



Qualitative analysis of clinical research coordinators' role in phase I cancer clinical trials



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ABSTRACT

Background: Clinical research coordinators play a pivotal role in phase I cancer clinical trials.

Purpose: We clarified the care coordination and practice for patients provided by clinical research coordinators in phase I cancer clinical trials in Japan and elucidated clinical research coordinators' perspective on patients' expectations and understanding of these trials.

Method: Fifteen clinical research coordinators participated in semi-structured interviews regarding clinical practices; perceptions of patients' expectations; and the challenges that occur before, during, and after phase I cancer clinical trials.

Discussion: Qualitative content analysis showed that most clinical research coordinators observed that patients have high expectations from the trials. Most listened to patients to confirm patients' understanding and reflected on responses to maintain hope, but to avoid excessive expectations; clinical research coordinators considered avoiding unplanned endings; and they aimed to establish good relationships between patients, medical staff, and among the professional team.

Conclusions: Clinical research coordinators were insightful about the needs of patients and took a meticulous approach to the phase I cancer clinical trial process, allowing time to connect with patients and to coordinate the inter-professional research team. Additionally, education in advanced oncology care was valuable for comforting participants in cancer clinical trials.

1. Introduction

Phase I clinical trials are designed primarily to evaluate the safety and toxicity of new agents, establish their pharmacokinetic properties, and determine appropriate doses for subsequent phase II and phase III studies. Recently, trials are being complicated by the promotion of “precision medicine.” Additionally, as American Cancer Society said that this kind of trials have the highest risk compared with other phases of trials. Therefore, they require research teams to consider the risks and benefits carefully [1]. The impact makes clinical trials more time consuming to explain to terminally ill research participants [2]. Patients enrolled in phase I cancer trials are usually those with advanced cancers that are refractory to standard treatments [3] and 90-days mortality rate is over 15% [4]. As the American society of clinical

oncology (ASCO) pointed out in 2015, these kinds of trials have improved their response rate as a therapeutic option for patients as participants [5]. However, there are three conceptual problems. (1) Phase I cancer trials provided many different compounds and regimens, and are highly variable. (2) The trials do not have therapeutic intent. (3) The drugs provided in the specific way for conducting trials, and the participants are exposed to the new agents in testing conditions.

Patients with advanced cancers who are refractory to standard treatments tend to have high expectations for the clinical benefits that may come from participating in clinical trials [6,7]. This is despite tumor response rates being typically only 4–10% [8,9] and grade 4 adverse events occurring in 14–30% of patients [8,10].

To manage patients' expectations appropriately, it is essential to promote and maintain high levels of scientific and ethical integrity in

Abbreviations: CRC, Clinical Research Coordinators; CRN, Clinical Research Nurses; CTN, Clinical Trial Nurses; RNC, Research Nurse Coordinators

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clinical research. Therefore, for early-phase clinical trials, multi-disciplinary approaches including clinical research coordinators (CRCs) are needed. Worldwide, CRCs comprise clinical research nurses (CRNs), clinical trial nurses (CTNs), research nurse coordinators (RNCs), and study coordinators. The preferred term in Japan is CRCs, because Japanese CRCs have various healthcare professionals such as nurses, pharmacists, lab technicians and others. Regarding the role of CRCs, some studies have reported that they are responsible for numerous aspects of clinical trials including patient protection, study coordination, data management, participant recruitment, compliance with regulatory requirements, and reporting [11–14].

Especially in phase I cancer clinical trials, where patients typically have severe physical and mental burdens, the care coordination and practice are critical parts of the CRC role. Therefore, it should be clear. Elucidating this activity will enhance the CRCs performance and improve the quality of clinical research; therefore, this study qualitatively examined the care coordination and practice provided by CRCs, and the associated challenges that they face in phase I cancer trials to improve educational resources.

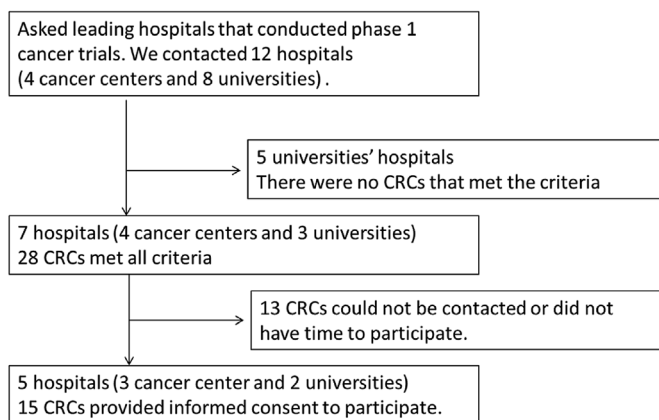
2. Materials and methods

We conducted semi-structured interviews with Japanese CRCs who were conducting phase I cancer trials and analyzed interview data using the qualitative content analysis method.

2.1. Participant recruitment

Inclusion criteria for this study participants included the following: (1) working at facilities conducting phase I cancer trials, (2) more than 2 years' experience as a CRC (based on the certification requirement of clinical research professionals), and (3) involved in at least three phase I cancer protocols (including being currently involved in one). We adopted the third inclusion criterion because we considered that formation of empirical knowledge requires being involved in phase I cancer protocols multiple times. There is no exclusion criteria.

For participant recruitment, we contacted twelve hospitals that conducted phase I cancer clinical trials and who met the inclusion criteria. The twelve hospitals comprised four cancer centers and eight university hospitals. Eight hospitals were designated as “Translational Research Centers” or “Clinical Research Centers” by the Japanese government. Then, seven hospitals reported having 28 CRCs who met the study criteria. There were no eligible CRCs in five hospitals. After contacting the 28 CRCs by mail or e-mail, 15 CRCs at 3 cancer centers and 2 university hospitals showed their intention to participate in the study. We obtained written informed consent from all participants



Note. CRCs = clinical research coordinators.

Fig. 1. Participants' recruitment. Note. CRCs = clinical research coordinators.

(Fig. 1).

2.2. Data collection

This study was approved by the Ethics Committee of the Graduate School of Medicine, University of Tokyo. Semi-structured interviews were conducted by one researcher (N.F.), who considered the interview content among the authors including one CRC (N.F.), two cancer nursing researchers (Y.Shi. and K.K.), and one nursing researcher who specialized in qualitative research (R.O.) before meeting the CRCs. This study was conducted in accordance with the Declaration of Helsinki.

The researcher met each CRC in a private room so that participants' privacy would be protected, explained the study purpose, informed them that their identities would be kept anonymous, and allowed them to ask questions for clarification. Then, written informed consent was obtained from each participant. There were no time constraints affecting interview length.

Interviews were audio recorded and then transcribed verbatim. Three sets of interviews were conducted: before, during, and after the trial. This method was devised based on the existing literature [6], a general trial timeline, and our clinical experience. Each set contained the following three topics: Patients: “What needs and expectations do patients and their families have?” (For example, physical conditions, mental conditions, and the participants' expectations); Clinical Practice: “How do you care for the patients and their families?” (For example, the collaboration with other team members); and Challenges: “What challenges do you face?” Participants were encouraged to provide detailed descriptions of their experiences (Fig. 2).

2.3. Data analysis

Qualitative content analysis was performed to divide the transcribed data [15] into content units; each had a specific meaning, and codes were created based on these. Codes were grouped based on similarities into “categories.” The units, codes, and categories were decided through deliberation among the researchers. Then, the data were classified based on the three topics of Patients, Clinical Practices, and Challenges (See Data Collection section and Fig. 2). Then, one coder with experience in hospital-based nursing (a practice nurse with advanced experience in oncology), conducting phase I cancer clinical trials, and conducting qualitative studies as a principal investigator validated the coding. We also calculated intercoder reliability regarding choices of code and unit, and the resulting level of agreement between coders was tentatively acceptable (77%). Therefore, the coder and the interviewer discussed the units that they disagreed until they reached consensus. Finally, the authors including two CRCs (N.F. and Y. Sa.), two cancer nursing researchers (Y.Shi. and K.K.), one nursing

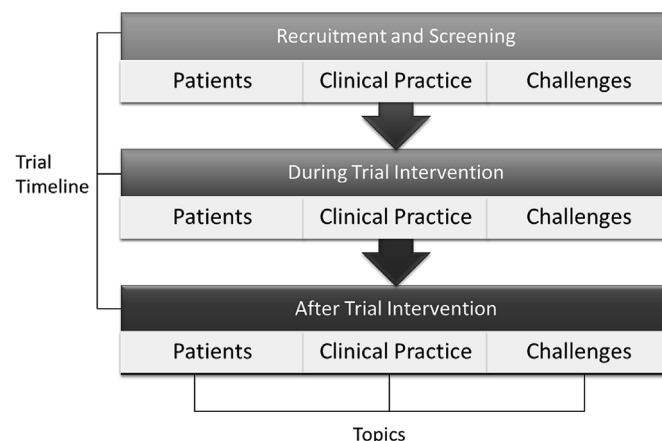


Fig. 2. Structure of interview guide.

Table 1
Demographic characteristics of participating CRCs (N = 15).

Characteristic		n	(%)
Sex	Female	14	(93)
	Male	1	(7)
Age (years) (Mean = 39.9)	30–39	8	(53)
	40–49	5	(33)
	≥50	2	(13)
	0–4	2	(13)
Length of professional career as a CRC (years) (Mean = 7.4)	5–9	8	(53)
	≥10	5	(33)
	0–4	2	(13)
Licensure	Nurse	13	(87)
	Pharmacist	2	(13)
No. of protocols involved in	3–9	7	(47)
	10–19	5	(33)
	≥20	3	(20)
	0–9	1	(7)
No. of patients cared for	10–49	8	(53)
	≥50	6	(40)
	0–9	1	(7)

Note. CRCs = clinical research coordinators.

researcher who specialized in qualitative research (R.O.), and two physicians working in phase I cancer clinical trials (F.N. and S.I.) confirmed the appropriateness of the codes and categories.

3. Results

3.1. Participants' characteristics

Participants' characteristics are shown in Table 1. Fourteen participants (93%) oversaw more than 10 patients undertaking phase I cancer trials. These patients in the trials required hospitalization. Interview durations ranged from 45 to 108 min (average 75 min).

3.2. Recruitment and screening

Information collected from the CRCs is shown in Table 2. We classified the codes for the patients' topics into three categories: (1) high expectations of the trial, (2) physical condition, and (3) mental

Table 2
CRC experiences regarding issues during trial recruitment and screening.

Topics	Category	Code	N = 15		
Patients	High expectations of the trial	Have high expectations	13		
		Will try anything to get better	11		
		Actively participate in trials through self-selection	6		
		Family members have high expectations	6		
		Do not have excessively high expectations when given adequate information	4		
	Physical condition	Good	8		
		Unstable	8		
	Mental condition	Nervous about receiving a new agent	7		
		Have received bad news about their prognosis	6		
		Afraid of dying	4		
		Refused to participate because it was a trial and they needed to be hospitalized	2		
		Clinical Practices	Helping patients to understand clinical trials	Listens to patients and reflects on their responses	12
				Makes the time to give patients information	9
Supports patients' hopes but discourages unrealistic expectations	9				
Explains cases where patients cannot participate in the trial	8				
Asks questions to confirm that patients understand	3				
Obtaining informed consent	Meets with patients after they have talked to an investigator		11		
	Counsels patients without an investigator during visit to hospital		10		
	Present at talks between an investigator and patients		5		
Challenges	Communication with severely ill patients		Level of explanation required depends on the patient's condition and attitude	5	
			Dealing with patients who are ineligible for a trial is difficult	3	
			Need to develop individualized communication strategies	1	
	Time shortage		Need more time to collect information on patients, assess their levels of understanding, and give them emotional support	3	
			Need to meet patients after the first visit in hospital to get more information	3	

Note. CRCs = clinical research coordinators.

condition.

Thirteen CRCs observed that some patients had excessively high expectations of treatment efficacy and 11 CRCs reported that patients would try anything to get better. Further, eight CRCs reported that patients were in good physical condition. The same number of CRCs had perceived an unstable mental condition. Finally, seven CRCs reported that patients were nervous about receiving the new agent.

Codes for the clinical practices topics were classified into two categories: (1) helping patients understand clinical trials and (2) obtaining informed consent. Twelve CRCs listened to the patients' comments and carefully explained how they would be treated, simultaneously assessing the patients' understanding and trying to help them maintain a positive attitude. Nine CRCs supported the patients' hopes; however, they discouraged their unrealistic expectations.

Codes for the challenges were classified into two categories: (1) communication with severely ill patients and (2) time shortage. Five CRCs believed that the level of explanation required was dependent on the severely ill patients' situation and attitude. The second, three CRCs, stated challenges related to difficulties in dealing with patients who were ineligible for trials and the need to meet with them again to explain things further.

3.3. During trial intervention

Information collected from the CRCs regarding issues experienced during trial intervention is shown in Table 3. Codes for the patients' topics were classified into three categories: (1) mental condition, (2) physical condition, and (3) high trial expectations.

Nine CRCs reported that patients' symptoms were initially under control; however, 7 CRCs reported patients' burden increased from their disease, and 6 CRCs considered that patients experienced increasing mental distress, especially before and after physical examinations.

Codes for the topics of clinical practices were classified into four categories: (1) making frequent contact, (2) involving medical staff in clinical trials (in addition to research staff), (3) supporting patients' autonomy, and (4) preparing for the post-trial period. Thirteen CRCs made frequent contact with patients to assess them for adverse events and 12 CRCs provided support for and gained the trust of patients and

Table 3
CRC experiences regarding issues during trial intervention.

Topics	Category	Code	N = 15	
Patients	Mental condition	Symptoms were initially under control	9	
		Increasing burden of disease	7	
		Increasing mental distress, especially before and after physical examinations	6	
		Worry about whether to continue to participate in the trial	5	
		Worry about continuing participation in the trial if adverse events are worse than anticipated	1	
		Worry about whether the drug will be effective when there are few adverse events	1	
	Physical condition	Some patients with cancer worsen rapidly	6	
		Some have pain	4	
		Physical condition rarely changes compared with before the trial	3	
	High expectations of the trial	Patients have high expectations	4	
		Family members have high expectations	2	
	Clinical Practices	Making frequent contact	Visits bedsides daily during hospitalization	13
			Visits to assess patients for adverse events	13
Visits to support patients and their family members, and to gain their trust			12	
Visits to inform patients of the trial schedule			5	
Collaborates and communicates with clinical nurses			10	
Involving medical staff in clinical trials		Shares information with other medical staff	8	
		Promotes good relationships between patients and staff	6	
		Coordinates between an investigator and patients	4	
Supporting patient autonomy		Requests bedside care from primary care team nurses	3	
		Maintains patients' quality of life	5	
Preparing for post-trial period		Helps patients and their families make informed decisions	4	
		Gives information to patients in advance to try not to upset them	5	
		Talks about what happens after the trial	3	
	Looks ahead to the patients' futures	2		
	Talks about all eventualities	2		
	Maintains family support after giving information to patient	2		
Challenges	Need for team approach	Prepares patients for post-trial treatment.	2	
		Assesses patients' ability to cope	2	
		Reinforcement of the inter-professional team approach is necessary	6	
		Need to coordinate a good relationship between patient and their investigator	2	
	Care for severely ill patients	Need for mental health professionals to help care for patients	2	
		Need to know about the daily workflow of nurses as a CRC	1	
		Encouraging patients to maintain hope but not raising unrealistic expectations is difficult	5	
		Unsatisfied with own skills in caring for deteriorating patients and seeks improvement	5	
		Recognizes and manages high-risk patients	3	

Note. CRCs = clinical research coordinators.

their family members. Six CRCs made pivotal efforts to promote good relationships between patients and staff, and 10 emphasized the importance of collaboration and communication with clinical nurses.

Codes for the topics of challenges were classified into two categories: (1) need for a team approach and (2) care for severely ill patients. Six CRCs considered that reinforcement of the inter-professional team approach was necessary, and five CRCs found that encouraging patients to maintain hope, but not raise unrealistic expectations, was difficult.

3.4. After trial intervention

Information collected from the CRCs regarding issues experienced after the trial intervention is shown in Table 4. Patients' topics codes were classified into four categories: (1) what patients do after the trial, (2) physical condition, (3) what patients think about the trial, and (4) mental condition.

All CRCs had patients who had participated in other phase I trials after participation in their trials. Twelve reported that almost all patients had progressive disease, which resulted in termination of their participation in the trials. Nevertheless, most CRCs said that patients' performance status after the trial was more stable than it was before the trial treatment. Moreover, nine CRCs observed that some patients received positive feedback after trial participation and seven said that other patients were shocked to hear their results.

Codes for the topic of clinical practices were classified into two categories: (1) relieving feelings of anxiety and abandonment and (2) handing over care responsibilities. Eight CRCs attentively listened to what patients had to say and tried to maintain open communication to

relieve the patients' feelings of being abandoned by the experts. The same number of CRCs said that they were concerned about a smooth handover of patients to the general medical care team.

Codes for the topics of challenges were classified into only one category: (1) involvement in post-trial care. Almost half of the CRCs said it was difficult to draw a clear line between the responsibilities of CRCs and those of the medical staff who took over the patients' care after the trial intervention.

4. Discussion

Our study revealed that CRCs who were involved in phase I cancer clinical trials played crucial roles. Critical findings included that CRCs listened to patients and reflected on responses to maintain hope; however, they avoided excessive expectations; CRCs considered well-planned withdrawal; and CRCs aimed to establish good relationships between patients, medical staff, and among the professional team.

4.1. Recruitment and screening

CRCs need well-balanced insight between patients' expectation and hope, sufficient communication and explanations, and support of patients' decision-making. Prior research showed that patients in this period face their first decision-making process [16], and they become "therapeutic optimists" as one of their coping strategies [17]. As CRCs reported, some patients with severe physical and mental burdens tend to have excessively high expectations regarding the efficacy of the trial treatment. Research professionals need to avoid providing their patients with unrealistic expectations and to need to maintain a sense of

Table 4
CRC experiences regarding issues after trial intervention.

Topics	Category	Code	N = 15
Patients	What patients do after trial	Some are enrolled in other trials	15
		Many are discharged or transferred to other hospitals	7
	Physical condition	Disease is progressive	12
		Physical condition is stable	10
	What patients think about the trial	Some give positive feedback about participation	9
		Few become upset	3
		Some are relieved after participation	2
	Mental condition	Some are shocked to hear the results	7
		Ask to be able to contact the CRC even after the trial is complete	5
		Hate the idea of having no treatment	4
			4
Clinical Practices	Relieving feelings of anxiety and abandonment	Listens to patients attentively	8
		Tells patients that the team is available for consultation even after the trial is complete	8
		Tells patients they can contact the CRC even after the trial is complete	8
		Gradually decreases frequency of visiting patients to affect a smooth transition to management by the original team	5
		Avoids mentioning transfer to another hospital to stop patients from feeling abandoned	4
	Handing over care responsibilities	Reduces patient anxiety and recommends various forms of diversion by talking with them	4
		Concerned about ensuring a smooth transition when referring patients back to the original care team	8
		Visits patients even after office hours are over	7
		Visits patients even after the trial is complete	6
		Recommends various forms of diversion	4
Challenges	Involvement in post-trial care	Drawing a clear line between the responsibilities of CRCs and those of medical staff taking over patients' care after the trial intervention is difficult	7
		Dealing with patients is especially difficult when the trial intervention has been ineffective and no other treatment option remains	4
		Hard to care for dying patients and their families	3
		Hard to spend time with patients after the trial	3
		Need to consider how to work as a member of the professional team after the trial	2

Note. CRCs = clinical research coordinators.

treatment-specific optimism to improve patients' mental health outcomes. Therefore, CRCs need well-balanced insight between maintaining hope and avoiding excessively high levels of expectation [18] in recruitment and screening. Since the complexity of clinical research is increasing and as Phase I cancer trials have the highest risks, CRCs need to carefully explain to patients how they will be treated, assessed the patients' understanding, and empathize with the patients' perspective.

Furthermore, it is important to explain to patients the possibility that they may not be able to participate in the trial because of the exclusion criteria. Almost all patients in phase I cancer trials have no remaining standard anticancer treatments available to them, which is likely why they have high expectations of trial treatments, as was the case in our study. However, these trials are mainly aimed at evaluating the safety and toxicity of new therapeutic agents, rather than assessing the therapeutic benefit of the trial drug. To help patients understand the trials, CRCs need to provide sufficient face-to-face communication to assess carefully patients' and their families' feelings and personal situations. This communication is also important into helping patients and their families make effective decisions.

Finally, CRCs considered meeting patients and their families without investigators to confirm their understanding. Although, investigators (clinicians), themselves, generally explained on the trials and obtained their consent in Japan. Compared with the U.S., the patient-doctor communication style of Japan tend to be more hierarchical and paternalistic [19], so many patients hesitated to ask their clinician honestly. Therefore, the advocate for the patient as one of the roles of CRCs is important.

4.2. During trial intervention

CRCs showed in our study that during trial intervention, patients' mental condition fluctuated, especially before and after evaluation. Therefore, CRCs need to maintain frequent contact, protect patients' autonomy, promote a team approach, and debrief patients after the study.

CRCs that participated in the study stated that they had frequent

contact with their patients to assess adverse events, confirm the trial schedule, and provide psychosocial support as needed. As showed above, in Japan, almost all phase I cancer trials had been conducted in inpatient setting. CRCs could see their patients frequently. On the other hand, CRCs should consider carefully the recruit of the terminally ill patients, because hospitalization usually restrains a person's activities. Previous reports have demonstrated that regular visits and attention from hospital staff are likely to be psychologically beneficial, and they allow for early detection of symptoms and prompt treatment of patients [20]. Moreover, frequent visits increase opportunities for communication between CRCs and clinical nurses or other medical staff members. The amount of attention patients receive during clinical trials makes them feel special and reinforces the perception that they are receiving the best possible care [6]. Frequent contact with patients is a principal role of CRCs, and they care about the relationship between patients and other medical staff by keeping a suitable distance from patients.

Furthermore, CRCs in this study supported patients and their families to help patients maintain their autonomy. A previous study showed that patients participating in trials sometimes feel they are not in control of their lives [6]. Placing a high value on patient quality of life can help address this. Because clinical trials can be coordinated most effectively by CRCs [11,14], maintaining a well-balanced relationship with patients and establishing good relationships between patients and medical staff is crucial. This also helps prepare for patient handover after trial participation is complete. Clinical trials are a temporary endeavor. They have time limitations; therefore, CRCs need to prepare for post-trial interventions.

4.3. Post-trial interventions

Our findings revealed that providing mental support and implementing a smooth transition are critical components of post-trial interventions.

As many CRCs said in our study and the literature showed, the patients' diseases are progressive and withdrawals are usually a result of toxicity [6]. As we already mentioned above, CRCs need to prepare

patients for these eventualities during the trials. To ensure a smooth transition when referring patients back to their clinical care teams from the research team, many CRCs need to stay in touch with their patients, even after their own roles as clinical research professionals have ended.

After the trial, they listened attentively to what the patients had to say, and help alleviate the disappointment that the new agent had been unsuccessful, while simultaneously reducing patients' fears about being abandoned. This approach was considered as executing a “well-planned withdrawal” [21]. This literature review showed that a satisfactory ending should be prepared for at the beginning of the trials and it should be a part of the whole process. An unplanned ending appears as a sudden cessation, and it could potentially enhance negative feelings of patients such as sadness, abandonment, and loss. Therefore, it is important to have a well-planned ending at the start of the trial.

CRCs in phase I cancer clinical trials need to comfort patients who are heavily burdened by the treatment process and whose condition fluctuates with their physical and psychosocial status [22–24]. Studies have shown the impact of psycho-oncological interventions for advanced cancer patients such as reducing symptoms, encouraging emotional adjustment, improving their knowledge about their disease and treatment, providing social support, and improving quality of life [25,26] Furthermore, researchers also need to consider the requirements for the support of cancer patients by multidisciplinary team members. Especially, CRCs need to collaborate with clinical nurses and social workers to mitigate the bad feelings in stressful time of their patients [27].

4.4. Study limitations

As with any qualitative research study, it is difficult to generalize our results. Furthermore, we had a small sample of 15 participants because phase I cancer trials in Japan are only conducted at some cancer centers and university hospitals. In future research, we recommend using a large sample of participants. Moreover, we recommend evaluating the direct patient care of CRCs, as this can affect patient outcomes.

5. Conclusions

Initially, CRCs assessed the obstacles to patients' accurate expectations and understanding of the clinical trials, and tried to manage these to maintain patients' hope. Thereafter, they attempted to establish good relationships by liaising between patients and medical staff even after the completion of the trial. CRCs were insightful about the needs of patients and took a meticulous approach to the phase I cancer clinical trial process, allowing time to connect with patients and to coordinate the inter-professional research team.

Conflict of interest

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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