Research integrity in randomized clinical trials

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REVIEW ARTICLE

Obstetrics

Research integrity in randomized clinical trials: A scoping umbrella review

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Abstract

Background: Randomized clinical trials (RCTs) are experiencing a crisis of confidence in their trustworthiness. Although a comprehensive literature search yielded several reviews on RCT integrity, an overarching overview is lacking.

Objectives: The authors undertook a scoping umbrella review of the research integrity literature concerning RCTs.

Search strategy and selection criteria: Following prospective registration (https://osf.io/3ursn), two reviewers independently searched PubMed, Scopus, The Cochrane Library, and Google Scholar, without language or time restrictions, until November 2021. The authors included systematic reviews covering any aspect of research integrity throughout the RCT lifecycle.

Data collection and analysis: The authors assessed methodological quality using a modified AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews) tool and collated the main findings.

Main results: A total of 55 relevant reviews, summarizing 6001 studies (median per review, 63; range, 8–1106) from 1964 to 2021, had an overall critically low quality of 96% (53 reviews). Topics covered included general aspects (15%), design and approval (22%), conduct and monitoring (11%), reporting (38%), postpublication concerns (2%), and future research (13%). The most common integrity issues covered were ethics (18%) and transparency (18%).

Conclusions: Low-quality reviews identified various integrity issues across the RCT lifecycle, emphasizing the importance of high ethical standards and professionalism while highlighting gaps in the integrity landscape. Multistakeholder consensus is needed to develop specific RCT integrity standards.

KEYWORDS
quality assessment, randomized clinical trial, research integrity, scoping, scoping review, umbrella review, umbrella review integrity issues

María Núñez-Núñez and Marta Maes-Carballo contributed equally to this work.

1 | INTRODUCTION

Randomized clinical trials (RCTs), ranked highest in the hierarchy of evidentiary validity, are essential for fostering quality health care.[1,2] They must be rigorous at all stages of design, execution, and reporting.[1] However, there is growing skepticism about their trustworthiness in light of various allegations of data fabrication and related retractions.[3,4] RCT integrity is under threat from a mix of unintentional errors, faulty methodology, and misconduct.[5–7] Women's health RCTs have been under recent scrutiny.[8,9]

With an emphasis on adherence to ethical standards and professionalism, the integrity of RCTs is underpinned by responsible research conduct.[10] Research integrity, as generally defined, is the conduct of research in a way that inspires confidence in the findings. It is different from bias, which captures internal validity or deviation from the truth due to deficiencies in a study design or execution. For research integrity, five principles have been reported: responsible research practices, transparent reporting, open-access science, valuing the diversity of research types, and recognizing all contributions to research activity.[11] Thus, integrity applies to the whole research lifecycle, from designing and proposing projects to their publication and dissemination.[12] Multiple initiatives by institutions, research groups, journals, and governmental bodies[11,13–16] provide general statements about science integrity as a whole. Except for the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use documents,[15] the existing initiatives are not specific to RCT integrity. As a first step, this deficiency requires an evidence synthesis to consolidate what has been published in this area. A literature search revealed several reviews on various aspects of integrity related to RCTs, but there were no overarching overviews.

In light of the above background, we conducted a scoping umbrella review to summarize the evidence contained within existing systematic reviews concerning RCT integrity, highlighting their main findings and identifying any gaps to be addressed in future research.

2 | METHODS

Following prospective registration (Center for Open Science, https://osf.io/3ursn), this scoping umbrella review was conducted using recommended methodology[17,18] and written to meet the requirements of the relevant reporting guidelines[19] (Appendix S1).

2.1 | Search strategy, data sources, and study selection

A comprehensive search strategy covering major electronic databases was deployed to capture peer-reviewed and gray literature. PubMed, Scopus, The Cochrane Library, and Google Scholar were searched from database inception until November 2021. References from the eligible primary articles were reviewed for potential additional articles. International experts taking part in an RCT integrity consensus[20] were consulted for additional references. The search term combination was developed iteratively through various pilot searches conducted to capture the concept of research integrity, defined as "research behaviour viewed from the perspective of professional standards."[8] We selected all systematic reviews about any aspect of integrity linked to the research lifecycle of RCTs. The final search combined the keywords and word variations of the following terms: "ethics," "integrity," "misconduct," "fraud," "dishonesty," "transparency," "responsible conduct of research," "questionable research practice," "questionable research," "duplicated publication," "fake," "inconsistent result," "retraction," falsification," and "plagiarism" (Appendix S2). EndNote X9 software (2023 Clarivate) was used to manage the searches downloaded. No language or time restrictions were applied.

The scoping nature of this umbrella review was developed during the conduct of the work. Selection criteria captured systematic reviews concerning any integrity issue applicable to RCTs, defined as a study design that randomly assigns participants into experimental or control groups to compare outcomes.[1] A systematic review was defined as an attempt to "collate all empirical evidence that fits prespecified eligibility criteria in order to answer a specific research question and uses explicit, systematic methods that are selected with a view to minimizing bias."[21] We excluded nonhuman studies, those focusing on the integrity of publications by an author or a group, and those that did not follow a systematic search for reviews.

Studies were selected through a multistep approach, including the deletion of exact and inexact duplicates, reading titles and abstracts, and assessment of full texts. Initially, after the removal of duplicates, a sample of 200 citations (titles and abstracts) was independently examined by two reviewers (MNN and MMC) to unify the selection criteria through discussion. Titles and abstracts were assessed for eligibility by two reviewers (MNN and MMC), and three reviewers (PC, ABC, and MF) double-checked the citations rejected as being research integrity but not RCT related or irrelevant citations. Then, full texts were obtained and assessed for eligibility by two reviewers (MNN and MMC). Potential disagreements or inconsistencies were resolved by arbitration by at least two of the four senior reviewers (PC, KSK, ABC, or MF). Rejected full-text articles were classified into four categories: not systematic review, not research integrity related, not randomized trial related, and outside the scope of review.

2.2 | Data extraction and study quality assessment

The characteristics of the included reviews and their quality were extracted by four reviewers (MNN, MMC, LM, and ABC) into a piloted electronic data extraction sheet. Each paper was evaluated independently by at least three reviewers to extract the quality assessment.

The methodological quality assessment was evaluated if the selected systematic reviews were well-described using a modified

version of AMSTAR,[2,22] a tool for systematic reviews of interventions evaluated in randomized and non-randomized studies. The original tool was adapted to tailor it to the types of reviews within our scope, retaining 16 questions, including seven that addressed critical weaknesses (Appendix S3 gives details of the modified quality assessment). The questions were designed for a binary "yes/no" answer and a "partial yes" when it was considered worthwhile to identify partial adherence to the standard. The critical domains were unchanged from those advised in the original tool: prospective registration, adequacy of the literature search, justification for excluding individual studies, risk of bias from individual studies being included in the review, appropriateness of meta-analytical methods where applicable, consideration of the risk of bias when interpreting the results of the review, and assessment of the presence and likely impact of publication bias. The overall quality was rated as "high" if there was ≤1 non-critical weakness; "moderate" if there was >1 non-critical weakness; "low" if there was one critical weakness with or without non-critical weaknesses; and "critically low" if there was >1 critical weakness with or without non-critical weaknesses. Three reviewers (MNN, MMC, and LM) held training meetings to learn and unify the quality assessment criteria, pilot testing six of 55 (11%) selected reviews. They completed the review quality assessment, initially working individually on one-third of the reviews and then collectively on them all. Disagreements were resolved by consensus or arbitration by a senior reviewer (ABC).

The main findings of each selected review were extracted initially by at least two of the seven reviewers (MMC, MNN, LM, ABC, KSK, MF, and PC). All of the initially extracted findings were then reviewed by one senior reviewer (PC). Finally, a consensus meeting of three reviewers (ABC, MMC, and MNN) summarized the findings statement extracted and delineated the integrity issue(s) covered by each selected review.

2.3 | Evidence synthesis

A descriptive analysis was performed, tabulating the characteristics and quality of the selected reviews. We classified the integrity issues and the main findings according to various integrity categories covering the RCT lifecycle as follows: general (overarching issues); design and approval (the process of proposing an RCT and obtaining approval for its protocol); conduct and monitoring (executing the study according to the approved protocol and overseeing its compliance with standard operating procedures and applicable regulatory requirements); reporting of protocol and findings (manuscript submission, peer-review and publication according to relevant ethics, statistics, and reporting guidelines); postpublication concerns (dealing with postprint complaints); and future research and development (emphasizing gaps that need to be addressed). Some reviews covered more than one integrity category and were assigned the main category by consensus (ABC and MMC) for tabulation.

3 | RESULTS

3.1 | Study selection

The initial search identified 4419 citations. After removing 597 duplicates, 3822 records were screened. A total of 3639 records were initially excluded. The full text of 183 citations was obtained for eligibility assessment (Figure 1). A total of 55 reviews[5,23–76] were included in the final appraisal. Only four of them included meta-analysis.[30,53,69,74] The list of excluded articles with reasons can be found in Appendix S4.

3.2 | Characteristics and quality of the included reviews

The characteristics of the included reviews are reported in Appendix S5. The publication dates of the included reviews ranged from 2003 to 2021, with 34 (62%) studies published within the past 5 years. There were 6001 studies in the included reviews, with the median number of studies per review being 63 and ranging from eight[32,34] to 1106.[48] The publication time range of the included studies was 1964 to 2021. Most of the reviews did not limit the included RCTs to a specific geographical area (49/55, 89%); some focused regionally on low–middle-income countries[25] and South East Asia,[48] and nationally on India,[62] China,[73] Brazil,[5] and the United States.[35] There was no patient involvement in the design, conduct, or interpretation of any of the included systematic reviews.

The overall quality was critically low in 53 (96%) reviews, and moderate[42] and high[54] in 1 (2%) each (Figure 2; Appendix S6). The four meta-analyses included were of critically low quality. Analyzing the rates of compliance with individual items, there were deficiencies, particularly in domains concerning the provision of the list of excluded studies (2 of 55, 4%) and the description of funding sources of the included studies (4 of 55, 7%). Only 13 (27%) of the reviews reported an explicit statement about prospective registration. The highest rates of compliance were in the domains relating to the reporting of conflict of interest of the reviewers (42 of 55, 76%) and duplicated study selection (35 of 55, 64%).

3.3 | Synthesis of findings

The integrity issues covered in the included reviews and their main findings were diverse (Table 1). Some recurrent findings were weakness of informed consent, ethical review, and follow-up; the lack of a standardized curriculum for the integrity of research for students, clinicians, and researchers, or the need for excellent and consistent peer-review; and reporting guidelines. Regarding misconduct, systematic detection was established only for plagiarism. Some reviews[28,35,46,49,54,63,74] were allocated to the future research section because their findings were related to currently

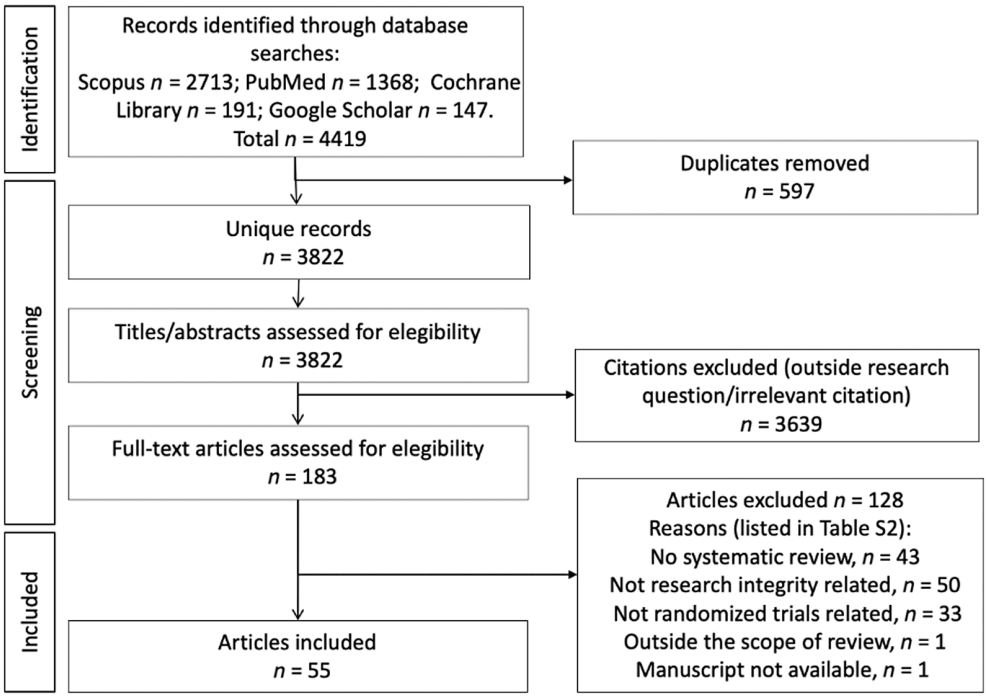

FIGURE 1 Flow chart of the systematic reviews included in the scoping umbrella review.

unsolved questions. Regarding the RCT integrity categories, 8 (15%) reviews focused mainly on the general aspects of RCTs, 12 (22%) on the design and approval, 6 (11%) on the conduct and monitoring, 21 (38%) on the reporting of protocol and findings, 1 (2%) on postpublication concerns, and 7 (13%) on future research and development.

The integrity issues covered were varied, with the most common being the importance of ethics (10 of 55, 18%) and transparency (10 of 55, 18%). Figure 3 shows the integrity issues according to categories. Ethics was featured as an issue across the categories. Transparency was featured as an issue in the reporting of protocols and findings (eight of 21; 38%) and the design and approval (two of 12; 17%) categories.

4 | DISCUSSION

4.1 | Main findings

The large body of evidence in this scoping umbrella review included over 6000 studies captured in 55 systematic reviews, with four of these reviews summarizing the findings using a meta-analysis. The overall quality of the majority of reviews was critically low, with weaknesses in critical areas. There was low compliance, particularly concerning the quality items relating to the list of excluded studies and the description of funding sources for the included studies, the reviewers' conflict of interest, and the extent of duplicated study selection. The main findings were heterogeneous and, in most circumstances, reached diverse conclusions that reduced the possibility of directly comparing the included reviews. The findings could be categorized under the heading's general aspects, design and approval, conduct and monitoring, reporting of protocols and findings, postpublication concerns, and future research and development, encompassing the entire RCT research lifecycle. The integrity issues covered by approximately two-fifths of the reviews focused on ethics and transparency of RCTs.

4.2 | Strengths and limitations

To the best of our knowledge, this is the first scoping umbrella review to identify and summarize research integrity issues specific to RCTs. The focus of our review was not on the risk of bias. One of this review's main strengths is its extensive search strategy, which was based on a wide conceptual framework and gave a global perspective by identifying a large number of RCT-related reviews connected to research integrity without regard to language or time restrictions. This allowed us to include diverse systematic reviews about any aspect of research integrity concerning the RCT lifecycle. The evidence, highlighting main review findings and gaps to be addressed in future research, was synthesized in a manner that is akin to scoping reviews[77] in that it allowed the mapping of the research conducted in the research integrity field, clarifying concepts (integrity categories and issues) covered in the literature. Hence, for reporting, we used the relevant scoping review guidelines.[19] This approach is more likely to assist with the completeness and transparency of reporting our work.

One of the main challenges we encountered when performing the literature search and selection was defining the terms research integrity, systematic review, and RCT. To solve this dilemma, preliminary

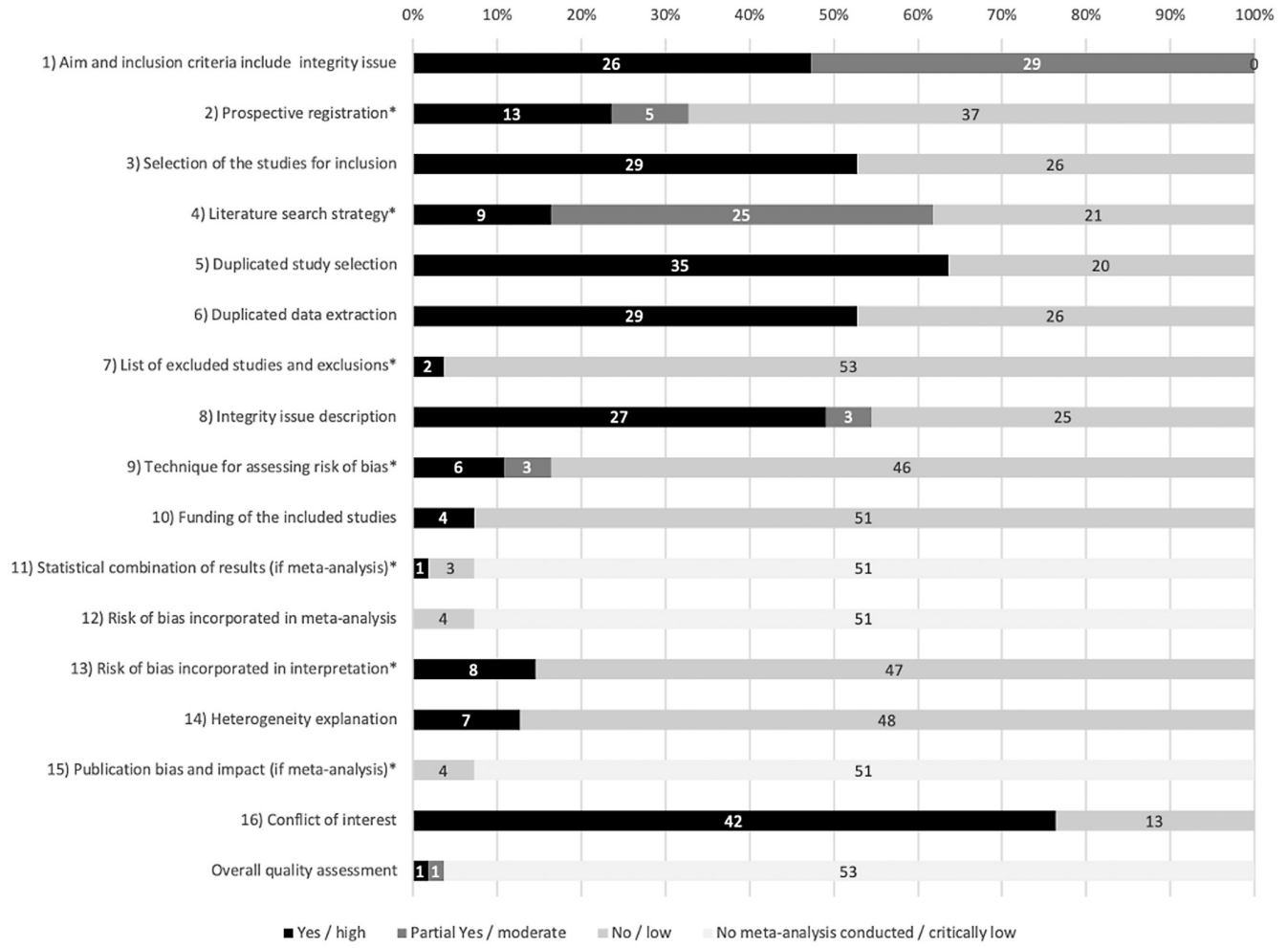

FIGURE 2 Overall quality assessment and rates of compliance of individual quality assessment items in the umbrella review of research integrity of randomized clinical trials. Critical items are marked with an "*".

literature reviews were performed to determine a clear, unambiguous definition of each term to implement the final search term combination and the selection criteria. These preliminary efforts made a clear way for the subsequent scoping umbrella review with which we captured a large number of reviews and studies within them related to the research integrity topic that comprehensively mapped the issues within RCTs.[18,78] Readers may hold different opinions on the inclusion or exclusion of specific review articles. For example, reviews on interventions to prevent integrity flaws[54] or RCT reporting extensions[79] may be considered ineligible by some. However, mapping is quite a broad exercise compared with quantifying effectiveness, e.g. in meta-analyses of RCT data. To ensure reproducibility and avoidance of errors, six reviewers were involved in the selection of articles in our review. Moreover, when a review, e.g. that of preventive interventions,[54] served to generate a statement in the international multistakeholder consensus paper,[20] its endorsement in a two-round Delphi survey lends credence to inclusion through the votes of the expert panel. Given the broad nature of the scoping umbrella review, the heterogeneity found among the findings of the articles was likely unavoidable as the research integrity topic itself is wide, and the included reviews fundamentally differ in their development, structure, context, and terminology. Thus, our review is able to establish a baseline as to "what has previously been done?" and "what does the literature say?" about research integrity related to RCTs.

Scope reviews are inclusive, adaptive, and iterative.[18,80,81] Like all reviews, they require rigorous methodology in their conduct to ensure that the results are trustworthy. In this regard, the reliability of the study selection and the data extraction process is key. Given the nature of variation in terminology and the dispersion of the topic across academic specialties, achieving reproducibility was identified as an early challenge in our work. We thus introduced various piloting exercises and multiple reviewers to minimize the risk of errors and omissions. Reviewers worked independently and in duplicate, with double-checks included throughout the work. In the extraction of findings, a particularly challenging task, seven reviewers participated to ensure accuracy in the determination of key facts. Despite this attention to detail in the implementation of the review, there remains a possibility of some errors. In the interest of openness, we provide all of our data extracted as detailed appendices to supplement what is reported in the main text.

TABLE 1 Characteristics of the reviews included in the scoping umbrella review of research integrity of randomised clinical trials and their main findings.

	Author	Year	Integrity issue	Main findings
1	Maccaro A	2021	Ethics	The majority of articles reporting ethical issues with the coronavirus disease 2019 (COVID-19) pandemic come from low–middle-income countries. The most typical theme found was the issue of resource allocation with personal protective equipment with COVID-19
2	Ni Y	2019	Misconduct prevention	Most postgraduate students are aware or relatively aware of the definition of research misconduct. The main reasons responsible for research misconduct are the unhealthy atmosphere of the society/institution, insufficient research ability, insufficient knowledge of academic norms, limitations of the education/evaluation system, lack of heteronomy/supervision, lack of guidance/training (in both research skills and research integrity), lack of self-discipline, and too much pressure to publish. About 10% to 32% of postgraduate students admitted that they had committed research misconduct
3	Awasthi S	2019	Plagiarism	Researchers and academics do not well understand the concept of plagiarism. Libraries play an essential role in detecting and deterring plagiarism activities by spreading the word about plagiarism. The use of antiplagiarism software may help detect and deter plagiarism. A plagiarism policy needs to be implemented in academic institutions
4	Stavale R	2019	Retraction of publications	The trend of publication retractions is increasing over time. Experimental studies (40) and literature reviews (15) accounted for 84.6% of the retracted articles. Within the health and life sciences fields, medical science was the field with the most significant number of retractions (34), followed by biological sciences (17). Among the retrieved articles, plagiarism was the main reason for retraction (60%). Missing data were found in 57% of the retraction notices, and 63% of the articles were still cited after their retraction
5	Guraya S	2017	Plagiarism	Key reasons leading to plagiarism are lack of awareness of research ethics, poor writing skills, and pressure to publish. Plagiarism can be avoided by educating undergraduate and postgraduate students on research and publication ethics. Editors, reviewers, and authors should rigorously check sources and consider the use of plagiarism detection software. Retraction notices by journals should highlight the reasons and backgrounds for retraction and specify whether the author or the publisher initiated the retraction. Allegations of potential plagiarism should be reviewed by a Faculty Plagiarism Committee of the author's institution(s) concerned
6	Wang J	2017	Retraction of publications	The number of retracted articles increased over time. The most common reason for retraction was because of a duplicated publication found elsewhere ($n=26$), followed closely by plagiarism ($n=22$) and presenting fraudulent data ($n=14$). Other reasons included scientific errors/mistakes ($n=11$), author misattribution ($n=7$), and compromised peer review ($n=7$)
7	Guraya S	2016	Misconduct prevention	Some universities offer generous grants and salaries to researchers with a high *h*-index and with more publications in elite journals. Job promotion and better job security are also often proposed to researchers who publish more often. This can result in the widespread publication of non-significant research with a high index of plagiarism that eventually leads to an increased frequency of retractions
8	Nicholls SG	2015	Ethics	Lack of consensus on the criteria and tools used to evaluate the quality of the ethics review process for clinical studies. No study reported using an underlying theory or framework of institutional review board quality/effectiveness to guide study design or analyses. The included studies varied substantially with respect to outcomes assessed, although tended to focus on structure and timeliness of ethics review
9	Hutchings E	2021	Data-sharing	Consent prior to the use of health data for secondary research was not universal nor always supported by legislation. There is a need to clearly state where data must be identifiable at the initial consent stage. Many articles concluded that neither consent nor being informed of the research without providing additional consent were sufficient

TABLE 1 (Continued)

	Author	Year	Integrity issue	Main findings
10	Paramasivan S	2021	Ethics	Indian literature was heavily focused on "knowledge" assessments of participants from lay/professional groups on various topics. Ethics committees were examined from multiple angles, and they were also the source of data in many studies. Healthcare students were often research participants. Studies that investigated the recruitment, informed consent process, models of informed consent tailored to the Indian context, and issues such as equity and justice in the context of clinical trials/research were far fewer in number or absent. Significant knowledge gaps exist in the informed consent and recruitment process
11	Natale P	2021	Recruitment challenges	Patient perspectives on recruitment and retention in randomized clinical trials (RCTs) were related to trust/mistrust in health professionals, patients, families, and institutions. Trials were perceived as an opportunity for some patients to access free and high-quality health care. Barriers identified to participating in trials: lack of clarity about the context and potential benefit of the trial, feeling pressured in making immediate decisions, being overwhelmed by the disease and treatment burden, having little knowledge of opportunities, being concerned about being randomized to the control arm and not gaining benefits from participating in the trial, loss of privacy, discrimination, and the notion of being experimented on with interventions that had unknown effects and lack of feedback from the RCT
12	Mirchev M	2020	Passive data	In the context of big data, patient data ownership is poorly researched, and the authors did not find consensus on policy decisions and legal regulations. The majority of publications on this topic come from the United States (3%–31%) and the United Kingdom (3%–25%)
13	Maher NA	2019	Passive data	Current methods of obtaining informed consent for passive data collection are inadequate (35 studies). No consensus on the ownership of passively collected data (eight studies) and concerns about security and storage of such data (15 studies) and data quality (12 studies) were found. Significant barriers still exist to using passively collected data for scientific and public health research (four studies)
14	Alemayehu C	2018	Barriers for an RCT	The greatest challenge that faced researchers in developing countries was the lack of financial (eight studies) and human capacity (nine studies). In addition, several other themes emerged from the research literature: ethical and regulatory system obstacles (seven studies), lack of research environment (eight studies), operational barriers (eight studies), and competing demands (eight studies)
15	Phillips, A	2017	Ethics	The majority of the selected articles recommended obtaining ethics approval to use anonymized samples and data. There is a concern over the effectiveness of most anonymization procedures to prevent reidentification. Even where individual identities may not be identifiable, there is still the risk of group harm that may not be protected by the anonymization process alone. This is particularly true in the context of genomic research
16	Djurisic S	2017	Barriers for an RCT	The main barriers to RCTs identified are: inadequate knowledge of clinical research and trial methodology, lack of funding, excessive monitoring, restrictive privacy law and lack of transparency, complex regulatory requirements, and inadequate infrastructures
17	Dupont JC	2016	Ethics	Obtained informed consent ($n = 320$; 33%) and research ethics ($n = 267$; 27%) were the most frequently addressed ethical domains in the field of pediatric oncology, compared with professionalism ($n = 173$; 18%) and public policy ($n = 143$; 15%). Ethical assessment of research protocols ($n = 65$; 7%) was the least common issue raised
18	McKeown A	2015	Transparency	In analgesic clinical trial publications, sample size calculations were frequently incompletely reported. Only 111 (65%) of 172 RCTs reported at least one element of a sample size calculation. Among these 111 RCTs, only 65 (59%) met all of the elements for reporting for sample size calculation as per CONSORT (Consolidated Standards of Reporting Trials) guidelines. Only 60 (54%) of these 111 articles included a justification for the assumed treatment effect to be detected. Randomized participants differed by ≥10% from the planned number of participants in 31 of 111 articles (28%). No significant differences in reporting of any or all elements were detected between publications of trials with industry and no industry sponsorship

(Continues)

TABLE 1 (Continued)

	Author	Year	Integrity issue	Main findings
19	Chapman S	2014	Transparency	Registration of surgical RCTs is increasing over time but remains suboptimal. The principle of open access data sharing is poorly endorsed in surgical research
20	Schellings R	2006	Ethics	Of 50 RCTs, non-compliance to study protocol was higher in the randomized consent experimental group compared with the control group in 65% of studies. Trials that employed an incomplete double consent design (participants only consent for the intervention received for the randomized arms) were associated with a higher rate of non-compliance (16%–21% vs. 3%–58%) and loss to follow-up (21%–44% vs. 25%–26%) compared with single consent (where only participants in the experimental arm had an explanation of the intervention received) or complete double consent design (whereby participants were told about both interventions studied)
21	Pietrzykowski T	2021	Ethics	Study participants demonstrated the highest level of understanding (over 50%) regarding voluntary participation, blinding (excluding knowledge about investigators' blinding), and freedom to withdraw at any time. Only a tiny minority of participants demonstrated comprehension of placebo concepts, randomization, safety issues, risks, and side effects
22	Karanatsios B	2020	Registry-based RCT	Most registry-based RCTs (15 of 17) were two-arm studies and had randomization performed at individual participant-level (15 of 17) studies. Primary and secondary outcomes were well defined in all studies. RCT duration ranged from 2 months to 2 years and 9 months. The follow-up duration of the studies ranged from 72 h to 12 years. Only three of 17 studies commented on the cost-effectiveness of the interventions studied
23	Houghton C	2020	Recruitment challenges	Several factors influence a person's decision to participate in a trial, including how the trial is set up and communicated, people's individualized circumstances, and the potential benefits of participation. Potential participants may have a genuine interest in contributing to scientific knowledge and improved care
24	Goldstein CE	2018	Ethics	Most of the articles do not support the distinction between research and clinical practice. Low-risk pragmatic RCTs should be allowed to be conducted with either no or simplified consent. Study information should only be disclosed if research participation adds risks over and above clinical practice. There is a disagreement about whether to disclose randomization. Oversight is time-consuming, costly, and complex
25	Olsen R	2016	Monitoring approaches	One hundred percent source data verification (SDV) may not be a rational method of ensuring data integrity and patient safety based on the high cost. Three of 22 publications showed that SDV has some value for detection of not initially reported adverse events and centralized statistical monitoring (CSM) captures atypical trends; 14 publications showed little objective evidence of improved data integrity with traditional monitoring, such as 100% SDV and sponsored queries as compared with reduced SDV, CSM, and remote monitoring. Eight publications proposed a potential for significant cost reductions of monitoring by reducing SDV without compromising the validity of the trial results
26	Treweek S	2013	Recruitment challenges	Interventions identified to be effective in increasing recruitment included: (1) telephone reminders to non-respondents (risk ratio [RR], 1.66 [95% confidence interval (CI), 1.03–2.46]; two studies, 1058 participants); (2) use of opt-out rather than opt-in procedures for contacting potential participants (RR, 1.39 [95% CI, 1.06–1.84]; one study, 152 participants; and (3) open designs where participants know which treatment they are receiving in the trial (RR, 1.22 [95% CI, 1.09–1.36]; two studies, 4833 participants). Other strategies such as offering financial incentives to trial participants, training recruiters, and greater coordination between trial recruiters and the use of video information had mixed results

TABLE 1 (Continued)

	Author	Year	Integrity issue	Main findings
27	Malicki M	2021	Reporting guidelines	Significant heterogeneity between different journals in the Instructions to Authors addressing: (1) authorship; (2) conflicts of interest; (3) data sharing; (4) ethics approval; (5) funding disclosure; and (6) International Committee of Medical Journal Editors Uniform Requirements for Manuscripts. Heterogeneity is explained by: (1) time (addressing of topics generally increased over time); (2) country (significant differences found between countries); (3) database indexation (considerable differences found between databases); (4) impact factor (topics were more often addressed in highest than in lowest impact factor journals); (5) discipline (topics were more often handled in Health Sciences than in other disciplines); and (6) subdiscipline (topics were more often addressed in general than in subdisciplinary journals). In the context of big data, patient data ownership is poorly researched, and the authors did not find consensus on policy decisions and legal regulations. Most publications on this topic arrive from the United States (3%–31%) and the United Kingdom (3%–25%)
28	Slade AL	2021	Transparency	Barriers to ethnically diverse recruitment include diverse participant engagement, the relevance of ethnicity to the research question, prominence of patient-reported outcomes, and the need to minimize investigator burden. Only 14 of 84 RCTs (17%) reported collecting data by ethnic groups despite eight of 14 (57%) of these RCTs being multicentered and multinational. The numbers of participants represented by ethnicity data were small (13%) in comparison to the total number of participants recruited across the 14 RCTs. The use of translated patient-reported outcome measures (PROMs) was not reported in any of the trial protocols or publications despite seven (88%) using PROMs that have been translated into other languages
29	El-Menyar A	2021	Retraction of publications	Of 124 manuscripts studied, six papers were retracted from high-impact journals, in which the average period until publication was 33 days. Retraction of papers occurred within 10 to 48 days
30	Hayden J	2021	Integrity training	Study quality and reporting of trials in the exercise for chronic low back pain field continue to be lacking. The majority of trials did not report registration information, are small, have insufficient follow-up length, and do not use the recommended core outcome measure set for the field. A total of 25 (9%) of the trials in this review were published in presumed predatory journals. The presumed predatory publication was associated with a missing conflict of interest (COI) statement (odds ratio [OR], 7.6 [95% CI, 3.0–19.1]), inadequate follow-up duration (OR, 11.2 [95% CI, 3.7–33.7]), incomplete study methods (OR, 12.1 [95% CI, 2.8–52.2]), and baseline reporting (OR, 4.3 [95% CI, 1.6–11.7]), and high risk of bias (OR, 2.7 [95% CI, 1.2–6.3]). All (100%) presumed predatory publications had missing trial registrations and inadequate sample sizes
31	Hayden AA	2020	Funding disclosure	Of the 98 studies, 47 (48%) reported favorable results, with five of these studies (10.6%) reporting industry affiliations. Of the 98 studies, 48 (49%) did not report the study funding source. Published studies with unknown funding sources were 5.9 times more likely to report conclusions favoring the biological treatment than those with reported funding sources ($P=0.015$)
32	Evuarherhe O	2019	Professional medical writing support (PMWS)	PMWS is positively associated with measures of overall quality of reporting of clinical trials: better adherence to CONSORT guidelines (OR, 1.44 [95% CI, 1.04–2.00]; $P=0.03$); improved quality of written English (81.1% with PMWS vs. 47.9%); more likely to be published in a journal with an impact factor ($P=0.001$) and higher mean impact factor ($P<0.001$); and lower incidence of reporting of non-prespecified outcomes. Time to publication from last patient visit in clinical trials was also reduced (18.6 months [standard deviation (SD), 13.2] vs. 30.8 months [SD, 11.7])
33	Weissgerber TL	2019	Transparency	The inappropriate use of bar graphs to display continuous data was the most common visualization problem in peripheral vascular disease journals. Of 180 articles, 47.7% used bar graphs to present continuous data, especially with small data sets. Other more effective presentation methods such as dot plots, box plots, and violin plots are recommended instead

(Continues)

TABLE 1 (Continued)

	Author	Year	Integrity issue	Main findings
34	Laothavorn	2019	Ethics	Journals with better ethical approval (EA) and informed consent (IC) instruction scores had a higher percentage of articles that adequately reported EA/IC. There were significant relationships between EA/IC statement scores and journals' instructions scores (EA: $P=0.002$; IC: $P=0.019$)
35	Darmon M	2018	COIs	The presence of a COI statement and the declared rate of COI and funding increased from 2001 to 2016. COI statements are shown by 243 of 374 (65%) articles, and 29 of 373 (7.7%) have declared COIs. Declared COIs were more frequent in 2011 to 2016 than in 2001 to 2010 (OR, 4.06 [95% CI, 1.15–25.79]) and in the higher quartile of a journal's impact factor (OR, 16.73 [95% CI, 3.28–306.20])
36	Montgomery P	2018	Reporting guidelines	The CONSORT-SPI (CONSORT for Social and Psychological Interventions) 2018 checklist extends nine of the 25 items from CONSORT 2010: background and objectives, trial design, participants, interventions, statistical methods, participant flow, baseline data, outcomes and estimation, and funding
37	Yelland L	2018	Transparency	Recruitment, randomization, or treatment errors were reported in 32 of 82 (39%) phase III RCTs published in leading medical journals in 2015, with a median of eight errors (range, 1–176). The three most commonly reported errors were ineligible participants inadvertently being randomized ($n=23$; 28%), participant receiving incorrect treatment ($n=4$; 5%), and participant randomized using incorrect baseline information ($n=2$; 2%)
38	Van der Steen JT	2018	Transparency	The determinants related to selective reporting found were related to: focus on preferred findings (36%); poor or overly flexible research design (22%); high-risk area and its development (8%); prejudice (7%); lack of resources including time (3%); doubts about reporting being worth the effort (3%); limitations in reporting and editorial practices (3%); academic publication system hurdles (3%); unfavorable geographical and regulatory environment (2%); relationship and collaboration issues (2%); and potential harm (0.4%)
39	Gewandtera J	2017	Transparency	There is a frequent lack of clarity in primary publications regarding whether data monitoring committees (DMC)/data and safety monitoring boards (DSMB) were used and the details of their role and composition. Of the 294 RCTs, 175 (59%) mentioned using a DMC/DSMB; 45 (26%) of these 175 reported all of the members' names. Only one article stated that a DSMB was not used. The remaining 119 articles did not report whether a DMC/DSMB was utilized, even though 59 had previously stated in a clinical trials registry entry or a published protocol that a DMC/DSMB was to be employed
40	Liu TY	2016	Reporting guidelines	Only 2 (3%) journals did not introduce any statistical reporting guidelines for authors, but there has been an improvement in the statistical requirements in Instructions to Authors over time. The four most common statistical issues relevant to research are: participant flowchart, "eligibility" criteria details, randomization information, and sample size calculation details. Concerning statistical analysis, statistical methods and the reasons for using them, novel methods should be explained, multivariate analysis and whether one-tailed or two-tailed tests should be used. The four most typical statistical issues relevant to the presentation are: reporting of actual outcomes, exact P value, whether to use the mean or median to describe the data, and tables and graphs that show them clearly
41	Adewuyi T	2015	Transparency	In surgical trials, the reporting of non-compliance to allocation and the handling of missing data were typically suboptimal; 45 of 82 (55%) studies reported non-compliance with treatment allocation; 52 of 82 (63%) studies reported primary outcome missing data. Of the 31 of 82 studies that explicitly stated that the analysis was by intention-to-treat, only 20 (65%) included all participants and were analyzed as randomized
42	Hunsinger M	2013	Authorship	Incomplete disclosure of author contributions was 99%. The types of incomplete disclosure are: articles reporting financial support without specifying for what the funds were used (34%), thanking individuals for support without specifying contributions (11%), not reporting the names of individuals providing specific forms of support (design 13%, conduct 11%, statistical 12%, writing 15%, administrative 12%, other 22%), and not reporting the affiliations of individuals providing support (design 85%, conduct 61%, statistical 46%, writing 40%, administrative 75%, other 81%)

TABLE 1 (Continued)

	Author	Year	Integrity issue	Main findings
43	Khalil J	2012	Transparency	The reporting of study characteristics necessary for the correct interpretation and application of the human study is incomplete. The percentage of studies that reported whether the experiment was conducted on an inpatient or outpatient basis was 71%, but only 47% of them reported the number of days participants spent as an inpatient or outpatient during the study. The number of participants in the study was reported at 98%; 80% reported the age of the participants and 91% reported the eligibility criteria for the study; 73% of the studies had IRB approval and 76% reported that informed consent was obtained; 43% reported the origin of the challenge strained studied and 88% reported on the details of the inoculum used; 84% of the studies reported on the method of clinical evaluation of the study outcome; 68% reported on the follow-up of participants; and 27% reported any detection of adverse events
44	Dulhunty JM	2011	Authorship	The eight tools for determining authorship are: (1) DiGiusto points system; (2) the Center for Healthy Communities authorship scale; (3) National Psychosis Research Framework guidelines; (4) Bhopal et al. ranking method; (5) authorship guidelines by Erlen et al.; (6) Rennie–Yank–Emanuel descriptive system; (7) CanChild Centre for Childhood Disability Research, McMaster University, Ontario, Canada author guidelines; and (8) HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) scoring system
45	Milette K	2011	Transparency	Only 25 of the 63 articles (39.7%) were classified as having adequately declared outcomes, including 9 (14.3%) with adequately declared primary outcomes and 16 (25.4%) with adequately declared secondary outcomes. Of the 38 articles (60.3%) that had inadequately declared outcomes, 15 (23.8%) declared multiple primary outcomes without appropriate statistical adjustment, 21 (33.3%) had undefined outcomes, 1 (1.6%) reported a previously published primary outcome without indicating it in the article, and 1 (1.6%) declared a primary outcome, but a previous report from the same RCT declared a different primary outcome. Only 13 of 63 (20.6%) of the RCTs were registered, but it was reported in the manuscript in one of 13. Only one study registered sufficiently precise outcome information to compare with the published outcomes, but registered and published outcomes were discrepant
46	Di Pietrantonj C	2005	COIs	The definitions of the source of funding varied largely across the studies, and the information on funding available in the primary studies was generally judged as inaccurate and insufficient to identify the source. The studies financed by industry are more likely to conclude in favor of the intervention produced by the funding bodies (RR, 1.58 [95% CI, 1.39–1.80] $I^2 = 75.7\%$ [$P < 0.001$])
47	Bekelman JE	2003	COIs	Industry-sponsored studies were more likely to be associated with proindustry conclusions (pooled OR, 3.60 [95% CI, 2.63–4.91]). When the studies were stratified into RCTs and other studies, the findings did not change significantly (pooled OR, 4.14 [95% CI, 2.72–6.32] for RCTs)
48	Avenell A	2019	Retraction of publications	The 12 retracted trial reports were cited 1158 times in publications of any kind by August 2016. The median number of citations for retracted trial reports was 84 (range, 14–323). Systematic reviews ($n = 68$), meta-analyses, narrative reviews, guidelines, and clinical trials cited at least one of the 12 retracted trial reports. Each retracted trial report was cited by a median of 11 of the 68 publications (range, 1–25). By 2018, only one of the 68 citing systematic reviews appeared to have undertaken a reassessment, which led to a correction. The 12 retracted trials were cited in nine effectiveness reviews and clinical guidelines in 2016: removing these trial reports would likely alter findings in five, unclear if the findings will change in one, and unlikely to change the findings in another three of these reviews and guidelines
49	Bordewijk E	2021	Misconduct prevention	Measures to counteract textual plagiarism are well implemented and tools to investigate other forms of research misconduct are rudimentary and labor-intensive, based on examples, not standardized, and lack formal validation
50	Pavlenko E	2020	Warehouses data access	Formal documentation on warehouse data users' roles and access levels needs to be defined. The governance of the data and review bodies to underpin this governance needs to be prespecified. The amount of access to the data set with the location and time period of access needs to be stipulated clearly

(Continues)

TABLE 1 (Continued)

	Author	Year	Integrity issue	Main findings
51	Garrison S	2016	Data-sharing	Most studies support the need for consent to use biobank data, although there is a lack of consensus on the level of consent (broad, study-by-study, categorial) required. Most studies support an opt-in consenting process. Participants were generally willing to share their samples and information with other academic institutions and more willing to provide broad consent for samples that were deidentified or anonymous compared with identifiable. Also, they were keener to have their data shared with commercial enterprises than national databases and federal repositories
52	Marusic A	2016	Misconduct prevention	The evidence base relating to interventions to improve research integrity is heterogeneous and incomplete
53	Kalkman S	2015	Ethics	There are three ethical considerations identified in the analysis of the literature on postlaunch pragmatic drug trials: (1) what level of oversight should pragmatic trials require; (2) do randomized patients face additional risks; and (3) is a waiver of informed consent ethically defensible? The literature does not specifically describe ethical challenges related to prelaunch pragmatic trials
54	Larson BP	2012	Peer-review process	There is a lack of an ideal peer-review model to maintain research integrity. The essential themes of the peer-review process were the structure and process of the peer-review system, the criteria referees for submitted manuscripts, and the ethical code of conduct for both author and referees
55	Marusic A	2011	Authorship	There were general themes common to all research disciplines: authorship perceptions, definitions and practices, defining order of authors on the byline, ethical and unethical authorship practices, and authorship issues related to student/non-research personnel-supervisor collaboration. The pooled prevalence of researchers reporting their own and others' experience of misuse of authorship was 29% (95% CI, 24–35). Authorship misuse was reported more often by researchers outside the United States and United Kingdom: 55% (95% CI, 45–64) for four studies in France, South Africa, India, and Bangladesh versus 23% (95% CI, 18–28) in the United States/United Kingdom or international journal settings

The primary purpose of our review was to map research integrity literature related to RCTs. The scoping nature of this review allows flexibility, and quality assessment is not considered mandatory.[18,80,81] However, we were careful not to skip the risk-of-bias assessment in order to expedite knowledge synthesis as others have also done.[82,83] This quality assessment of the reviews included was made possible through modification of the AMSTAR 2 tool.[22] An alternative tool, ROBIS,[84] has been reported to be more cumbersome in its implementation.[85] It is important to highlight that the main purpose of AMSTAR 2, in its original version, is to evaluate the review of interventions. Thus, some original elements do not strictly apply in our review. For example, instead of asking about the components of the PICO structured question, our modified tool captured an explicit objective stated concerning the purpose of the review. However, in another example, the item concerning publication bias[86] did not require much modification as this aspect of an included systematic review required assessment in our scoping umbrella review. When applying this modified version to evaluate reviews addressing research integrity issues across the RCT lifecycle, we readily admit to the possibility of there being some misclassification of the individual quality items. We also acknowledge that the requirements across the quality domains are dynamic and changeable over the years, particularly as the publication time ranged from 2003 to 2021 for the reviews included. We made an overt effort to minimize this risk by first adapting the AMSTAR 2 tool to make it more suitable for our scoping umbrella review and then ensuring the reliability of quality assessment through piloting and multiple assessments. The subjective character of data extraction regarding quality items is plain for everyone to see, so we accept that readers may disagree with our evaluations. We transparently provide all of our assessments for others to re-evaluate if they so wish. The overall low quality of the included reviews does not necessarily cast doubt on whether there is any integrity issue within RCTs; it simply shows that the methodological quality of reviews in this area needs improvement in the future.

With respect to the extraction of main findings, integrity issues, and their categorization, we went to the extreme of assessing each paper at least three times using seven reviewers who frequently debated the key messages of each included review. Others may differ in their take-home messages when they assess the same literature. Knowing what results to extract and how to synthesize them is not always straightforward. We targeted our evidence synthesis strategy to collate the main findings for mapping them across the entire RCT lifecycle in line with our formulated objective. By mapping, we intended to outline the range of evidence in our field, a task that was problematic given that the reviews included provided both qualitative and quantitative data. The descriptive approach we have taken is likely to be informative for the reader. It was not our intention to make specific recommendations for the conduct and reporting of RCTs; we wished to collate a repository of the evidence and determine what further step is required to impact the integrity of RCTs.

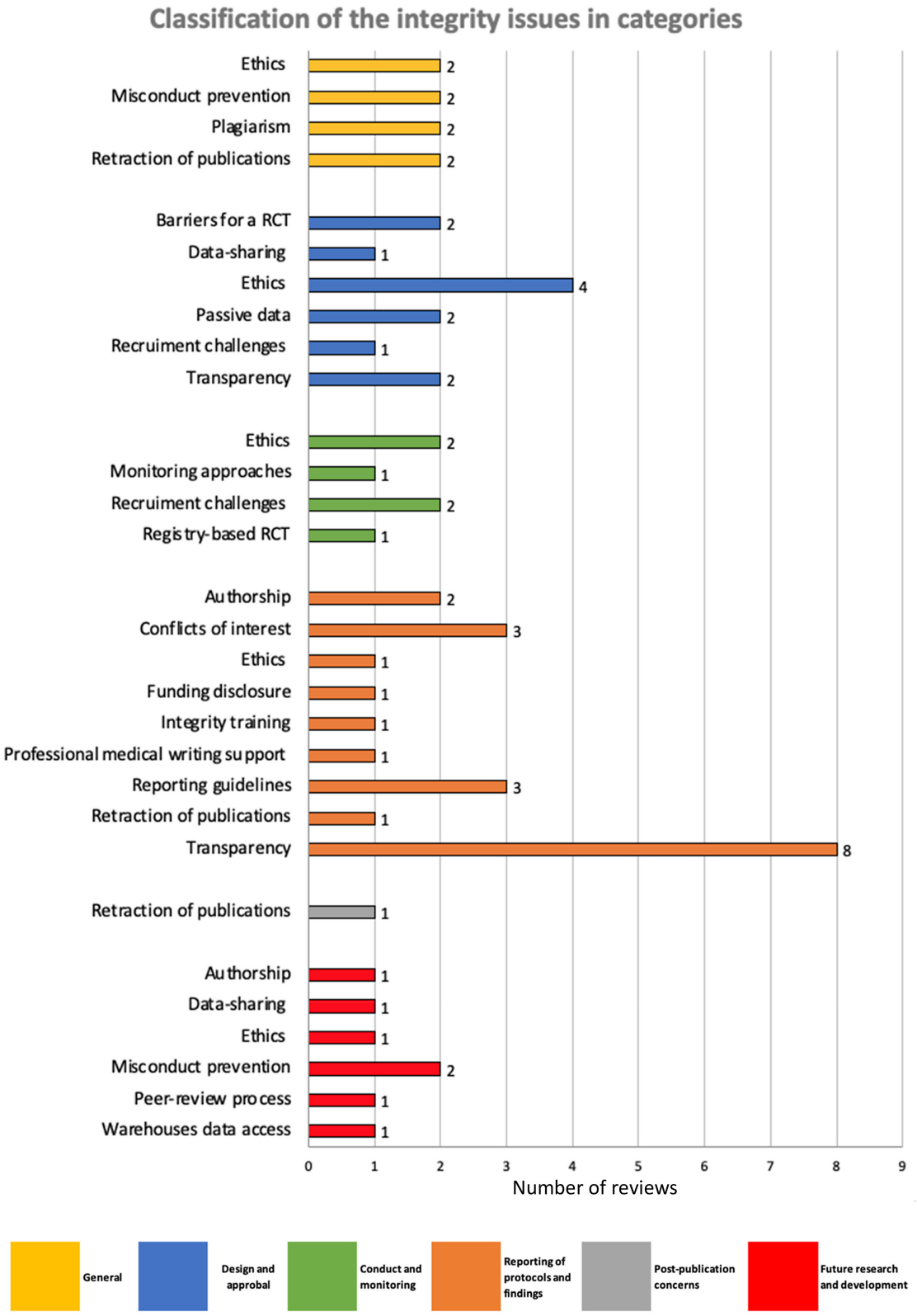

FIGURE 3 Main findings of the reviews included in the scoping umbrella review of research integrity of randomised clinical trials classifying issues into categories.

4.3 | Implications

Issues concerning research integrity may currently be more relevant in women's health RCTs[8,9,87]; however, evidence mapped concerning integrity issues across all medicine permits greater generalizability. Research integrity of RCTs requires attention to high ethical standards and professionalism with respect to methodology concerning design and statistics at the one end and obsession with adherence

to protocol in conducting and reporting at the other end of the spectrum. Taking the adequacy of consent in RCT as an example captured through the included reviews,[48,65] we highlight the unethical Tuskegee experiments[88] about which Tobin wrote: "*Despite 15 journal articles detailing the results, no physician published a letter criticizing the Tuskegee study. Informed consent was never sought; instead, Public Health Service researchers deceived the men into believing they were receiving expert medical care*." These articles remain not retracted from the literature formally to this date. Thus, ethics and consent standards need to be recognized as important alongside data-related integrity. The mixed task of maximizing methodological rigor, preventing innocent errors, and detecting deliberate misconduct is not for one responsible officer to undertake; it is for everyone involved to take integrity seriously. Thus, academic organizations, trial funders, researchers, publishers, journals, editors, peer-reviewers, and the broader clinical trial community, including consumers, all have to play a role.[10] There is no shortage of words from worldwide institutions stressing the importance of research integrity. There are plenty of declarations on the principles of scientific integrity, including the Hong Kong Principles,[11] the European Code of Conduct for Research Integrity,[89] the Montreal Statement,[90] and the Singapore Statement.[87] Nevertheless, there are still multiple reports of fraud and questionable research practices with clinicians, authors, editors, and institutions haggling over retractions and corrections. In this background, our scoping umbrella review has highlighted the low quality of research integrity literature related to RCTs, mapping the diverse range of results and conclusions reported in reviews.

What is now crucial is to set international benchmarks for RCT integrity standards through a consensus of experts that generates recommendations building on the findings of this review. Once developed, these could be used to underpin specific policies to prevent and mitigate risks to the integrity of RCTs. It is easy for us to say, but it cannot be hidden from sight that institutions frequently have a knee-jerk reaction to ad hoc initiatives. It is time that they decode integrity principles into research practice within a plan that aims to change the academic culture. Education strategies to enhance research integrity and patient and public involvement related to RCT integrity would no doubt need to accompany any coordinated action.[91–93]

5 | CONCLUSIONS

A diverse set of research integrity issues covering the RCT lifecycle have been summarized in our scoping umbrella review, collating a large but mainly low-quality body of evidence. The key findings of this comprehensive overview emphasize ethical standards and professionalism. Many gaps in the RCT integrity landscape were recognized. There is a need to develop an international multistakeholder consensus to arrive at specific RCT integrity recommendations.

AUTHOR CONTRIBUTIONS

KSK, MF, and AB-C conceived the study and, together with PFWC and JZ led the development of the protocol and provided supervision and mentorship. MN-N and MM-C, who wrote the first draft, coordinated and incorporated the comments from co-authors and together with AB-C and LEM contributed to the development of search strategy and data extraction. YK provided specific expertise on research integrity and critically appraised the review and provided intellectual input to the manuscript. All authors also provided specific expertise on research integrity and contributed to developing a search strategy. All authors critically contributed to citation selection, data extraction, reviewed successive drafts of the manuscript, provided important intellectual input, and approved the final version for publication.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

All data is available in table, figures and supplementary material.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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