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KEY CONCEPTS IN CLINICAL EPIDEMIOLOGY

Harm outcomes applicable for most meta-analyses of randomized trials of biomedical interventions: a key concept in clinical epidemiology

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Abstract

Randomized trials are used to evaluate health care interventions because they minimize confounding and selection bias through randomization. Harms reporting in trials remain suboptimal, despite established guidelines. To improve transparency and clinical relevance, trialists should share information about harms—whether assessed systematically or nonsystematically. Nonsystematically assessed adverse events warrant greater attention, as they are often underreported or inconsistently documented. Trialists should specify what was measured, when, and by whom. For each study arm, tables or data should be available that include all harms observed. For dichotomous outcomes, tables or data should include the number of people who experienced each harm in each group: the number of participants at risk of harms (ie, randomized individuals); the number of deaths; participants with one or more adverse events; withdrawals (discontinuations) due to harms; and the total number of events, if appropriate. Thresholds should not be used to limit the sharing of information about harms. Zero events should be included for harms systematically assessed. For combined adverse events, such as the proportion of participants with one or more serious adverse events, researchers should report or share data for all component events (eg, deaths, major cardiovascular events, cancers, infections, and psychiatric events). Better harms reporting could improve evidence synthesis, enhance interpretability, and support informed clinical decision-making as well as patient safety. © 2026 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

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1. Background

Randomized controlled trials (RCTs) should measure outcomes specified in Core Outcome Sets (COS), when available. These consensus-based, condition-specific (and occasionally, intervention-specific) outcome lists should be explicit about, and explain the rationale for, considering potential harms [1,2]. Terminology for harms varies [3]; ''adverse events'' (AEs) are unwanted outcomes that may or may not be caused by treatment, whereas ''adverse effects'' are considered treatment-attributable [4]. Transparent reporting of all outcomes—regardless of the results—remains a shared responsibility of authors, journals, and peer reviewers [5,6]. Although benefit outcomes have received considerable attention [7], appropriate reporting of harms in randomized trials is equally essential for knowledge synthesis and informed decision-making [8]. Several influential meta-analyses have revealed important treatment-related harms not apparent in individual trials, particularly when rare events were involved [9−12].

The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) Harms statement emphasizes the impact that harms reporting in trials might have on evidence synthesis [13]. For instance, harms categorization by primary trial authors may result in inconsistent reporting due to varying definitions of severity and seriousness across studies [14]. Further, trials of biomedical products often report harms according to standardized terminology (such as the Medical Dictionary for Regulatory Activities [MedDRA system] or Common Terminology Criteria for Adverse Events [CTCAE]) for each group [15]. Timing and frequency of assessments also matter; for instance, collecting information only at study end risk inaccurate recall of participants' experiences. The Medical Publishing Insights & Practices (MPIP) initiative—a collaborative effort involving pharmaceutical companies and the International Society for Medical Publication Professionals—emphasizes the need to report clinically relevant harms clearly [16]. MPIP discouraging vague statements such as ''generally safe'' or ''well tolerated,'' and encourages inclusion of detailed harm data when appropriate [16]. The initiative also recommends reporting numerators and denominators for all clinically important events [8,16]. Although systematic reviewers are encouraged to prespecify methods for identifying and analyzing harms [13], numerous systematic reviews omit harms data, reflecting persistent underreporting in primary trials [17]. This is a major problem; improving the identification and reporting of harms must begin at the trial planning stage [18]. Trial protocols and systematic review protocols should prespecify both benefit and harm outcomes as well as methods for collecting and analyzing harms systematically, using the same level of rigor as benefits [19]. Nonsystematic collection of harms data is much more complicated at every stage and good solutions/guidance are somewhat lacking [20,21].

1.1. Aim: core harm outcomes in randomized trials

Given the high prevalence of outcome reporting bias and spin for harms [22,23] improving transparency, data sharing, and reporting quality in both primary studies and systematic reviews is essential [18]. Building on current recommendations, trialists should adopt minimum standards for harm reporting, while incorporating intervention-specific details when needed [8].

In this Key Concepts in Clinical Epidemiology article, we outline strategies to improve the reporting and synthesis of adverse events in meta-analyses of randomized trials of biomedical interventions. Drawing on updated Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) [24] and Consolidated Standards of Reporting Trials (CONSORT) [25] guidelines, we aim to reinforce and operationalize existing standards by identifying harm outcomes that are applicable in many trials of biomedical interventions.

2. Standardizing minimal harm reporting in randomized trials

Harm analysis in RCTs remains underdeveloped—improved methods and clearer reporting are needed to detect and interpret adverse events more effectively [26]. Harm outcomes are commonly included in core outcome sets (COS), either as individual or combined outcomes [27]. However, challenges persist regarding both methodology and the need to include harms in a COS. Developers should carefully evaluate the need to include core harm outcomes, considering the scope and objectives of the COS [1,2]. For COS focused on specific intervention types—such as radiotherapy or chemotherapy—developers should also include intervention-specific harms. For condition-specific COS covering all interventions, COS developers should remind the reader that trial-specific adverse events must still be considered and reported. Integrating harms into COS is critical because, as emphasized by Outcome Measures in Rheumatology (OMERACT) [28], trials frequently quantify benefits more rigorously than harms [29−31]. Continued labeling or flagging of adverse events is essential to allow independent and transparent evaluation of both anticipated benefits and potential harms [2]. A COS framework that mandates consideration of core harm outcomes—defined broadly when all intervention types are included, or specifically when tailored to an intervention—alongside core benefit outcomes, will support more complete assessment of both harms and benefits. This approach ensures that harms relevant to each intervention are evaluated and reported consistently, ultimately improving the evidence available for clinical decision-making and patient care.

3. Harms reporting for serious adverse events

The CONSORT harm statement recommends collecting and reporting the number of participants experiencing one or more serious adverse events (SAEs) for each study group [8]. Authors should share results for each type of event (ie, individual components). As shown in Box 1, regulators define SAEs as those that result in death, disability, hospitalization, or other events that require further intervention to prevent additional harms [32]. SAEs are defined and classified by systems such as MedDRA and International Council for Harmonization (ICH) [33], and although reporting frameworks are inconsistently applied, they offer rigor comparable to fully prespecified definitions and are more robust than ad hoc or post hoc approaches.

Combined—composite—outcomes, such as SAEs, combine multiple events to improve both statistical and operational efficiency. Combined outcomes should be prespecified in the protocol with all components listed (eg, death, cardiovascular events, and cancer). When components differ in importance or frequency, overall results can be misleading [34]. To ensure transparency and accurate interpretation, all individual components should therefore be reported separately [35]. Both the number of events and the number of participants affected by harms should be reported for each study arm, including a breakdown of individual components—even if no events occur when harms are systematically assessed—to improve clarity, support interpretation, aid clinical risk-benefit assessment, and enable meta-research [13]. This also applies to groups of harms that may be created post hoc or during the analysis to increase power by aggregating different preferred terms into higher-order terms when using structured language such as MedDRA or CTCAE.

Box 1 Constituents of a SAE

Death—When death is an outcome of the adverse event.

A life-threatening situation—A substantial risk of death at the time of the adverse event or if continued use of the product might result in death.

Hospitalization (initial or prolonged)—Emergency room visits that do not result in admission should be evaluated under other serious outcomes.

Disability or permanent damage—A substantial disruption of a person's ability to conduct normal life functions.

Congenital anomaly/birth defect—An exposure to a medical product prior to conception or during pregnancy that may have resulted in an adverse outcome in the child.

Required intervention to prevent permanent impairment or damage—Necessary intervention to prevent lasting harm to a body function or structure.

Other serious treatment events—Important events that do not fit the above categories but may jeopardize the patient and require medical or surgical intervention to prevent further harm.

4. Updates from the SPIRIT and CONSORT statements

The 2025 updates to the SPIRIT [24] and CONSORT [25] statements were revised to incorporate recent methodological advances and user feedback, addressing persistent reporting deficiencies—especially in harms, outcome definitions, protocol deviations, and statistical methods.

Incorporating harm evaluation should begin at the earliest stages of trial planning, starting with the protocol [36]. The SPIRIT statement outlines essential protocol elements that promote transparency and ensure comprehensive documentation of planned procedures [24]. Planning must clearly define objectives that address both potential benefits and potential harms. Prespecification of harms in both the protocol [24] and statistical analysis plan [37] is critical, including the rationale for selected harms, methods for their assessment, and planned statistical approaches, thereby support reproducibility and transparency. Such standardized guidelines should be followed to ensure harms are identified and evaluated consistently [18]. Trialists should also specify criteria for modifying interventions or comparators, such as dose adjustments in response to observed harms. These transparent data sharing mitigates meta-analysis concerns, including selective outcome reporting and inconsistent definitions, thereby strengthening the evidence base and improving confidence in trial findings.

Adherence to standardized reporting guidelines, such as CONSORT, enhances transparency, reproducibility, and reliability of clinical trials [6]. Consistent reporting reduces bias, supports high-quality meta-analyses, and enhances the overall credibility of research. For the harms section, key recommendations include clearly defining and reporting harm outcomes, whether or not they were systematically assessed. Reports should specify what was measured, when, and by whom. Trialists following best practices, in line with CONSORT guidelines, should report the number of participants per group who were randomized, treated, and included for the primary outcome [7]. For each trial arm, it is essential to detail the number of participants at risk for harms, those experiencing one or more AEs, withdrawals (discontinuations) due to harms, and deaths. Rather than emphasizing the total number of AEs—which may obscure clinical relevance—trialists should provide a breakdown of the number of participants

experiencing each specific AE in each group. Such detailed reporting, placed in the main text or in supplementary materials, facilitates interpretation and supports robust meta-analyses. Including zero-event data for systematically collected harms are also critical to prevent selective outcome reporting [38]. Even mild or moderate harms may lead to treatment discontinuation and withdrawal, though reasons are often complex. Because nonadherence and loss to follow-up may reflect harm-related intolerance [4], reporting these outcomes—eg, in a flow diagram—is essential for transparency.

Data sharing in clinical trials typically include (1) the underlying data generated during trial; (2) a data dictionary describing the structure, content, and meaning of each variable; and (3) key analytic materials such as the protocol, data management plan, statistical analysis plan, and analytic code. Aggregate data may be shared through institutional repositories (eg, those affiliated with the coordinating center's university), public repositories, or mechanisms established by the trial team. Most sharing requires a data use agreement that should prohibit attempts to reidentify or contact trial participants, specify requirements for planned outputs (eg, publication and acknowledgment), and restrict nonapproved uses or redistribution. Requesting that trialists report what was collected is more useful than prescribing how trials should be conducted. Transparent data sharing helps address limitations encountered in meta-analyses, including selective reporting and inconsistent outcome definitions. The concept of ''reporting'' has evolved; although early reporting guidelines emphasized minimum essential elements, contemporary standards encourage comprehensive documentation. This may extend beyond the main text to supplementary materials and appendices. As long as relevant information is publicly accessible, whether in tables, appendices, or online repositories, it should be considered acceptable and consistent with current best practices in transparent reporting.

5. Conclusion

SPIRIT and CONSORT provide explicit guidance on defining and reporting harms whether or not systematically assessed. For each study arm, trials should report the number of participants, those experiencing one or more AEs, withdrawals (discontinuations) due to harms, deaths, the number of participants with each specific AE—including zero events for systematically assessed harms—without applying arbitrary thresholds. For combined adverse events outcomes such as SAEs, researchers should prespecify and clearly define all components (eg, deaths, major cardiovascular events, cancers, infections, and psychiatric events) in the protocol, use consistent classification systems (eg, MedDRA or ICH), and report both the number of affected participants and total event counts. Clear component-level breakdowns—preferably in tables—are essential to support clinical interpretation and allow reviewers to reconcile component data with aggregate SAE counts. Comprehensive harms reporting promote transparency and reproducibility. Incorporating intervention-specific harms into core outcome sets with a relevant scope, along with the harm outcomes identified here for use in most meta-analyses of randomized trials, will enhance evidence synthesis, improve interpretability, and support informed clinical decision-making as well as patient safety.

6. Further reading

The updated guidelines from SPIRIT: [24].
The updated guidelines from CONSORT: [25].

CRediT authorship contribution statement

Robin Christensen: Conceptualization, Investigation, Methodology, Supervision, Visualization, Writing − original draft. **Dorthe B. Berthelsen:** Conceptualization, Investigation, Methodology, Visualization, Writing − original draft. **Peter Tugwell:** Conceptualization, Investigation, Methodology, Writing − review & editing. **Su Golder:** Conceptualization, Investigation, Methodology, Writing − review & editing. **Riaz Qureshi:** Conceptualization, Investigation, Methodology, Writing − review & editing. **Evan Mayo-Wilson:** Conceptualization, Investigation, Methodology, Visualization, Writing − review & editing. **Lee S. Simon:** Conceptualization, Investigation, Methodology, Writing − review & editing. **Joey Kwong:** Conceptualization, Investigation, Methodology, Writing − review & editing. **Paula R. Williamson:** Conceptualization, Investigation, Methodology, Writing − review & editing. **Sunita Vohra:** Conceptualization, Investigation, Methodology, Writing − review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data were used for the research described in the article.

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