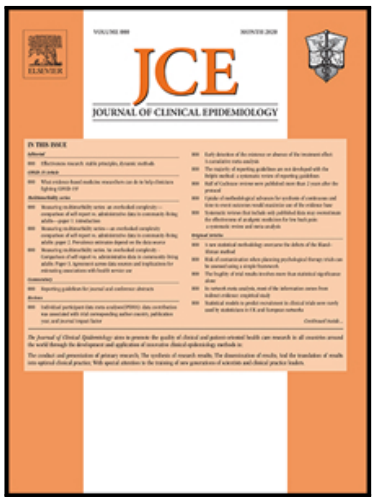

Commentary: Time to improve the reporting of harms in randomized controlled trials

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Title Page

Commentary: Time to improve the reporting of harms in randomized controlled trials

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Estimates of treatment effects in randomised controlled trials (RCTs) are comprised of efficacy and harm outcomes. Similarly, treatment decisions rely on accurate knowledge of both efficacy and harms. Harms can be measured as pre-specified outcomes and may be detected through systematic assessment (e.g., checklists or laboratory tests) or emergent non-anticipated events detected through systematic or non-systematic assessment (e.g., regular application of questionnaires (systematic) or spontaneous reporting (non-systematic)).[1 2] The frequency of harm outcomes detected in RCTs vary depending on how the outcomes were collected, the frequency of the collection, and also on factors such as the condition under investigation, the investigational treatment, demographic characteristics of the participants, and time dependence between treatment implementation and the development of the adverse event. The many different ways to identify and measure harms in RCTs generates multitudes of complex data and arbitrary decisions regarding reporting are often used.[3] To compound the problem, clinical trials are typically designed, analysed and reported to focus on efficacy outcomes,[4] and harms tend to receive less attention at both the design stage as well as in reports of published RCTs.[5 6]

Lack of reporting or selective reporting of harms in published clinical trials also impacts the ability of systematic reviews to synthesize harm outcomes[7], which can promote a false impression of safety and misinform clinical and policy decisions. The recognition that the quality and

quantity of harm outcomes reporting were suboptimal[8] led to the development of a reporting guideline to inform the better reporting of harms in RCTs, the (Consolidated Standards of Reporting Trials) CONSORT Harms extension.[9] CONSORT Harms was published in 2004 and comprised 10 reporting items proposed to ensure adequate reporting of harms in RCTs (Box 1). [9] The publication also addressed issues related to the terminology around harms as applied in RCTs. With the term "harms" recommended over the reassuring term "safety", and advised that the common expression "side effects" should be avoided as it downplays the importance of harms as outcomes.[9]

In 2017, we conducted an overview of reviews to analyse changes in the reporting of harms in RCTs, in relation to the milestone of the publication of the CONSORT Harms guidance in 2004. Sixteen years have passed since the publication of CONSORT Harms, but emerging evidence and our own experiences suggest reporting practices have remained substandard and inconsistencies in terminology persist. We aimed to investigate this supposition and to establish whether an update to CONSORT Harms is needed, and if needed, to inform what level of detail such an update might entail.

Impact of CONSORT Harms on reporting practices: Public trust in clinical trial evidence requires transparent and complete assessment and reporting of harm outcomes

We identified 13 reviews that assessed the reporting of harms in RCTs using the items of the CONSORT Harms checklist and reported quantitative results that could be extracted for further analysis. Details on the sources of information and search strategies are described in Appendix 1 (Supplementary material). We compared summaries of the CONSORT Harms items reported in RCTs published pre (≤2004) and post (>2004), and overall across trials regardless of the year of publication. We also examined the range of terminology used to refer to harm outcomes across reviews to assess the impact CONSORT Harms had on the adoption of a more consistency terminology to refer to harms.

Six reviews analysed trials published pre (≤2004) and post (>2004) the publication of CONSORT Harms and presented results for both periods separately; five reviews evaluated only trials published post-CONSORT Harms; one review only assessed trials pre-CONSORT Harms; and one review covered trials published in both pre and post periods but presented overall results and as such only had the combined data analysed.

Table 1 summarizes the proportion of trials reporting each item of the CONSORT Harms checklist according to publication periods. Based on the crude pooled rates, the reporting of each of the items of the checklist seemed to improve following the publication of the guideline statement, with one exception. Nevertheless, overall reporting of CONSORT Harms items remained lower than 50% for most of the items.

Figures from the post period provide an overview that may best approximate contemporary practice. The items most consistently reported post-CONSORT Harms pertain to the Introduction section (**item 1** (n=643/1201, 54%) "*If the study collected data on harms and benefits, the title or abstract should so state*"), the Results section (**item 6** (n=633/1201, 53%) "*Describe for each arm the participant withdrawals that are due to harms and their experiences with the allocated treatment*"), **item 7** (n=645/1201, 54%), **item 8** (n=688/996, 69%), and to the Discussion section (**item 10** (n=579/996, 58%),"*Provide a balanced discussion of benefits and harms with emphasis on study limitations, generalizability, and other sources of information on harms*"). The remaining five items were reported in less than 50% of RCTs published in the post period. Few RCTs published in the post period (65/508, 13%) reported **item 9** ("*Describe any subgroup analyses and exploratory analyses for harms*"). Of note, four reviews excluded item 9 from their assessment deeming that this item would not be expected to be reported in trial reports.

Shifting the assessment and reporting culture

The results of this review exercise showed that, overall, there has been only a slight improvement in the reporting of harms in clinical trials post publication of CONSORT Harms. Nevertheless, the reporting of harms in RCTs remains suboptimal as most trials report less than half of the CONSORT Harms items. This is in line with the earlier findings of other groups that had previously indicated the need for improvement in the reporting of harms in clinical trials and attempted to provide recommendations to complement CONSORT Harms.[10]

It is interesting to consider the potential impact of the main CONSORT statement for RCTs on the increased reporting of some CONSORT Harms items, such as item 6 (describe for each arm the participant withdrawals that are due to harms) and 7 (provide the denominators for analyses on harms). For instance, an evaluation of RCT reports among journals endorsing CONSORT found that sixty-nine of 81 meta-analyses showed a relative benefit from CONSORT endorsement on completeness of RCTs reports.[11] As the CONSORT statement promoted the widespread use of a diagram to report participant flow, including numbers and reasons for exclusions of participants after randomisation, this may have positively impacted the expected standards for harms reporting. Notably, across periods, item 7 ("*Provide the denominators for analyses on harms*") was the only item with demonstrated overall increased reporting among trials. The main CONSORT statement is endorsed in the guidance to authors of many scientific journals[11 12] but only a limited number mention CONSORT Harms in their submission instructions.[13] It is possible that authors' lack of awareness of the CONSORT extension to harms undermines the reporting. Indeed, there is evidence that journals supporting reporting statements positively impact the quality of reporting.[14 15] We encourage journals to promote the CONSORT extension to harms (and other CONSORT extensions) in their guide to authors. Furthermore, the main CONSORT statement refers to primary and secondary outcomes but leaves harm outcomes as a separate entity, which some may interpret to signify than harms events are less important than efficacy outcomes.

An integration of CONSORT Harms items into the main CONSORT statement should be considered to highlight the importance of providing a balanced summary of both efficacy and harm in the main report of RCT results.

An interesting note from our review is that items comprising multiple components, e.g., item 4 ((i) mode of data collection, (ii) timing, (iii) attribution methods, (iv) intensity of ascertainment, and (V) harms related monitoring and stopping rules), and item 8 ((i) presentation of absolute risk per arm; (ii) per adverse event type; (iii) per grade; (iv) per seriousness, and (v) appropriate metrics for recurrent events, (vi) continuous variables, (Vii) and scale variables) were assessed by some reviews as individual components, whereas other reviews reported an overall reporting proportion for the item. This demonstrates that items comprised of multiple components present challenges to the evaluation of reporting practices. In turn, it is fair to expect that items with multiple components could, in some instances, present difficulties to authors when reporting RCT results and could conceal incomplete reporting. Editors and authors should pay particular attention to multicomponent items to ensure each component are reported – even if data were not collected or results were negative. Future updates of CONSORT and CONSORT Harms should avoid items comprising multiple components to facilitate uptake and usability.

One of the original CONSORT Harms aims was to promote the use of standard terminology with regards to harm outcomes. There have been additional publications, pre- and post-CONSORT Harms, discussing definitions of terms characterising events of harms and the importance of standardisation.[16 17] The review found that the use of 'safety' and 'side effects' receded in the period after the checklist was published, suggesting a positive impact of CONSORT Harms in reducing the use of misleading terms. However, the language 'safety', which can be misleadingly interpreted as absence of harms,[9] is still prominent. This may be explained by area-specific preferences or even challenges in

translations from different idioms to the English language, issues that do not justify the potential inappropriate impact on clinical decisions and patient outcomes. Continued efforts across the clinical trial arena are needed to promote consistent terminology in harms reporting.

It should be acknowledged that changes of reporting practices over time are shaped by multiple factors (types of trials done, training and awareness of investigators, reviewers and editors, and requirements of funders, among others). Therefore, these changes in reporting should not be causally attributed only to the publication of the CONSORT Harms document. In our overview, we could not address potential confounders that may have made trials post-2004 different in ways that might have also affected the reporting of harms. Finally, judging the uptake of reporting guidelines can be highly subjective. For example, it is possible that judgments on what is a balanced discussion could be more of a philosophical consideration than a pragmatic one, thus challenging the adjudication of the reporting of item 10 of the CONSORT Harms checklist. Another example of the subjective decisions that might take place in judging reporting are the reviews that derived different scoring criteria to assess the same 10-items checklist of CONSORT Harms.[18 19] Given this is an overview of reviews, and such judgements could have varied between reviews, it is possible that there are inconsistencies in assessments across reviews that cannot be accounted for and that could have partially impacted our findings.

In conclusion, the reporting of harms in RCTs seems to have improved in the years after the publication of CONSORT Harms, but the improvement was limited. The empirical evidence supports the need for an update of CONSORT Harms to better align the reporting of harm outcomes with those of efficacy outcomes. It has passed the time for trialists and the scientific community to recognise the relevance of harms for patients and healthcare decisions. Harm outcomes are highly relevant for patients and, therefore, should be fully recognized as an outcome during the design, conduction and reporting of trials.

Conflict of Interests Disclosure

To the author's knowledge, no conflict of interest, financial or other, exists.

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Table 1: **Reporting of CONSORT Harms items pre and post publication and overall results.**

Item	Pre-CONSORT Harms				Post-CONSORT Harms			
	Reviews (n)	RCTs (n)	RCTs adhering to item	%	Reviews (n)	RCTs (n)	RCTs adhering to item	%
1. If the study collected data on harms and benefits, the title or abstract should so state	8	552	258	47	11	1,201	643	54
2. If the trial addresses harms and benefits, the introduction should so state	8	552	186	34	11	1,201	419	35
3. List addressed adverse events with definitions for each (with attention, when relevant, to grading, expected vs unexpected events, reference to standardized and validated definitions, and description of new definitions)	8	552	161	29	11	1,201	486	40
4. Clarify how harms-related information was collected (mode of data collection, timing, attribution methods, intensity of ascertainment, and harms related monitoring a stopping rules, if pertinent)	8	552	246	45	11	1,201	527	44
5. Describe plans for presenting and analysing information on harms (including coding, handling of recurrent events, specification of timing issues, handling of continuous measures, and any statistical analyses)	8	552	206	37	11	1,201	373	31
6. Describe for each arm the participant withdrawals that are due to harms and their experiences with the allocated treatment	8	552	246	45	11	1,201	633	53
7. Provide the denominators for analyses on harms	8	552	229	42	11	1,201	645	54

8. Present the absolute risk per arm and per adverse event type, grade, and seriousness, and present appropriate metrics for recurrent events, continuous variables, and scale variables, whenever pertinent	8	552	270	49	10	996	688	69
9. Describe any subgroup analyses and exploratory analyses for harms	8	552	48	9	7	508	65	13
10. Provide a balanced discussion of benefits and harms with emphasis on study limitations, generalizability, and other sources of information on harms	8	552	307	56	10	996	579	58

Box 1 CONSORT Harms items.[9]

Paper Section	CONSORT Harms Extension 2004	Items
Title and Abstract	If the study collected data on harms and benefits, the title or abstract should so state	1
Introduction	If the trial addresses harms and benefits, the introduction should so state	2
Methods	List addressed adverse events with definitions for each (with attention, when relevant, to grading, expected vs unexpected events, reference to standardized and validated definitions, and description of new definitions)	3
	Clarify how harms-related information was collected (mode of data collection, timing, attribution methods, intensity of ascertainment, and harms related monitoring a stopping rules, if pertinent)	4
	Describe plans for presenting and analysing information on harms (including coding, handling of recurrent events, specification of timing issues, handling of continuous measures, and any statistical analyses)	5
Results	Describe for each arm the participant withdrawals that are due to harms and their experiences with the allocated treatment	6
	Provide the denominators for analyses on harms	7
	Present the absolute risk per arm and per adverse event type, grade, and seriousness, and present appropriate metrics for recurrent events, continuous variables, and scale variables, whenever pertinent	8
	Describe any subgroup analyses and exploratory analyses for harms	9
Discussion	Provide a balanced discussion of benefits and harms with emphasis on study limitations, generalizability, and other sources of information on harms	10