ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 9, Issue 3, 2016

Online - 2455-3891
Print - 0974-2441

Research Article

PROCESS MODEL OF THE TRIAL SITE QUALITY MANAGEMENT SYSTEM

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Received: 07 February 2016, Revised and Accepted: 15 February 2016

ABSTRACT

Objective: The necessity of ensuring the implementation of planned objectives concerning quality, costs and timing of clinical trials (CT) in a modern complex and changing environment determines the importance of a systematic approach to CT quality management. The paper aims to substantiate and design on the base of process approach quality management system (QMS) at trial site.

Methods: To build a process model of a trial site QMS we used Integration Definition Function Modeling (IDEF0) methodology.

Results: General approaches to the process model of QMS have been developed, its core processes have been explicated, its input, outputs, and their interrelation according to the application of International Organization for Standardization (ISO) standard ISO 9001:2015 have been implemented. The main process chart which includes five base CT processes has been designed. The consistency of these processes has been substantiated and described with the general framework for QMS implementation at trial site provided.

Conclusion: Our model can be used at trial sites as a framework for designing QMS in the process of ISO standards implementation in order to meet quality standards and achieve high efficiency of work. The advantage of the proposed model is in flexibility and perspective modification according to trial site specificity and needs.

Keywords: Trial site, Quality management system, Process model.

INTRODUCTION

Dynamic changes that have been occurring in clinical trials (CT), cause an intensive development of scientific and applied research regarding quality assurance and control, targeted at integrating and systematizing the already known management approaches, involving new concepts and methodologies. The globalization of CT, increasing the number of participants and trial sites, the complexity of research designs, involving other parties on the basis of outsourcing into CT - these and other factors have influenced the formation of the concept of quality management in CT and reformed the sustainable approach according to modern characteristics of the pharmaceutical market and its needs [1]. The stable trend of growth in the value of new drugs creation and increasing competition among pharmaceutical companies have led to the fact that the rational use of resources and time is no less important than achieving compliance with the quality requirements in the organization and conduct of CT [2-4].

The need for ensuring the implementation of planned objectives concerning quality, costs, and timing of the CT in the complex and changing environment of the XXI century determines the importance of a systematic approach to CT quality management [5]. In addition, designing the Quality management system (QMS) of CT according to the requirements of ISO 9001:2015 is a prerequisite for an integrated CT QMS which combines and allows to consider industry guidelines ICH on a single basis: The requirements of Good Clinical Practice ICH E6 and the methodology of risk management ICH Q9 as well as approaches to quality planning [6].

A significant role in ensuring the proper conduct of clinical study of a drug belongs to trial sites - health institutions where activities directly related to the conduct of CT is performed by agreement with the manufacturer (Sponsor) [7].

At trial sites the compliance of CT conducting with all the corresponding requirements are under the responsibility of the investigator, systematically monitored and evaluated by Sponsor, who has to ensure quality control systems and is responsible for the quality of CT in accordance with the guidelines of Good Clinical Practice. In addition, monitoring encourages the Sponsor to engage the required number of expert monitors and a significant investment of resources. Thus, the total cost of monitoring procedures during CT ranges from 200 000 USD for Phase I to about 1.6 mln. USD for Phases III and IV ranges from 9.33% to 13.60% of the total CT budget [8]. Therefore, to select clinical sites, Sponsors assess medical institution capabilities for properly conducting and performing the CT protocol (technical equipment, recruitment of the required number of subjects that meet the inclusion criteria, personnel qualifications, etc.) as well as their ability to provide the high quality of CT. This should significantly reduce the frequency and scope of trial site monitoring, and, consequently, prevent increase of Sponsor's expenses due to of discrepancies and violations of protocols.

The processes of globalization that have recently gained an increasing scale in the pharmaceutical development and research are contributing to the growing number of medical institutions and researchers who may be involved in a CT as trial site, especially in regions that are considered by Sponsors to be attractive in terms of research because of a number of economic and technical advantages [2,9,10]. All this is leading to an increased competition among trial sites that are interested in participating in a higher number research projects and enhancing their reputation in terms of high quality of CT [10].

This determines the relevance of implementing risk-based approaches during CT, especially in the implementation of monitoring by Sponsor, which is increasingly reflected in scientific papers [11-14]. Thus, the research project ADAMON has designed a sound methodology for risk assessment and on-site monitoring in CT and practical tools for its implementation [15].

However, despite a large number of publications focused on this subject, to date there are no clear requirements for the implementation of quality management and risk-based approach at trial site. Consequently,

it is essential that approaches to designing QMS at trial sites should be developed, which will assure CT conducting effectively and compliance with the protocol, the guideline on Good Clinical Practice and applicable regulatory requirements, ensuring strict implementation of all contractual arrangements with Sponsor and other stakeholders. In the previous studies, we have defined the general scheme of management at study site [6]. Accordingly, the aim of the present work is processing and clarifying the structure of QMS at the trial site.

METHODS

To develop the structure of QMS at the trial site, we have to identify its detailed process model, which allows determining the precise sequence and relationship of processes, materials, and information flows that connect them, resources and controls that are necessary for implementing processes and the most responsible and critical quality CT stages. To build such a process model, we have used the Integration Definition Function Model (IDEF0) [16,17].

RESULTS

One of the principles of quality management is the process approach that allows to achieve the desired results during work optimization as a combination of processes more effectively [18,19]. Process approach is established by ISO 9001:2015 standard as the basis for development, implementation and improvement of QMS effectiveness to enhance customers' satisfaction with meeting their requirements [18]. The importance of process approach implementation in trial site activities predetermines its advantages such as the focus on the result (evidence-based data on the efficacy and safety/tolerability of a drug), providing a clear understanding and performing requirements for CT conducting tasks by staff and trial site administration; a high level of coordination of all CT processes and their continuous improvement; transparency in management and an opportunity of identifying errors and deficiencies [18].

According to ISO 9001:2015, QMS is aimed at achieving results as for the quality objectives in order to meet stakeholders' needs, expectations and requirements of, therefore the initial step in trial site QMS designing should be a clear definition of the term "quality of CT."

Thus, following the definition of CT Transformation Initiative, the quality of CT is an effective solution to scientific challenges concerning the risks and benefits in the use of the studied health technology, protecting research subjects [5,20]. This formulation allows to define a dual focus of trial site quality policy and its main aspects. On one hand, it is obtaining reliable data as a result of CT which allows to make conclusions identical to those based on correct data. On the other hand, it is protecting the rights, safety, and well-being of trial subjects in accordance with ethical and legal norms of conducting CT.

Based on the meaningful definition of CT quality, the following step of designing QMS is to determine the stakeholder's needs, expectations, and requirements which have priority for trial site during conducting research. Thus, according to process model of CT management at trial sites described in our previous study, the result of this process is obtaining evidential data on the efficacy and safety/tolerability of a drug [11]. First, these data meet needs of the Sponsor (or contract research organization - CRO), manufactures of an investigated drug who initiate this research for further registration. The Ethics Committee is also among the Consumers of data obtained in CT at the health institution that makes ethical evaluation and monitoring of CT [7,21]. Regulatory bodies (State Expert Center of Ministry of Health of Ukraine - MoHU) are the stakeholders, stating the requirements for conducting CT, making assessment of compliance with these requirements during the study and carrying out an examination of registration materials, including clinical data of study drugs. Data obtained in CT published in scientific professional journals and included in systematic reviews are used by health workers and scientists, influencing decision-making in science and practice [7]. Finally, in view of the expected implementation of the study drug in medical practice, stakeholders are hospitals, patients, and consumers who are expected to gain access to an effective and safe drug therapy [22].

The analysis of the list of stakeholders in CT enables us to formulate the requirements for trial site activity. According to our previous studies, the input into the process of CT management at trial site is investigational medicinal product, reference drug and documents, and assuring performing research. Making an impact on the formation of output flows, stakeholders put forward the corresponding demands, needs, and expectations to the reference of CT management at trial sites: The requirements of good clinical practice, regulatory documents and protocol, ethical requirements for CT, expectations and agreement on the terms of research performance, financial arrangements, and requirements of the contract concluded by sponsor and trial sites.

Based on the above mentioned and the result of ISO 9001: 2015 analysis, we have designed a model of CT quality management at trial sites, which is process-based (Fig. 1).

In this connection, we have proposed to identify four base blocks in the CT quality management model at trial sites: "Processes of vital cycle," "Measurement, analysis and assurance of QMS," "Fulfillment of the responsibility of senior authorities management for quality control," "Management of resources and documentation." The "processes of vital cycle" block represents the main processes of QMS at trial sites that are directly related to planning, organizing, and closing CT.

The first stage was the development in accordance with the principles of the IDEF 0 methodology process charts "To provide services in research and experimental development in medical science," which generally characterizes the activities of trial sites and includes the main blocks of QMS processes discussed above (A0) (Fig. 2). In this chart, the block "management of resources and documentation" is divided into two separate processes "management of resources" (A2) and "management of documentation" (A5) because they have different input and output flows and can have different "owners" - persons who are responsible for the proper process implementation.

Besides, the key elements of process management are included into the process chart, which is represented in the regulatory documents and guidelines ST-HN MoHU 42-7.0:2008 "Good clinical practice" and ST-HN MoHU 42-7.1:2014 "Investigation of bioequivalence," and elements of process execution, including resources, infrastructure, and trial site personnel. The processes identified in the A0 flow chart are complex, since each of them includes a lot of components, making it mandatory to describe them.

To realize the responsibility of senior management for quality management, administration of CT sites has to perform a continuous analysis of QMS, based on information about the effectiveness and efficiency of its operation, received at different stages of CT management.

At the same time, informing of the staff about the QMS work proves to be internally, ensuring the involvement of all staff into the quality management of CT and understanding the importance of assuring the performance of their duties, their achieving compliance with CT goals. It is obligatory that the trial site administration should also perform the process of risk control, aimed at evaluating, monitoring, informing, and reviewing CT quality risks.

Resources management at trial sites includes the following processes: Managing staff, managing infrastructure, and operating of measuring devices. The process "processes of vital cycle" (A3) is complex, and it includes several sub processes. After Sponsor or CRO sends requests for study, the principal investigator analyzes this application and makes the corresponding decision about participation in CT. On the basis of analyzing the study protocol results, the analysis of contract,

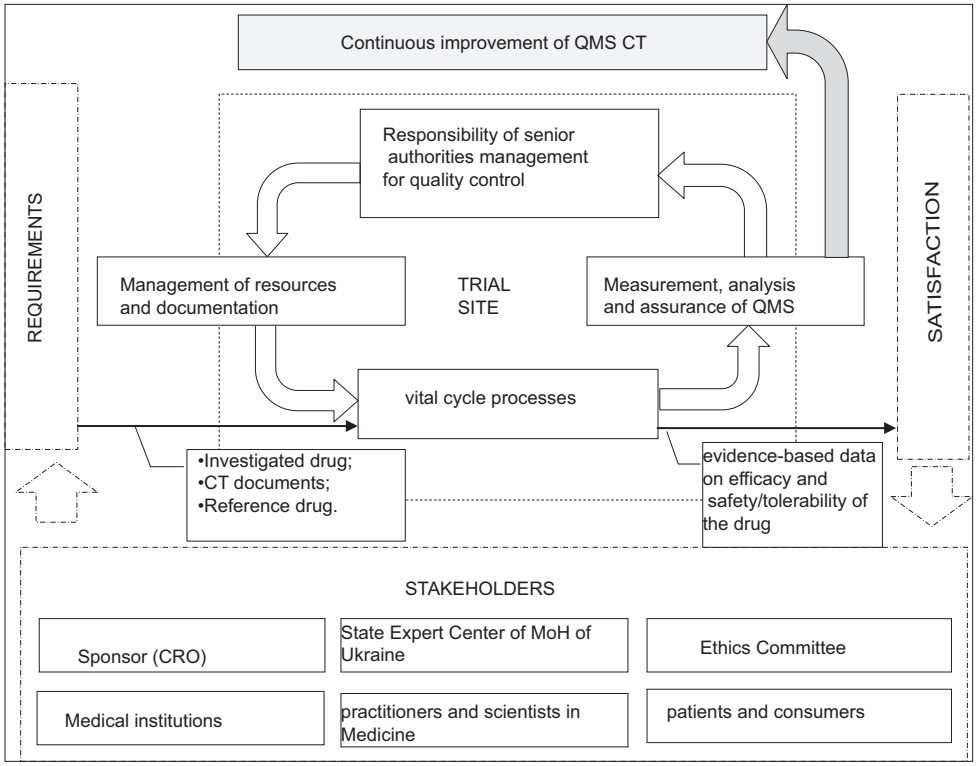

Fig. 1: Implementation of ISO 9001:2015 standard into trial site activity

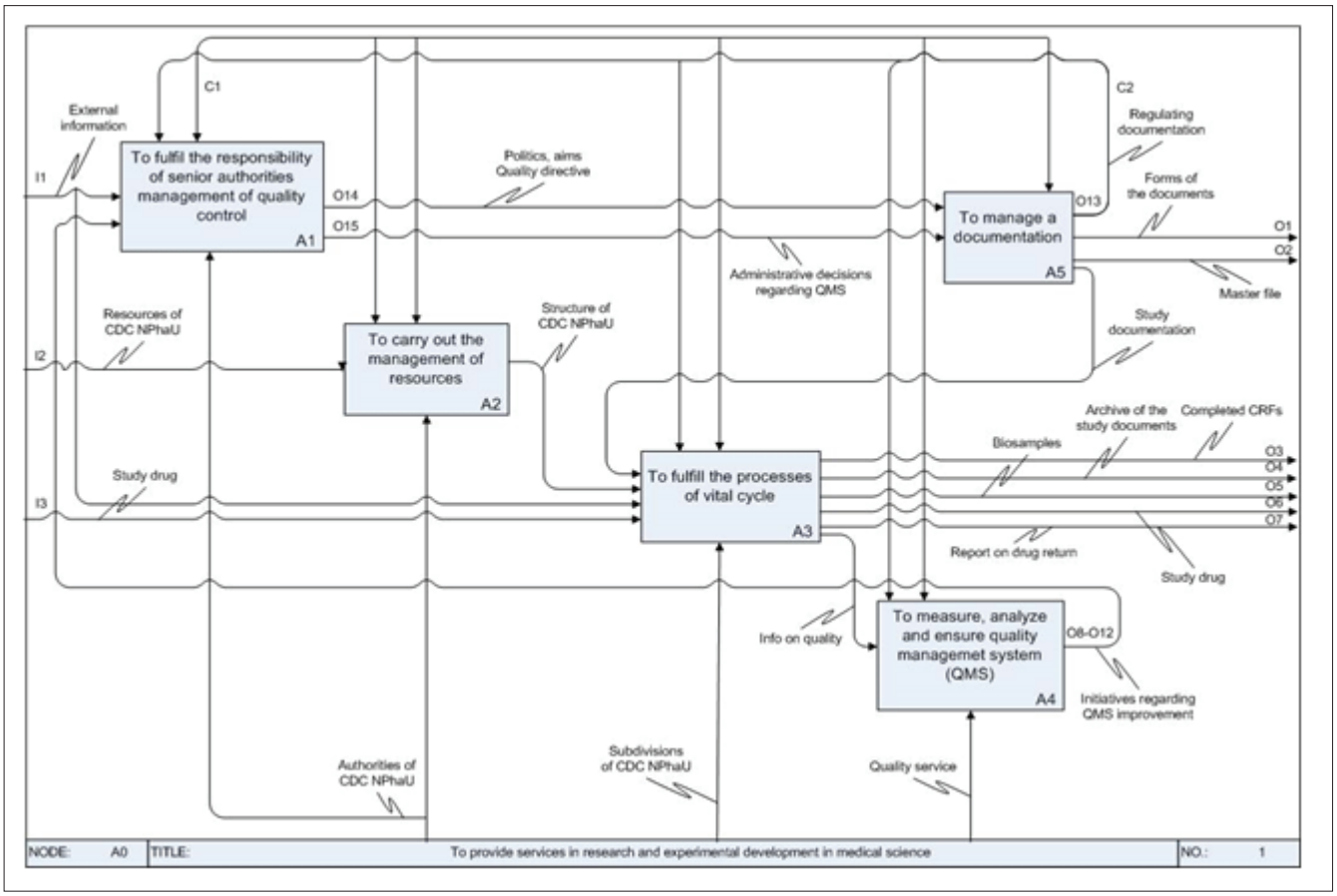

Fig. 2: Process A0 chart "to provide services in research and experimental development in medical science"

protocol signing, and formulation of a specification are performed. On having analyzed the study protocol, the need for consumables, supplies materials, and equipment is outlined with their further substantiated purchasing.

Before CT starts, an on-entry checkup of reference and investigational drugs supplied by the Customer is necessarily carried out, with the proper storage provided. The preliminary activities are followed with involving research subjects, clinical procedures according to CT protocol, resulting in received data on investigated and reference drugs. Data are recorded in source medical documentation, to be subsequently properly verified, registered in the CRFs, and delivered to the customer.

Given the fact that one of the principles of quality management states the need for continuous improvement as one of the goals of the organization, an essential part of the trial site QMS is the process of measurement, analysis, and improvement (A4). This process involves planning and carrying out internal audits at trial sites, managing the appropriate services, corrective and preventive actions, and implementing validation procedures.

DISCUSSION

Taking into account intensified competition at clinical trial market, increasing quality and regulatory requirements, implementation of ISO 9001:2015 standard becomes a task of high priority for trials site management. General principles for QMS designing in clinical trials have been discussed in the numerous papers which provide general approaches of quality management focusing on Sponsor activities [1,5, 9,10,19]. But the role of clinical trial site management still is unclear despite its critical significance in clinical trial quality assurance. The clarified structure of QMS at the trial site presented in current research provides novel approach for trial site management. The process model of QMS at the trial site designed by IDEF0 methodology is compliant with fundamentals of ISO 9001:2015 standard and provides the framework for its implementation. Clear determination of stakeholders' needs and requirements gives deep understanding of principles and requirements for process management at trial sites. According to this, appropriate methods for processes control and metrics for quality assessment can be developed and that is the essential element of "CHECK" stage of the Deming-Shewhart cycle. Accurate inputs and outputs of each process, determined in QMS structure, provide precise trial conducting at trial site, personnel coordination and control. On the base of this structure the appropriate system of documents should be created (standard operating procedures, duty regulations) which is the second stage of QMS designing. Moreover, proposed QMS structure gives better understanding of resources and infrastructure management at trial site. This helps to decrease costs and avoid timeline incompliance during clinical trial conducting, preclude fails in Sponsor or CRO requirement fulfillment. This aspect becomes of critical importance in modern conditions of clinical trials market and current practices when about 50% sites fail to reach the planned recruitment targets and more than 95% milestones are missed in clinical trials [22].

CONCLUSIONS

The process model described in this paper has been tested and assessed at the Clinical and Diagnostics Center of National University of Pharmacy, which is the trial site of Phases I-II and bioequivalence studies as part of quality management implementation. The elements of this model can be modified and implemented at another trial site, considering specific features, peculiarities regarding CT and trial site specificity, the process of subject recruitment, and other characteristics. The advantage of the process model based on ISO 9001:2015 is in flexibility and perspective modification according to trial site specificity and needs. The approaches outlined in the paper provide a general framework for designing QMS at trial sites, which can be used in the process of ISO standards implementation. The following stage in this research is further decomposition of the proposed process model in order to identify critical CT processes and to start the development of regulatory documentation as process guidelines and standard operating procedures.

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