УДК 615.038
DOI: 10.15587/2519-4852.2018.145593

EVALUATION OF OPPORTUNITIES FOR THE USE OF MODERN METHODS FOR CORRECTION AND PREVENTION OF RISKS IN THE QUALITY CONTROL OF CLINICAL TRIALS

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Для організації та проведення клінічного випробування (КВ) на високому рівні необхідно постійно контролювати його якість, оскільки виникнення невідповідностей може загрожувати здоров'ю та безпеці досліджуваних, а також призводити до втрати даних КВ або їх ненадійності. В цілому, для ефективного контролю якості проведення КВ доцільним є постійне поліпшення системи управління якістю усіх сторонучасників КВ, у тому числі на місці проведення випробування. Сучасні нормативні вимоги включають в себе вказівку на необхідність постійного проведення процесу поліпшення системи менеджменту якості для забезпечення належного рівня виконання процесу, зокрема, системи корекції і попередження виникнення невідповідностей.

Метою *даної роботи стало оцінити можливості і проблеми застосування сучасних методик усунення та попередження ризиків при управлінні якістю КВ.*

Матеріали та методи. *Для досягнення поставленої мети був проведений мета-аналіз джерел літератури з використанням технології пошуку PICO та аналіз існуючих нормативно-регуляторних документів щодо наявності в них методик, інструкцій та алгоритмів вибору і застосування інструментів для усунення та запобігання виникненню невідповідностей під час організації та проведення КВ.*

Результати дослідження. *Проведенедослідження показало, що регуляторні органи бачать необхідність у впровадженні стандартизованих систем менеджменту якості КВ для підвищення кількості кваліфікованих МПВ, а також більш суворій відповідності принципам ICH GCP. Аналіз нормативної документації показав відсутність єдиних гармонізованих вимог до проведення процесів усунення та попередження виникнення невідповідностей в рамках організації та проведення КВ.*

Висновки. *Організація і проведення КВ ЛЗ вимагає постійного контролю якості процесів, що проводяться, для забезпечення отримання цілісних і достовірних даних щодо досліджуваного препарату.Враховуючи відсутність нормативних вимог, що регламентують проведення процесу усунення та попередження виникнення невідповідностей, видається доцільною розробка алгоритму роботи з CAPA-планом і методики його складання, а також СОП для стандартизації проведення даного процесу*

Ключові слова: *управління якістю клінічних досліджень,CAPA-план, коригуючи дії, попереджувальні дії, управління ризиками*

1. Introduction

The ultimate goal of any clinical trial (CT) of a new drug is to obtain high-quality, integral and reliable data on the efficacy, safety and benefits of the developed drug. In order to organize and conduct CT on a high level, it is necessary to continuously monitor its quality, as the occurrence of non-conformances can threaten the health and safety of the trial subjects, as well as lead to loss of data or their uncertainty [1, 2].

2. Formulation of the problem in a general way, the relevance of the theme and its connection with important scientific and practical issues

The non-conformances that may arise could be detected at different stages of CT: as a result of internal monitoring, monitoring by sponsor, inspections, audits, during the assessment of the trial subjects by study staff at the clinical site (CS), during data processing, analysis and synthesis, during CT quality control, as well as during regulatory inspections, audits. At each of the stages of the CT discovering of non-conformances will be carried out by different participants of the CT [3, 4]. In the work of Munish Mehra et al. it has been shown that a later discovery of non-conformances and, consequently, their later correction leads to an increase in the cost of conducting the trial in general [5].

In order to minimize the impact of the non-conformances on trial subjects safety and the integrity of the data and to prevent such non-conformances in the future, companies involved in the organization and conducting of CT must have a program for managing the conducted trial quality, as well as performing corrective and preventive actions [6].

Today, the planning, organizing and conducting of CT using the Quality-by-Design concept for trial quality management are popular. With its use, it is possible to prevent non-conformances occurrence by improving the design of the research protocol, detailed planning of CT and quality control. In addition, this concept emphasizes that the norm should be to prevent the occurrence of non-conformances, and not to eliminate them when detected, as well as root case analysis. Another indisputable advantage is the possibility of using this concept at all stages of the life

cycle of quality control. It is recommended to use a risk-informed approach for identifying and managing critical issues for quality [7].

In general, for the effective CT quality control, it is expedient to continuously improve the quality management system (QMS) of all parties who participate in the CT, including the clinical site.

3. Analysis of recent studies and publications in which a solution of the problem are described and to which the author refers

CT QMS according to Meeker-O'Connell et al. includes a combination of senior management development and quality assurance, compliance with standards, understanding of consumer needs, compliance with policies and procedures, adequate training, implementation of quality control, use of risk-based monitoring and audits, the existence of a strict corrective and preventive action policy, as well as ensuring a continuous improvement process [8].

Current regulatory requirements include an indication of the need for a continuous process of the QMS improvement to ensure the proper level of the process execution, in particular, the system of corrective and preventive actions for non-conformances. However, methods that can be used for this purpose during organizing and conducting the CT are not clearly identified in the regulatory documents, which means the necessity of an efficient and convenient method of application development by each party involved in the CT process independently.

One of the methodical tools used in modern QMS, including in CT, is the CAPA-planning method. Despite the recent popularity of the risk management and risk-based monitoring methodology use as one of the tools to increase the effectiveness of CT planning, organizing and conducting, the use of such an instrument as CAPA-planning, not only does not contradict this concept, but can become one of the methods of solving the implementation of a risk-oriented tool in the CT processes.

4. The field of research considering the general problem, which is described in the article

Taking into account all the above, it is expedient to conduct the analysis of scientific publications and existing regulatory documents for the identification of general requirements, which should be met by the methods of carrying out work on the non-conformances correction and prevention during CT organizing and conducting. It is necessary to develop a convenient and effective method to conduct work in this area within the planning, organizing and conducting of CT processes. Also, within the framework of quality management it is expedient to create a complex of activities for the continuous detection and further management of identified risks, and the creation of an algorithm for working with this process is necessary.

5. Formulation of goals of article

The purpose of this work is to evaluate the problems and possibilities of applying modern methods of risk correction and prevention in CT quality management.

6. Presentation of the main research material (methods and objects) with the justification of the results

Materials and methods. In order to establish the current state of non-conformances correction and prevention process in CT QMS, a meta-analysis of literature sources using PICO search technology was conducted for this purpose, the SagePub database was used. The key words included: clinical trial/ trials, quality management, quality assurance, corrective action, preventive action, corrective action preventive action, risk prevention, quality management system and their combinations. Selection criteria were: the publication period – 2012–2017, the language of publications - English, the type of publications - scientific articles.

At the next stage, the analysis of existing regulatory documents was carried out on the availability of methods, instructions and algorithms for the selection and application of non-conformances correction and prevention tools during organizing and conducting CT of new drugs. Methods of meta-analysis, abstraction, synthesis and generalization were used in this work.

Results and discussion

A total of 336 articles were found during the search on the given keywords (Fig. 1). Scientific publications included articles on clinical trials, some aspects of medical education, patients' with various diseases quality of life, cases in medical practice description, dental technologies, etc.

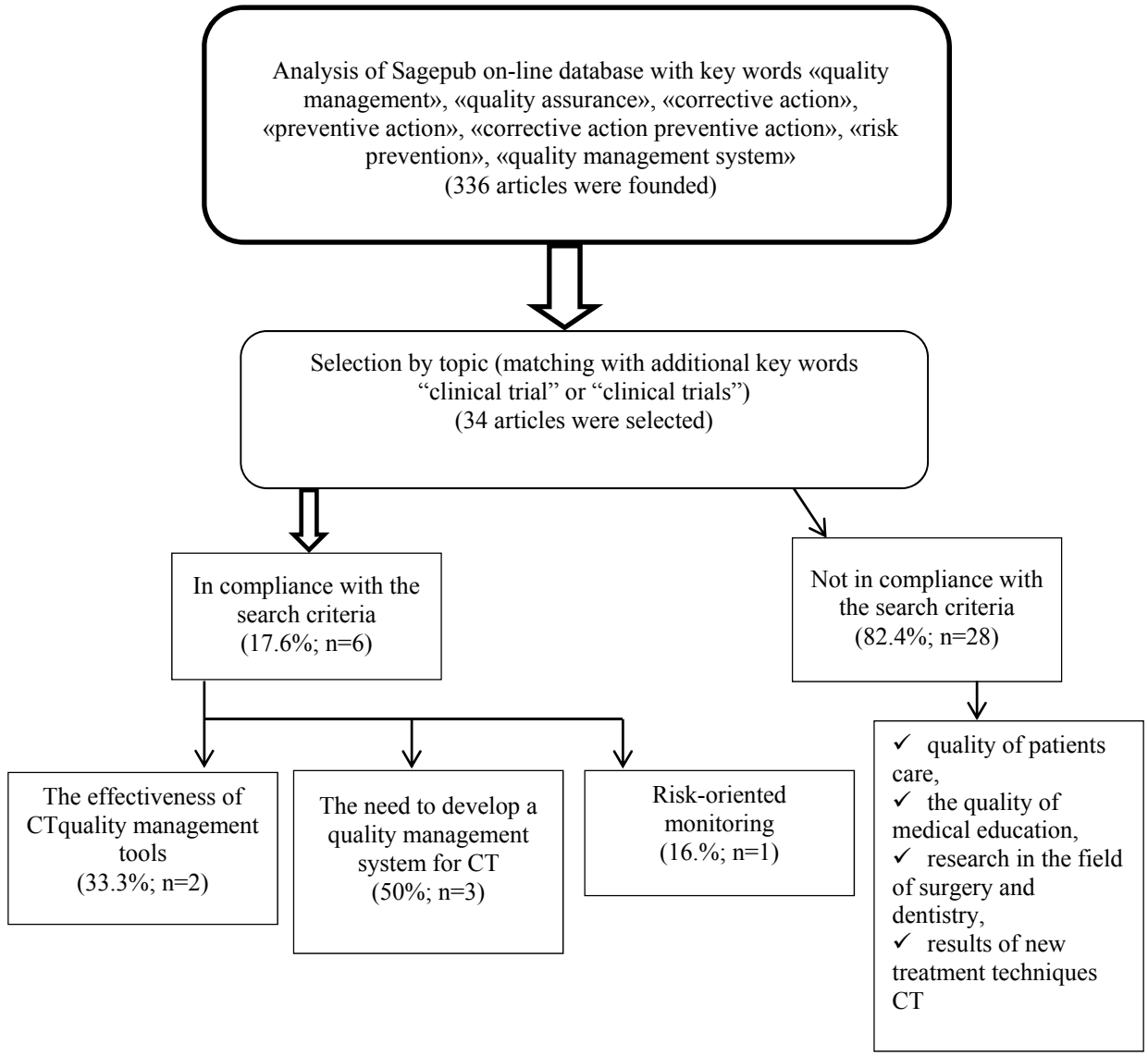

Fig. 1.Scheme of conducted scientific publications meta-analysis

At the next stage, selected scientific publications were filtered according to their relation to CT planning, organizing and conducting field - 34 articles (10.1 %). Among them, there were articles devoted to the patients' care quality, problems of the medical education quality, researches in the field of surgery and dentistry, as well as the results of new treatment methods CT, etc.

Further, 6 articles (17.6 %) were selected for future analysis as a result of their screening on compliance with the CT organizing and conducting topic through the abstracts reading (Fig. 1). The key indicators for assessing the article for compliance with the specified search criteria were the content of current guidelines for quality management of new drugs CT. Of the 6 articles that met the search criteria, 33.3 % were devoted to the effectiveness of CT quality management tools, 50 % -the need to develop a CT QMS, and 16.7 % -risk-oriented monitoring in CT (Fig. 1).

The analysis of the selected publications showed (Table 1) that the key issues highlighted in them were the study of factors that determine the need for implementation of QMS in CT, the establishment of an effective system of quality management that operates at all stages of organizing and conducting of CT, management of non-conformances within the framework of the CT quality management concept, application of the Quality-by-Desing concept for quality management during organizing and conducting of CT, as well as the benefits of using risk-based monitoring [4–9].

Table 1

Analysis of the main recommendations for CT quality management

Authors, year	Title	Key issues regarding CT quality management
Mehra M., Kurpanek K., Petrizzo M., Brenner S., McCracken Y., Katz T., Gurian M. 2014	The life cycle and management of protocol deviations	Discussion of the importance and necessity of correction and prevention of trial protocol deviations, as well as effective ways to do this
Meeker-O'Connell A., Borda M. M., Sam L. M. 2015	Enhancing quality and efficiency in clinical development through a clinical QMS conceptual framework: concept paper vision and outline	The importance of the QMS in the processes of CT organizing and conducting, as well as the main elements that should be included in its structure
Callery-D'Amico S., Sam L. M., Grey T. H., Greenwood D. J.2016	Trans Celerate's clinical Quality management system: issue management	A brief overview of non-conformances management within the framework of the developed CT QMS concept
Meeker-O'Connell A., Glossner C., Behm M., Mulinde J., Roach N., Sweeny F., Tenaerts P., Landray M. 2016	Enhancing clinical evidence by proactively building quality into clinical trials	Possibilities of Quality-by-Design concept use for quality management during organizing and conducting of new drugs CT
Meeker-O'Connell A., Sam L. M., Bergammo N., Little J. A. 2016	Trans Celerate's clinical Quality management system: from vision to a conceptual framework	Rationale for the need of a QMS in CT concept development, a description of the development stages and key elements of the concept
Brosteanu O.,Schwarz G., Houben P., Paulus U., Strenge-Hesse A., Zettelmeyer U., Schneider A., Hasenclever D. 2017	Risk-adapted monitoring is not inferior to extensive on-site monitoring: results of the ADAMON cluster-randomized study	Advantages of risk-oriented monitoring using on CS

In 2016 Trans Celerate company conducted a survey of FDA, EMA, as well as regulatory agencies from Canada, Germany, Brazil, China, Mexico, South Korea and Japan, the results of which showed their high interest in the development of CT quality management field [8]. Regulatory authorities of every country during the survey formulated a number of the most important reasons, according to their opinion, for the need of standardized CTQMS implementation [8]. Some of the given opinions were connected to the same points of CT QMS standardization, so such opinions we grouped together for further analysis. On the next stage, based on the results of this survey we analyzed the percentage of the given by regulatory authorities points. The views of the regulatory authorities in the article on the importance of CT quality management standards development were grouped into 7 categories: benefit for CS, advantages for patients, the lack of a single standard for CT quality management, increasing the number of qualified CS, the importance of CT QMS harmonization, the possibility to reduce review time for regulatory authorities and implementation will facilitate more strict compliance with ICH GCP requirements.

Fig. 2 shows the calculated by us percentage between the categories of the reasons for the need of a systematic approach to the CT QMS implementation, which were stated by the regulatory authorities.

The results showed that the majority of surveyed regulatory authorities (55.56 %) see the advantages for patients in implementation of such kind of system. The second place took the reason "benefit for CS" –marked by 44.44 % of respondents. One third (33.33 %) of regulatory authorities noted the presence of common harmonized specific quality standards for pharmaceutical manufacturing (ICH Q9-10) and the absence of ones for the CT field, also 22.22 % of respondents paid attention to the importance of CT QMS harmonization. According to the surveyed regulatory authorities' opinion the implementation of such kind of standard will facilitate more strict compliance with ICH GCP requirements (22.22 %) and will allow to increase the number of qualified CS (11.11 %). Such results show the high interest of different countries regulatory authorities in CT QMS harmonizing.

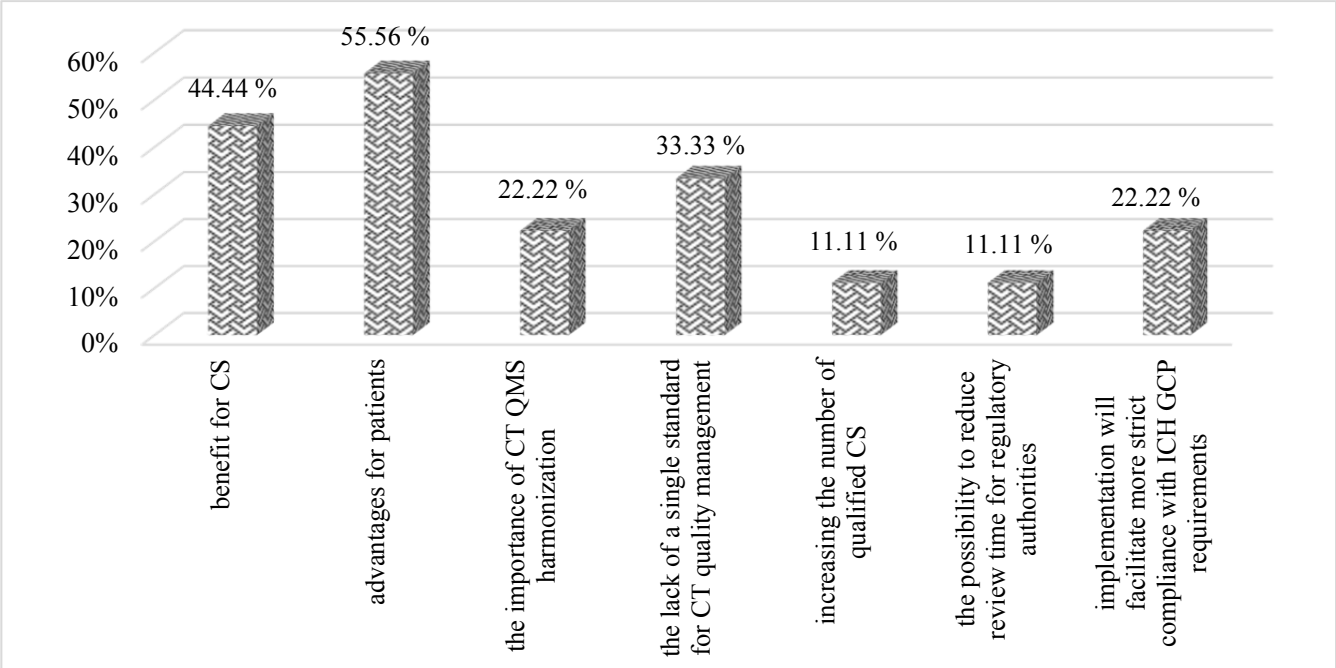

Fig. 2. Reasons for the need of the CTQMS implementation according to the regulatory authorities' opinion

Another key aspect that was addressed in the analyzed publications was CT quality management, taking into account the Quality-by-Design concept, which is based on risk-oriented approaches to quality [7–9].The key to these approaches is the early detection of possible risks for the CT quality, their correction and prevention of appearance in the future. This task could be solved through the conducting of monitorings, inspections, audits, which benefits both the CS and the regulatory authorities. In industry to correct and prevent repeated appearance of risks the CAPA (corrective action and preventive action) tool is used for a long time. The point of its use is in correction of risks, which were founded on any stage of product manufacturing (corrective action) and implementation of changes in manufacturing process, which prevent the repeated appearance of founded risk (preventive action), and in that way its improves the manufacturing quality in general. The level of technologies growth in manufacturing field doesn't leave doubt in the effectiveness of this tool use.

In general, the use of CAPA-planning method for CT quality management has the following advantages:

1. allows to identify the problem and the ways to solve it;
2. helps to verify if the solution is really effective;
3. minimize any risks or potential problems that may arise in the future.

As the best way organizations on the basis of prospective analysis of ten create centralized cross functional process to correct and prevent the future appearance of non-conformances. Such kind of processes could include [3]:

– requirements for documentation, which comply with the level of influence
– corrective and preventive actions (CAPA)
– communication plan
– requirements for analytics(including the stakeholders identification) and etc.

Creation of such kind of process by each party involved in CT organizing and conducting, what leads to:

a) labor costs by skilled personnel who is responsible for carrying out such actions;

b) increase the number of documents that needed to be developed;

c) material costs for carrying out the analysis and development of a complex of events aimed at non-conformances correction and prevention and etc.

Also, the developed complex of events has to include root case analysis, as well as corrective actions, which correspond to the founded non-conformances[3].

The conducted analysis of regulatory documents, which regulate QMS in pharmacy (ICH Q8 [10], ICH Q9 [11], ICH Q10 [12], ICH GCP [13], Guideline «Bioequivalence studies» [14] and also standard ISO 9001:2015 [15]), on recommendations on CAPA method use during CT organizing and conducting availability showed that they don't contain methodological description and requirements to this process performing (table 2).

Thus, in paragraph 10 of standard ISO 9001:2015 «Improvement» the cases have been discussed in which organizations need to take steps to correctnon-conformances, as well as their possible examples, among which [15]:

a) take steps to manage non-conformances and their consequences;

b) assessment of the need for action to correct the cause of non-conformance;

c) analysis of the effectiveness of corrective actions which were made;

d) saving of documented information on the nature of the non-conformance and the actions which were made.

Table 2

Regulation of the CAPA-planning method use for the correction and prevention of non-conformances

Regulatory document	The situation with regard to the work with the CAPA-plan process
ICHQ8	Not specified
ICHQ9	Not specified
ICHQ10	The necessity of the CAPA system for correction of non-conformances found in manufacturing has been discussed
ICHGCP	Not specified
Guideline «Bioequivalence studies»	Not specified
ISO 9001:2015	«The organization must identify and choose the opportunities for improvement and take any necessary actions to meet the requirements of consumers.»

The essence of this paragraph of the standard is to correct the identified non-conformances and prevent their re-occurrence, which may be made by using the CAPA method, although the standard itself does not determine the form of the necessary improvements at pharmaceutical manufacturing. This means that the document leaves the right to choose a method to achieve the desired result by the organization.

Paragraph 3.2.2 of ICH Q10 (Pharmaceutical quality system) [12] contains information on the need for a CAPA system in the pharmaceutical industry at all stages of the product's life cycle (Table 2). The standard specifies the possible goals of the CAPA method use at each stage of the drug's life cycle, but does not provide guidance on its use, except that the use of this methodology should improve the quality of the product or the process.

The absence of any guidance on the use of the CAPA-planning method for CT quality management in regulatory documents leaves the development of a methodology, as well as the necessary documents, for the application of this method to the party being checked, which may be a CS, trial sponsor, CRO, etc. This means that each organization that being checked is forced to develop its own techniques, SOPs, procedures, etc. for correction and prevention of risks, that requires time and effort from the qualified staff, and sometimes money, but not each of the developed methods of work organizing and documenting of this process is effective and easy to apply. The absence of regulations on forms of work with CAPA-planning method creates the uncertainty in the process of developing such kind of systems, as each organization that is checked has the right to develop its own methodology. Unification of guidelines on the application of this method for CT quality management will reduce costs for the CT organization and conducting, the time work on the correction and prevention of non-conformances by the qualified personnel and will allow the party which being checked to organize their work during the inspection, audits or monitoring more effectively. Another important advantage of unifying the work with CAPA-plans is the elimination of the need for ongoing trainings with personnel on the new forms, SOPs, etc. use. However, it can also lead to problems of interaction between the parties involved in the process of work with the CAPA-plan, in the process of its preparation, registration and implementation, since each party may have its own point of view on the way in which this process should take place.

7. Conclusions from the conducted research and prospects for further development of this field

1. The organizing and conducting of CT requires continuous monitoring of the quality of the processes carried out to ensure receiving of complete and reliable data on the study drug.

2. The regulatory authorities see the need to implement standardized CT quality management systems to increase the number of qualified CS, as well as more strict compliance with the ICH GCP principles.

3. The use of the CAPA-planning method to correct and prevent the appearance of risks during CT new drugs organizing and conducting can close the cycle of actions between identifying the problem and the action to solve it.

4. The analysis of regulatory documents showed the absence of unified harmonized requirements for carrying out this type of processes within the framework of CT organizing and conducting.

5. Based on this, it seems expedient to develop an algorithm for work with CAPA-plan and the method of its development, as well as SOPs to standardize this process execution.

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Дата надходження рукопису 28.08.2018

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