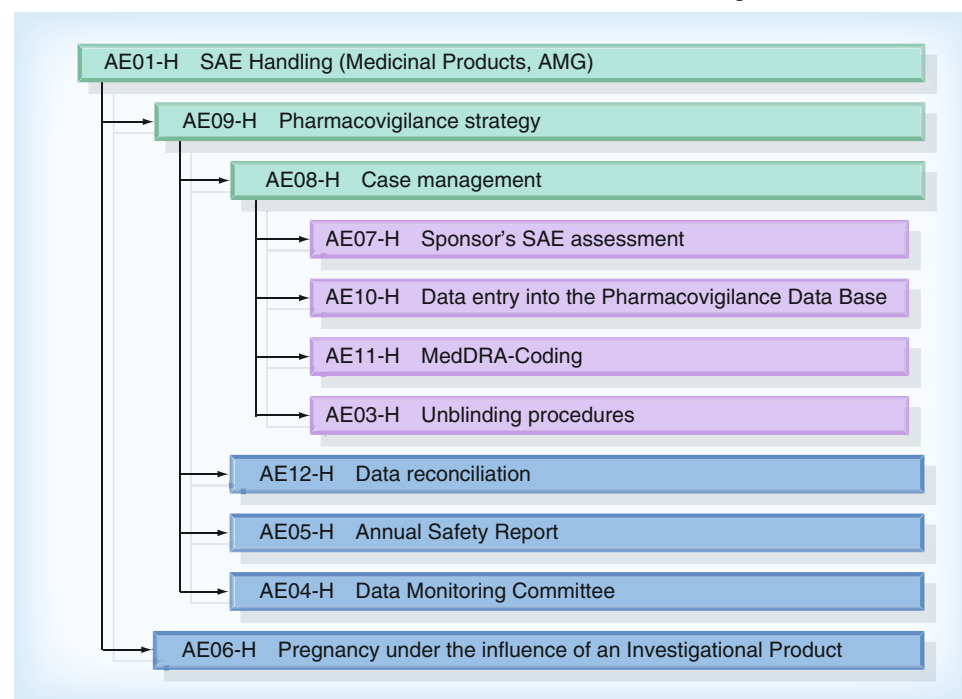


Figure 3. Hierarchical structure of the concerted pharmacovigilance standard operating procedures.

AMG: German Drug Law; SAE: Serious adverse events.

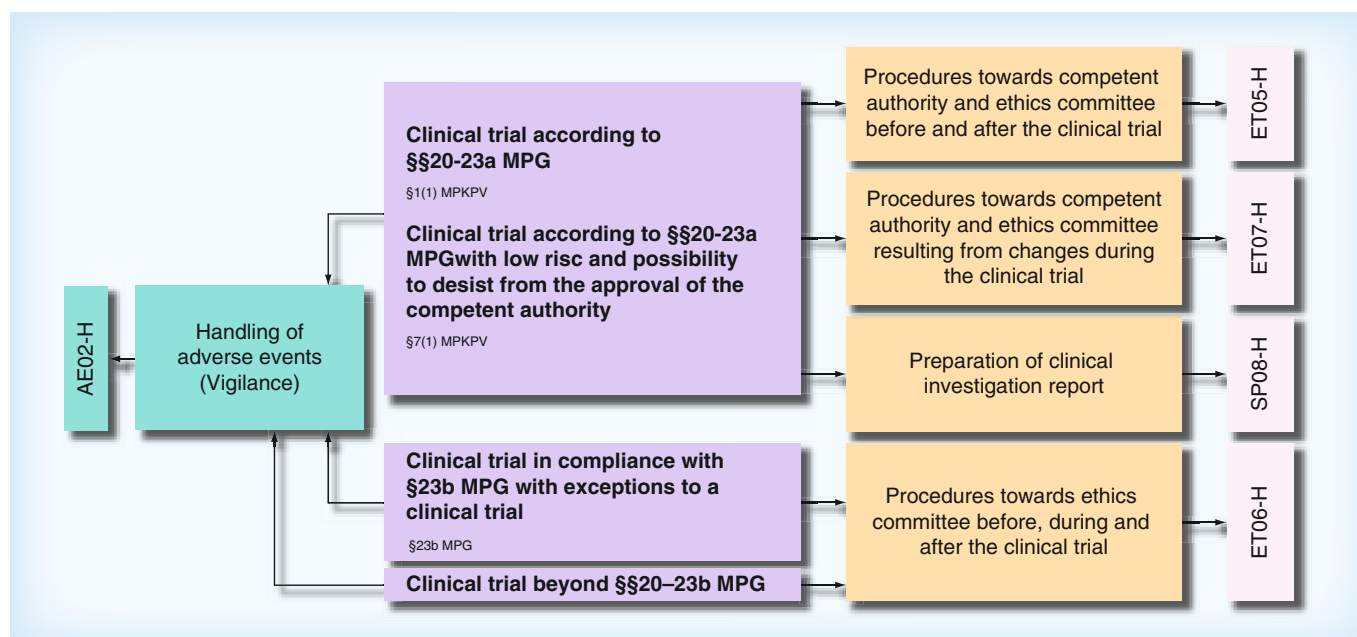


Figure 4. System of concerted standard operating procedures for clinical trials with medical devices.

AE02-H: Serious adverse events handling in clinical trials with medical devices; AMG: German Drug Law; ET05-H: Procedures towards competent authority and ethics committee before and after clinical trials with medical devices; ET06-H: Procedures towards ethics committee in clinical trials beyond AMG and MPG or according to §23b MPG; ET07-H: Subsequent changes in clinical trials according to AMG or MPG; MPG: German Act on Medical Devices; SP08-H: Clinical investigation report in clinical trials with medical devices.

process due to variable structures of the ZKS/KKS had to be tackled by introducing designated paragraphs intended for local specification. In approved concerted SOPs these paragraphs display standard processes which are visualized by greying them out. They can be implemented unchanged or adapted to local (structural) conditions. Each ZKS/KKS had to implement a document control thus ensuring that only valid copies of these SOPs are used as templates for local implementation.

As the described concerted SOPs are accessible on the TMFe.V. website [101] for all interested parties free of charge, they can be implemented by, for example, study groups, competence networks and contract research organizations, and particular processes can be specified.

The SOP system in the context of multinational trials
For the conduct of multinational clinical trials the SOPs of the complete monitoring module and the SOPs regulating processes related to the data monitoring committee, trial master file, investigator site file, and the template for the trial protocol/clinical investigation plan were translated into English. These SOPs provide options to adapt appendices (e.g., the table of contents for the trial master file/investigator site file and checklists) according to national specifications respectively.

Experiences with the SOP system & sustainability
For the dissemination of the described SOP system the TMFe.V. implemented a central document-management system where each SOP is accessible [101]. Download statistics show that on average approximately 50 nonmembers of the KKS-Network (e.g., study groups, competence networks or contract research organizations) have already adopted SOPs of the presented SOP system. This finding is further supported by the number of institutions placing questions and regular requests together with the considerably high number of participants in the corresponding webinars.

For the dissemination of the SOP, project tutorials and webinars, organized by the TMFe.V., were run upon its completion. The tutorials gave an overview of SOP modules whereas the webinars gave a valuable insight into the individual SOPs. Each 2-h webinar addressed another excerpt of the SOP collection: obligations towards ethical committees and regulatory authorities, planning of monitoring activities, (pharmaco)vigilance, biometry, medical device trials, and the templates for trial sites and site management organizations. With a total of 200 webinar participants the expectations of the organizers were exceeded considerably.

Hitherto, each ZKS/KKS has been audited repeatedly with great acceptance of its SOPs by the auditors.

Box 1. Modular structure of the system of harmonized standard operating procedures.

GE

- GE01-H: Preparation, implementation and maintenance of SOPs
- GE02-H: Archiving of trial-related documents
- GE03-H: Contracting

SP

- SP01-H: Trial protocol
- SP03-H: Trial master file
- SP04-H: Investigator site file
- SP05-H: Premature termination of clinical trials
- SP07-H: Final report (medicinal products, AMG)
- SP08-H: Final report (MPG)

Pharmacovigilance

- AE01-H: SAE handling (medicinal products, AMG)
- AE02-H: SAE handling (MPG)
- AE03-H: Unblinding procedures
- AE04-H: Data monitoring committee
- AE05-H: Annual safety report
- AE06-H: Pregnancy under the influence of an investigational product
- AE07-H: Sponsor's SAE-assessment
- AE08-H: Case management
- AE09-H: Pharmacovigilance strategy
- AE10-H: Data entry into a pharmacovigilance database
- AE11-H: MedDRA-Coding
- AE12-H: Data reconciliation

MO

- M001-H: Prestudy visit
- M002-H: Initiation visit
- M003-H: MO visit during a clinical trial
- M004-H: Close out visit
- M005-H: MO planning

ET

- ET01-H: Ethics committee (medicinal products, AMG)
- ET02-H: Informed consent
- ET03-H: Subject insurance
- ET04-H: Competent authority (medicinal products, AMG)
- ET05-H: Competent authorities (MPG)
- ET06-H: Procedures towards ethics committee in clinical trials beyond AMG and MPG or according to §23b MPG

QS

- QS01-H: Auditing
- QS02-H: Preparation, attendance, and follow-up of audits and inspections
- QS03-H: Fraud and misconduct
- QS04-H: On-site audits

Module investigational medicinal products

- PP01-H: Investigational medicinal products

AMG: German drug law; BI: Biometrics; ET: Ethical and regulatory topics; GE: General procedures; MO: Monitoring; MPG: German Act on Medical Devices; QS: Quality control and assurance; SAE: Serious adverse events; SOP: Standard operating procedures; SP: Clinical study preparation.

Likewise numerous inspections in ZKS/KKS and some Competence Networks in Medicine resulted in no objections concerning the locally implemented SOPs.

From the beginning a continuous update of the SOP system was planned and is maintained by the KKS-Network and the TMFe.V., because SOPs are living documents with a vital capacity for adjustment to changing regulations and procedure advancements.

Discussion

Since the ZKS/KKS were founded at university hospitals, German legislation regulating clinical trials has been changed fundamentally as the implementation of quality assurance strategies also became obligatory for IITs with medicinal products [3,11] and medical devices [5]. Therefore the foundation of the QM working group prior to these amendments turned out to be a prospective step.

The QM working group established a system of comprehensive concerted SOPs for central management processes in multicentre clinical trials which are arranged in a modular structure. The designated SOP modules were generated according to the sponsor and investigator responsibilities stated in the international GCP standards (ICH-GCP [1] and ISO 14155:2011 [8]) as well as in national regulations. These SOPs facilitate the cooperation of ZKS/KKS and ensure high quality standards within all members of the KKS-Network. They consider the characteristics of IITs and the variable structures of the individual ZKS/KKS that was accomplished by introducing designated paragraphs for local specifications (see 'Modus operandi of the QM working group'). A comparable SOP system comprised of a smaller number of documents was developed in the UK. In contrast to the SOP system presented in this paper, these SOPs illustrate information concerning obligatory processes in text format [16,102] without a distinct structure presenting a description of process steps and allocated functions. The SOP templates for trial sites (PZ module; Box 2) are offered as the basis of a QM system with consistent standards enhancing and ensuring continuity and constant procedure quality at trial sites. Using SOPs can be regarded as a competitive advantage as their implementation increases confidence of sponsors in the excellence of a trial site [9]. Download statistics already revealed a wide circulation of this source of knowledge.

This unique SOP system developed by the KKS-Network is highly valued by the European Clinical Research Infrastructures Network (ECRIN) [103] which was founded to promote the conduct of multinational clinical trials in Europe and to enhance multinational cooperation in medical research. Before providing their services ECRIN partner institutions have

to comply with minimum standards defined within ECRIN policies, among which is the local implementation of SOPs. By ECRIN the presented SOP system is regarded as a sound basis and valuable source of information to constitute the intended QM standards for multinational/translational IITs.

Nonetheless, this SOP system also has its limitations. Within the KKS-Network the individual facilities vary in structure and use different data management and IT solutions resulting in different processes which cannot be harmonized. Consequently the comprehensive system of concerted SOPs does not comprise SOPs in these fields, although, active exchange of experience and stirring discussions on how to implement regulations for clinical data management take place within respective working groups regularly. For multinational clinical trials efforts are made with the involvement of several ZKS/KKS to establish a verifiable open quality standard for data management (ECRIN Data Centre Standards) which can also be used for certifications [17].

In each EU member state the council directives affecting clinical trials with medicinal products [2] and medical devices [18–21] were implemented into national regulations independently resulting in varying requirements. Although the SOPs are valid for national and multinational clinical trials this fact rendered it impossible to develop SOPs with ready-to-use procedures, checklists, trial protocol or manual templates for multinational clinical trials. During the planning phase of multinational clinical trials the national regulatory framework of each participating country has to be made clear in a first step. As the

Box 1. Modular structure of the system of harmonized standard operating procedures (cont.).

BI

- B101-H: Statistical trial design
- B102-H: Randomization
- B103-H: Statistical analysis plan
- B104-H: Interim analysis
- B105-H: SAS programming
- B106-H: SAS program-validation
- B107-H: Statistical report

AMG: German drug law; BI: Biometrics; ET: Ethical and regulatory topics; GE: General procedures; MO: Monitoring; MPG: German Act on Medical Devices; QS: Quality control and assurance; SAE: Serious adverse events; SOP: Standard operating procedures; SP: Clinical study preparation.

structure of all attached checklists and templates is sufficiently flexible, these requirements can then be incorporated. However, requirements can also result in divided responsibilities between a member of the KKS-Network and a national study office.

Future perspective

The maintenance of the presented SOP system which will be supported by the KKS-Network and the TMFe.V., implies a substantial amount of work that has to be accomplished with limited resources. In order to make the documents easier to assimilate and to update, the QM working group discusses new strategies to streamline them by including flowcharts. Moreover a hierarchical document structure is intended for the next generation of concerted SOPs by transferring ancillary procedures into appendices or working instructions.

Box 2. Standard operating procedures templates for trial sites and site management organizations.

General procedures

- PZ-GE01: Preparation, implementation and maintenance of SOPs in investigational sites
- PZ-GE02: Training of site staff

Contracting

- PZ-VG01: Handling of requests – feasibility
- PZ-VG02: Trial cost calculation including identification of additional, trial-related expenses
- PZ-VG03: Contracting

Clinical trial conduct

- PZ-SD01: Preparation of trial start
- PZ-SD02: Patient enrolment
- PZ-SD03: Trial documentation and query management
- PZ-SD04: Archiving of trial related documents
- PZ-SD05: Patient information process and informed consent
- PZ-SD06: Serious adverse events handling on trial sites
- PZ-SD07: Premature termination of clinical trials

Quality assurance

- PZ-QS01: Preparation of on-site audits and inspections

SOP: Standard operating procedure.

Currently European Regulations harmonizing regulatory requirements within all member states are open for discussion. Thus it would be possible to develop concerted SOPs with ready-to-use appendices, thereby easing the conduct of multinational clinical trials.

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Executive summary

Background

- The (coordinating) centers for clinical trials, supported by the Federal Ministry of Education and Research, established quality management systems and a quality management working group within the KKS-Network.

Results

- Output is an standard operating procedure (SOP) system with a modular structure covering most trial aspects taking into account the characteristics of the academic environment, thereby establishing standardized procedures for German investigator-initiated trials, which are also applicable for multinational investigator-initiated trials.
- The SOP modules were generated according to the sponsor and investigator responsibilities stated in the international GCP standards and the national regulations.
- Translations into English are available for SOPs describing processes for multinational trials.
- The concerted SOPs are accessible on the TMFe.V. website for all interested parties free of charge and download statistics already reveal a wide circulation of the documents.

Future perspective

- The KKS-Network and TMFe.V. will support the future maintenance and the progress of the SOP system presented here.

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- This guideline is valid worldwide – it is considered mandatory reading. It is the international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects.
- 2 Directive 2001/20/EC of the European Parliament And The Council. *OJEC* (2001).
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- 13 Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3', 2011/C 172/01) (2011).
 - This detailed guidance gives a comprehensive overview of requirements for the collection, verification and reporting of adverse events and adverse reactions which occur in a clinical trial falling within the scope of Directive 2001/20/EC.
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