International Journal of Nursing Studies

The need for clarity and consistency in defining and reporting primary outcomes

--Manuscript Draft--

Manuscript Number:	NS-D-21-00704
Article Type:	Editorial
Keywords:	
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EDITORIAL

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Correspondence we received on a recently published paper (Wang et al., 2021) highlights the importance of prospective clinical trial registration (Gray, 2021). When registering a clinical trial prospectively, researchers publicly set out details of trial methodology before enrolling participants. Prospective registration of clinical trials is a requirement for subsequent publication of results in the *International Journal of Nursing Studies.* This policy reflects the recommendations of the International Committee of Medical Journal Editors (ICMJE):

> *"the ICMJE requires, and recommends that all medical journal editors require, registration of clinical trials in a public trials registry at or before the time of first patient enrolment as a condition of consideration for publication" (ICMJE, 2019p.13)*

Registration increases transparency about the conduct of the trial, including the analyses that were planned. Prospective registration reduces the likelihood of publication bias arising from selective reporting and encourages researchers to be much clearer about any analyses that were planned and undertaken only after the researchers had the opportunity to identify patterns in the data that were gathered.

A tendency to selectively report only positive results undermines the basis of statistical inference, produces biased estimates of effect in meta-analyses and is believed to be a major contributor to the so called replication crisis in science. This phenomenon, whereby published results cannot be replicated by others, was originally identified in psychology, but it is widespread (Ritchie, 2020). Even apparently robust studies subject to peer review have been implicated in the replication crisis.

Studies with 'negative' (i.e. not statistically significant) results are less likely to be published because authors are less likely to submit such studies for publication (Dwan et al, 2013). Evidence that journals are less likely to publish such results once submitted is less clear cut (Dwan et al, 2013) although this may be a product of the advance selection by authors. This is an acknowledged problem and study registration at least permits such studies to be found.

The selective reporting of outcomes *within* a study is a less widely recognised. Of 20 empirical studies of outcome reporting bias identified by a systematic review, only 5 considered selective outcome reporting bias (Dwan et al, 2013). The consequences of such selective reporting are very similar to the consequences of publication bias. In very simple terms if a study of effectiveness measures 20 different outcomes that were all independent of each other and unaffected by the treatment being studied, the study has a 64% chance of producing one or more statistically significant results.

Multiple outcomes and comparisons always increase the risk of false positives but with selective outcome reporting the risk of false positive results is much higher than it appears to be. While it is unlikely that all outcomes in a study are completely independent of each other, it is perhaps a better starting assumption that for any published studies the chance of a false positive result is a product of the number of reported outcomes plus an unknown number of unreported outcomes multiplied by the chosen significance level. For many published studies at least one significant result could easily be more likely than not even in the absence of any effect. Shifting emphasis away from significance testing and on to estimation based on confidence intervals, as we advocate at the *International Journal of Nursing Studies* (Griffiths and Needleman, 2019), is a partial remedy, but selective reporting can still introduce biased estimates.

Prospective registration of trials allows consumers of published research, including all readers of this journal, to compare what researchers set out to investigate as set out in the trial's registration with what they subsequently report in publications. Professor Gray has made this comparison for Wang

et al's (2021) study and we are grateful to him for pointing to inconsistencies between the registration record and reported trial results.

The particular issue that Gray points out, a discrepancy between the originally stated primary outcome and the primary in a particular report is a common one (Goldacre et al., 2019). We have seen other recent examples in papers that we have published (Chou, 2020, Gray et al., 2020, Kao et al., 2018). A common feature of the response from the authors is an apparent naivety concerning the importance of clearly and consistently stating the primary outcome. The primary outcome is not the outcome selected by the authors after analysis to be the focus of the paper in hand, nor is it the outcome that provides the most 'interesting' result. Such selections are often based on levels of statistical significance or a large effect size.

The primary outcome is whichever outcome the investigator stated in the protocol was the primary outcome, which should be the most important among the many outcomes that are to be examined in the study. It follows that there can only be a single primary outcome. Ensuring that there is a single primary outcome that is stated and consistently reported provides a partial mitigation for the problem of high false positive rates noted above.

The primary outcome must be defined at the time the study is designed and certainly should not be informed by the data acquired or the results of the analysis of data. It should be used to determine the required sample size in designing the study. Secondary outcomes might be taken into account when determining sample sizes but the primary determines the ultimate 'power' of the study and the statistical error rates associated with traditional statistical significance testing apply only to that outcome. Authors wishing to report outcomes other than the primary or those undertaking secondary analyses of existing data sets to test new hypotheses have many options available if such analyses cannot be included in the original report. Changing the stated primary and, in some cases, presenting a sample size calculation that implies the study was designed with that primary in mind is not one of those options. Omitting the original primary outcome because the results show no statistically significant effect (which may have happened in the reporting of Wang et al's study) is simply not an option.

As Gray's letter reminds us, whilst prospective trial registration is important and necessary, it is not in itself sufficient to ensure consistency between trial registration and articles arising from these trials. It is our clear expectation at the *International Journal of Nursing Studies* that the primary outcome stated in a paper is the primary outcome identified in the trial protocol and we have long been clear about the need for authors to transparently link different publications arising from the same study (Norman and Griffiths, 2008). However, along with other nursing journals the *International Journal of Nursing Studies* could do better. Checking the protocol against the article submitted for publication and checking whether any discrepancies between the protocol and the article are legitimate or otherwise would support our goal of disseminating high quality rigorous research to inform nursing practice and policy.

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Conflict of Interest Disclosures

The authors declare that they have no competing interests.