Trials

COMMENTARY

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Improving the capture and reporting of adverse events in clinical trials of non-pharmacological interventions: learnings from the PaCCSC/CST membership

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Abstract

Background Accurate capture and reporting of adverse events (AEs) in clinical trials is critical to understanding the potential harms of prospective interventions. Current AE-reporting frameworks are specifically constructed for pharmacological interventions and adaptation of these frameworks imparts the risk of excluding AEs unique to non-pharmacological interventions that have not yet been defined. As a result, clinical trials of non-pharmacological interventions seldom include a systematic method to capturing and reporting AEs, often using no method at all. These gaps make it likely that AEs in trials of non-pharmacological interventions are underreported, providing insufficient information about the safety of such interventions prior to their implementation in clinical practice. In addition, clinical trials focus primarily on participants receiving the intervention, with current AE-reporting frameworks not designed to capture potential harms to other personnel involved (i.e. family/carers, and clinical and research staff). A series of collaborative group discussions with consumers and interdisciplinary clinical trialists, and case study analyses were conducted to explore gaps in the capture and reporting of AEs specific to non-pharmacological trials, and their mitigation.

Main body Two case examples are provided. The first case example highlights that current methods are inadequate, resulting in inconsistencies in capturing AEs, influenced by the environmental context of the clinical trial. The second case example highlights the need for both systematic and simplified AE-reporting frameworks, particularly for clinical trials conducted in medically complex populations where participants may be at high risk of experiencing AEs. We recommend future trials of non-pharmacological interventions adopt a four-step framework that incorporates: (1) enhanced trial protocol development to define the participant, environmental context in which the intervention is taking place and identify other personnel involved; (2) pre-specify anticipated AEs in trial protocol; (3) selection of the most appropriate measurement system to define, report and grade AEs; and (4) develop corrective and preventative action plans.

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Conclusion We provide recommendations for an AE-reporting framework for future trials that encompass risks unique to non-pharmacological interventions and all individuals involved. By focusing on these directions, we can streamline the process of capturing and reporting AEs and contribute to more impactful and sustainable outcomes.

Keywords Adverse events, Non-pharmacological, Risk management, Clinical trials, Intervention, Harm, Case study, Framework, Safety

Background

"*Medicine is not only a science; it is also an art. It does not consist of compounding pills and plasters; it deals with the very processes of life, which must be understood before they may be guided*". This adage (Paracelsus, sixteenth century) reminds us that before any medical intervention can be safely initiated, be it pharmacological or non-pharmacological, it is essential to understand the mechanism, benefits, and potential harms of the treatment. This understanding should incorporate a holistic approach whereby we consider the impact of the intervention on the whole person, not just the disease process.

Accurate capture and reporting of adverse events (AEs) in clinical trials is critical to understanding the potential harms of prospective interventions. Yet clinical trials of non-pharmacological interventions rarely incorporate a systematic method of capturing and reporting AEs, and often use no method at all [1]. Current AE-reporting frameworks, such as the International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Guideline for Good Clinical Practice (ICH-GCP) [2] and the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) [3], are specifically constructed for pharmacological interventions. They also focus on trial participants and do not capture harms to participants' family/carers and clinical/research staff.

The Cochrane Handbook for Systematic Reviews of Interventions defines AEs, as "*any unfavourable or harmful outcome that occurs during, or after, the use of a drug or other intervention, but is not necessarily caused by it*". In contrast, the ICH-GCP defines an AE as "*any untoward medical occurrence in a patient… administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment*". By extension, a serious AE (SAE) is defined as "*any untoward medical occurrence that at any dose; a) results in death, b) is life-threatening, c) requires inpatient hospitalisation or prolongation of existing hospitalisation, d) results in persistent or significant disability or incapacity, or e) is a congenital anomaly or birth defect*" [2, 4]. The ICH-GCP specifically defines AEs in the context of a "pharmaceutical product", and non-pharmacological interventions are not referred to directly in their definition.

As per ICH-GCP compliance requirements, clinical trials of pharmacological interventions have strict systems for defining, recording, and reporting AEs and SAEs. There is an emphasis on reporting biologically mediated AEs with physical manifestations and the NCI-CTCAE grading system, designed for cancer clinical trials, is frequently used [3].

There is less clear guidance for capturing and reporting AEs in trials of non-pharmacological interventions, and a possible emphasis upon non-biologically mediated psychological AEs [1]. Investigators commonly refer to the ICH GCP framework for definitions and terminology related to AEs, whilst the NCI-CTCAE framework is used for systematically naming and grading specific AEs [2, 3]. Adaptation of these reporting frameworks imparts a risk of excluding AEs unique to non-pharmacological interventions, such as a participant's emotional distress if they cannot complete a mindfulness-based intervention. In addition, manufacturers of pharmacological products include an Investigator's Brochure for unlicenced products or a Summary of Product Characteristics (SmPC) for licenced products [5]. These documents, developed according to ICH-GCP guidance, detail potential AEs based on pre-clinical and clinical data. The development of such documents is not standard practice for non-pharmacological interventions, and most are evaluated without this documentation [2]. Consequently, there is a lack of clarity regarding non-pharmacological intervention AEs, predisposing to ambiguity and inadvertent exclusion of important safety data [6].

Through a series of collaborative group discussions with consumers and interdisciplinary clinical trialists and case study analyses, we identified a need for clear guidance on capturing and reporting AEs in clinical trials of non-pharmacological interventions. This paper, led by two Australian Collaborative Trials Groups (Palliative Care Clinical Studies Collaborative (PaCCSC) and Cancer Symptom Trials (CST)) aims to (i) share case examples of AE-reporting in clinical trials of non-pharmacological interventions and (ii) provide recommendations and a framework to aid the systematic capture and reporting of AEs experienced by all individuals involved in clinical trials.

Main text

Case examples

The following case examples describe the process and insights gained from AE capture and reporting in two recent Australian randomised controlled trials (RCTs) of non-pharmacological interventions. Beyond these examples, it is crucial to highlight that the methodological aspects discussed resulted from consultations with members of the PaCCSC and CST collaboratives.

Example #1—the TIGER trial

The TIGER (rehabili**T**ation **I**n lun**G** canc**ER**) study was a RCT of a home-based exercise and supportive care program for people with non-operable non-small cell lung cancer (Fig. 1) which aimed to improve participants' physical capacity (ACTRN12614001268639) [7]. The intervention was individually tailored and consisted of aerobic and resistance exercise and symptom self-management. Trained physiotherapists and nursing staff delivered the intervention by telephone and participants self-reported their outcomes.

The trial protocol defined SAEs as any event occurring either during or up to 60 min following the intervention or outcome assessment which met the standard SAE definition [2]. AEs were defined as falls not resulting in injury, severe breathlessness, new or progressive pain, neurological deficits, altered mental status, palpitation, and progressive fatigue [8]. Research staff recorded AEs and SAEs following intervention and outcome assessment. Only SAEs were reported to ethics committees.

An example of an incident which was not reported as an AE occurred when a participant tripped and fell at home whilst completing their exercises. It was reported by a family member at the next home visit, but as there was no injury at that time it was only recorded in the field notes of the visiting staff member as per protocol guidelines, without further review. Should this incident have occurred within the hospital, it would have been reported through the hospital's risk management system and a medical review would be conducted, regardless of severity.

This example demonstrates that environmental factors, such as the trial location, may result in inconsistencies in AE-reporting in clinical trials of non-pharmacological interventions. There may be a higher risk of AEs not being captured in community settings compared to hospital settings, as many existing reporting frameworks are designed for structured clinical environments and may not be easily adaptable to the less controlled and resource-limited community settings.

	Population	Intervention	Comparator	Outcome
Example 1: TIGER (6)	Community-dwelling adults with non-operable non-small cell lung cancer	An individually tailored home-based rehabilitation program Aerobic and resistance exercise, behaviour change and symptom self-management	Usual care	Improve physical capacity; Improve health related quality of life and symptoms
Example 2: PRESERVE (8)	Adults with advanced cancer admitted to palliative care units across four Australian hospitals	Delirium prevention strategies across six domains: sleep, vision and hearing, hydration, orientation, mobility, and family engagement	Usual care - waitlisted sites	Intervention adherence; Feasibility of delivering the intervention; Delirium incidence and severity; AEs including falls, complaints and other according to NCI-CTCAE

Fig. 1 PICO table for TIGER and PRESERVE case examples

Example #2—the PRESERVE pilot study

The PRESERVE (**PR**event delirium through **E**ating and drinking, **S**leep, **E**xercise, **R**eorientation, **V**ision and hearing, and **E**nabling family) pilot study was a phase II cluster RCT of a multicomponent non-pharmacological delirium prevention intervention (Fig. 1). It aimed to determine the feasibility and acceptability of the six domain non-pharmacological intervention prevention strategies for people with advanced cancer admitted to palliative care units (ACTRN12617001070325p) [9].

The trial protocol pre-specified the following AEs of interest: falls, complaints about intervention delivery or implementation, death and others [10]. AEs were captured by research nurses on case report forms (CRFs) during the intervention period and reviewed by site investigators, according to the NCI-CTCAE and descriptively in the event of a complaint [3]. Recorded AEs were reported at trial end. Most (69%) participants experienced an AE (162 in total), but none was attributed to the intervention [9].

The PRESERVE pilot study demonstrated a comprehensive and complementary approach to proactively capturing and reporting AEs in a RCT of a non-pharmacological intervention, utilising both quantitative and qualitative methods. However, the AE data collection and review processes were time-consuming for site staff, given the high number of AEs. Ideally, AE-reporting frameworks should be both systematic and simplified, particularly those conducted in medically complex populations where participants may be at high risk of AEs due to their underlying disease and/or concurrent interventions [11].

Current AE-reporting frameworks

Typically, clinical trials capture participant-related AEs which are then attributed by the site principal investigator (PI) and reported to ethics/governance bodies and/or the data safety and monitoring committee, as required. These AEs are expected to be transparently reported in dissemination activities upon trial completion. Currently, these AEs are limited to predominantly physical symptoms graded against established measuring systems (Fig. 2A). As discussed, there are AEs that cannot be graded according to existing measurement systems. Furthermore, incidents occurring within the environmental context of a trial can impact not only the participant, but other individuals such as clinical and research staff, and family and caregivers, who are not captured in current frameworks and likely under-reported as AEs in publications (Fig. 2B).

Recommendations

We propose future trials of non-pharmacological interventions adopt a four-step framework (Fig. 3) to enhance

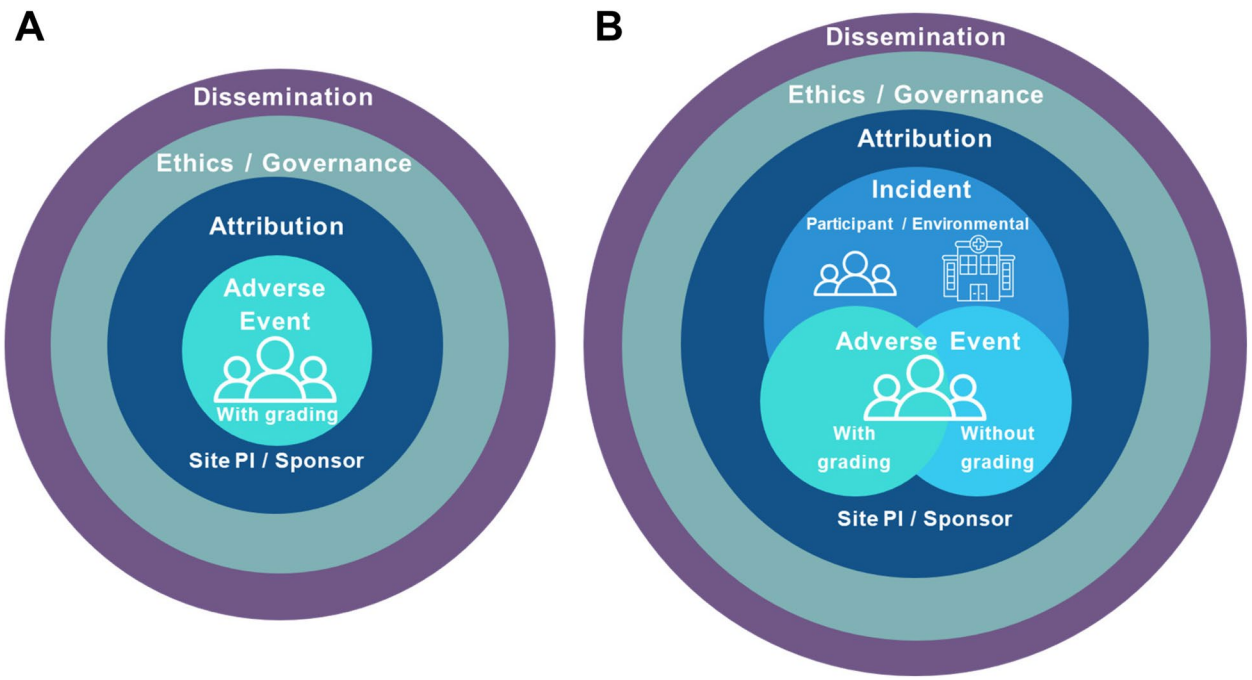

Fig. 2 **A** Traditional AE-reporting frameworks capture AEs that only impact trial participants that can be graded according to current measuring systems. **B** Sponsors and investigator teams need to consider potential AEs that cannot be graded in this way, as well as the importance of capturing AEs that may occur within the environmental context of a trial, and how to best capture and report them

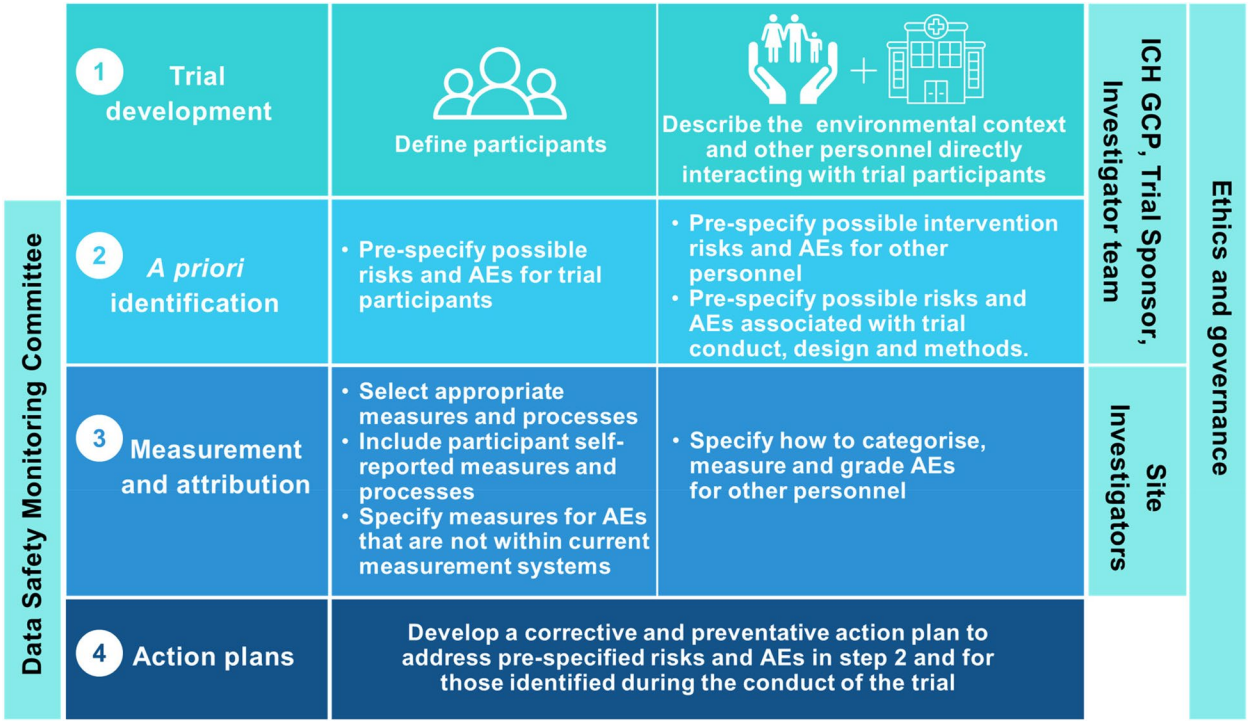

Fig. 3 A 4-step framework for the accurate capture and reporting of AEs in clinical trials

the quality of AE data, facilitate the capture of AEs occurring within the environmental context, and streamline the reporting process. The four steps are as follows:

1. Trial protocol development: Trial protocols should clearly define the participant and the environmental context in which the intervention will be administered and identify individuals (e.g. family, clinical staff) who will interact directly with the participant during the trial (referred to as "other personnel" herein).
2. A priori and proactive approach to identify AEs and other risks: It is essential to pre-specify any anticipated AEs in the trial protocol. Sponsors should encourage the development of an Investigator's Brochure or SmPC, as per Chapter 7 of the ICH-GCP guidelines (Fig. 3) [2, 5]. Additionally, environmental risks and harms to other personnel should be identified using a risk management approach and outlined in the trial protocol. The current guidance regarding risk management and assessment in clinical trials from the Australian National Health and Medical Research Council does not refer to other personnel [12]. Therefore, a general risk assessment matrix, such as the one provided by the Australian Commission on Safety and Quality in Healthcare [13], is recommended. For further general guidance on risk management and assessment, refer to the Australian and New Zealand Standard AS/NZS 4360:2004 [14].
3. Measurement and attribution: Investigators and sponsors need to select the most appropriate measurement system to define, report and grade AEs. Commonly used measurement systems include the Medical Dictionary for Regulatory Activities [15], the Systematized Nomenclature of Medicine—Clinical Terms terminologies [16], and the NCI-CTCAE classification [3]. Furthermore, measurement systems need to allow participants to self-report AEs, potentially capturing AEs staff may not consider noteworthy until they become more severe. They may also foster improved communication between participants and researchers, ultimately leading to enhanced decision-making regarding trial interventions and long-term participant wellbeing [17]. Non-pharmacological trial protocols should incorporate guidance on the grading and reporting of AEs that fall outside current measurement systems. Research staff responsible for safety monitoring and reporting should seek access to data collected in the hospital incident reporting system and/or clinical field notes to check for potential AEs not captured in the trial reporting system. Additionally, guidance on categorisation, measurement, and grading of other risks (as identified in step 2) should be included.

4. Develop corrective and preventative action plans: This proactive approach involves systematically analysing processes to pre-emptively address and prevent AEs or risks identified in step 2, as well as any AEs identified during the conduct of the trial, and implement corrective measures to prevent their recurrence, ensuring ongoing improvement and compliance. At the site level, this includes increasing the awareness of AEs that fall outside current AE-reporting frameworks, and risks that impact other personnel. For example, participants and carers should be informed of their responsibility to promptly report AEs to research staff, regardless of perceived relatedness to the trial. Similarly, clinical and research staff, and carers have a responsibility to report any incidents they themselves experience.

Limitations

The case studies presented in this paper are drawn from Australian trials conducted by the authors' research group. Whilst these provide valuable insights, future work could explore similar challenges and strategies in other international contexts to broaden the applicability of the findings. A significant limitation of this investigation is the scarcity of published literature. It is imperative to establish the extent of AE underreporting, but the lack of data across various practice and trial domains complicated any estimation. Additionally, the examples provided are based on a series of collaborative discussions within our network of palliative care and cancer clinical researchers and consumers and may not be representative of the AE-reporting experiences of other research groups. These examples are also based on our collective recollection of the AEs, as they were either not reported, or identified retrospectively.

Conclusions

The proposed framework is designed to facilitate the capture and reporting of AEs that do not fit within current measuring systems, as well as incidents occurring within the environmental context of a trial that may impact participants and/or other personnel. Going forward, a primary direction is the operationalisation of the proposed four-step framework, which involves a multifaceted approach aimed at enhancing the efficiency and effectiveness of research. Other aspects such as incorporating guidance on budgeting and resourcing within the framework will be essential to ensure feasibility of research studies. We recognise the resource implications of adopting this framework, but believe it is an investment that will enhance long-term efficiency in reporting, ensure regulatory compliance, and bolster the integrity and credibility of research studies. Researcher training to adapt to the proposed processes and equip them with the knowledge and skills to elevate the overall quality of their research is also required. By focusing on these directions, we can streamline the process of capturing and reporting all AEs and foster a culture of innovation and excellence within our research community, ultimately contributing to more impactful and sustainable outcomes.

Abbreviations

AE	Adverse event
CRF	Case report form
CST	Cancer Symptom Trials
ICH-GCP	International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Guideline for Good Clinical Practice
NCI-CTCAE	National Cancer Institute's Common Terminology Criteria for Adverse Events
PaCCSC	Palliative Care Clinical Studies Collaborative
PI	Principal investigator
PICO	Population, Intervention, Comparator and Outcomes
PRESERVE	**PR**event delirium through **E**ating and drinking, **S**leep, **E**xercise, **R**eorientation,**V**ision and hearing, and **E**nabling family
RCT	Randomised controlled trial
SAE	Serious adverse event
SmPC	Summary of Product Characteristics
TIGER	rehabilit**T**ation**I**n lun**G** canc**ER**

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Authors' contributions

All authors (RSM, JP, VY, BF, CM, AH, LE, DD, LB, IG, JS, AC, SF, MA) actively participated in consultations, engaged in collaborative discussions, contributed ideas for methodological aspects, and reviewed and approved the final manuscript. Co-first authors, RSM and JP, drafted the manuscript and created the figures for this paper.

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Competing interests

The authors declare that they have no competing interests.

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