Oral Agents

Challenges with self-administered medication adherence in clinical trials

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BACKGROUND: In oral agent clinical trials, patients may not be adherent to self-administration of study medication; this nonadherence can affect validity and reliability. Many factors contribute to nonadherence to protocol requirements, and managing patients with fidelity issues is the responsibility of the research team.

OBJECTIVES: The aim is to identify which group (patients, physicians/principal investigators, nurses, or other personnel) research nurses report as most responsible for protocol nonadherence and to characterize the most observed causes and contributors to nonadherence within each group.

METHODS: Sixty-seven protocol nurses completed a nine-question survey developed from pilot data. Descriptive statistics and ordinal regressions addressed the objectives of the study.

FINDINGS: More than half of the nurses observed clinical trial nonadherence in their practices. Nurses identified challenges regarding physician, patient, and nurse factors. The most frequently identified causes included patients’ forgetfulness, refusal to undergo study procedures, inadequate family or caregiver support to complete study activities, ineffective communication, and collaboration within the research team.

KEYWORDS
adherence; oral agents; protocol; research; assessment; patient-reported outcomes

DIGITAL OBJECT IDENTIFIER
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study by Flock et al. (2017), in which the researchers interviewed oncology nurses caring for patients on clinical trials, challenges included knowledge deficits on details, logistics in the protocol, and scope of the trial. In addition, there was a perceived need for advanced skills in responding to and managing patients’ expectations, perceptions, and emotional concerns (Flock et al., 2017).

**ECONOMIC COSTS OF BREAKING PROTOCOLS:** Although there are potential clinical costs to current and potential patients if protocols are violated, penalties also may be levied from the FDA. Penalties could be a warning letter; disqualifications, restrictions, or debarments; and even criminal prosecutions, prison, or fines. Therefore, it is essential to address the cause of patients’ nonadherence to oral medication and protocol requirements in clinical trials. In conducting a clinical trial to demonstrate the effectiveness of a drug, the protocol guidelines must be vigorously followed to obtain rigorous and usable data for analysis and improved patient outcomes (Friedman, Furberg, DeMets, Reboussin, & Granger, 2015).

Sponsors of clinical trials can mount pressure on the research team to meet maximum accrual within a specific time frame. In an effort to meet this accrual goal and not lose the outside grant funding, the research team may decide to enroll patients who are not likely to adhere to the protocol requirements and may not be appropriate candidates for the study (Agoritsas et al., 2011). The role of the sponsor, patient–provider relationship, disease, treatment, patient characteristics, and socioeconomic factors significantly affect adherence. Physicians and research nurses subscribe to the notion that patients are most likely to deviate from the protocol requirements because of the side effects from the study medication and the tests and procedures they must complete while in the study (Agoritsas et al., 2011).

**PROTOCOL BREAKS:** Sweetman and Doig (2011) reviewed 80 studies to determine how often studies reported protocol violations; they found 15%–24% containing protocol violations. Violations were categorized into one of five types: enrollment, randomization, study interventions, patient compliance, and data collection. Liberal criteria were applied, and only violations that affected safety were considered. Thirty-two percent of the studies evaluated failed to provide useful information on protocol violations (Sweetman & Doig, 2011).

The FDA and clinical trial sponsors continue to refine designs and monitoring for protocol violations, but drug developments, such as oral agents, provide emerging challenges that result in knowledge gaps (Muluneh et al., 2018). Clinical trial nurses are well-positioned to observe protocol violations, ensuring patient safety. The current study addresses knowledge gaps about nonadherence to oral agents in clinical trials, as reported by clinical trial nurses.

**ADHERENCE AND NONADHERENCE:** According to the World Health Organization, adherence to oral agent administration and protocol requirements is affected by healthcare systems or patient–provider relationship, disease, treatment, patient characteristics, and socioeconomic factors (Zolnierek & Dimatteo, 2009). Communication can be challenging, particularly in the exchange of information among healthcare providers.

Primary underlying causes for noncompliance of protocol requirements include time-consuming, demanding procedures; complicated protocols (difficult-to-understand requirements); and inadequate interprofessional communication. According to Given, Spoelstra, and Grant (2011), 50 years of research across diseases found an overall nonadherence rate of 25%. Carelessness about taking medications (80%), forgetting to take medication (30%–60%), purposely skipping doses (35%), late dosing (27%), concerns about side effects (17%), and not understanding written materials about the prescription (20%) were listed as some of the reasons for nonadherence in oral agent clinical trials (Given et al., 2011).

**ORAL AGENTS:** With the introduction of clinical trials, the approach to patient treatment has been revolutionized. Clinical trials involving the comparison of new treatments to standard treatments have contributed to a better understanding of treatment benefits and risks. In terms of moving science forward, clinical trials are considered the gold standard contributing to clinical science and improved patient care (Hammer, Eckardt, & Barton-Burke, 2016). Use of oral agents in clinical trials has increased since 2005, and exponential growth is predicted (Moody & Jackowski, 2010). Globally, an estimated 25%–50% of all new antineoplastic agents in development will be oral agents (Oncology Nursing Society, 2017; Weingart et al., 2008). This growth continues despite the significant challenges that promote nonadherence to oral agents (Spoelstra et al., 2013). Many patients with cancer believe that oral agent medications are not as toxic as IV chemotherapy and, as such, willingly choose the oral option over IV (Weingart et al., 2008). These decisions are made without the knowledge that chemotherapeutic agents have a narrow therapeutic index and different toxicity profile, placing patients at increased risk for harmful effects (Weingart et al., 2008).
Because oral agents have the potential to cause harm, it becomes the responsibility of the healthcare team to examine better ways to collaborate with staff, particularly nursing staff, to support patients and address nonadherence and safety issues to improve care (Weingart et al., 2008).

It is an ethical imperative that patients and caregivers be educated to understand the potential dangers associated with oral agents. Providers must collaborate with nurses to care for patients receiving oral agents to ensure patient and caregiver safety during treatment by monitoring and facilitating adherence. Healthcare providers should identify barriers and implement strategies to ensure adherence to improve clinical outcomes (Weingart et al., 2008).

RESEARCH NURSES: Nurses play a significant role from the inception of the study to completion. Roles include effective operation of research protocols in collaboration with the principal investigator and study sponsor, assessment of patients for protocol eligibility through personal interviews and medical record reviews, collaboration with the interprofessional team, coordination, evaluation, and follow-up with patients participating in the clinical trial. Research nurses contribute significantly to research integrity, care coordination, evaluation, and follow-up of the clinical trial (Bevans et al., 2011). The nurse input expedites the conduct of different phases of the trial and correlates to the enhanced quality of the trial (Spilsbury et al., 2008). In a role delineation study of clinical trial nurses, Purdom, Petersen, and Haas (2017) determined the practice as being multidimensional. An eight-dimensional model was delineated that included care, manage study, expert, lead, prepare, data, advance science, and ethics.

Objectives
The purpose of the current study is to identify which group (patients, physicians/principal investigators, nurses, or other personnel) research nurses report as most responsible for protocol nonadherence to oral agents and characterize the most observed causes and contributors to protocol nonadherence within each group.

Methods
The current study took place at a National Cancer Institute (NCI)–designated comprehensive cancer center. A convenience sample of all oncology research nurses was invited to participate (N = 232). The inclusion criterion was being a research nurse engaged in the management of patients on clinical trials. Sixty-seven nurses completed the study for a response rate of 29%.

Procedures
The survey was conducted using a Qualtrics tool and was sent via intranet with two subsequent reminders. The survey site remained open for a four-week period. Because this was a qualitative improvement initiative, institutional review board approval was not required.

Survey Development and Validation
A pilot survey of 10 oncology research nurses in the same NCI-designated comprehensive cancer center was conducted to identify perceived barriers to the challenges in protocol requirement compliance. Data from the pilot study were used to generate the questions for the current study. In addition, nurse content experts evaluated the pilot findings and determined the four different populations to be examined. The populations included patients, physicians/principal investigators, nurses, and other personnel. The investigator-developed survey included nine questions; four questions characterized demographics and practice setting, and five questions examined compliance to oral agents and protocol requirements in clinical trials. Nurses

FIGURE 1.
CONTRIBUTORS TO PROTOCOL NONADHERENCE

CONTRIBUTORS TO NURSE NONADHERENCE
- Missing an item in the research timeline
- Procedures not scheduled according to the research timeline
- Difficulty communicating protocol requirements to the patients
- Lack of or ineffective communication with community providers about need for specific laboratory tests per protocol requirement
- Study materials not given to patients (e.g., research diaries, study calendars)

CONTRIBUTORS TO PATIENT NONADHERENCE
- Forgetting to take the study medication
- Not understanding the protocol process
- Not documenting when the study drug was taken per protocol
- Inconsistent follow-up with laboratory testing
- Patient refusal to undergo study procedure
- Inadequate family or caregiver support to complete study activities
- Not taking medication as prescribed

CONTRIBUTORS TO PHYSICIAN/PRINCIPAL INVESTIGATOR NONADHERENCE
- Orders not written in a timely manner
- Study orders not released when written
- Study prescription not released to the correct pharmacy
- Ineffective communication with the research nurse or staff
- Study assessment (i.e., performance status) not completed with patients in a timely manner

CONTRIBUTORS TO OTHER PERSONNEL NONADHERENCE
- Local hospitals not reporting a patient’s hospitalization during the study
- Not reporting information to the sponsor in a timely manner
- Not performing the required tests per protocol
first were asked to rank which of four groups (patients, physicians/principal investigators, nurses, or other personnel) was most associated with nonadherence. Additional questions then established rankings for group-specific contributors to protocol nonadherence reported in the literature. The number of categories varied by group, with each having a “fill in other” category. There were seven patient contributors, five physician/principal investigator contributors, five nurse contributors, and three other personnel contributors, as seen in Figure 1. These questions provided ranking of contributions within each group.

**Analysis**

Descriptive statistics were completed for demographic variables and were used to characterize the populations (patients, physicians/principal investigators, nurses, or other personnel) most associated with nonadherence. Descriptive statistics also were used to characterize the percentage of observed nonadherent trial participants. To evaluate which group was associated with each rank, an ordinal regression was used, with rank as the dependent variable and group categories as the predictor. Similarly, to determine the association between the ranks assigned to sources of nonadherence to oral agents within each of the groups, four ordinal regressions (one for each group) were completed.

**Results**

The sample included 67 nurses. Overall, respondents worked in a variety of research settings and capacities, with 31 having more than five years of experience and 60 spending 76%–100% of work time in clinical trials (see Table 1).

Observation of nonadherence in clinical trials indicated that only 33 nurses reported that 25% or less of protocols were in compliance with protocol regulations. Remaining nurses indicated that 26%–50% (n = 25), 51%–75% (n = 4), or 76%–100% (n = 5) of protocols were in violation of protocol adherence. The nurses ranked the groups most responsible for protocol nonadherence as patients, followed by physicians/principal investigators. The patients and/or physicians/principal investigators were ranked first or second by 56 respondents.

**Sources of Nonadherence**

The results of the ordinal regression analyses indicated that the percentage of clinical trial nurses assessed as being nonadherent was not significant (p > 0.05). All sources of nonadherence were significant (p < 0.05) for those ranked at least first or second in importance.

**PATIENT SOURCES:** Research nurses identified the top two patient sources for nonadherence as the patient forgetting to take the study medication and not taking the medication as prescribed. Patients not understanding the protocol process, not documenting when the study drug was taken, and inconsistent follow-up with laboratory testing were identified as the next three top patient sources. The least frequently identified sources of patient nonadherence were patient refusal to undergo procedures and inadequate family caregiver support.

**PHYSICIAN/PRINCIPAL INVESTIGATOR SOURCES:** Research nurses identified ineffective communication as the most common cause of nonadherence, which was followed closely by the study assessment not being completed in a timely manner. The next two were study orders not released when written, closely followed by orders not written in a timely manner. The lowest reported causes were study scripts not being released to the correct pharmacy and other.

**RESEARCH NURSE SOURCES:** Time frames, with regard to missing study items, and procedure schedule were the top two sources of nonadherence with research nurses. This was followed closely by the study assessment not being completed in a timely manner. The next two were study orders not released when written, closely followed by orders not written in a timely manner. The lowest reported causes were study scripts not being released to the correct pharmacy and other.

**OTHER PERSONNEL SOURCES:** The top ranked sources for other personnel sources of nonadherence included the local
hospitals not reporting the patient being hospitalized, not performing required protocol tests, and not reporting to the sponsor in a timely manner. These three sources accounted for 96% of nonadherence to protocol requirements.

Other Sources of Nonadherence
Components of the survey had options for respondents to write in other factors they felt contributed to patient nonadherence, and additional issues were revealed. When condensed into several categories, primary items listed included scheduling, rigid and complex protocol and procedure requirements, and the need for frequent clinical visits during the trial. In addition, measurements not documented in a timely manner or within an acceptable time frame also were listed. An example is physicians not cosigning the informed consent and their dictation within the given time frame. Principal investigators not adhering strictly to protocol requirements was listed as a contributing factor to nonadherence to protocol requirements.

Institutional factors were listed, with a focus on the treating physicians who often make dose modifications outside protocol parameters and being unsupportive of the other research staff, particularly the research nurses. Also noted were changes in patient appointments often being made without the knowledge of the research nurses. Communication was a common theme, emphasizing the treating physicians’ failure to collaborate with research nurses on the timeline of requirements. Of concern was the issue of pressuring the research nurses to enroll patients who are not fully eligible and waiving protocol-required tests with the intent of logging a deviation. Last, pharmacists not getting the investigational medicines ready in a timely manner contributed to protocol violations.

Respondents also commented on issues with the EPIC™ software system (EPIC FACTOR). Primary concerns emphasized timelines not being built fully or correctly (e.g., screening, follow-up), difficulty in finding outside test results and progress notes from local treating physicians in the software system, and orders placed in EPIC not being performed. Respondents had much to add about communication with other departments, inpatient and outpatient teams, discrepancies in the interpretation of protocol requirements, and difficulties in balancing priorities with other team members to meet the patient and protocol requirements.

Limitations
A limitation of the current study was the data being obtained from a single network with extensive clinical trial experience. As such, the findings may not be generalized to other settings. In addition, the survey included perspectives only from the research nurses instead of perspectives from other members of the research team and patients. The low response rate, although within range of survey response rates (Burns & Grove, 2010), may have been because the survey was available only for four weeks. Last, the survey was set up in a way that participants completing the survey could not move onto the next question without completion of the previous question; this limitation could have been why some nurses did not complete the survey.

Discussion
The current study characterized which groups are associated with protocol violations and which violations are most common in patients, physicians/principal investigators, nurses, and other personnel. The results provide a granular view of protocol violations but can be interpreted as providing two common themes; communication and organization appear to be the overarching themes responsible for protocol violations identified by clinical trial nurses across groups.

The current study specifically focused on oral agents, which is unique and provides important insights to enhance clinical trials in this area. The benefits of oral agents for patients with cancer include their ease and convenience; flexibility in timing and location of administration; sustainment of good quality of life; cost efficiency when compared to inpatient and ambulatory treatment options; and that they are the less invasive treatment option (Batlle et al., 2004). The benefits derived from clinical trials with oral agents are numerous; however, for optimal usage of these agents, policies must be in place to validate the quality and integrity of the data provided by the research team. Patients enrolled in clinical trials must be adherent to the oral medication and protocol requirements to establish the efficacy and safety of any study drug and make judgment on its clinical significance. According to McCue et al. (2014), nonadherence to protocol requirements in clinical trials not only leads to reduced rates of response but also increases medical cost.

In the current study, the rate of observed violations is higher than in earlier reports that found 5%–24% of trials containing protocol violations (Macias et al., 2004; Sprung et al., 1996); this difference is not surprising because the current study includes a broader range of violations based on nurses’ observations. This is an important issue for further research because it provides insight for future exploration and potential intervention.

Although patients were identified as the group most responsible for protocol breaks, the sources within each of the remaining groups are also potentially important targets for remediation. Viewed broadly, physician/principal investigator, nurse, and other personnel sources, across these groups, indicated that errors in scheduling or missing required procedures, lack of reporting,
and errors in communication were most responsible for nonadherence. To address these issues, emerging technologies may be helpful.

The more effective use of technology to enhance the organization of clinical trials offers significant opportunities to improve study organization and communication. As significant time and funds are invested in clinical trials, expanding health information exchange (HIE) to enhance the sharing of patient-level electronic health information among different organizations could reduce some errors identified in the current study (Vest & Gamm, 2010). With the use of HIE, previously unavailable patient-level information is made available to healthcare providers; this sharing will enhance communication between the research team and the patient’s local physician’s office. The research team needs to educate all parties about the importance of clinical trials and how information generated from such trials is beneficial to clinicians in making informed decisions that affect health and health care (Lavis, Robertson, Woodside, McLeod, & Abelson, 2003).

Electronic solutions that could revolutionize clinical trials are evident with new technology (Idenburg & Dekkers, 2016). Clinical trials should implement electronic data capture to improve data collection, management, and analysis, and enhance communication of results among healthcare providers (Idenburg & Dekkers, 2016). It is feasible to include cloud-based methodologies, which include electronic trial master file, electronic source documentation, and risk-based monitoring, in research clinical trials (Idenburg & Dekkers, 2016). Data from these systems easily can be clustered and entered into the cloud, and such data can be aggregated into a clinical data warehouse, which simply can be accessed by patients, caregivers, and healthcare providers (Idenburg & Dekkers, 2016). These sources are not new to clinical trials but remain in use. A suggested intervention to enhance communication is regularly scheduled conference calls for all staff and locations involved in the study to discuss challenging issues and share ideas to resolve pending issues (Roll et al., 2013). With a platform for group participation in the study, the research team can draw knowledge from others, and such knowledge can be used as a tool to address or prevent impediment to the study implementation (Roll et al., 2013).

Implications for Nursing

The clinical trial nurses in the current study identified the study participants/patients as the primary source of nonadherence, with the top two reasons being forgetting to take the study medication and not taking the medication as prescribed. These reasons parallel those seen in oral cancer treatments outside of clinical trials (Muluneh et al., 2018). Interventions to address these sources of nonadherence have been developed and are available in the Oncology Nursing Society’s Oral Adherence Toolkit (Oncology Nursing Society, 2016). The toolkit includes solutions for improving nonadherence, which include, but are not limited to, the use of tools like medication diaries, alarm clock reminders for pill taking, and follow-up telephone calls by research nurses. Education on the importance of laboratory timelines and prompt completion of standard laboratories and research laboratories are essential. In addition, patients need to be informed about how to store the study medication, the dosage and how to self-medicate, and the time of administration of the study medication. Patients need to understand what the implications of dose omission, delayed administration, overdose, and side effects of the medication mean for their health and how nonadherence can mean reduced efficacy of the study medication. Nurses need to provide repeated teaching for improving adherence to medication and protocol requirements, thereby improving patient safety, and self-monitoring for adverse effects (Roop & Wu, 2014).

Conclusion

Clinical trial nurses share a critical responsibility with physicians/principal investigators in providing information to study participants to ensure their safety and the fidelity of the scientific knowledge gained from their participation in a clinical trial. The current study suggests that nonadherence is more common than earlier reports (which are limited to safety errors). The stringent evaluation of clinical trial procedures, data, and reporting are effective safeguards that may mitigate any effects of the non-safety-related errors, but further examination of these errors is important for the development of new treatment.

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