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SCIENTIFIC SUBSTANTIATION OF STANDARD OPERATIONAL PROCEDURES ROLE IN QUALITY ASSURANCE SYSTEM IN CLINICAL DRUG TRIALS

RESUME

The article is invited to develop the scientifically grounded approaches to the generation of standard operational procedures (SOPs) system in clinical sites in order to systematize the processes regulation and assure the effective use of SOPs. Structural scheme of SOPs in clinical trial has been developed, its internal interaction and place in the quality assurance system in clinical trials has been determined, the classification-functional structuring of SOPs in clinical sites has been proposed and the basic groups of processes have been given.

Key words: clinical trial, quality assurance, standard operational procedures, process regulation.

STATEMENT OF THE PROBLEM

Clinical trials (CT) are essential and important stage in drug life cycle. On the base of clinical trial results appropriate authorities make a decision on investigational drug licensing and permit its entry into pharmaceutical market. The major condition to assure proper CT conduct is compliance with Good Clinical Practice requirements and study protocol. It enables to get reliable and validate results and assure patient safety and wellness. Lately, issues of proper clinical trials planning, organization and statistical analysis of obtained data have become very topical. Nowadays range of regulatory documents have been developed that contain requirements regarding ethical and scientific aspects of quality CT conduct, planning and statistical analysis model development, and regulate conduct of the parties involved in CT [1, 3-6]. In the 14th principle GCP guidelines

determines the need to apply the system of procedures to assure CT quality in all aspects. The quality assurance and control system should be fixed in standard operational procedures (SOPs) which should be introduced on the each stage of CT planning and conduct from starting of protocol development till data statistical analysis. This testifies to the important role and critical significance of SOPs in the CT quality assurance system, and make most demanded the problem of its development, successful implementation and introduction to the stuff training program.

In modern practice SOPs become meaningful and essential part of CT sites functioning. CT organization implies the execution of a huge volume of work and initiates performance of a great amount of processes, so the entire scope of SOPs is required. Lack of systematic approach in SOPs development can lead to its inconsistency, contradiction and duplication. It happens in cases when some part of process is described in several SOPs, which fixed different responsible person for its performing, or when some processes are not regulated in SOPs at all [7].

Non-systematic processes regulation initiated by urgent necessity, without a sound reason and informed understanding of its purpose and need, leads to fragmental coverage with SOPs operations and tasks, which don`t have consistent manual. It is clear that in this case SOPs implementation cannot be effective [2, 7]. Thus, creation of consistent system of regulatory documentation becomes an urgent problem and requires scientific substantiation of processes regulation and creation models of its development.

ANALYSIS OF RECENT RESEARCH AND PUBLICATIONS

Analysis of publications relating to the use of SOPs in CT has enabled to determine the relevance of the development and effective implementation of SOPs in trial sites [2]. In some sources the problems of proper development of documented procedures, the importance of using them to ensure compliance with the requirements of GCP and study protocol are considered [2, 5]. However, there is no theoretical and methodological substantiation of approaches to date to

develop SOPs and create single coherent regulatory documentation system at trial sites.

SORTING OUT THE UNSOLVED BEFORE PART OF THE PROBLEM

Despite the availability of publications that discuss the importance of SOPs at trial sites, remains relevant the issues regarding scientific justification of approaches to the creation and implementation of effective CT processes regulation, which is part of their standardization and quality assurance.

FORMATION THE PURPOSE OF ARTICLE

Systematizing of regulatory documentation at trial sites and assuring the efficiency of its implementation during the study require justifying of the approaches to the creation of SOPs and determining their scope distribution.

THE MAIN STUDY MATERIAL

Standard operating procedures are the means that allow the sponsor of the clinical trial to ensure the compliance with GCP in planning, conducting and analyzing CT results. SOPs introduction creates uniform conditions for the implementation of functions, which provides the unification of processes and minimizes the risk of inconsistencies. Creating SOPs complex requires a significant investment of time and labor, but the result of this labor-intensive work is clear and internally consistent documentation system, easy to use, providing each employee with detailed information on how he should performs his functions. Conduct of structural and logical analysis has enabled to determine that the use of complex SOPs in CT provides the following benefits:

- availability of documented CT procedures;
- reduce time and cost to control the functions;
- maximum uniform performing of procedures;
- effective staff training;

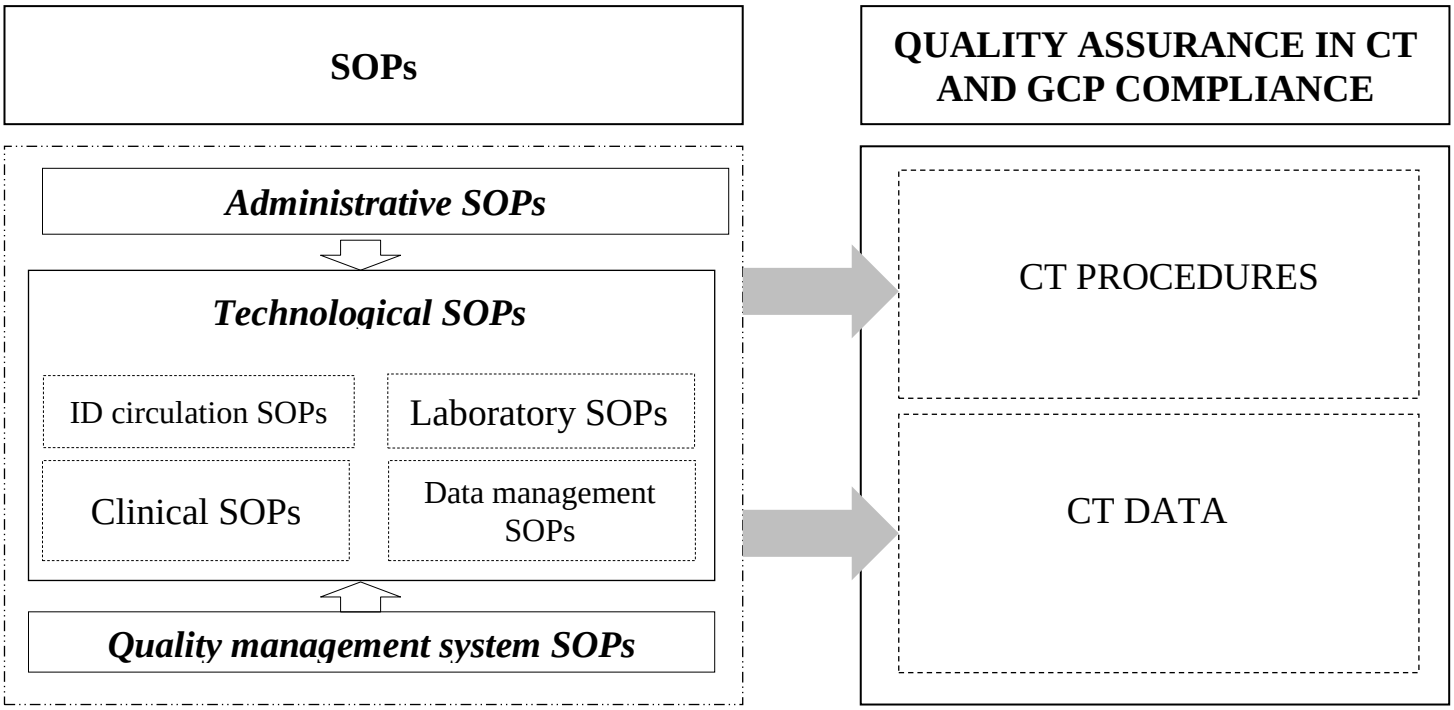
- assistance in monitoring and audits.

CT processes regulation should be standard, which will provide a unified internally coherent system of regulatory documents for trial site. One of the first stages of this standard development is to define the processes that need to be documented and create a structure of regulatory documentation. Selection of CT processes requires their classification according to the functions that are performing in the process execution, or according to the basic logical stages of clinical trials.

To ensure a unified SOP system, we propose a structural diagram of SOPs in CT quality assurance (QA) system, which determines the distribution of SOPs scope in trial site, their internal interactions and place in the QA system (Fig. 1). According to the proposed model three blocks of SOP at trial site have been identified, which should have a clearly defined scope. Administrative SOPs should describe the processes of planning, monitoring, coordination, organization, working with staff and other management processes at trial site. Considering these types of processes, administrative SOPs are more general and primarily describe the main principles of processes. Moreover, they are very much associated with technological SOPs that regulate the performance of basic executive CT processes: laboratory, clinical SOPs, data management SOPs and investigational drug (ID) circulation SOPs. These SOPs are very detailed, accompanied by graphical material and contain clear instructions and directions. Development of technological SOPs should be done in coordination with the SOPs of quality management system, which will greatly facilitate and reduce time spent on preparing of trial site for monitoring and audit and provide their further proper conduct.

On the base of this model, and after analyzing the list of processes performing during CT according functional purpose, classification and functional structure of SOPs at trial site has been proposed (Fig. 2). The following groups of processes have been identified within this structure:

1. Administrative. (Development of SOPs, staff training, CT planning, clinical center assessment on capability of CT conduct, CT organization and trial



site preparing,

organization of the research group work, study protocol development and its validation, computer security management, study closure etc.).

Fig. 1. Structural scheme of SOPs role in clinical trial quality assurance system.

2. Clinical (patient recruitment, obtaining personal written informed consent, case report form (CRF) completion, biospecimen handling etc.).

3. Laboratory (blood test performing, biochemical blood analysis performing, thermometer calibration etc.).

4. Processes that regulate investigational drug (ID) circulation (ID labeling, handling of unused ID samples, receipt and storage of ID, transportation and distribution of ID, providing trial subject with ID etc.).

5. Data management processes (data recording, data entry to a computerized database, data protection against unauthorized access, coding, data storage, database development, data verification, archiving, etc.).

6. The processes of the quality management system (preparation for monitoring, preparation for audits, implementation of quality control procedures, etc.).

7. Statistical analysis processes (statistical analysis plan development, interim statistical analysis, data analysis, compiling of statistical reports, etc.).

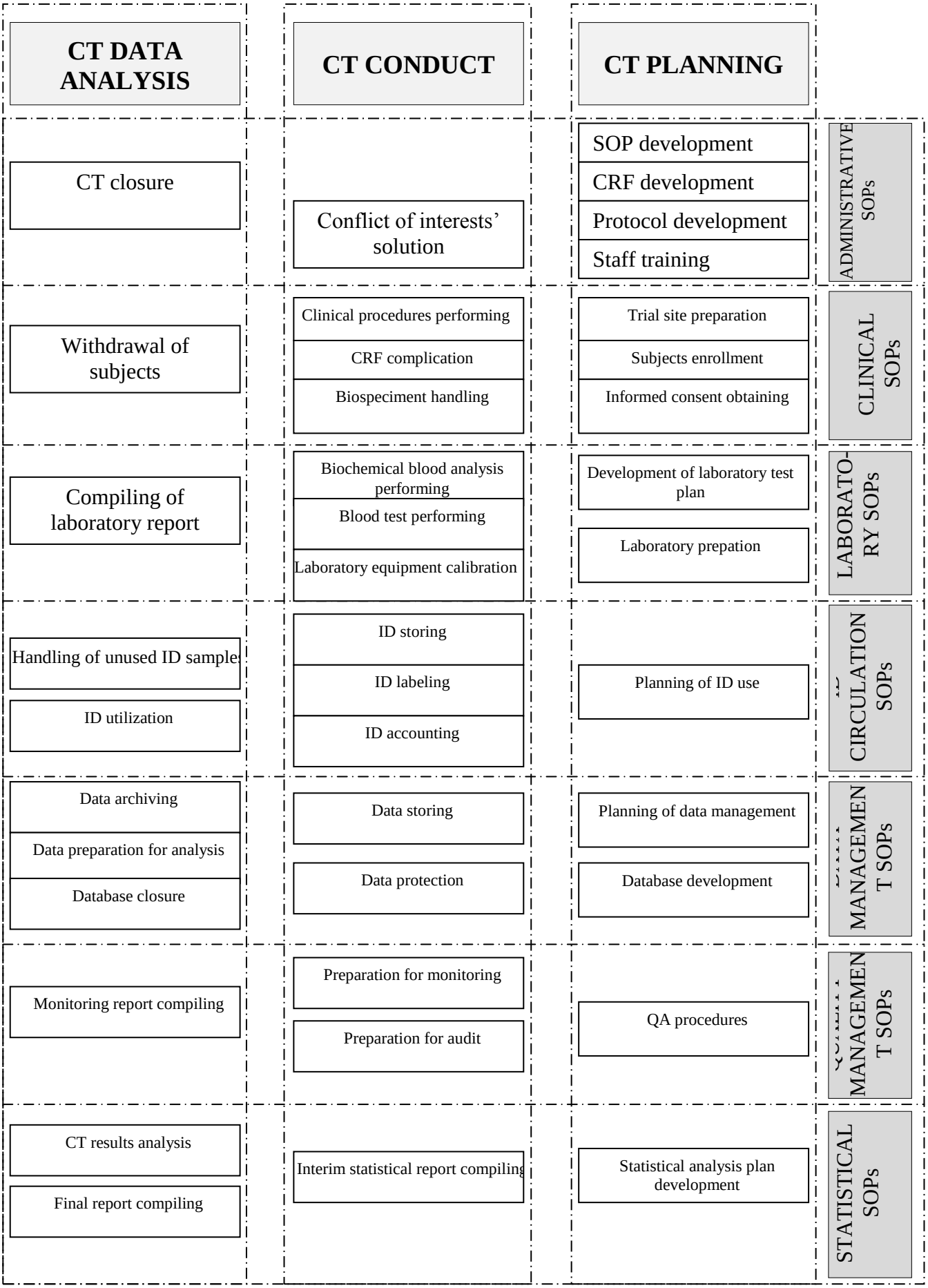


Fig. 2. Classification-functional model of processes regulation in CT.

SOP classification should be used in their coding (code assigning) to provide quick and easy management of regulatory documents. Especially it becomes appropriate in application a computer database with service of SOPs search, upgrade and management of existing versions of SOPs. Using the proposed structure will delineate the scope of SOP and quickly and effectively manage regulatory documents.

Timely and scientifically substantiated development of SOPs ensures proper implementation of CT procedures and obtaining reliable data, which is the principal basis for CT quality assurance and its compliance with GCP.

Implementation of the CT processes regulation model can justify and systematize names of SOPs, determine their place in the CT quality system. Moreover, using this model enables to avoid the unsystematic processes regulation, which leads to the creation of many inactive formal documents, complicating the work of personal. Using scientifically substantiated model of processes regulation allows effective managing SOPs at the trial site and improving the level of processes compliance with SOPs requirements.

Thus, the urgency of proper CT processes regulation testifies to the need of appropriate methods of SOPs development and implementation in the trials sites work.

FINDINGS AND PROSPECTS FOR FURTHER RESEARCH

1. In order to systematize the regulatory documentation and ensure the effectiveness of its use during the study the need of development of scientifically grounded approaches to the creation of SOPs at trial site has been analyzed and identified.

2. To ensure appropriate scientific justification of processes regulation structure of SOPs in CT has been developed, which determines the distribution of SOPs scopes at a trial site, their internal interaction and place in the QA system.

3. During the research classification and functional structure of SOPs at a trial site has been proposed, within which were identified key groups of CT processes.

4. Scientific approaches to SOP systemization at a trial site, substantiation of their role in the quality control system and classification of their structure is the scientific and theoretical basis for the proper CT processes regulation, analysis of existing and development of new SOPs, and creating a system to assess their compliance, which is subject of further research in this direction.

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