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Original Article

Participation in and withdrawal from cancer clinical trials: A survey of clinical research coordinators

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ABSTRACT

Objective: Poor accrual and withdrawal are the main reasons for the failure of cancer clinical trials. As clinical research coordinators (CRCs) work at the frontlines of clinical trials, CRCs can best identify the main factors that influence patient participation and dropout and suggest potential remedial measures. This study aimed to investigate participation and withdrawal in cancer clinical trials through a survey of CRCs. Furthermore, we collected suggestions of CRCs to increase patient participation and reduce withdrawal from cancer clinical trials.
Methods: This cross-sectional survey among 100 CRC nurses currently coordinating cancer clinical trials and having more than six months of experience was conducted at four hospitals in South Korea between March and August 2021. We designed a questionnaire based on prior studies, and the key items included characteristics of respondents, characteristics of clinical trials, clinical trial participation, and withdrawal.
Results: Patients refused to participate due to concern about adverse events (46.5%) and negative perception of clinical trials (44.4%). The main reasons for study withdrawal were disease progression (71.5%), adverse events (10.6%), and withdrawal of consent due to personal issues (5.5%). The provision of sufficient explanation was suggested as a remedial measure for increasing consent to participate (67.4%) and reducing withdrawal (21.8%).
Conclusions: A survey of CRCs revealed the reasons governing patient participation and withdrawal in cancer clinical trials, thereby providing a novel insight into strategies for promoting subject enrollment and reducing withdrawal from cancer clinical trials.

Introduction

Oncology is one of the most active fields of new drug development and clinical trials. However, poor accrual hampers participant enrolment and completion of clinical trials.[1,2] Only 2%–5% of adult cancer patients participate in clinical trials, and 25% of cancer clinical trials fail to recruit sufficient patients.[3] Participants can voluntarily withdraw or be involuntarily withdrawn from clinical trials. Withdrawal reduces the statistical power of clinical trials due an insufficient sample size and is one of the main reasons for clinical trial failure.[3–5] The reasons for withdrawal vary and may include health status deterioration, study violation, and investigator's decision, although voluntary withdrawal and loss to follow-up are the commonest reasons for withdrawal.[5,6] Thus, improving accrual and reducing withdrawal are essential for ensuring a successful clinical trial.

Clinical research coordinators (CRCs), such as research nurses, are core research professionals who coordinate and manage clinical trials.[7,8] In South Korea, new CRCs receive 40 h of training, and experienced CRCs receive 24 h of advanced training.[7] CRCs perform tasks, such as screening study subjects, patient education and acquisition of informed consent, scheduling clinical visits and contacting study subjects, completing case report forms, observing adverse events, and liaising with researchers and sponsors.[9–11] As CRC nurses work on the front lines from the beginning to the end of clinical trials,[12] they can best identify the main reasons for participation and withdrawal from clinical trials and suggest potential remedial measures. Many studies have assessed motivations for or barriers to clinical trial participation as well as the reasons for study withdrawal by surveying the participants or physicians.[4,13–16] However, CRCs may have different perceptions, from those of other nurses or physicians, about clinical trials.[17,18] Nevertheless, few studies have surveyed CRCs who coordinate cancer clinical trials. Previously, a study investigated 15 CRCs who coordinated phase 1 cancer clinical trials to determine their practices, perceptions of patient expectations, and the challenges that occur before, during, and after clinical trials.[19] With regard to the challenges in the recruitment phase, the maximum number of respondents (n = 5) cited that the level of explanation required depended on the

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patient's condition and attitude.[19] Furthermore, CRCs emphasized the need for a multidisciplinary approach during clinical trials.[19] A recent study qualitatively evaluated the perceptions of 21 CRCs about barriers to enrolling adult cancer patients and categorized responses into five themes: clinical trial protocol (e.g., frequent laboratory testing and hospital visits), communication barriers and cultural beliefs, financial barriers, patient status (e.g., performance status and comorbidities), and physician commitment.[20] The study identified some measures that can facilitate patient accrual, including the simplification of clinical trial protocols and addressal of communication barriers by increasing institutional and physician commitment.[20] In both studies, CRCs averred that sufficient explanation to patients and cooperation with other medical staff were essential for increasing patient enrollment in cancer clinical trials. Although these studies focused on the perception of CRCs, the small number of respondents and the qualitative study design limit the generalizability of the study's results.

Therefore, this cross-sectional survey of CRC nurses aimed to investigate participation and withdrawal in cancer clinical trials. Furthermore, we collected suggestions from CRCs on strategies to potentially increase enrollment and reduce withdrawal in cancer clinical trials.

Methods

Setting

This cross-sectional survey was conducted at four hospitals in Seoul, South Korea. Since 2010, Korea has ranked among the global top 10 countries with regard to the number of clinical trials.[21] All study centers were secondary or tertiary hospitals that were actively conducting cancer clinical trials. Data were collected for a six-month period between March and August 2021. This study was approved by the Institutional Review Board (Approval No. ewha-202111-0013-01) and all respondents provided informed consent prior to their participation in this study.

Questionnaire development

Based on earlier studies, we designed a questionnaire (Appendix 1) with key items that included the characteristics of respondents, characteristics of clinical trials, clinical trial participation, and study withdrawal.[22–24] Terminologies in the questionnaire were defined as follows: “study withdrawal” indicates the subject's voluntary or involuntary withdrawal (including discontinued intervention due to disease progression) from clinical trials at any point during the study period; “withdrawal of consent” was the subject's voluntary withdrawal of informed consent at any time following the provision of consent to participate in a clinical trial; “duration of enrollment” indicates the length of time from initiation of the clinical trial to completion of enrollment; “length of study” was the length of time from initiation to completion of the clinical trial.

Survey procedure

We used a convenience sampling strategy to collect surveys from 100 CRC nurses who were currently coordinating cancer clinical trials and had more than six months of clinical trial coordination experience. CRCs who consented to participate in the survey were asked to complete a questionnaire on the basis of one of the completed cancer clinical trials that they has coordinated. There was no overlapping clinical trial. Most (91%) of the questionnaires were retrieved directly, and some (9%) were returned via e-mail.

Data analysis

Descriptive statistics were used to summarize the survey results. Continuous data were non-normally distributed and are represented by the median with the range or the interquartile range (IQR). All analyses were performed using R version 4.1 (R Foundation, Vienna, Austria).

Results

Characteristics of respondents and clinical trials

The characteristics of the 100 CRCs and the corresponding clinical trials are presented in Tables 1 and 2, respectively. In the majority of the clinical trials, the numbers of targeted and actual enrollment were less than 10. Most subjects were aged 50 years or older and had never participated in clinical trials. The median duration of enrollment and length of study were 13 and 18 months, respectively.

Clinical trial participation

The CRCs responded that subjects learned about enrollment in the clinical trials from their physicians (97%), were motivated to participate in clinical trials because of expectations of treatment benefit (75%), trust in medical staff (24%), and economic benefits (1%). Of the 100 clinical trials included in the survey, 54 had enrolled subjects without any refusal of consent from the eligible patients who were invited to participate in the study. In the remaining 46 clinical trials, 151 [19.1% (IQR 10.6%–32.1%)] potential subjects refused to participate after being assessed for eligibility. Common reasons that were discerned by the CRCs for the patient's refusal to participate were concerns about adverse events (30.5%) and negative perception of clinical trials (29.8%) (Figure 1).

The CRCs indicated that the poor understanding of clinical trials by potential subjects is the principal challenge in obtaining consent for study participation (51%), followed by the fear of the risks of participating in clinical trials (23%) (Figure 1). Forty-six CRCs suggested measures to increase the number of enrollments from eligible patients. Most CRCs (67.4%) emphasized the importance of providing a detailed explanation about clinical trials, included information on the need for the research, research drugs, expected effects and risks, and research procedures, to potential subjects. Some of them suggested the utilization of audiovisual educational materials or online programs to improve the transfer of information to enhance the subject's understanding of the trial. Some CRCs (28.3%) suggested the need to improve the awareness of clinical trials through mass media. Other potential strategies included the reduction of blood sampling and sharing of patient experiences by other subjects.

Withdrawal

Withdrawal rates were 11.9% (IQR 0–55.1%) across the 100 cancer clinical trials. Figure 2 shows the reasons for study withdrawal, which includes mainly disease progression (70.6%), followed by adverse events (10.4%), withdrawal of consent (10.4%), lack of effectiveness (3.8%), use of contraindicated drugs (2.6%), and others (2.1%). Reasons for withdrawal of consent included personal issues (5.9%), frequent visit

Table 1
Characteristics of respondents.

Characteristics	Respondents (n = 100)
Female, n (%)	100 (100.0)
Age (years), median (range)	37 (25–47)
Research experience (months), median (range)	62 (6–216)
Affiliation	
Tertiary hospital, n (%)	98 (98.0)
Secondary hospital, n (%)	2 (2.0)
No. of clinical trials coordinated, median (range)	11 (1–40)
Phase 1, median (range)	1 (0–14)
Phase 2, median (range)	3 (0–11)
Phase 3, median (range)	5 (0–22)
Phase 4, median (range)	0 (0–10)

Table 2
Characteristics of clinical trials.

Characteristics	Clinical trials ($n = 100$)
Study phase	
Phase 1, *n* (%)	16 (16.0)
Phase 2, *n* (%)	28 (28.0)
Phase 3, *n* (%)	52 (52.0)
Phase 4, *n* (%)	4 (4.0)
No. of enrollments	
Targeted enrollments, median (range)[a]	6 (1–64)
Actual enrollments, median (range)[a]	8.5 (1–55)
Types of cancer	
Gastric, *n* (%)	15 (15.0)
Breast, *n* (%)	15 (15.0)
Lung, *n* (%)	12 (12.0)
Hepatobiliary, *n* (%)	10 (10.0)
Lymphomas, *n* (%)	9 (9.0)
Colon, *n* (%)	5 (5.0)
Others, *n* (%)	34 (34.0)
Demographics of subjects	
Male (%), median (IQR)	60.8 (40.0–85.0)
Age 18–29 years (%), median (IQR)	0 (0–0)
Age 30–39 years (%), median (IQR)	0 (0–6.5)
Age 40–49 years (%), median (IQR)	12.1 (0–25.2)
Age 50–59 years (%), median (IQR)	33.3 (13.5–50.0)
Age $\geq$ 60 years (%), median (IQR)	34.7 (14.3–70.4)
Previous experience of clinical trial (%), median (IQR)	0 (0–12.8)
Duration of enrollment (months), median (range)	13 (1–60)
No. of visits, median (range)[b]	21.5 (3–150)
Length of study (months), median (range)	18 (1–96)

IQR: interquartile range.
[a] In the case of a multicenter clinical trial, the number corresponds to the enrollments at each hospital.
[b] In 12 clinical trials, visits were planned until disease progression.

schedule (0.9%), frequent blood sampling and examination (0.7%), insufficient economic benefit (0.7%), and other reasons (2.1%).

Figure 3 shows the suggested measures to reduce study withdrawal. The CRCs suggested the provision of sufficient detailed explanation in advance before study enrollment (21.3%), supplementing the number of research staff (19.1%), simplifying protocols (11.2%), education programs (11.2%), economic benefits (10.1%), reducing wait time (9.0%), and a good attitude and attention from medical staff (6.7%). Other suggestions included improvement of the patient's adherence to oral drugs (e.g., through digital devices), interdepartmental cooperation, and an independent cancer clinical research room (e.g., dedicated room for the administration of consent and completion of case report form).

Discussion

The results of this study indicate the perceptions of 100 CRCs who were surveyed with regard to participation in and withdrawal from cancer clinical trials as well as the measures suggested by the CRCs to increase patient participation and reduce withdrawal in cancer clinical trials. With regard to the motivation for participation, we found that the principal motivation was medical benefit, which is consistent with the finding of a previous survey that was conducted several years ago wherein the majority of the nurses (92%) reported that subjects participated in clinical trials due to their wish for a cure.[17] This motivation apparently remains unchanged over time. Furthermore, the result was similar to the perceptions of patients and physicians that the prospect of receiving better treatment was the main reason for participation in clinical trials.[18] Moreover, patients in South Korea indicated their willingness to participate in clinical trials because of an expectation of better treatment (78.3%).[25]

In this study, the principal reasons for refusal to participate were concerns about adverse events and a negative perception about clinical trials. Concern about adverse events was the main reason for refusal to participate in several studies. Approximately 46% of patients refused to participate in antithrombotic trials due to concerns about adverse events[26] and, in a survey of Korean patients, apprehension about adverse events accounted for 83.9% of the reasons for refusal to participate.[25] However, the reasons for refusal to participate in clinical trials may vary. A systematic review and meta-analysis study summarized the reasons from 15 studies and showed that desire for other treatment, desire to choose own treatment, avoidance of protocol-based treatment, or preference for standard treatment were the commonest reasons for refusal to participate in clinical trials.[13] Other reasons included lack of sufficient explanation about the study, financial concerns, and dislike of participating in an experiment.[13,27]

The CRCs in our survey responded that they faced difficulties in making patients understand how the need for the clinical trial should overcome their concerns and negative perceptions. Thus, lack of sufficient explanation was one of the reasons for the patient's refusal to participate.[27] Therefore, the CRCs suggested that sufficient explanation should be provided to patients to increase their participation in clinical trials. In particular, some CRCs felt that the physician's explanation was more helpful than that of the nurses' explanation. This finding is consistent with the previous suggestions of CRCs that emphasized physician commitment.[20] However, most physicians do not have enough time to explain clinical trials to their patients.[28]

Disease progression was the main reason for study withdrawal because this study investigated cancer clinical trials. This result was consistent with that of previous studies. A study of 20 patients who withdrew or were withdrawn from cancer clinical trials showed that, in accordance with the clinical trial protocol, 13 patients (65%) were withdrawn due to disease progression.[14] Another phase 1 cancer clinical trial reported that disease progression accounted for 57.6% of the reasons for study withdrawal.[29] Disease progression is an uncontrollable factor that results in study withdrawal. Controllable factors included loss to follow-up, medication nonadherence, frequent visit schedule, frequent blood sampling and examination, insufficient economic benefit, and wait time, which accounted for 3.8% of study withdrawals in our study.

Adequate explanation about the necessity and protocol of clinical trials might reduce withdrawal of consent due to inconvenience (e.g., visit schedule, blood sampling/tests, and wait time). A previous study reported that communication between subjects and research staff reduces the intention to drop out.[4] Nonetheless, it might be difficult to devote much time to clinical trials because the number of clinical trials per CRC is excessively high, and the physician, who has a large impact on the motivation for participation by patients, is also burdened by medical tasks besides those in the clinical trials. Approximately 56% of research staff claimed that they did not have adequate support staff.[28] Therefore, the CRCs in our study suggested the supplementing of research staff as a secondary measure.

Furthermore, public education programs are needed to change the negative perception about clinical trials and to convey the positive effects of clinical trials. Although many measures have been developed to protect clinical trial subjects, patients still exhibit high reluctance to participate in clinical trials. Therefore, improving awareness of clinical trials through various media and in-hospital education programs will increase the participation rate of subjects.[30]

This study has some limitations. First, as this study surveyed CRCs who were responsible for cancer clinical trials, it is difficult to generalize the results to clinical trials for other diseases. Second, perceptions about

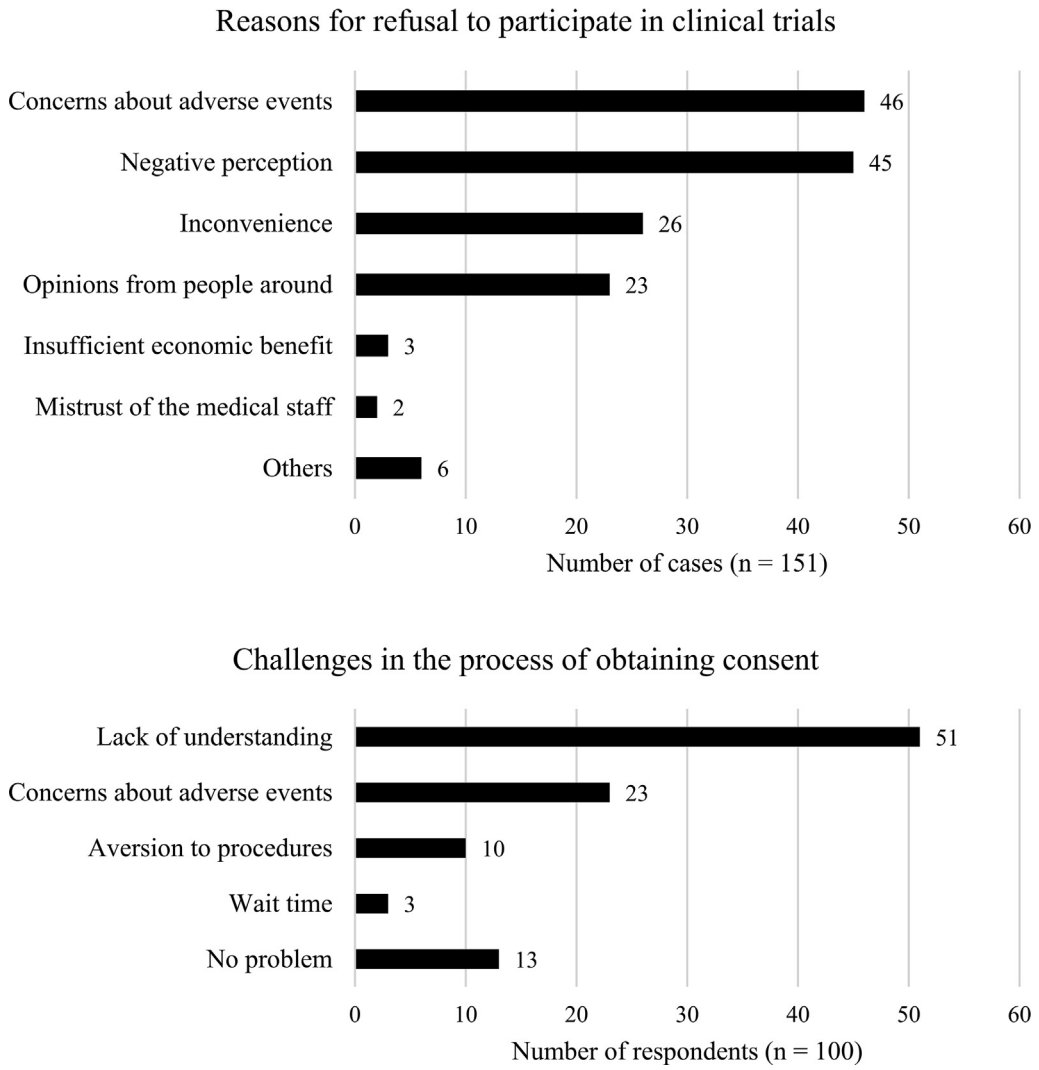

Figure 1. Reasons for refusal and challenges to the informed consent process.

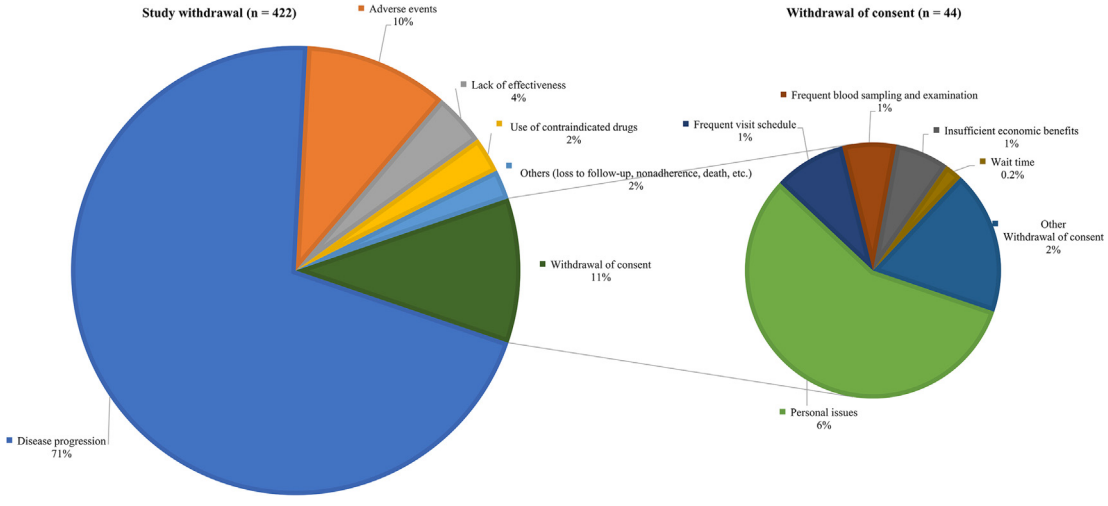

Figure 2. Reasons for study withdrawal and for withdrawal of consent.

clinical trials might differ between CRCs and subjects. In a previous study, a wide gap between research staff and patient attitudes and beliefs about cancer clinical trials was identified.[18] This limitation may have been partially addressed because of the number of cases for each reason of refusal, study withdrawal, and withdrawal of consent that were collected in our study.

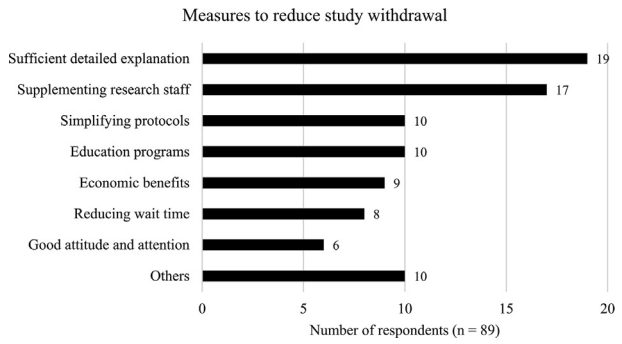

Figure 3. Measures to reduce study withdrawal.

Nonetheless, the strength of this study is that the results of this study have significance because comprehensive information on participation and withdrawal in cancer clinical trials was investigated through a survey of CRCs, who are primarily responsible for actual clinical trial management.

Conclusions

The results of this study provide a novel insight into strategies for promoting subject enrollment and reducing withdrawal in cancer clinical trials. Research staff need to elaborate the information and procedures of clinical trials for enrolling subjects by reducing their vague fears about risks and to reduce study withdrawal.

Supplementary material

To access the supplementary material accompanying this article, visit the online version of the *Asia-Pacific Journal of Oncology Nursing* at https://doi.org/10.1016/j.apjon.2021.12.015.

Declaration of competing interest

None declared.

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