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Original Article

Effect of evidence-based nursing management of protocol compliance in anticancer drug clinical trial

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ABSTRACT

Objective: This study aimed to construct evidence-based anticancer drug clinical trial nursing management norms to ensure the safety and quality of clinical trial nursing.
Methods: This before-after study was carried out to complete the evidence implementation in a cancer hospital in Shanghai, China. Seven review indicators were developed and reviewed in one phase I clinical trial center and two oncology wards. The corresponding evidence-based intervention program was formulated, and the completion rate of good clinical practice certification, protocol training, delegation of duties, qualification rate of administration, sampling and document recording in anticancer drug clinical trials before and after implementation were compared.
Results: After implementation, the completion rate of protocol training, delegation of duties, and the qualification rate of document recording were significantly higher than those of the baseline review, whereas the completion rate of good clinical practice certification and the qualification rate of sampling did not significantly differ from those observed at the baseline review. There was no administration or infusion device-related protocol deviation during the baseline and post reviews.
Conclusions: Anticancer drug clinical trial nursing management norms and relevant standard operating procedures were constructed. The results showed that the implementation of this intervention improved the standardization of nurse qualification procedures and the nursing original document recording in anticancer drug clinical trials, and nursing-related protocol deviation could be reduced to a certain extent.

Introduction

In 2020,[1] 24% of new cancer cases and 30% of cancer-related deaths worldwide occurred in China. Cancer has become a major disease threatening human health in China and around the world. Drug therapy is an important means of anticancer treatment. There is an urgent clinical need to encourage the research and development of new anticancer drugs and improve the prognosis of patients with cancer.[2] A drug clinical trial is a systematic study of experimental drugs in the human body before marketing to evaluate their safety and effectiveness.[3] From 2009 to 2018,[4] 1493 trials of 751 new tested anticancer drugs were launched in China, and the number of pilot projects, new drug research and development, and clinical trial institutions launched every year continues to rise. With the increasing number of clinical trial projects, more attention has been given to quality supervision and quality control. Any intentional or unintentional protocol deviation (PD)/protocol violation will directly affect the rights and interests of the subjects and the integrity, authenticity, and effectiveness of the data.[5]

The protocol refers to the document describing the purpose, design, methodology, statistical considerations, and organization and implementation of the clinical trial.[6] It is jointly developed by pharmaceutical, medical, and statistical experts. After being reviewed by ethics experts, it is signed and approved by the investigator and the sponsor. All study staff, such as doctors, nurses and pharmacists, must strictly follow the

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protocol throughout the trial[7] to ensure the rights and interests of the subjects and the authenticity and reliability of the data. At the beginning of the clinical trial design, various factors that may affect the trial are considered as much as possible; however, due to the numerous personnel, complex design, conditions, and links involved in the implementation process of the trial, PD is often inevitable.

In China, a survey examined the quality of 949 medical records involved in 27 drug clinical trials conducted by the hospital from 2010 to 2016 and found 176 cases of PD, accounting for 18.55%.[8] In an investigation of 126 registered anticancer drug clinical trials being conducted at a cancer hospital in Liaoning Province from 2017 to 2019, it was found that among 1155 PDs, improper drug use was one of the most common PDs, including missing drugs, improper oral drug use, improper infusion configuration, overdose or insufficient dose, wrong use of auxiliary drugs, subjects losing drugs, taking the wrong drugs, and so on.[9] Another survey showed that the most common PDs were improper use and management of test drugs, the omission of laboratory tests, incorrect procedures, out-of-visit window, and so on.[10]

As one of the main members in the clinical trial, nurses directly participate in the clinical trial administration, verification, sample collection, inspection, necessary nursing evaluation, relevant propaganda and education, process coordination and many other links prone to PD as mentioned above. However, an investigation showed that nurses were generally unfamiliar with the basic knowledge, quality control, and ethics of clinical trials.[11] Lack of knowledge and nursing management norms or quality supervision may lead to a series of PD problems. The process of anticancer drug clinical trials cannot be separated from the direct participation of nurses. Any omission or error will directly affect the reliability and authenticity of the research results.[12] However, at present, there is still a lack of a unified qualification procedure for nurses to participate in clinical trials and nursing management norms for clinical trials in China, which leads to certain loopholes and hidden dangers in clinical trial nursing management and limits the development of specialized nursing.

Therefore, it is urgent to establish clinical trial nursing management norms to ensure nurses' compliance with the protocol and to avoid nursing-related PDs. Research and evidence-based practice (EBP) are important ways to ensure that nurses deliver safe and effective care, improve care quality, and promote good nursing practice.[13] The purpose of this study was to apply the best evidence of nursing management of protocol compliance in anticancer drug clinical trials to practice and construct nursing management norms. Based on this, this study aimed to standardize the nursing processes of clinical trials, reduce the incidence of nursing-related PD, and ensure that nurses implement the trial plans in strict accordance with the protocol. We also hope that this study can provide a basis for the establishment of anticancer drug clinical trial nursing management norms in China.

Methods

This study was based on the "evidence implementation model" and methodological framework proposed by the evidence-based nursing center of Fudan University.[14] The model takes clinical problems as the starting point, takes knowledge translation as the purpose, takes implementation science as the methodological guidance, and aims to build a sustainable evidence ecosystem. It was formed by the evidence-based nursing center of Fudan University through 15 years of theoretical exploration and empirical research into EBP. Now, it has become one of the most commonly used methodological guidelines for EBP and evidence implementation in the field of nursing in China.

The model includes four phases: preparation, implementation, evaluation, and maintenance, and consists of 14 steps. The preparation phase includes theoretical preparation, construction of the PIPOST, retrieval of evidence, evaluation of the evidence quality, and the formation of an evidence summary. The implementation phase includes the construction of evaluation indicators, barrier analysis, the construction of action strategies, leadership incentives, and the establishment of facilitating factors. The evaluation phase includes the designing of the implementation research and measuring the outcomes. The maintenance phase includes sustainability analysis and the construction of an updated plan. This study was completed following these steps.

Study sample

The study was conducted in one phase I clinical trial center and two oncology wards of a cancer hospital in Shanghai, China. The clinical trial projects, subjects, and nurses participating in the clinical trial in the above wards were included in the study. Inclusion criteria: (1) clinical trial projects: clinical trials started and carried out in the phase I clinical trial center and oncology wards of the hospital; (2) subjects: clinical trial subjects enrolled in a clinical trial in the phase I clinical trial center and oncology wards of the hospital; (3) nurses: nurses that were participating in the clinical trials in the phase I clinical trial center and oncology wards of the hospital. Exclusion criteria: (1) clinical trial projects: clinical trial suspension or termination; (2) subjects: subject drop out or withdrawal. Study sample selection: (1) clinical trial projects and subjects: convenience sampling was adopted, and subjects meeting the inclusion and exclusion criteria during the review period were enrolled; (2) nurses: 59 nurses in three wards were included in the baseline and post reviews.

Procedures

Phase I: preparation phase

First, the clinical question of the study was how to standardize the nursing management of protocol compliance in anticancer drug clinical trials. Then, the question was structured by PIPOST,[15] in which P (population) refers to the target population of evidence implementation and clinical application. In this study, it referred to the clinical trial subjects and the nurses participating in clinical trials; I (intervention): refers to a series of interventions. The study included the construction of a nurse qualification access process, the formulation of clinical trial nursing standard operating procedures (SOP), and the construction of quality evaluation indicators for nurse protocol compliance; P (professional): refers to the multidisciplinary professionals involved in the evidence implementation process. In this study, it referred to the clinical supervisors and nurses participating in the clinical trial; O (outcome) refers to the factors expected to change in response to the intervention implementation. The outcomes in this study were the qualified rate of nurses, the nursing-related PD rate, and the qualified rate of nursing-related original documents. S (setting) refers to the scenario analysis of evidence applications and the analysis of the gap in the evidence. In the study, the included wards lacked clinical trial nursing management norms and nursing quality evaluation indicators. T (type of evidence) refers to the type of evidence, which tends to adopt high-quality and integrated secondary research evidence. The types of evidence included in this study included guidelines, evidence summaries, systematic reviews, meta-analyses, and expert consensuses.

The project team was established, including two leaders and seven members. The two leaders (one head nurse and one nurse) had received training from the evidence-based nursing center of Fudan University and were responsible for project quality supervision and coordination, project implementation, evidence retrieval and other preliminary research, data collection, data analysis, and so on. Among the seven members, one director and one deputy director of the nursing department were responsible for the overall planning of the project, one director of the clinical trial center was responsible for the supervision and consultation of clinical trial-related issues, two head nurses were responsible for the project implementation and supervision, and two nurses were responsible for the data collection.

Following the "6S" evidence model,[16] the project team systematically searched the guidelines, evidence summary, systematic reviews, meta-analysis, and expert consensus on the nursing management of protocol compliance in anticancer drug clinical trials from domestic and

Table 1
The formation process of review indicators.

Categories	Evidence	Review indicators
Personnel preparation	1. Nurses should know and understand the laws and regulations related to the research and comply with the most stringent laws or regulations.[17] 2. Study staff participating in the implementation of clinical trials shall have the corresponding education, training, and experience to undertake the work of clinical trials.[6,18] 3. Investigators and clinical trial institutions delegate individuals or units to undertake clinical trial-related duties and functions shall ensure that they have the corresponding qualifications, and establish complete procedures to ensure that they perform clinical trial-related duties and functions and generate reliable data.[6] 4. All study staff participating in the clinical trial shall clarify their respective division of labor and responsibilities in the trial and record them in the documentation of the delegated duties to ensure the authenticity, completeness and accuracy of the clinical trial data.[6,17,18] 5. All study staff must learn the protocol, and find and confirm the information as needed at any time.[6]	Indicator 1: Nurses participating in clinical trials should receive GCP certificates Indicator 2: Protocol training of nurses should be carried out before the clinical trial initiation Indicator 3: Nurses participating in clinical trial should be delegated their duties
Administration quality	6. During the clinical trial, the investigator shall ensure that all personnel participating in the clinical trial fully understand the protocol and test drugs.[6,17] 7. They shall ensure that the test drug is used according to the protocol and shall explain the correct usage of the test drug to the subjects.[6,17,18] 8. The whole process of clinical trial shall be carried out in strict accordance with the quality management standard operating procedures.[6,17,18] 9. Nurses shall obtain the doctor's instruction before distributing and using the test drug, and double-check with the pharmacist or the designated study nurse to ensure the correct dose and accurate time of administration.[17] 10. Records of the quantity and dosage of the test drug used by each subject shall be kept, and the quantity of the test drug used and remaining shall be consistent with the quantity provided by the sponsor.[6,17] 11. The storage temperature, transportation conditions (whether it is necessary to keep away from light), storage time limit, preparation method and process of drug solution, requirements for drug infusion device, and so on, of the test drug shall be clearly specified. The proper usage of the test drug shall be provided to all relevant personnel.[6,17] 12. The test drug recovered from the subjects and not used shall be returned to the sponsor or destroyed by the clinical trial institution after the sponsor's delegation of duties.[6]	Indicator 4: The clinical trial administration should comply with the protocol, including drug name, dosage, solvent, pretreatment or auxiliary medication, administration time, administration interval, administration route, administration sequence, and so on. Indicator 5: The infusion device should comply with the protocol
Sampling quality	13. The management, detection, transportation, and storage of samples collected in clinical trials shall ensure the quality.[6] 14. Different biological samples, such as frozen tissue, slides, blood, serum and urine, and so on, should comply with the best practice standards and follow the protocol as fully as possible.[17] 15. Study staff involved in the collection, storage, and delivery of samples must obtain relevant qualifications and be trained in standard operating procedures to understand the whole process of biological sample collection and storage in detail.[17] 16. Samples shall be collected at the specified time, and the actual and planned sampling time shall be recorded.[18]	Indicator 6: The sampling plans should be implemented and comply with the protocol, including sampling time points, times of sampling, sampling volume, and so on.
Original documents	17. Standard operating procedures for document management shall be formulated.[6] 18. All information about the subjects must be clearly and legally recorded.[6,17,18] 19. It shall be ensured that all adverse events are recorded in the subject's medical records and case report forms.[6,17] 20. All subject records shall be written in ink, not pencil.[17] 21. It is forbidden to erase or overwrite errors, and it is not allowed to use correction fluid for modification. The modification of source data should leave a mark and cannot cover up the initial data. The modifier should sign and date, and record the reasons for the modification.[6,17,18] 22. The investigator or designated study staff shall record and explain the protocol deviation.[6,17] 23. The essential documents for the clinical trials used to apply for drug registration shall be kept for at least 5 years after the test drug is approved for marketing. For clinical trials not used for drug registration, the essential documents shall be kept for at least 5 years after the termination of the trials.[6]	Indicator 7: The records and signatures of nursing-related original documents should be complete and timely

foreign guide websites, association websites and databases, evaluated the quality of the obtained literature, and finally involved three pieces of literature, including two guidelines[17,18] and one expert consensus.[6] Subsequently, the relevant evidence was extracted, and the included evidence was graded. The feasibility, appropriateness, meaningfulness, and effectiveness of the evidence were evaluated according to the JBI FAME Scale.[19] Eventually, twenty-three pieces of best evidence, including personnel preparation, administration quality, sampling quality, and original documents, were included.

Phase II: implementation phase

According to the included evidence, after discussion and decision-making, the project team finally formulated seven review indicators (Table 1) and determined the corresponding review methods and data collection methods. To clarify the current situation of nursing quality before the intervention, a baseline review was carried out from May to September 2021, including 59 nurses in the three wards of the phase I clinical trial center and oncology wards. A total of 26 clinical trials, 148 administrations, 140 samplings, and 140 administration-related nursing

original documents were randomly selected. The results of the baseline review (Table 2) showed that indicators 4–5 related to the administration quality were 100%, and there was no administration-related PD during the baseline review. However, other indicators still need to be improved, especially the completion rate of GCP certification, protocol training, delegation of duties, and the qualification rate of document recording. Based on the baseline review results, the project team discussed and analyzed the barriers and facilitating factors of each review indicator and formulated corresponding action strategies (Table 3).

Phase III: evaluation phase

This before-after study was carried out in one phase I clinical trial center and two oncology wards from September to November 2021.

Personnel preparation

- Standardization of the access and qualification: We organized the project team to study and discuss relevant policies and guidelines, formed a unified qualification standard for nurses participating in clinical trials, and formulated *The Nursing Management Norms for Anticancer Drug Clinical Trials.*
- Standardization of the protocol training and delegation of duties: We established a standardized protocol training process and provided a specific training time and place. Training methods such as e-mail, telephone, and on-site could be allowed, and the training records were required to be completed on time. We also established a standardized delegation of duties process that was signed and agreed upon in writing by the sponsor, and the principal investigator considered it acceptable. A specific form was created to record whether the nurse had been delegated duties and the time to facilitate the review of clinical supervisors.
- Standardization of GCP qualification management: Due to the uncertain GCP certification time, the clinical supervisor usually organizes nurses in need to participate in the GCP training held every 1–2 years. We stipulated that the GCP certificate acquisition time and photos should be entered into the nursing management system software in time for the review of the clinical supervisor.
- Organization of learning and training: We made courseware for the nurses and organized their learning and training to improve their awareness of the access and qualification process.

Administration quality

- No substandard indicators.

Sampling quality

- Standardization of the clinical trial sampling operation: We formulated the clinical trial sampling operation specification and SOP and trained the relevant nurses. Inception conferences and nurse training were carried out to familiarize the staff with the sampling plans and specific details before clinical trial initiation. We also standardized the content and process of checking the physician orders, and the specific requirements were noted in the physician orders or they issued corresponding orders when necessary.
- Strengthening of the subjects' education during the intensive sampling period: We provided the study participants with an education manual to guide them in understanding the sampling procedures/timing and take care to protect their intravenous line access during the intensive sampling period to avoid catheter displacement, catheter blockage, difficulty in blood collection, and so on. While improving the puncture technique, we arranged for special nurses (usually nurses with high seniority and rich clinical trial experience) to take charge of the clinical trial sampling tasks.
- Preparation of the clinical trial sampling schedule: Due to the different sampling plans in the different protocols, there were many and complex sampling points, and it was difficult to remember them all. Therefore, a sampling schedule was made, and the sampling time points and relevant requirements were indicated to facilitate the verification before sampling. In addition, the sampling handover process was improved. Nurses were required to hand over the unfinished sampling plans and corresponding requirements when changing shifts to avoid the occurrence of PDs, such as sampling omissions and out-of-sampling windows.

Table 2
Baseline and post review results [*n* (%)].

Characteristics		Baseline review	Post review	χ^2	*P*
Personnel preparation	Indicator 1: GCP qualification	*N* = 59	*N* = 59	–	–
	Yes	41 (69.49)	41 (69.49)		
	No	18 (30.51)	18 (30.51)		
	Indicator 2: Protocol training	*N* = 26	*N* = 25	14.162[a]	0.000
	Yes	11 (42.31)	23 (92.00)		
	No	15 (57.69)	2 (8.00)		
	Indicator 3: Delegation of duties	*N* = 26	*N* = 25	18.988[a]	0.000
	Yes	10 (38.46)	24 (96.00)		
	No	16 (61.54)	1 (4.00)		
Administration quality	Indicator 4: Administration	*N* = 148	*N* = 140	–	–
	Qualified	148 (100)	140 (100)		
	Unqualified	0 (0)	0 (0)		
	Indicator 5: Infusion device	*N* = 148	*N* = 140	–	–
	Qualified	148 (100)	140 (100)		
	Unqualified	0 (0)	0 (0)		
Sampling quality	Indicator 6: Sampling	*N* = 140	*N* = 144	–	0.242[b]
	Qualified	138 (98.57)	144 (100)		
	Unqualified	2 (1.43)	0 (0)		
Original documents	Indicator 7: Document record	*N* = 140	*N* = 140	12.992[a]	0.000
	Qualified	125 (89.29)	139 (99.29)		
	Unqualified	15 (10.71)	1 (0.71)		

[a] Chi-square test.
[b] Fisher exact method.

Original documents

- Standardization of nursing relevant original document recording and management: We formulated nursing relevant original document recording and management specifications and SOP and trained nurses. Before clinical trial initiation, the relevant documents to be signed and recorded were clarified, and the document information was reviewed for completeness and accuracy.

Data collection

The homemade *Quality Review Form for Nurses' Protocol Compliance* was used for baseline and post review, which included four sections:

Table 3
Analysis of barriers, facilitating factors, and action strategies.

Review indicators	Barriers	Action strategies	Facilitating factors
Personnel preparation Indicator 1: Nurses participating in clinical trials should receive GCP certificates Indicator 2: Protocol training of nurses should be carried out before the clinical trial initiation Indicator 3: Nurses participating in clinical trials should be delegated their duties	① There were disputes about the qualification; ② There was no standardized and unified access process and qualification examination standard; ③ For novices, there was no protocol training or delegation of duties process; ④ Shift nurses were unable to complete the protocol training and delegation of duties in time; ⑤ The protocol training time and place were not fixed; ⑥ GCP certification time and method were uncertain; ⑦ Nurses were unfamiliar with the access process or qualification criteria.	① Improve the access process and qualification review standards; ② Construct the standardized protocol training and delegation of duties process; ③ Prepare the relevant training courseware and organize learning and training to improve nurses' awareness of access and qualification process.	① The management supports and hopes to establish standardized anticancer drug clinical trial nursing management norms and personnel access process; ② Each ward in the hospital can provide protocol training time, place and other resources; ③ Relevant learning and training can be carried out after morning meetings.
Administration quality Indicator 4: The clinical trial administration should comply with the protocol, including drug name, dosage, solvent, pretreatment or auxiliary medication, administration time, administration interval, administration route, administration sequence, etc. Indicator 5: The infusion device should comply with the protocol	The baseline review results of indicators 4–5 were both 100%, and there were no noncompliance indicators.	–	–
Sampling quality Indicator 6: The sampling plans should be implemented to comply with the protocol, including sampling time points, times of sampling, sampling volume, etc.	① Nurses' high dependence on CRC; ② Unfamiliar with sampling plans and relevant requirements; ③ The subjects education was insufficient and they did not cooperate with the sampling plans; ④ Different protocols had different sampling plans, there were many and complex sampling points, and the sampling window was usually narrow, resulting in great difficulty in remembering the process; ⑤ Lack of standards for clinical trial sampling management; ⑥ Imperfect handover of sampling plans and corresponding requirements when nurses change shifts.	① Inception conference and nurse training should be carried out to be familiar with the sampling plans and specific details before the clinical trial initiation; ② Prepare the sampling schedule, indicating sampling time points and relevant requirements for verification before sampling; ③ Improve the sampling handover process. Nurses should hand over the unfinished sampling plans and corresponding requirements when changing shifts; ④ Formulate standardized sampling management specifications; ⑤ Prepare the education manual for subjects to guide them to cooperate with the sampling plans.	① They can reach a consensus with all investigators and provide nurse training related to the sampling plans of the protocol; ② The wards have sufficient human resources and can arrange special sampling nurses.
Original documents Indicator 7: The records and signatures of nursing-related original documents should be complete and timely	① Nurses' high dependence on CRC; ② The nursing original documents to be signed and recorded have not been clarified; ③ Nurses usually forgot or were unable to complete document recording in time when the workload was heavy; ④ There was no standard for the management of nursing original documents and records.	① The relevant documents to be signed and recorded should be clarified, and document information should be reviewed for completeness and accuracy before the clinical trial initiation; ② Organize relevant learning and training to improve nurses' awareness of recording and signing; ③ Formulate standardized nursing document recording and management specifications.	① They can reach a consensus with all investigators and clarify the documents to be signed and recorded before the clinical trial initiation; ② Nurse representatives usually attend the inception conference and can participate in the verification and confirmation of relevant documents.

personnel preparation, administration quality, sampling quality, and original documents. Personnel preparation (indicators 1–3) involved reviewing the GCP certificates, protocol training records, and delegation of duties records. Administration quality (indicators 4–5) involved reviewing whether the medication date, drug name, dosage, solvent, pretreatment medication, medication sequence, medication duration, and infusion device complied with the protocol. Sampling quality (indicator 6) involved reviewing whether the sampling exceeded the time window and whether the sampling was complete. Original documents (indicator 7) involved reviewing whether the relevant documents, records, and signatures were complete and whether the modifications met

the specifications. After unified training, three nurses from the project team adopted a combination of on-site observation and retrospective review, collected data by viewing the relevant certificates and records, and then evaluated and recorded them accurately in the review form.

Data analysis

SPSS 22.0 (IBM Corp, Armonk, NY, US) was used for statistical analysis, and $P < 0.05$ was considered statistically significant. The counting data were described as frequencies and percentages. For the counting data analysis, the chi-square test and rate ratio increases were used. Fisher's exact method was used when the data did not meet the preconditions of the chi-square test.

Ethical considerations

This project was registered as a nursing quality improvement activity within the hospital and therefore did not require ethical approval.

Results

The results of the baseline review and post review are shown in Fig. 1 and Table 2.

Personnel preparation

- Indicator 1: During the baseline review, there were 59 nurses in three wards, of which 41 had obtained a GCP certificate and 18 had not. The completion rate of GCP certification at the post review was the same as that of the baseline review.
- Indicator 2: During the baseline review, 26 clinical trials were randomly selected, of which 15 had incomplete protocol training records. During the post review, 25 clinical trials were randomly selected, of which 2 had incomplete protocol training records. The completion rate of protocol training at the post review was significantly higher than that of the baseline review ($P < 0.01$).
- Indicator 3: During the baseline review, 26 clinical trials were randomly selected, of which 16 had incomplete delegation of duties signatures. During the post review, 25 clinical trials were randomly selected, of which 1 had incomplete delegation of duties signatures. The completion rate of delegation of duties at the post review was also significantly higher than that of the baseline review ($P < 0.01$).

Administration quality

- Indicator 4: 148 times of intravenous administration were reviewed at baseline, and 140 times were reviewed again after the intervention. There was no administration-related PD during the review periods, and the qualified rate of administration was 100%.
- Indicator 5: there was no inappropriate use of the infusion device during the baseline review and post review, and the qualified rate of the infusion device was 100%.

Sampling quality

- Indicator 6: A total of 140 cases of sampling were reviewed at baseline. During the review period, it was found that 2 cases were out of the sampling window, and there was no sampling omission or insufficient sampling. A total of 144 cases of sampling were reviewed again after the interventions, and there was no out-of-sampling window, sampling omission, or insufficient sampling. The qualified rate of sampling at the post review was higher than that of the baseline review, but the difference was not statistically significant ($P > 0.05$).

Original documents

- Indicator 7: During the baseline review, 140 administration-related nursing original documents were checked, of which 9 had signature or record omissions and 6 had incomplete document information. During the post review, 140 administration-related nursing original documents were checked, of which 1 had signature or record omissions. The qualified rate of document recording at the post review was significantly higher than that of the baseline review ($P < 0.01$).

Discussion

Personnel preparation

At present, the number of studies on the qualifications and responsibilities of research nurses/research coordinators is increasing[20–22];

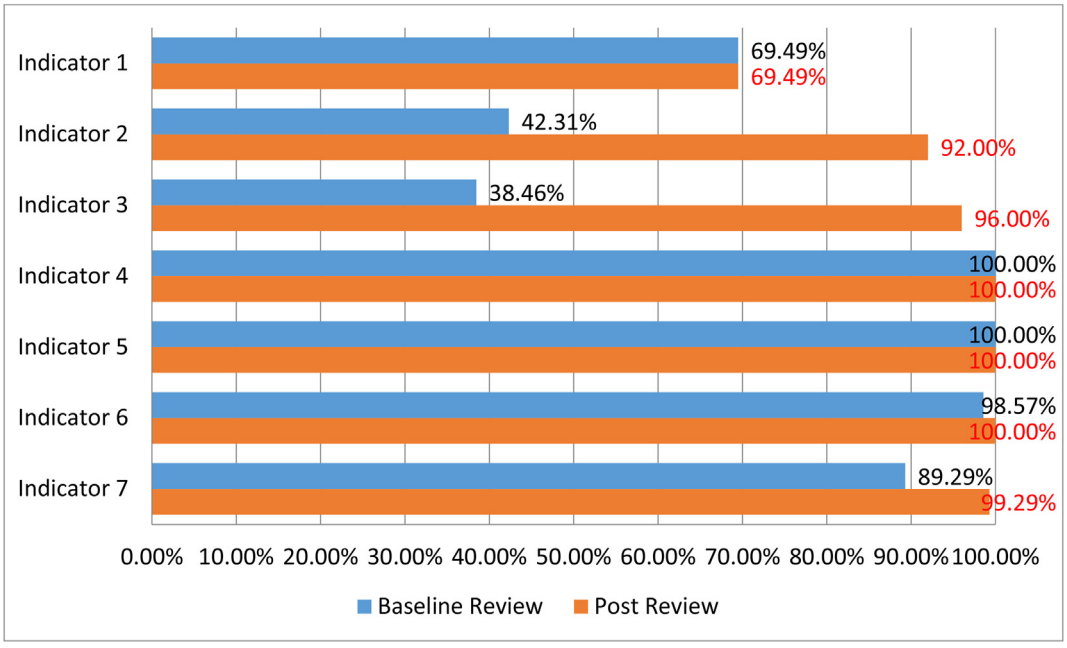

Fig. 1. Changes in baseline and post-review indicators.

however, the nurses mainly involved in the study were different from the research nurses. The nurse discussed in the studies referred to those who specifically provided direct care for subjects in clinical trial institutions and mainly participated in clinical trial medication, sample collection, relevant original document recording, and so on. This role has not been described by accurate terms or definitions in China.[17] In clinical practice, some domestic studies[12,23] have divided this role into full-time and part-time and considered that both should receive training in GCP, basic clinical trial knowledge, protocols, and relevant nursing SOPs.

There is still a lack of unified standards for the qualification, access, training requirements, and scope of responsibilities of nurses participating in clinical trials in China. There is no standard process for qualification or access in clinical practice. The main problems in the baseline review included the low coverage of GCP certification, the weak awareness of protocol training and the delegation of duties signature, the failure of new nurses to complete the training or delegation of duties in time, and the failure to complete the training in time after the update of the protocols.

In view of the problems found during the baseline review, the project team was established to study and discuss the relevant policies and guidelines, formulate the SOP for the qualification, standardize the access process from GCP certification and protocol training to the delegation of duties, improve the access process of updating protocols and novices, and clarify the position conditions so that a unified standard process could be followed in clinical practice. We also hope to provide a reference for the establishment of unified qualification standards for nurses participating in anticancer drug clinical trials in China. The results showed that the interventions were effective in improving the completion rate of protocol training and the delegation of duties. However, in terms of GCP certification, since offline GCP certification had not been organized during the study and the online GCP certification had not been uniformly recognized, the completion rate of GCP certification had not changed compared with the baseline review. The GCP certification method is still controversial. The requirements for personnel qualification are different in different trials. Subsequently, the project team will further explore and unify the standards.

Administration quality

Clinical trials involve a large number of nursing operations, in which administration and sample collection are the core links. The improper use or management of study drugs is one of the most common PDs.[10,24] Nurses should learn and follow consistent SOPs to reduce the various operation variations and experimental errors and ensure the accuracy and reliability of the data.[12] Therefore, standardizing drug administration in clinical trials and strictly following the protocol is an inevitable requirement to ensure the quality of trials and the safety of subjects.

In terms of clinical trial administration, the baseline review results showed that the qualified rate of administration was 100%, and there was no PD. However, there were still errors or incomplete information in some physician orders. In addition, due to the high dependence of nurses on clinical research coordinators (CRCs), there are certain hidden dangers in clinical trial administration. Therefore, this study also formulated a SOP for clinical trial administration, standardized the administration nursing process, clarified the contents of checking physician orders, prepared a key information manual of study drugs, organized nurses' learning and training, and made checklists to be confirmed by the corresponding CRC and executive nurse before administration to ensure the safety of the subjects and the quality of clinical trial administration. The qualified rate of administration remained 100% at the post review, and there was no administration-relevant PD.

Sampling quality

Anticancer drug clinical trials test the safety and effectiveness of anticancer drugs, evaluate their pharmacokinetics and pharmacodynamics, and collect data on adverse reactions and efficacy.[25] Data are the core of anticancer drug clinical trials,[26] and sample collection directly affects the authenticity and accuracy of data, which is one of the key factors for the success or failure of the trial.[27] During an anticancer drug clinical trial, especially a phase I clinical trial, according to the requirements of the protocol, blood samples can be collected dozens of times within a day after drug administration.[28] During the intensive sampling period, there are many and complex blood collection time points. There are strict requirements for the timing of each blood collection and the sampling window is usually narrow. There will be some hidden dangers in clinical trial sampling without standardized management. Therefore, it is necessary to establish standardized specimen collection procedures and formulate and strictly implement the sampling SOP[27] to avoid sampling-related PD.

In terms of clinical trial sampling, the baseline review results showed that there were two cases out of the sampling window, and the sampling qualified rate was 98.57%. The main reasons for the two cases included the high dependence of the executive nurses on the CRC, their unfamiliarity with the sampling plans and corresponding requirements, and the imperfect handover of sampling plans and corresponding requirements when the nurses changed shifts. In addition, there were some other problems, such as inadequate education resulting in the subjects' failure to cooperate with the sampling collection and corresponding requirements, the narrow sampling window, the many and complex blood collection time points making it difficult to remember them all, and so on. Therefore, this study formulated a SOP for clinical trial sampling, standardized the sampling nursing process, prepared the sampling schedule, marked the time points and corresponding requirements of each sampling, made an intensive sampling education manual for the subjects to guide them in cooperating with the sampling plans, arranged for special nurses to take charge of the clinical trial sampling tasks, and improved the sampling handover process to reduce sampling-related PDs. Although the difference was not statistically significant ($P > 0.05$) between the baseline and post reviews, it was necessary to eliminate hidden dangers and avoid PD as much as possible, which is also a basic requirement to protect the rights and interests of the subjects and ensure the authenticity of the data.

Original documents

In clinical trials, source data are regarded as the basis for traceability, and source documents are the original documents carrying the source data.[29] As one of the source documents of clinical trials, nursing-related original documents should be recorded and preserved in accordance with the relevant provisions of the GCP and the management requirements of clinical trial documents. However, clinical trial documents are numerous and diverse and are prone to deficiencies in document management, such as incomplete document retention, non-standard document retention, untimely document recording, and non-standard record modification.[30] The original document contains the information and data record of the clinical trial process, which reflects the compliance of the trial process with the protocol, GCP and current management requirements. It is also the first-hand data and key basis for the drug regulatory agency to supervise and approve new drugs. Therefore, it is necessary to standardize the management of clinical trial documents.

This study mainly focused on the paper nursing original documents. During the baseline review, it was found that there were problems such as missing or untimely document signatures or records and incomplete document information. Therefore, this study formulated a SOP for the management of nursing relevant original documents and records, standardized the recording and management process of clinical trial nursing documents, routinely reviewed whether the document information was complete and accurate before the clinical trial initiation, clarified the relevant documents that needed to be signed and recorded, and trained the relevant nurses. The results showed that the qualified rate of document recording was significantly improved after the intervention ($P <$

0.01).

Limitations

At present, there is still a lack of unified standards for the qualification, access, and training requirements of nurses participating in clinical trials in China. During this study, there were still disputes about the GCP certification method. The requirements for personnel qualification are different in each clinical trial and this need to be further discussed and unified. In addition, this study was only carried out in three wards of our hospital. With the increasing number of clinical trials to ensure the safety of the subjects and the nursing quality, it is necessary to promote the intervention and results of this study in relevant departments of hospitals and other medical facilities involved in clinical trials.

Conclusions

Based on the evidence, through the construction of nursing management norms of protocol compliance in anticancer drug clinical trials, this study has established standardized systems and SOPs in many aspects, such as personnel preparation, administration quality, sampling quality, and original documents, to provide evidence for clinical trial nursing operation and management and ensure the safety of subjects and the quality of clinical trial nursing. The results showed that through the evidence implementation of nursing management of protocol compliance in anticancer drug clinical trials, standardizing the nurses' qualification, administration, sampling and original document recording process, the standardization of nurse qualification procedures and the nursing original document recording could be improved, and nursing-related PD could be reduced to a certain extent.

Authors' contributions

Conceived and designed the analysis: Xiaoju Zhang, Zhenqi Lu, Qionghua Gu, Rui Yang, Jian Zhang. Collected the data: Rui Yang, Fengzhen Chen, Yang Yang, Linli Gu. Contributed data or analysis tools: Rui Yang, Qionghua Gu. Performed the analysis: Rui Yang, Qionghua Gu. Wrote the paper: Rui Yang, Qionghua Gu, Fengzhen Chen, Yang Yang, Linli Gu, Jian Zhang, Zhenqi Lu, Xiaoju Zhang.

Declaration of competing interest

None declared.

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