Title: Research integrity in randomised clinical trials: an umbrella review.

María Núñez-Núñez* (1, 2), Marta Maes-Carballo* (3, 4), Luciano E. Mignini (5), Patrick FW Chien (6), Yacoub Khalaf (7), Mohamed Fawzy (8), Javier Zamora (2, 9), Khalid Saeed Khan (10, 11), Aurora Bueno-Cavanillas (2, 11)

1. Pharmacy Department. University Hospital Clínico San Cecilio, Granada, Spain
2. Biomedical research institute of Granada (IBS-Granada), Granada, Spain.
3. General Surgery Department. Breast cancer Unit, Complexo Hospitalario de Ourense, Ourense, Spain
4. General Surgery Department. Hospital Público Verín, Ourense, Spain
5. Mastology Unit. Grupo Oroño, Rosario, Argentina
6. Department of Obstetrics & Gynaecology, RUMC, Penang, Malaysia
7. Guy's & St Thomas' Hospital Foundation Trust, UK
8. IbnSina (Sohag), Banon (Assiut), Qena (Qena), Amshag (Sohag) IVF facilities, Egypt.
9. Clinical Biostatistics Unit. Hospital Ramón y Cajal (IRYCIS), Madrid, Spain.
10. Preventive Medicine and Public Health, University of Granada Faculty of Medicine, Granada, Spain.
11. Consortium for Biomedical Research in Epidemiology and Public Health (CIBERESP-Spain), Madrid, Spain.

* These authors contributed equally to this work.

Running title: Research integrity in RCT: Umbrella review

***Corresponding Author:**

Khalid S. Khan

Email: profkkhan@gmail.com; Phone: +44 7977 559415

Present address: Preventive Medicine and Public Health, University of Granada, Faculty of Medicine. Av. Innovación s/n. CP 18016. Granada, Spain.

ABSTRACT

Background: The trustworthiness of randomised clinical trials (RCTs) is suffering a crisis of confidence.

Objectives: We undertook an 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, Cochrane Library and Google Scholar, without language or time restrictions until November 2021. We included systematic reviews covering any aspect of research integrity throughout the RCT lifecycle.

Data collection and analysis: We assessed methodological quality using a modified AMSTAR-2 tool and collated the main findings.

Main results: There were 55 relevant reviews summarising a total of 6001 studies (median per review 63; range 8-1106 studies). The overall quality of 53 (96.4%) reviews was critically low. Eight (14.6%) reviews focused on the general aspects of a RCT, 12 (21.8%) on the design and approval, 6 (10.9%) on the conduct and monitoring, 21 (38.2%) on the reporting of protocols and findings, one (1.8%) on post-publication concerns and 7 (12.7%) on future research and development. The integrity issues covered were varied, the most common being the importance of ethics (10/55, 18.2%) and transparency (10/55, 18.2%).

Conclusions: Various research integrity issues covering RCT lifecycle, captured from mostly low-quality reviews, provided a broad overview emphasising the need for high level of ethical standards and professionalism. Many gaps in the RCT integrity landscape were also identified. There is a need to generate multistakeholder consensus to create specific RCT integrity standards.

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Tweetable abstract: Existing evidence syntheses concerning integrity issues in the research lifecycle of randomized clinical trials need consolidation through consensus of stakeholders.

Key words: “research integrity”, “randomised clinical trial”, “umbrella review”

INTRODUCTION

Randomised clinical trials (RCTs), ranked highest in the hierarchy of evidentiary validity, are essential for fostering quality healthcare(1, 2). They must be rigorous at all stages of design, execution and reporting(1). However, there is growing scepticism 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).

With an emphasis on adherence to ethical standards and professionalism, the integrity of RCTs is underpinned by responsible research conduct(8). Research integrity, as generally defined, is the conduct of research in a way that inspires confidence in the findings. Five principles have been reported: responsible research practices, transparent reporting, open-access science, valuing the diversity of research types and recognising all contributions to research activity(9). Thus, integrity applies to the whole research lifecycle, from designing and proposing projects to their publication and dissemination(10). Multiple initiatives by institutions, research groups, journals and governmental bodies(9, 11-14) provide general statements about science integrity as a whole. Except for the International Council for Harmonization(13) documents, 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 an umbrella review to summarise the evidence contained within existing systematic reviews concerning RCT integrity, highlighting their main findings and identifying any gaps to be addressed in future research.

METHODS

Following prospective registration (Center for Open Science, https://osf.io/3ursn), this umbrella review was conducted using recommended methodology(15) and written to meet the requirements of the relevant reporting guidelines(16, 17) (Appendix S1).

Search strategy, data sources and study selection

A comprehensive search strategy covering major electronic databases was deployed to capture peer-reviewed and grey literature. PubMed, Scopus, 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 (see the accompanying paper, prospective registration: osf.io/bhncy) 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 was used to manage the searches downloaded. No language or time restrictions were applied.

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 pre-specified eligibility criteria in order to answer a specific research question and uses explicit, systematic methods that are selected with a view to minimising bias"(18). We excluded non-human studies, those focussing 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 multi-step approach, including deletion of exact and inexact duplicates, reading titles and abstracts, and assessment of full-texts. Initially, after the removal of duplicates, a sample of the 200 citations (titles and abstracts) was independently examined by two reviewers (MN-N and MM-C) to unify the selection criteria through discussion. Titles and abstracts were assessed for eligibility by two reviewers (MN-N and MM-C), and three reviewers (PC, AB-C 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 (MN-N and MM-C). Potential

disagreements or inconsistencies were resolved by arbitration by a least two of the four senior reviewers (PC, KSK, AB-C or MF). Rejected full-text articles were classified into four categories: not systematic review; not research integrity related; not randomised trial related; and outside the scope of review.

Data extraction and study quality assessment

The characteristics of the included reviews and their quality were extracted by four reviewers (MN-N, MM-C, LM and AB-C) 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 evaluated if the selected systematic reviews were well-described using a modified version of AMSTAR-2(19), a tool for systematic reviews of interventions. 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). 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 overall quality was rated as "high" if there was $\leq$1 non-critical weakness; "moderate" if there were >1 non-critical weakness; "low" if there were one critical weakness with or without non-critical weaknesses; and "critically low" if there were >1 critical weakness with or without non-critical weaknesses. Three reviewers (MN-N, MM-C and LM) held training meetings to learn and unify the quality assessment criteria, pilot testing 6/55 (11%) selected reviews. They completed the review quality assessment, initially working individually on a third of the reviews and then collectively on them all. Disagreements were resolved by consensus or arbitration by a senior reviewer (AB-C).

The main findings of each selected review were extracted initially by at least two of the seven reviewers (MM-C, MN-N, LM, AB-C, KSK, MF and PC). All the initially extracted findings were then reviewed by one senior reviewer (PC). Finally, a consensus meeting of three reviewers (AB-C, MM-C and MN-N) summarised the findings statement extracted and delineated the integrity issue(s) covered by each selected review.

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); post-publication concerns (dealing with post-print complaints); and, future research and development (emphasising gaps that need to be addressed). Some reviews covered more than one integrity category and were assigned the main category by consensus (AB-C and MM-C) for tabulation.

RESULTS

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, 20-72) were included in the final appraisal. Only four of them included meta-analysis(27, 51, 67, 72). The list of excluded articles with reasons can be found in Appendix S4.

Characteristics and quality of the included reviews

The characteristics of the included reviews were reported in Appendix S5. The publication dates of the included reviews ranged from 2003 to 2021; with 34 studies (62%) published within the last 5 years. There were 6001 studies in the included reviews, with the median number of studies per review being 63 and ranging from 8(29, 31) to 1106(46). Most of the reviews did not limit the included RCTs to a specific geographical area (49/55, 89.1%); some focused regionally on low-middle income countries(22) and South-East Asia(46), and nationally on India(60), China(72), Brazil (5) and USA(32). 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 reviews (96.4%), and moderate(40) and high(52) in one (1.8%) each (Figure 2, Appendix S6). The four meta-analyses included were of critically low quality. Analysing the rates of compliance with individual items, there were deficiencies, particularly in domains concerning the provision of the list of excluded studies (2/55, 4.0%) and the description of funding sources of the included studies (4/55, 7.3%). Only thirteen (26.6%) 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 (42/55, 76.4%) and duplicated study selection (35/55, 63.6%).

Synthesis of findings

The integrity issues covered in the included reviews and their main findings were diverse (Table1). Some recurrent findings were weakness of informed consent, ethical review and follow-up, the lack of a standardised 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(25, 32, 44, 47, 52, 61, 72) were allocated in the future research section because their findings were related to currently unsolved questions. Regarding the RCT integrity categories, 8 (14.6%) reviews focused mainly on the general aspects of RCT, 12 (21.8%) on the design and approval, 6 (10.9%) on the conduct and monitoring, 21 (38.2%) on the reporting of protocol and findings, 1 (1.8%) on post-publication concerns, and 7 (12.7%) on future research and development.

The integrity issues covered were varied, the most common being the importance of ethics (10/55, 18.2%) and transparency (10/55, 18.2%). Figure 3 shows the integrity issues according to categories. Ethics featured as an issue across the categories. Transparency featured as an issue in the reporting of protocols and findings (8/21; 38.1%) and the design and approval (2/12; 16.7%) categories.

DISCUSSION

Main findings

The large body of evidence in this umbrella review included over 6 thousand studies captured in 55 systematic reviews, with four of these reviews summarising the findings using 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 making a direct comparison between the included reviews. The findings could be categorised under the heading's general aspects, design and approval, conduct and monitoring, reporting of protocols and findings, post-publication concerns, and future research and development, encompassing the entire RCT research lifecycle. The integrity issues covered by around two-fifths of the reviews focused on ethics and transparency of RCTs.

Strengths and limitations

To the best of our knowledge, this is the first umbrella review to identify and summarise research integrity issues specific to RCTs. 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 synthesised in a manner that is akin to scoping reviews(73) 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(16). As no specific reporting tool exists for umbrella reviews, this approach is more likely to assist with the completeness and transparency of reporting of 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 literature reviews were carried out 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 umbrella scoping review with which we captured a large number of

reviews and studies within them related to the research integrity topic that comprehensively covered the issues within RCTs(74, 75). Given the broad nature of the umbrella review, the heterogeneity found amongst 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, terminology, etc. 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.

Umbrella reviews, like all reviews, 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 the academic specialities, achieving reproducibility was identified as an early challenge in our work. We thus introduced various piloting exercises and multiple reviewers to minimise 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 our data extracted as detailed appendices to supplement what is reported in the main text.

The primary purpose of our review was to describe research integrity literature related to RCTs. However, we were careful not to skip the risk of bias assessment in order to expedite knowledge synthesis. This quality assessment of the reviews included was made possible through modification of the AMSTAR 2(19) tool. It is important to highlight that the main purpose of this tool, in its original version, is to evaluate the review of interventions. So, when applying its modified version to evaluate reviews addressing research integrity issues across RCT lifecycle, we readily admit to the possibility of there being some misclassification of the individual quality items. We made an overt effort to minimise this risk by first adapting the AMSTAR 2 tool to make it more suitable for our review and then ensuring the reliability in quality assessment through piloting and multiple assessments. The subjective character of data extraction regarding quality items is plain for everyone to see, so we transparently provide all our assessments for others to re-evaluate if they so wish.

With respect to extraction of main findings, integrity issues, and their categorisation, 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 result to extract and how to synthesise 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 on the integrity of RCTs.

Implications

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. The mixed task of maximising methodological rigour, 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 organisations, trial funders, researchers, publishers, journals, editors, peer-reviewers, and the broader clinical trial community, including consumers, all have to play a role(8). 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: the Hong Kong Principles(9), the European Code of Conduct for Research Integrity(76), the Montreal Statement(77), the Singapore Statement(78), etc. to name a few. 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 umbrella review has highlighted the low quality of the 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 with ad hoc initiatives. It is time that they decode integrity principles into research practice within a plan that aims to change 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(79-81).

CONCLUSIONS

A diverse set of research integrity issues covering the RCT lifecycle have been summarised in our umbrella review, collating a large but mainly low-quality body of evidence. The key findings of this comprehensive overview emphasise ethical standards and professionalism. Many gaps in the RCT integrity landscape were recognised. 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 PC and JZ-R 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 LM 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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Ethics/Institutional Review Board Statement

Ethical review and approval was not required for this study because the scoping umbrella review relies on retrieving and synthesising of data from existing published systematic reviews and meta-analyses.

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Conflicts of Interest

The authors declare no conflict of interest.

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Figure 1. Flow chart

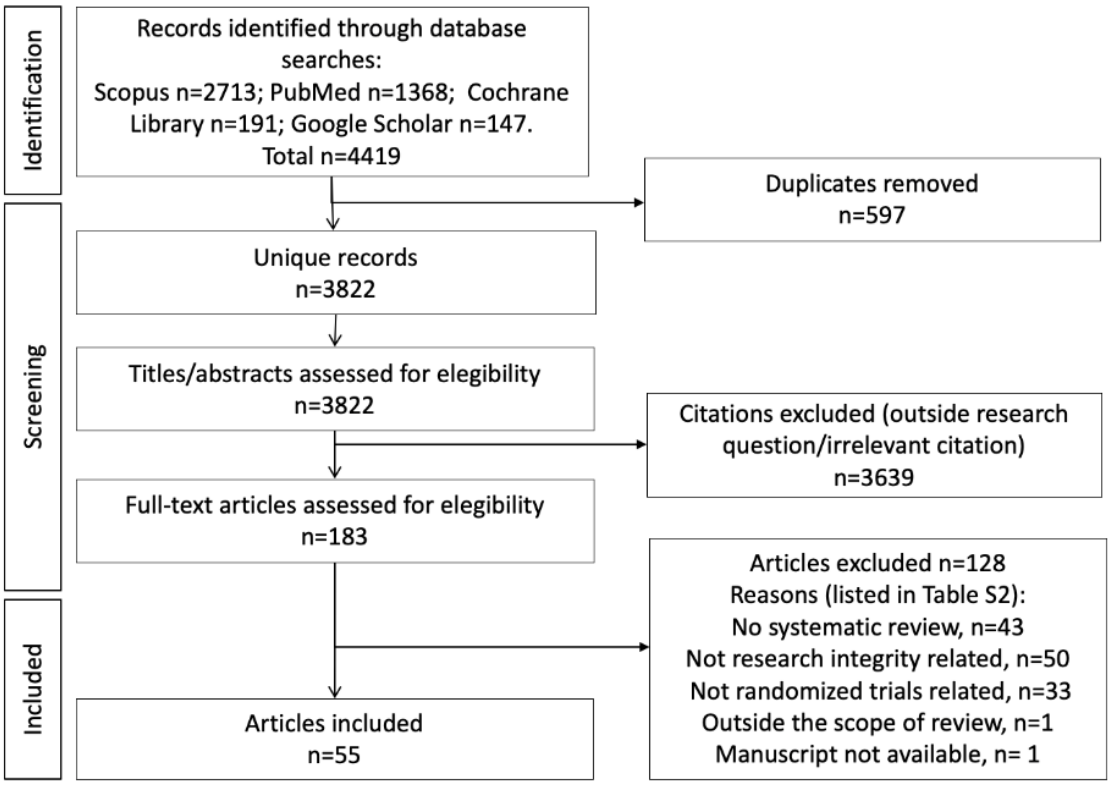

Figure 2: Overall quality assessment and rates of compliance of individual quality assessment items in the umbrella review of research integrity of randomised clinical trials. Critical items are marked with "*".

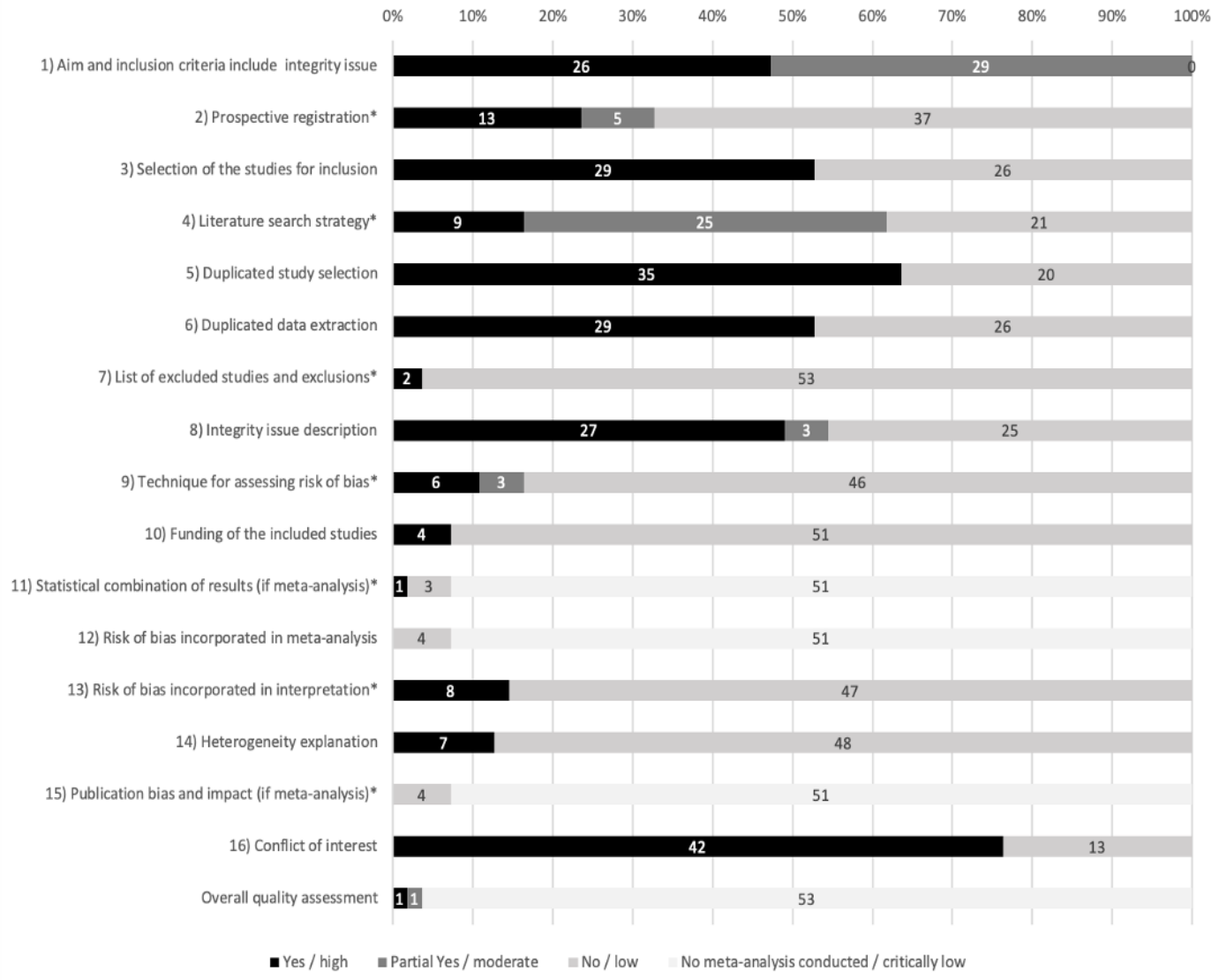

Figure 3: Main findings of the reviews included in the umbrella review of research integrity of randomised clinical trials classifying issues into categories.

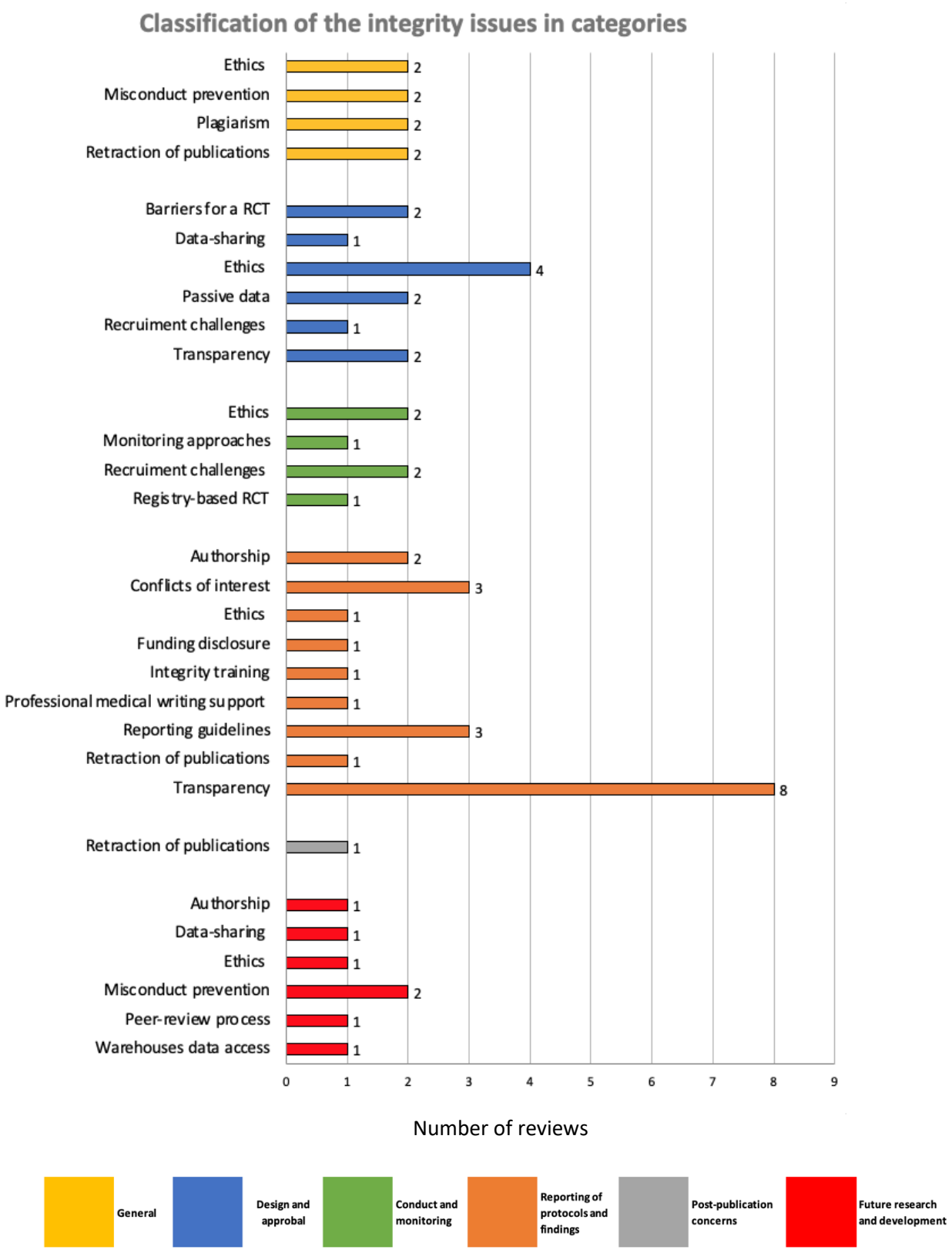

Table 1: Characteristics of the reviews included in the umbrella review of research integrity of randomised clinical trials and their main findings.

	Author	Year	Integrity issue	Main findings	Main statements related
General					
1	**Maccaro A**	**2021**	Ethics	The majority of articles reporting ethical issues with the Covid pandemic come from LMIC. The most typical theme found was the issue of resource allocation with personal protective equipment with Covid.	3 (General)
2	**Ni Y**	**2019**	Misconduct prevention	Most postgraduates 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, too much pressure to publish. About 10–32% of postgraduate students admitted that they had committed research misconduct.	2 (General)
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 anti-plagiarism software may help detect and deter plagiarism. A plagiarism policy needs to be implemented in academic institutions.	2 (General)
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	2 (General)

				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.	2 (General)
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) or presenting fraudulent data (n=14). Other reasons included scientific errors/mistakes (n=11), author misattribution (n=7), and compromised peer review (n=7).	2 (General)
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.	2 (General)
8	**Nicholls SG**	**2015**	Ethics	Lack of consensus on the criteria and tools used to evaluate the quality of the ethics review	3 (General)

				process for clinical studies. No study reported using an underlying theory or framework of IRB 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.	
Design and approval					
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.	10 (Design and approval); 42 (Reporting of protocols and 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.	8-11 (Design and approval)
11	**Natale P.**	**2021**	Recruiment challenges	Patient perspectives on recruitment and retention in 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 healthcare. 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 randomised 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.	8 (Design and approval); 20 (Conduct and monitoring)

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 USA (3-31%) and the UK (3-25%).	7 (Design and approval)
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 (8 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 (4 studies).	7 (Design and approval); 21 (Conduct and monitoring)
14	**Alemayehu C**	**2018**	Barriers for a RCT	The greatest challenge that faced researchers in developing countries was the lack of financial (8 studies) and human capacity (9 studies). In addition, several other themes emerged from the research literature: ethical and regulatory system obstacles (7 studies), lack of research environment (8 studies), operational barriers (8 studies), and competing demands (8 studies).	11; 12 (Design and approval)
15	**Phillips, A**	**2017**	Ethics	The majority of the selected articles recommended obtaining ethics approval to use anonymised samples and data. There is a concern over the effectiveness of most anonymisation 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 anonymisation process alone. This is particularly true in the context of genomic research.	7 (Design and approval)
16	**Djurisic S**	**2017**	Barriers for a RCT	The main barriers to randomised clinical trials 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.	2 (General); 9; 11; 12 (Design and approval)
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 paediatric 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.	8 (Design and approval)
18	**McKeown A**	**2015**	Transparency	In analgesic clinical trial publications, sample size calculations were frequently incompletely reported. Only 111 (65%) out of 172 RCTs reported at least one element of a sample size calculation. Amongst these 111 RCTs, only 65 (59%) RCTs met all the elements for reporting for	15 (Design and approval)

				sample size calculation as per CONSORT guidelines. Only 60 (54%) of these 111 articles included a justification for the assumed treatment effect to be detected. Randomised participants differed by ≥10% from the planned number of participants in 31 out 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.	
19	**Chapman S**	**2014**	Transparency	Registration of surgical RCTs is increasing over time but remains sub-optimal. The principle of open access data sharing is poorly endorsed in surgical research.	17 (Design and approval); 38 (Reporting of protocols and findings)
20	**Schellings R**	**2006**	Ethics	Out of 50 RCTs, non-compliance to study protocol was higher in the randomised consent experimental group compared to the control group in 65% of studies. Trials that employed an incomplete double consent design (participants only consent for the intervention received for the randomised arms) were associated with a higher rate of non-compliance (16-21% versus 3-58%) and loss to follow up (21-44% versus 25/26%) compared to 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).	8; 9 (Design and approval); 42 ((Reporting of protocols and findings)
Conduct and monitoring					
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, randomisation, safety issues, risks, and side effects.	8 (Design and approval); 22 (Conduct and monitoring); 42 (Reporting of protocols and findings)
22	**Karanatsios B**	**2020**	Registry-based RCT	Most Registry-based RCTs (15/17) were two arm-studies and had randomisation performed at individual participant level (15/17) studies. Primary and secondary outcomes were well defined in	21 (Conduct and monitoring)

				all studies. RCT duration ranged from 2 months to 2 years and 9 months. The study's follow-up duration ranged from 72 hours to 12 years. Only 3/17 studies commented on the cost-effectiveness of the interventions studied.	
23	**Houghton C**	**2020**	Recruiment challenges	Several factors influence a person's decision to participate in a trial, including how the trial is set up and communicated, people's individualised circumstances, and the potential benefits of participation. Potential participants may have a genuine interest in contributing to scientific knowledge and improved care.	20 (Conduct and monitoring)
24	**Goldstein C E**	**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 randomisation. Oversight is time consuming, costly and complex.	7 (Design and approval); 22 (Conduct and monitoring); 42 (Reporting of protocols and findings)
25	**Olsen R**	**2016**	Monitoring approaches	One hundred per cent Source Data Verification (SDV) may not be a rational method of ensuring data integrity and subject safety based on the high cost. Three out of 22 publications showed that source data verification (SDV) has some value for detection of not initially reported adverse events and centralised statistical monitoring (CSM) captures atypical trends; fourteen publications showed little objective evidence of improved data integrity with traditional monitoring, such as 100 % SDV and sponsored queries as compared to 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.	27 (Conduct and monitoring)
26	**Treweek S**	**2013**	Recruiment challenges	Interventions identified to be effective in increasing recruitment included: 1) telephone	20 (Conduct and monitoring)

				reminders to non-respondents (risk ratio (RR) 1.66, 95% CI 1.03 to 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 to 1.84; one study, 152 participants; 3) open designs where participants know which treatment they are receiving in the trial (RR 1.22, 95% CI 1.09 to 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.	
Reporting of protocols and 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) 6) sub-discipline (topics were more often addressed in general than in sub-disciplinary 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 USA (3-31%) and the UK (3-25%).	38 (Reporting of protocols and findings)
28	**Slade A.L.**	**2021**	Transparency	Barriers to ethnically diverse recruitment include diverse participant engagement, the	13 (Design and approval); 53

				relevance of ethnicity to the research question, prominence of patient-reported outcomes, and the need to minimise investigator burden. Only 14/84 RCTs (17%) reported collecting data by ethnic groups despite 8/14 (57%) of these RCTs being multi-centred and multi-national. 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 (PROM)s was not reported in any of the trial protocols or publications despite 7 (88%) using PROMs that have been translated into other languages.	(Reporting of protocols and findings)
29	**El-Menyar A**	**2021**	Retraction of publications	Out of 124 manuscripts studied, six papers were retracted from high impact journals, in which the average period till publication was 33 days. Retraction of papers occurred within 10–48 days	41 (Reporting of protocols and findings)
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. Nine per cent (25) of the trials in this review were published in presumed predatory journals. The presumed predatory publication was associated with a missing conflict of interest statement (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). 3. All (100%) presumed predatory publications had missing trial registrations and had inadequate sample sizes.	17 (Design and approval); 37 (Reporting of protocols and findings)

31	**Hayden A A**	**2020**	Funding disclosure	Forty-seven of the 98 studies (48%) reported favourable results, with 5 of these studies (10.6%) reporting industry affiliations. Forty-eight of the 98 studies (49%) did not report the study funding source. Published studies with unknown funding sources were 5.9 times more likely to report conclusions favouring the biological treatment than those with reported funding sources (p=0.015).	38; 46 (Reporting of protocols and findings)
32	**Evuarherhe O**	**2019**	Professional medical writing support	Professional medical writing support 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); lower incidence of reporting of non-pre-specified outcomes. Time to publication from last patient visit in clinical trials was also reduced (18.6 [SD 13.2] months vs 30.8 [SD 11.7] months.	40 (Reporting of protocols and findings)
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. Out 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.	49 (Reporting of protocols and 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).	42 (Reporting of protocols and findings)

35	**Darmon M**	**2018**	Conflicts of interest	The presence of a COI statement and the declared rate of COI and funding increased from 2001 to 2016. COI statements are shown by 243/374 (65%) articles, and 29/373 (7.7%) have declared COI. Declared COI were more frequent in 2011–2016 than in 2001–2010 (OR 4.06; 95% CI 1.15–25.79) and in the higher quartile of a journal's impact factor (OR of 16.73; 95% CI 3.28–306.20).	46 (Reporting of protocols and findings)
36	**Montgomery P**	**2018**	Reporting guidelines	The CONSORT-SPI (CONSORT for Social and Psychological Interventions) 2018 checklist extends 9 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.	49 (Reporting of protocols and findings)
37	**Yelland L**	**2018**	Transparency	Recruitment, randomisation or treatment errors were reported in 32 out 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 error was ineligible participants inadvertently being randomised n=23 (28%), participant receiving incorrect treatment n=4 (5%) and participant randomised using incorrect baseline information n=2 (2%).	51 (Reporting of protocols and findings)
38	**Van der Steen J.T.**	**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%); unfavourable geographical and regulatory environment (2%); relationship and collaboration issues (2%) and potential harm (0.4%).	51 (Reporting of protocols and findings); 80 (Future research and development)
39	**Gewandtera, J**	**2017**	Transparency	There is a frequent lack of clarity in primary publications regarding whether or not "Data	26 (Conduct and monitoring); 52

				Monitoring Committees/Data and Safety Monitoring Boards" 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 or not 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.	(Reporting of protocols and findings); 74 (Future research and development)
40	**Liu T Y**	**2016**	Reporting guidelines	Only two (3%) journals did not introduce any statistical reporting guidelines for authors, but there has been an improvement in the statistical requirements in Instruction to Authors over time. The 4 most common statistical issues relevant to research are: participant flowchart, "eligibility" criteria details, randomisation 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 4 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, tables and graphs that show them clearly.	38; 45 (Reporting of protocols and findings)
41	**Adewuyi T**	**2015**	Transparency	In surgical trials, the reporting of non-compliance to allocation and the handling of missing data were typically suboptimal; 45/82 (55 %) studies reported non-compliance with treatment allocation; 52/82 (63 %) studies reported primary outcome missing data. Of the 31 out of 82 studies that explicitly stated that the analysis was by intention-to-treat, only 20 (65 %) included all participants and were analysed as randomised.	51 (Reporting of protocols and findings)
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	44; 46 (Reporting of protocols and findings)

				(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%).	
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 have 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 follow up of participants, and 27% reported any detection of adverse events.	49 (Reporting of protocols and findings)
44	**Dulhunty J M**	**2011**	Authorship	The 8 tools for determining authorship are: 1) DiGiusto points system; 2) The Center for Healthy Communities (CHC) 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; 8) Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) scoring system.	44 (Reporting of protocols and findings)

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 13/63 (20.6%) of the RCTs were registered, but it was reported in the manuscript on 1/13. Only 1 study registered sufficiently precise outcome information to compare with the published outcomes, but registered and published outcomes were discrepant.	17 (Design and approval); 54 (Reporting of protocols and findings)
46	**Di Pietrantonj C**	**2005**	Conflicts of interest	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 favour of the intervention produced by the funding bodies (RR 1.58 (95% CI: 1.39 to 1.80); I2= 75.7%; p<0.001).	46 (Reporting of protocols and findings)
47	**Bekelman JE**	**2003**	Conflicts of interest	Industry-sponsored studies were more likely to be associated with pro-industry 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% CI2.72-6.32 for RCTs).	46 (Reporting of protocols and findings)
Post-publication concerns					

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 to 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 to 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 9 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 3 of these reviews and guidelines.	67; 68 (post-publication concerns)
Future research and development					
49	**Bordewijk E**	**2021**	Misconduct prevention	Measures to counteract textual plagiarism are well implemented, tools to investigate other forms of research misconduct are rudimentary and labour-intensive, are based on examples, are not standardized, and lack formal validation.	50 (Reporting of protocols and findings); 78 (Future research and development)
50	**Pavlenko E**	**2020**	Warehouses data access	Formal documentation on warehouse data users' roles and access levels need to be defined. The governance of the data and review bodies to underpin this governance needs to be pre-specified. The amount of access to the dataset with the location and time period of access needs to be stipulated clearly.	70 (Future research and development)
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 de-identified or anonymous compared with identifiable. Also, they were	70 (Future research and development)

				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.	69 (Future research and development)
53	**Kalkman S**	**2015**	Ethics	There are three ethical considerations identified in the analysis of the literature on post-launch pragmatic drug trials: (i) what level of oversight should pragmatic trials require; (ii) do randomized patients face additional risks; and (iii) is a waiver of informed consent ethically defensible? The literature does not specifically describe ethical challenges related to pre-launch pragmatic trials.	71; 72 (Future research and development)
54	**Larson B.P**	**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.	75 (Future research and development)
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% to 35%). Authorship misuse was reported more often by researchers outside USA and UK: 55% (95% CI 45% to 64%) for 4 studies in France, South Africa, India and Bangladesh vs 23% (95% CI 18% to 28%) in USA/UK or international journal settings.	74 (Future research and development)