Enhancing Adverse Event Identification and Management in Early-Phase Oncology Clinical Trials: The Emerging Role of Advanced Practice Providers

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Authors' disclosures of conflicts of interest are found at the end of this article.

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Abstract

Background: Adverse events (AEs) are unintended, harmful effects that occur in clinical trials, particularly in early-phase oncology clinical trials (EPOCT), where the risk of adverse effects from experimental therapies is high. Effective AE identification and management are essential for ensuring patient safety, improving outcomes, and advancing research. Advanced practice providers (APPs) play a key role in detecting and managing AEs, serving as a bridge between clinical care and research. However, their full impact on EPOCT remains underexplored. **Purpose:** This integrative review examines existing literature on AE identification, reporting, and management in EPOCT. It explores the role of APPs in managing AEs, emphasizing their impact on patient outcomes, clinical trial efficiency, and oncology science. **Methods:** A systematic search of peer-reviewed literature from 2020 to 2025 was conducted using various databases. Inclusion criteria were studies addressing AE management in EPOCT, patient-reported outcomes (PROs), and APP roles. Studies unrelated to oncology, AE management, or health-care providers were excluded. **Results:** Findings highlight the variability in AE reporting and the growing utility of electronic PRO tools in capturing timely and accurate data. Advanced practice providers contribute significantly to outpatient AE management, reducing emergency visits and improving treatment adherence. However, challenges remain, including underreporting with clinician-based tools, lack of standardized APP training, and limited comparison to physician-led AE management. **Conclusion:** APPs serve as key players in enhancing AE reporting and improving clinical trial processes. Future research should focus on standardizing structured training programs for APPs and comparative studies assessing the effectiveness of APP-led care.

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An adverse event (AE) refers to an undesirable experience or effect that occurs during a clinical trial, especially those testing experimental drugs, such as in early-phase oncology clinical trials (EPOCT; Veitch et al., 2021). Early-phase oncology clinical trials comprise phase I and II clinical trials that are designed to evaluate the safety, tolerability, and initial efficacy of investigational therapies (Barber et al., 2022). These clinical trials often enroll patients with advanced or metastatic cancer who have exhausted standard-of-care treatment options, making AE monitoring important due to the potential for unexpected or severe toxicities.

Adverse events frequently occur in healthcare settings such as hospitals and clinics but may also arise in home environments, where patient care often involves complex processes. Advanced practice providers (APPs) play a vital role in clinical trials, particularly in oncology, where they contribute to patient care, research oversight, and improved access to experimental therapies (Braun-Inglis et al., 2022). Advanced practice providers often serve as consistent points of contact, enabling more frequent patient evaluations and symptom monitoring. Their ability to independently assess, manage, and triage AEs allows clinical research centers to increase patient enrollment and maintain protocol adherence. Adverse event management and reporting in clinical trials directly impact patient safety, quality of care, and the development of therapeutic interventions (Liukka et al., 2020). As the number of APPs in oncology continues to grow, their involvement in clinical trials has the potential to enhance patient outcomes and expand the availability of cutting-edge treatments.

Advanced practice providers serve as links between patients, clinicians, and research protocols (Barber et al., 2022). Their expanding role in EPOCTs supports evidence-based practices while refining clinical guidelines and integration into multidisciplinary research teams. They are uniquely positioned to optimize AE management, enhance clinical trial efficiency, and ensure timely, high-quality care for patients receiving investigational therapies. This review aims to explore, analyze, and address aspects of AE identification and management in EPOCTs, with a focus on improving patient outcomes and enhancing the role of APPs.

SEARCH STRATEGIES

The search for relevant articles started at MD Anderson Research Medical Library where the core databases included CINAHL, PubMed, and Ovid. The search was also expanded to University of Texas Medical Branch (UTMB)–Health Moody Medical Library and was performed on its advanced platform. These databases are specifically tailored to nursing and health-care professionals, making them a valuable resource for finding peer-reviewed articles related to practice and patient care. These databases also offer access to a collection of research particularly useful for identifying studies on clinical trials, AE management, and evidence-based practices in oncology. Expanding the search to the UTMB Health Moody Medical Library provided broader access to specialized resources that aided in the retrieval of high-quality literature that was relevant to this review.

A comprehensive search in these databases was conducted using keywords that included "adverse events." Boolean search methods were used, such as "adverse event" AND "early phase oncology clinical trials" OR "healthcare" AND "advanced practice providers." Consideration was also given to the fact that these phrases could have synonyms. For example, adverse events could also be described as side effects, toxicities, or complications. The delimiters included date range, which included studies published within the past 5 years (2020–2025). The rationale for focusing on date range within the past 5 years was because of the advances in cancer therapies and the roles of APPs that have changed in recent years. The past 5 years have seen developments in immunotherapies, targeted therapies, and personalized medicine, and these therapies are associated with unique AEs that require up-to-date research to understand and manage effectively (da Silva Lopes et al., 2023). English-language studies found in peer-reviewed journals were looked upon primarily for this literature review. The study design of the articles was carefully evaluated. The articles selected included meta-analyses, systematic reviews, retrospective/prospective studies, and both quantitative and qualitative studies to ensure a broad

understanding of the types, causes, and impacts of adverse events.

The articles were selected based on the research focus, which was AE management in EP-OCT (Figure 1). Peer-reviewed articles with full-text availability specifically exploring implications in oncology, PROs, and the role of APPs were selected. A total of 1,659 articles resulted with all the delimiters included in the search criteria. A total of 1,532 records were excluded due to irrelevance, duplication, or lack of full-text availability. When inclusion of the role of APPs was examined, the number of articles was reduced to 127. Articles that exclusively examined AEs associated with individual oncology drugs without offering insights into general AE management strategies were excluded from this review. Articles that discussed AEs in a non-oncology setting or unrelated medical fields were excluded, along with articles that did not examine the role of APPs, nurses, or health-care providers. Also, articles that did not address PROs or experiences were excluded. These criteria enabled the literature review to focus on implications related to AE management, patient outcomes, quality care, and roles in clinical trials. Therefore, the exclusions included 40 articles from non-oncology settings, 35 that lacked emphasis on APP or health-care provider roles, 22 that omitted PROs, and 15 that focused exclusively on drug-specific adverse events. After review, 15 articles were ultimately selected for inclusion based on their relevance and alignment with the research objective.

RESEARCH SYNTHESIS

Advanced practice providers play a role in easing the impact of AEs, improving patient outcomes, and enhancing clinical trial efficiency. The common findings from these multiple studies analyzed included emphasizing AE monitoring with PRO tools and the expanding role of APPs in clinical research (Table 1).

Electronic Patient-Reported Outcomes Tools

Traditionally, AE monitoring and reporting relied on the health-care professional's assessment, which can lead to underreporting of the severity and frequency of symptoms (Kennedy et al., 2021). Patient-reported outcomes are direct reports from patients about their symptoms, health status, or treatment effects without interpretation by clinicians (Kennedy et al., 2021). These reports are used in clinical trials and health-care settings to capture the patient's perspective on adverse events, treatment burden, and quality of life. Patient-reported outcomes have been used as predictors of early treatment discontinuation due to severe side effects, allowing for timely intervention (Peipert et al., 2024).

Kennedy and colleagues (2021) emphasize the need for incorporating electronic PRO tools to complement clinician assessments. Patients, clinicians, and trial staff stated that they saw the potential of electronic PRO tools to capture comprehensive symptom data that in turn helped with increased symptom accuracy, timely data for clinical decision-making, and improved communication of patient experiences (Kennedy et al., 2021). Patient-reported outcome systems provided direct insights from patients regarding their health status, treatment tolerability, and symptom burden. This enables timely intervention, which is critical for assessing both the safety and efficacy of novel therapies, particularly in early-phase clinical trials (McMullan et al., 2023). In addition, real-time symptom reporting helps health-care providers proactively address worsening symptoms before they escalate into severe adverse events (Lopes et al., 2020). However, many limitations and challenges remain regarding the broader adoption of these tools. These include digital literacy, difficulty integrating the tools into the clinic workflow, the accessibility and usability of these tools, as well as patient interest and engagement.

A study by Watson and colleagues (2022) further reinforces the importance of incorporating PROs in AE monitoring. Of 219 evaluable patients, 81 experienced a high-grade (3/4) clinician-reported symptom, and of these, only 32 (40%) and 26 (32%) patients concordantly reported these as either severe or very severe, and interfering with daily life either "quite a bit" or "very much," respectively (Watson et al., 2022).

The use of electronic PROs aligns with capturing treatment-related AEs from patient perspectives. The strength of such a tool includes real-time documentation that captures a more accurate and detailed assessment of AEs (Peipert et al., 2024). It also allows for more direct patient approaches

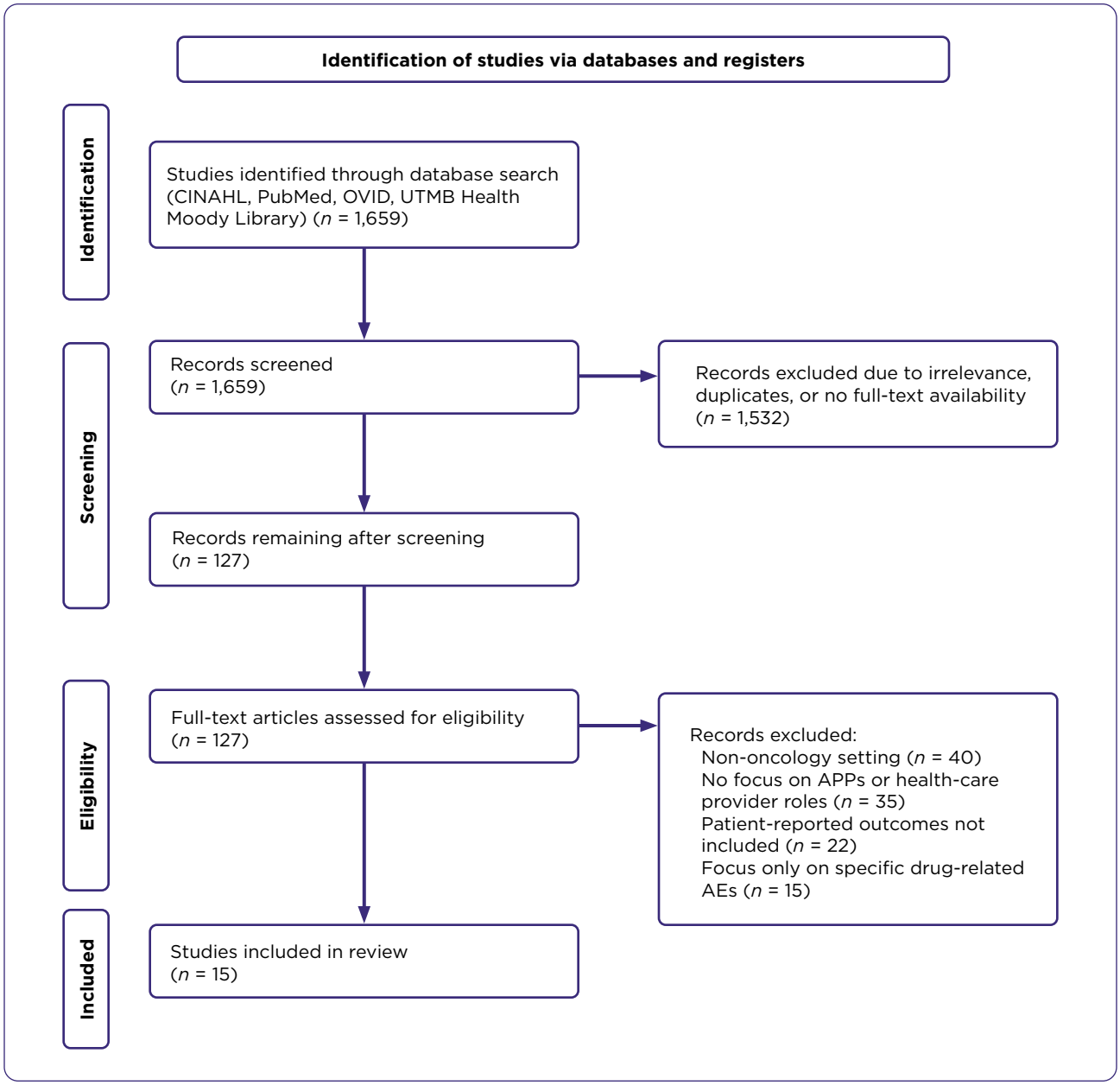

Figure 1. PRISMA flow diagram. Adapted from Moher et al. (2009).

and can be integrated into clinical trial workflows, allowing for timely detection and faster responses on developing toxicities.

A limitation is a reliance on self-reported data, which can vary due to individual perception and differences in health literacy (Kennedy et al., 2021).

Measuring AEs

Adverse events vary significantly in presentation, sometimes resembling disease progression. They can also manifest as various autoimmune responses, affecting organs such as the skin, gastrointestinal tract, endocrine glands, and lungs. Adverse events can be long-lasting or surface months into treatment and beyond, further adding to the symptom burden patients are already enduring (Xie et al., 2021).

Several measurement instruments are used to assess various variables related to patient outcomes, AE reporting, and patient experience in EPOCTs. The Common Terminology Criteria for

Table 1. Integrative Review Table

Author and year	Research question	Design, method, and sample	Data collection/ instruments	Findings	Limitations
Barber et al., 2022	How do APPs manage grade 3 to 4 AEs in early-phase clinical trials in an outpatient setting, potentially avoiding emergency center visits and hospital admissions?	Retrospective review of outpatient clinic visits for patients enrolled in phase I to II clinical trials. 808 patients with advanced or metastatic solid tumors, totaling 2,697 clinic visits, seen by 10 APPs.	Electronic medical records reviewed for patient characteristics, AE management, and frequency of emergency center referrals.	Most grade 3 to 4 AEs were managed in the outpatient clinic, with only 1.4% of visits resulting in emergency referrals. Patients with higher baseline risk factors (e.g., low albumin, high LDH, poor performance status) were more likely to require emergency care. APP experience was associated with a decreased likelihood of emergency referrals.	Single-center study with patient heterogeneity; findings may not generalize to smaller, community-based settings.
Biniakewitz et al., 2021	What are the unique challenges and adverse event profiles of older adults with cancer undergoing ICI therapy?	Single-institution retrospective study and case study. 38 older adult patients (age ≥ 75) with melanoma treated with ICIs (nivolumab, pembrolizumab, ipilimumab) between 2016–2018.	Retrospective review of EHR assessing frequency, severity, and timing of irAEs using CTCAE grading.	Median therapy duration was 7.4 months; median irAE onset was 81 days. 47% experienced grade 1–3 irAEs; 24% discontinued therapy due to irAEs, higher than rates in clinical trials.	Single-center, retrospective design; lack of comparison to younger populations; small, homogenous sample.
Braun-Inglis et al., 2022	What are the attitudes, beliefs, and roles of oncology APs in clinical research, and how can their involvement be optimized to enhance clinical trial accrual, conduct, and protocol development?	Nationwide online survey distributed to oncology APs through the Association of Community Cancer Centers and Harborside. 408 oncology APs, including nurse practitioners, clinical nurse specialists, physician assistants, and pharmacists practicing in across the US	65-item validated survey addressing demographics, attitudes, beliefs, and roles in clinical trials.	91% of respondents believe APs should participate in clinical research, and 73% express interest in greater involvement. Only 37% routinely explore clinical trials for patients, with lack of time, inadequate trial awareness, and undefined roles as barriers.	Convenience sample with potential bias toward APs already engaged in research; low response rate and overrepresentation of certain demographic groups.

Note. AE = adverse event; APP = advanced practice provider; CTCAE = Common Terminology Criteria for Adverse Events; ePRO = electronic patient-reported outcome; EPOCT = early-phase oncology clinical trial; EHR = electronic health record; ETD = early treatment discontinuation; FACT-GP5 = Functional Assessment of Cancer Therapy-General; HC = high-confidence; HR = hazard ratio; ICI = immune checkpoint inhibitor; irAE = immune-related adverse event; LDH = lactate dehydrogenase; LC = low-confidence; NHS = National Health Service; PRO = patient-reported outcome; QOL = quality of life; RCT = randomized controlled trial; SMT = symptom management theory; VRd = bortezomib, lenalidomide, dexamethasone; KRd = carfilzomib, lenalidomide, dexamethasone.

Table 1. Integrative Review Table (cont.)

Author and year	Research question	Design, method, and sample	Data collection/ instruments	Findings	Limitations
Le-Rademacher et al., 2020	Can the Adverse Event Burden Score (AE Burden Score) provide a more comprehensive and flexible measure for summarizing AEs in cancer clinical trials?	Development of the AE Burden Score, validated using data from two randomized, double-blind, placebo-controlled trials. 176 patients with advanced non-small cell lung cancer (NCCTG 97-24-51) and 83 patients with desmoid tumors (A091105).	Adverse event data graded using Common Terminology Criteria for Adverse Events (CTCAE) and calculated using the AE Burden Score metric.	The AE Burden Score integrates severity and frequency of AEs, providing toxicity assessment. Treatment arms had higher AE burdens compared to placebo, with differences in AE patterns over time. The score highlighted early dropout due to high toxicity in certain patients.	Requires predefined weight functions for AEs; limited generalizability due to the use of data from only two trials.
Kennedy et al., 2021	What are the perspectives of patients, clinicians, and trial staff on the use of electronic PRO systems for monitoring adverse events in early-phase clinical trials?	Qualitative study through semi-structured interviews. 16 patients, 16 trial and clinical staff from two NHS trusts and a trial unit in England.	Interviews analyzed using framework analysis.	Patients often under-reported mild symptoms in traditional settings. Both patients and staff saw potential in ePRO to capture comprehensive symptom data. Increased symptom accuracy, timely data for clinical decision-making, and improved communication of patient experiences. Concerns over data volume, attribution of symptoms, and patient safety management in real-time.	Limited generalizability due to small sample and specific location in England.

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Table 1. Integrative Review Table (cont.)

Author and year	Research question	Design, method, and sample	Data collection/ instruments	Findings	Limitations
Liukka et al., 2020	What are the key elements of action immediately after AEs in health-care organizations?	Integrative literature review of studies (2009-2018) on actions post-AEs, using a five-stage process based on Whittemore and Knafl's method. 25 studies involving healthcare professionals, patients, and family perspectives.	Systematic database search and quality scoring of selected studies.	First Victims: Emphasis on open communication, empathy, apology, and organizational responsibility. Second Victims: Need for emotional and peer support, coping strategies, and organizational policies. Third Victims: Organizational action plans, support services, and structured response protocols. Cross-cutting: Empathy, ethical communication, and transparent apology are critical across all victim groups.	Limited to peer-reviewed articles, lacking input from international guidelines; findings may not generalize across diverse healthcare contexts.
Lopes et al., 2021	How can longitudinal characteristics of adverse events (AEs) be incorporated into reporting to enhance understanding of treatment quality in cancer clinical trials?	Development and application of a novel AE reporting method using longitudinal metrics, tested with data from a randomized phase III trial. 716 patients with metastatic colorectal cancer treated with irinotecan or oxaliplatin.	Individual patient AE data analyzed for metrics of AE load (severity over time), onset time (early vs. late), and maximum grade.	Novel metrics provide a more comprehensive toxicity profile than traditional reporting. Longitudinal data reveal treatment-specific AE patterns that inform clinical decision-making.	Retrospective analysis, potential variability in AE data completeness, and limited generalizability due to single dataset focus.

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Table 1. Integrative Review Table (cont.)

Author and year	Research question	Design, method, and sample	Data collection/ instruments	Findings	Limitations
da Silva Lopes et al. 2023	How can an eHealth-enhanced model using electronic PROs improve the monitoring and management of immune-related adverse events (irAEs) in patients undergoing immune checkpoint inhibitor therapy?	Development and implementation of an eHealth-enhanced chronic care model (eCCM) across four stages, tested in a bicentric longitudinal randomized controlled trial (IePRO study). Patients receiving immune checkpoint inhibitors across two Swiss university hospitals.	ePRO data collected via a mobile application based on the PRO-CTCAE framework; triage nurses utilized the UKONS 24-hour triage tool to assess and manage symptoms.	The model facilitated proactive symptom management and timely interventions. Integration of ePROs into care improved patient-provider communication and symptom monitoring, though technical and workflow barriers persisted.	Implementation challenges include integration with existing EHRs and resource requirements for training and data handling.
Mathew et al., 2020	How has the Symptom Management Theory (SMT) been used and to what extent in research and practice involving adults with cancer?	Concept analysis using Fawcett and DeSanto-Madeya's framework and Silva & Sorrell's theory-testing criteria; systematic review of 20 studies 20 studies involving adults with cancer; various designs including RCTs, cross-sectional, qualitative, and secondary analyses.	Systematic database search (CINAHL, MEDLINE, PsycINFO, EMBASE, CENTRAL, Google Scholar); use of PRISMA guidelines; extracted study characteristics.	SMT has empirical adequacy in 80% of studies; symptom experience dimension most studied; SMT used to an adequate extent in only 35% of studies.	Lack of studies testing entire SMT; limited comparative studies; inconsistent application of theory concepts across studies.
Mazzarella et al., 2024	Can an iRAE Likelihood Score (ILS) effectively identify immune-oncology-related events that correlate with improved survival outcomes?	Retrospective analysis using a scoring system to classify IRAEs in patients in early-phase immunotherapy trials. 202 patients treated with immune-oncology agents in phases I–II trials at a single center.	Medical records reviewed to assess IRAE types, with scoring based on diagnostic evidence, immune response, timing, and known associations.	High-confidence IRAEs (ILS ≥ 5) strongly correlated with improved outcomes, unlike low-confidence IRAEs. Patients with HC IRAEs had significantly longer progression-free and overall survival.	Single-center design.

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Table 1. Integrative Review Table (cont.)

Author and year	Research question	Design, method, and sample	Data collection/ instruments	Findings	Limitations
McMullan et al., 2023	How effective and user-friendly is the developed ePRO system for patients with inflammatory diseases in capturing therapeutic response and treatment tolerability?	Usability testing of a custom ePRO system with cognitive interviews and the "Think Aloud" method. 9 patient participants and 7 research nurses.	Tasks completed on an ePRO app, with cognitive interviews to gather feedback on usability and satisfaction.	User feedback: Patients found the app straightforward but suggested minor improvements. Nurses appreciated the clinician dashboard's ease of use. Technical issues: Two patients faced device compatibility issues, and suggestions were made to improve navigation and visual cues.	Small, single-site sample with potential device limitations affecting generalizability.
Peipert et al., 2024	Are patient-reported experiences of AEs associated with early treatment discontinuation in multiple myeloma patients?	Prospective survey study analyzing responses to a single-item FACT-GP5 scale during the induction phase of a phase III trial. 1,058 patients with newly diagnosed multiple myeloma receiving bortezomib (VRd) or carfilzomib (KRd)-based regimens.	Patient responses on the FACT-GP5 at baseline and during treatment at 1, 2.8, and 5.5 months, categorized into "high adverse event bother" and "low adverse event bother."	High AE bother was significantly associated with increased odds of early treatment discontinuation across all time points. Worsening GP5 scores by two or more categories also correlated with higher early treatment discontinuation risk.	Single-trial data with a homogenous population; further validation in diverse settings is required.
Veitch et al., 2021	To what extent do clinicians underreport symptomatic AEs in phase I clinical trials, and how does this compare with PROs?	Prospective observational study comparing clinician and patient reports of symptomatic AEs. 243 patients enrolled in phase I clinical trials at Princess Margaret Cancer Centre.	Patients used the PRO-CTCAE tool, and clinicians used standard CTCAE assessments.	Clinicians reported significantly fewer AEs compared to patients, particularly in categories like sexual health and cognition. Poor to moderate agreement between patient and clinician AE reports. Higher clinician-reported AEs were associated with worse survival outcomes, but this was not observed with patient-reported AEs.	Single-center study, English-speaking participants only, and limited generalizability.

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Table 1. Integrative Review Table (cont.)

Author and year	Research question	Design, method, and sample	Data collection/ instruments	Findings	Limitations
Watson et al., 2022	How do PRO-CTCAEs compare with clinician-reported adverse event grading for patients in phase I clinical trials?	Prospective single-center observational study using PRO-CTCAE surveys and clinician-graded CTCAE reports. 219 patients with advanced solid tumors enrolled in phase I clinical trials.	PRO-CTCAE surveys administered at baseline and mid-treatment cycles, assessing AE severity and interference. Clinician-reported AEs documented per CTCAE v4.0.	Discrepancies: Only 40% of high-grade clinician-reported AEs were reported by patients as equally severe, with greater alignment in low-grade cases. Impact on dose: PRO-reported interference scores correlated with dose reductions, suggesting the clinical relevance of patient-reported interference.	Single-site study and data collected at limited timepoints, with no AE attribution.
Xie et al., 2021	How consistent and adequate is the reporting of irAEs in RCTs of PD-1/ PD-L1 inhibitors?	Systematic review using the Harms extension of CONSORT guidelines to evaluate irAE reporting in RCTs. 44 RCTs involving 23,759 patients treated with PD-1/PD-L1 inhibitors across various cancer types.	Data on irAE reporting practices were extracted from published RCTs and evaluated against an adjusted CONSORT checklist.	Inconsistent reporting of irAEs, with 39% of studies tabulating data in supplementary materials and only 7% including clear definitions. Combined therapy trials exhibited higher reporting quality. No significant improvement in reporting quality over 5 years.	Lack of a targeted checklist for irAEs; focused on specific ICIs without broader generalization.

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Adverse Events (CTCAE), which is currently in version 5, is a standardized approach to reporting toxicity and assessing treatment-related risks, with events typically graded based on severity from mild (grade 1) to life-threatening (grade 4; Xie et al., 2021). It provides a consistent framework for reporting AEs related to cancer treatments, including chemotherapy, immunotherapy, and radiation therapy. The CTCAE categorizes 837 AE terms across 26 system/organ classes, with most AEs assigned one of five severity grades: 1 (mild), 2 (moderate), 3 (severe), 4 (life-threatening), and 5 (fatal; Le-Rademacher, et al., 2020). The strength of this tool is that it is an objective measure for assessing AEs, thereby providing consistency throughout different studies. CTCAE is also endorsed by regulatory agencies in the US such as the Food and Drug Administration and the National Institutes of Health, making it a tool for evaluating treatment safety (Kennedy et al., 2021).

Limitations include underreporting or downgrading of symptoms by the health-care provider, especially for subjective toxicities such as pain or fatigue. The CTCAE focuses on acute toxicities, making it less effective in capturing long-term or late-onset effects of treatment, such as immune-related AEs (Mazzarella et al., 2024).

Role of APPs

Advanced practice providers in EPOCTs can help minimize emergency center visits. In the study by Barber and colleagues (2022), APPs managed grade 3 to 4 AEs in an outpatient clinic, with only 1.4% of visits resulting in emergency room referrals. This led to fewer treatment interruptions and improved patient adherence to investigational therapies. Maintaining a consistent relationship with patients and facilitating communication between them and research teams can provide additional opportunities for APPs to closely monitor for AEs. Mild symptoms are frequently overlooked and underreported by both patients and clinicians, yet they can signal serious conditions that may affect their quality of life (Xie et al., 2021). Patients, especially older adult patients, may underreport symptoms due to concerns about treatment discontinuation. Therefore, APPs are instrumental in establishing trust and encouraging symptom reporting (Biniakewitz et al., 2021). The study by Biniakewitz and colleagues (2021) highlights APPs as key players in proactive symptom monitoring and early identification of AEs. Advanced practice providers further contribute to clinical research by educating patients on symptom recognition and emphasizing the importance of adherence to clinical trial protocols (Braun-Inglis et al., 2022).

Despite their growing role, there are several challenges to APP involvement in clinical research. These include a lack of formal training in clinical trial methodology and limited integration into research leadership roles, along with time constraints. A lack of standardized protocols for APP involvement in clinical research and limited availability of training programs reduces APPs' ability to effectively manage AEs (Braun-Inglis et al., 2022).

Frameworks

Across the multiple studies reviewed, theoretical models were not referenced. However, several studies discuss frameworks related to patient safety, AE management, and the evolving role of oncology care providers. The study by Biniakewitz and colleagues (2021) on immune-related AEs in older adults with cancer receiving immune checkpoint inhibitor therapy incorporates the Geriatric Oncology Framework. The study acknowledges the physiological changes in aging, such as reduced renal, hepatic, and immune system function, that impact drug metabolism and toxicity in older adults (Biniakewitz et al., 2021). The Geriatric Oncology Framework emphasizes age-specific considerations in cancer treatment, including comorbidities, functional status, and treatment tolerance. The study by Braun-Inglis and colleagues (2022) combines health services research, workforce role theory, and clinical trial recruitment models to explore APPs' potential in oncology research. The compatibility between these frameworks strengthens the study's argument for expanding APP roles in clinical trials.

Many articles use the symptom management theory (SMT), which is a middle-range theory that guides symptom assessment and treatment. This theory can be used to guide nursing interventions for patients experiencing multiple symptoms, such as those with cancer, by promoting self-care and preventative strategies (Mathew et al., 2020). The study by Kennedy and colleagues (2021) focuses on online monitoring of patient-

reported AEs in EPOCTs. The study examines how patients perceive, interpret, and report symptoms, which aligns with SMT's focus on symptom experience, management strategies, and outcomes. The study by Le-Rademacher and colleagues (2020) aligns with SMT by assessing how patients experience, perceive, and report AEs over time in cancer clinical trials. The study by Mazzarella and colleagues (2024) uses the SMT and focuses on developing an AE likelihood score to better classify AEs in patients undergoing immunotherapy. The study by McMullan and colleagues (2023) focuses on the development of an electronic PRO system for patients and applies SMT by evaluating how patients perceive, track, and report their symptoms using the electronic platform.

IMPLICATIONS FOR RESEARCH

Based on the literature review, some information gaps are evident.

Late-Onset AEs

Many patients on immunotherapies may experience toxicities weeks or months after they have started treatment. While CTCAE is effective in capturing acute toxicities, it has limitations in identifying and assessing long-term or late-onset AEs, such as immune-related AEs. This can lead to underreporting of delayed toxicities that can occur later in the treatment course or during long-term follow-up periods. In addition, CTCAE relies heavily on health-care professional driven data and often fails to fully capture the patient experience, especially for subjective toxicities like fatigue and pain (Watson et al., 2022). This gap can result in incomplete documentation of long-term AEs.

APP-Led vs. Physician-Led AE Management

There is a lack of studies that compare and evaluate the effectiveness of APP-led compared with physician-led AE management in EPOCTs. A retrospective study by Barber and colleagues (2022) examined the role of APPs in managing grade 3 to 4 AEs among patients with advanced or metastatic solid tumors enrolled in EPOCTs. This included managing serious conditions such as immune-related colitis, severe dermatitis, pneumonitis, and endocrinopathies through timely interventions such as corticosteroids, imaging, lab monitoring, and specialist referrals, demonstrating that APP-led care can reduce acute care utilization while maintaining high-quality treatment. The study found that APPs effectively managed these severe AEs in an outpatient setting, suggesting that APP-led management can potentially reduce the need for acute care services (Barber et al., 2022).

Impact of Standardized Training Programs for APPs

Another research question is the impact of standardized training programs for APPs on the identification, management, and reporting of AEs in EPOCTs. Formal training programs can equip APPs with the skills to detect early toxicities, assess severity, and intervene promptly, while improving their use of CTCAE, PROs, and supporting their integration into research teams.

SUMMARY

Adverse events affect patient safety and clinical trial performance, especially in EPOCTs. This review examines the expanding role of APPs in managing AEs within this setting. Advanced practice providers play an essential role in monitoring, reporting, and mitigating AEs, improving patient outcomes, and preventing treatment interruptions. They contribute to clinical trial success by proactively identifying and managing treatment-related AEs, often reducing emergency visits and enhancing patient adherence to investigational therapies.

Advanced practice providers' routine involvement in AE surveillance, patient education, and protocol adherence reflects a shift toward a more collaborative, multidisciplinary approach to clinical trial conduct. However, barriers such as lack of formal research training, limited integration into leadership roles, and challenges in adopting electronic PRO systems persist. The review highlights the integration of PRO tools alongside clinician assessments to improve AE reporting accuracy. These tools enabled real-time symptom monitoring, thus reducing the risk of underreporting. Enhancing the role of APPs within clinical trials and utilizing advanced symptom monitoring tools can strengthen AE management, ultimately improving clinical trial outcomes.

The review also identified gaps in research, including the lack of standardized APP training programs in clinical trials, limitations of the CTCAE

in capturing long-term toxicities, and the absence of direct comparisons between APP-led and physician-led AE management. Addressing these gaps could lead to improved AE reporting, enhanced patient safety, and a greater role for APPs in clinical trial leadership. Future research should focus on optimizing AE management in clinical practice while emphasizing the growing role of APPs in clinical trials as a leading element for advancing both oncology care and research innovation. ●

Disclosure

The author has no conflicts of interest to disclose.

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