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Development of the model for the non-conformance correction and prevention process in clinical trials

The use of the CAPA-planning method to correct and prevent the risks emergence when organizing and conducting clinical trials (CT) of new drugs can close the cycle of actions between identifying the problem and the action to solve it. Our preliminary analysis of regulatory documentation showed the lack of unified harmonized requirements for this type of processes when organizing and conducting CT.

Aim. To develop the algorithm for using the CAPA-planning method during the process of non-conformance correction and prevention when organizing and conducting CT.

Materials and methods. The practical approaches used to develop CAPA-plans were assessed. The algorithm for the process of non-conformance correction and prevention was created. Methods of meta-analysis, abstraction, synthesis and generalization were used in this work.

Results. Our analysis of the experience of using organizational structures for designing CAPA-plans has shown that the most convenient and effective for work is the form of drafting and execution of the CAPA-plan in the form of a consolidated table of all non-conformances identified. Quality management of CT using the CAPA-planning method is a multi-stage process that begins with non-conformance identification during the inspection or control and ends with the documented correction and prevention of all non-conformances identified.

Conclusions. A review of the existing methods for organizing CAPA-plans indicates the absence of the general principles for their drafting, registration and work with them. The algorithm for the interfunctional process for non-conformance correction and prevention with the help of the CAPA-planning method has been developed.

Key words: clinical trial quality management; corrective action; preventive action; risk management

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Розробка моделі процесу усунення та попередження виникнення невідповідностей при організації та проведенні клінічних випробувань лікарських засобів

Використання методу планування CAPA для корекції та попередження виникнення ризиків під час організації та проведення клінічних випробувань (КВ) нових ліків може закрити цикл дій між виявленням проблеми та діями з її вирішення. Наш попередній аналіз нормативної документації показав відсутність уніфікованих гармонізованих вимог до цього типу процесів у рамках організації та проведення КВ.

Метою даної роботи було розробити алгоритм використання методу CAPA-планування під час процесу корегування та попередження виникнення невідповідностей при організації та проведенні КВ.

Матеріали та методи. Оцінені практичні підходи, які були використані для розробки CAPA-планів. Створено алгоритм процесу виправлення та попередження виникнення невідповідностей. У роботі використані методи мета-аналізу, абстракції, синтезу та узагальнення.

Результати. Аналіз досвіду використання організаційних структур для розробки CAPA-планів показав, що найбільш зручною і ефективною для роботи є форма складання CAPA-плану у формі зведеної таблиці всіх виявлених невідповідностей. Управління якістю КВ за допомогою методу CAPA-планування – це багатоетапний процес, який починається з виявлення невідповідності під час інспекції або контролю та закінчується документально оформленою корекцією та запобіганням виявлених невідповідностей.

Висновки. Огляд існуючих методів організації CAPA-планів показав відсутність загальних принципів їх складання, реєстрації та роботи з ними. Ми розробили алгоритм для міжфункціонального процесу для виправлення та попередження невідповідностей за допомогою методу CAPA-планування.

Ключові слова: управління якістю клінічних випробувань; коригувальні дії; превентивні дії; управління ризиками

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Разработка модели процесса по устранению и предупреждению появления несоответствий при организации и проведении клинических исследований лекарственных средств

Использование метода CAPA-планирования для коррекции и предотвращения возникновения рисков во время организации и проведения клинических исследований (КИ) новых лекарств может закрыть цикл действий между выявлением проблемы и действиями по ее решению. Наш предварительный анализ нормативной документации показал отсутствие единых согласованных требований к этим типам процессов в организации и проведении КИ.

Целью этой работы было разработать алгоритм использования метода CAPA-планирования в процессе коррекции и предотвращения несоответствий при организации и проведении КИ.

Материалы и методы. Были оценены практические подходы, которые были использованы для разработки CAPA-планов. Создан алгоритм для коррекции и предотвращения несоответствий. В этой работе были использованы методы мета-анализа, абстракции, синтеза и обобщения.

Результаты. Наш анализ опыта использования организационных структур для проектирования CAPA-планов показал, что наиболее удобным и эффективным для работы является форма составления CAPA-планов в виде сводной таблицы всех выявленных несоответствий. Управление качеством КИ с использованием метода планирования CAPA представляет собой многоэтапный процесс, который начинается с идентификации несоответствий во время проверки или контроля и заканчивается документированием коррекции и предотвращения всех выявленных несоответствий.

Выводы. Обзор существующих методов организации CAPA-планов свидетельствует об отсутствии общих принципов их составления, регистрации и работы с ними. Мы разработали алгоритм межфункционального процесса коррекции и предотвращения несоответствий с помощью метода CAPA-планирования.

Ключевые слова: контроль качества клинических исследований; корректирующие действия; превентивные действия; управление рисками

Regulatory authorities from different countries are aware of the need to implement standardized clinical trial (CT) quality management systems (QMS) to increase the number of qualified clinical sites (CS), as well as more strict compliance with the ICH GCP principles [1, 2].

The analysis of the resent scientific publications showed that the key issues in the field of CT quality assurance currently are the study of factors that determine the necessity of QMS implementation in CT, creation of an effective system of quality management that operates at all stages of organizing and conducting CT, management non-conformances in the framework of the CT quality management concept, the use of the Quality-by-Design concept for quality management when organizing and conducting CT of drugs, as well as the benefits of the risk-oriented monitoring using to improve the CT quality [3-5].

Recently, the use of risk management and risk-based monitoring methodology as a tool to improve the effectiveness of CT planning, organizing and conducting processes is gaining popularity. The method of CAPA-planning, which is used in modern QMS, including in CT, is one of the methods for solving the implementation of a risk-oriented instrument in the CT processes [3, 5-6].

The use of the CAPA-planning method to correct and prevent the risks emergence when organizing and conducting CT of new drugs can close the cycle of actions between identifying the problem and the action to solve it. Our preliminary analysis of regulatory documentation showed the lack of unified harmonized requirements for this type of processes when organizing and conducting CT [7-10].

This means that each party involved when organizing and conducting CT of new drugs, which in order to improve the quality of its activities, requires a process of non-conformance correction and prevention, and needs to develop this kind of measures on its own. Effective implementation of such an interfunctional process requires development of the methodology and the algorithm of work, the standard operating procedure (SOP), accompanying documentation for filling in the course of work on the non-conformance correction and prevention, etc. In turn, it requires cost of money, work time of the skilled staff, creates psycho-emotional stress on the staff that can negatively affect the quality of work they perform.

On this basis, we consider it expedient to develop an algorithm for work with the CAPA-plan and the method of its drafting, as well as the SOP to standardize this process.

The aim of this work was to develop the algorithm for using the CAPA-planning method during the process of non-conformance correction and prevention when organizing and conducting CT.

Materials and methods

To achieve this goal the practical approaches used to develop CAPA-plans were assessed based on the results of 8 audits; some of them were carried out at the Clinical and Diagnostics Center of the National University of Pharmacy (CDC NUPh). Then, based on the results of the analysis, the algorithm for the process of non-conformance correction and prevention when organizing and conducting CT was developed. Methods of meta-analysis, abstraction, synthesis and generalization were used in this work.

Results and discussion

To conduct the process of non-conformance correction and prevention identified during the inspection of the regulatory body, sponsor audit or monitoring by management effectively it is very important to grade non-conformances by the severity of the threat to the CT process. When organizing and conducting CT the absence of non-conformances, which are especially critical is important, and if they arise, this fact should be detected and corrected in a timely manner. To date, this process is carried out with the help of the CAPA-planning method, but the lack of regulatory requirements for the method and form of this process can be an obstacle to the effective implementation of the non-conformance correction and prevention that are divided into three categories:

a) critical;
b) major;
c) minor.

Table 1

Classification of non-conformances by the degree of the threat seriousness to the process of conducting clinical trial

Category of non-conformances	Characteristics
Critical	• violation of the safety, well-being and confidentiality of the subjects; • cases of unreliability or the lack of data; • inconsistency, insufficiency or timeless corrective action in relation to significant non-conformance
Major	• significant and unreasonable non-compliance with the applicable GCP requirements; • a series of deviations from GCP requirements in one area / field, indicating systematic weaknesses in quality control; • non-compliance with legal requirements, including requirements for annual reporting
Minor	• non-conformances that do not affect the rights, health and well-being of the trial subjects, as well as the integrity of the key data

During the generalization of the characteristics of each of the non-conformance categories according to the normative documents and scientific publications [7, 11-12], we have formed the following criteria for non-conformances assigning to a particular category, which are presented in Tab. 1 and we suggest using them in practice.

This classification of non-conformances allows not only to evaluate the quality of the CT procedures performed, but also simplifies the work on their correction and prevention, for example correction of critical non-conformances should be a priority.

Carrying out any CT processes must be documented. This fact also applies to the process of CAPA-planning. To select the most effective form of organizing the draft of CAPA-plans the practical approaches used to compose CAPA-plans were assessed. We analyzed 8 CAPA plans: 3 (37.5 %) of the EMA and FDA audits conducted at CDC NUPh, 3 (37.5 %) samples of plans for the U.S.A. clinical sites, 1 (12.5 %) – the Republic of the Philippines, 1 (12.5 %) – Great Britain [11, 13-15].

The forms of the CAPA-plans organization were part of the SOP for work with the process of non-conformance correction and prevention of the party, which was checked (62.5 %) and the party conducting the control (37.5 %). Since there are no single requirements for the CAPA-plans organizing, it is possible to organize a plan according to the form:

a) the party, which is checked;

b) the party that conducts the control;

c) agreed by both parties – if both parties have a documented form, it is necessary to hold an additional meeting, discussion and agreement on a joint decision on the work with the CAPA-planning process.

Table 2

Comparative characteristics of different organizational structures of CAPA-plans

Organizational structure of CAPA-plan	Benefits	Disadvantages
Consolidated table of all non-conformances identified	• classification of the non-conformance identified by the seriousness degree; • indication of the responsible person; • ease of use and storage; • structuring; • indication of regulatory requirement paragraphs related to non-conformance; • in a form of the integral document; • availability of a comment field	• variety of the existing forms; • the lack of information on the effectiveness of the actions and the staff training
Description of individual non-conformances	• indication of the non-conformance cause; • indication of the assessment of the effectiveness of the actions taken; • description of the personnel training; • availability of a comment field	• a separate document for each non-conformance; • the absence of classification according to the non-conformance seriousness degree; • inconvenience of storage and use; • the possible risk of the document part loss; • the absence of the ponsible person indication

No.	Non-conformance	Grading	Corrective/preventive action	Responsible person	Date

Fig. 1. The general structure of CAPA-plans organized as a consolidated table

The results of the analysis of the organizational structures of CAPA-plans have shown that most plans are compiled in the form of a consolidated table of all non-conformances identified (62.5 %) and in the form of description of individual non-conformances (37.5 %) (Tab. 2).

The common information in both organizational structures was information about non-conformances identified, corrective actions and the date of execution. In addition to these points, the plans organized in the form of a consolidated table contain the classification of the non-conformances identified into critical, major and minor, recommendations for the correction of the non-conformance identified, the person who will be responsible for the effective and timely corrective or preventive actions, as well as the place for comments. As the advantages of this structure convenience the structuring, pointing out regulations for the specific process, etc., can be considered, and one of the most important advantages of this structure is the inclusion of all non-conformances identified in a single document, which makes the structure convenient for use, and also prevents non-fulfillment of the corrective or preventive action because of an unidentified part of the document loss. Fig. 1 shows the overall structure of such kind of plans.

Regarding the CAPA-plans, which are organized in the form of description of individual non-conformances, in addition to general points, as in the form of a consolidated table, the reason for the non-conformance occurrence identified, a description of the personnel training, the effectiveness of the corrective or preventive action implementation are additionally indicated. Significant disadvantages of this type of the CAPA-plan organizational structure are the lack of indication of the non-conformance severity identified, as well as the inconvenience of their use. Since there is a risk of part of the plan loss and non-implementation of the subsequent corrective or preventive actions due to non-identification of the part of the document loss, as the description of each non-conformance is a separate document, and the CAPA-plan itself is essentially a set of documents. In this connection, there are also various factors associated with the work and storage of this type of the CAPA-plan organizational structure. Fig. 2 presents an example of such kind of plans.

Thus, our analysis of the experience of using organizational structures for designing CAPA-plans has shown that the most convenient and effective for work is the form of drafting and execution of the CAPA-plan in the form of a consolidated table of all non-conformances identified.

In view of all of the above, we have developed an algorithm for non-conformance correction and prevention with the help of the CAPA-planning method.

Quality management of CT using the CAPA-planning method is a multi-stage process that begins

Section I

Non-conformance identified:

Section II

Root case analysis:

Section III

The resolution proposed:

Section IV

Documentation of the staff retraining:

Fig. 2. An example of the CAPA-plan, which is organized in the form of a description of separate non-conformances

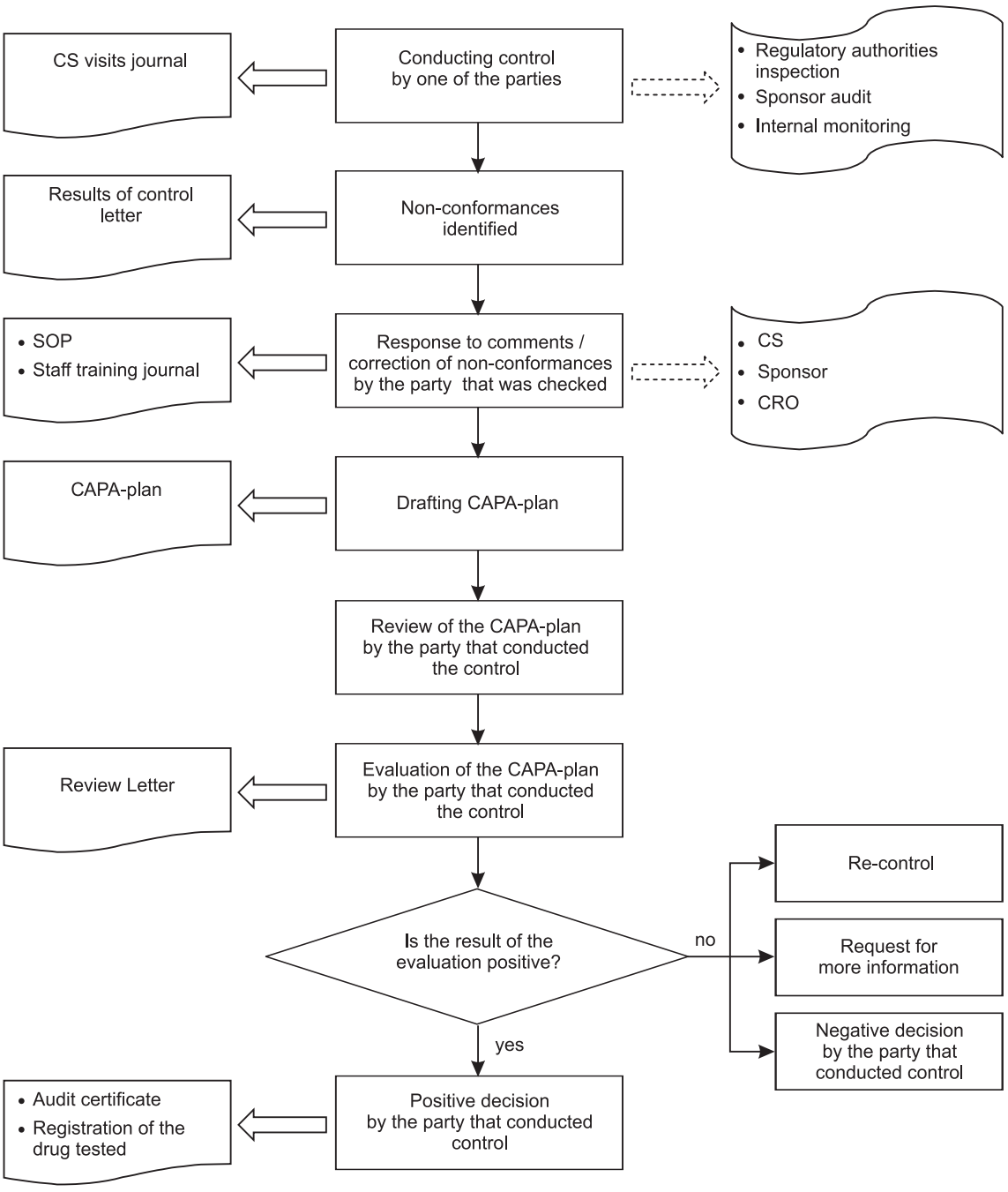

Fig. 3. The block diagram of the interfunctional process algorithm for non-conformance correction and prevention with the help of the CAPA-planning method

with non-conformance identification during the inspection or control by the party that conducts the control (these include: regulatory inspections, audits of the sponsor, or internal monitoring). Further, upon receiving of the comments made by the party that conducted the control, the party which was checked (clinical site (CS), sponsor, contract research organization (CRO)), should eliminate all non-conformances; measures should be taken to prevent the reappearance of non-conformances identified, and the documentary evidence of the measures taken must be provided to the party conducted the control (regulatory authority, sponsor, internal management), which is the CAPA-plan. With the effective execution of this process, a positive conclusion on inspection / audit / monitoring will be made after reviewing and evaluating the CAPA-plan by the party conducted the control. Fig. 3 shows a block diagram of the interfunctional process algorithm for non-conformance correction and prevention with the help of the CAPA-planning method.

Each of the steps in this process is reflected in the relevant documents created / corrected by one of the parties (that conducts the control or which is checked). For example, the control by the party that conducts the control will be accompanied by the relevant entries in the logbook of visits to the CS, and comments from them will be received by

the party, which is checked, in the form of a letter with the results. The most important stage for the CT quality management in this process is the stage of a response to the comments by the party that was checked and the correction of non-conformances identified during the process of control by the party that conducted it, which may result in a revision of the existing SOP or creation of new ones, if necessary, as well as conducting trainings with the staff, which should be recorded by the relevant records in the staff training journal.

The main document, which accompanies the entire process of non-conformance correction and prevention, is the CAPA-plan drafted and agreed by all parties. Non-regulation in normative documents requirements to the process itself, as well as its documentary design may lead to uncertainty at this stage of the work on the CT quality management. The form of the CAPA-plan structure can be a part of the SOP for the work with the CAPA-planning process both by the party conducted control and the party checked. The absence of requirements by one of the parties leads to drafting the CAPA-plan according to the form of the other party. However, if there are forms on both sides, there is a situation that requires an additional settlement and agreement to continue work on non-conformance correction and prevention.

The final version of the CAPA-plan is sent to the party that conducted the control, upon completion of work on it by the party which was checked. When there is a positive result of the control, the party, which was checked, can obtain a certificate of successful inspection / audit passing, the possibility to register the drug studied. If the result of the performed corrective and preventive actions is evaluated as unsatisfactory, a possible request for additional information on the non-conformances identified, the re-control or refusal to register a new drug could be considered as a result.

An integral part of carrying out the work on correction and prevention of future non-conformances is monitoring of the effectiveness and implementation of corrective or preventive action developed after the completion of work on implementation of all activities described in the CAPA-plan within the framework of the quality management system. This stage will allow to check on the number of procedures, equipment, etc., that are effective and useful for improving the quality of organizing and conducting CT. Equally important is the timeliness of such monitoring in due time.

The algorithm developed by us for work on the process of non-conformance correction and prevention with the help of the CAPA-planning method was tested and implemented in the work of the CDC NUPh, the SOP was developed.

CONCLUSIONS

A review of the existing methods for organizing CAPA-plans indicates the absence of the general principles for their drafting, registration and work with them. The algorithm for the interfunctional process for non-conformance correction and prevention with the help of the CAPA-planning method has been developed in order to increase the level of quality management in the process of organizing and conducting CT.

In the future, it is planned to conduct an analysis of the interaction of the parties involved in the process of CAPA-planning in the course of non-conformance correction and prevention in CT. In addition, it is necessary to examine what staff is involved in drafting the CAPA-plans and whether they have the necessary qualification for participation in this process.

Conflict of interests: authors have no conflict of interests to declare.

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