ABC of Methodology

This is a Section of *Epidemiologia e Psichiatria Sociale*, that regularly covers methodological aspects related to the design, conduct, reporting and interpretation of clinical and epidemiological studies. We hope that these articles will help develop a more critical attitude towards research findings published in the international literature and, additionally, will help promote the implementation of original research projects with higher standards in terms of design, conduct and reporting.

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Outcome reporting bias in clinical trials

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Randomised controlled trials (RCTs) are designed and powered to measure one single outcome, called *primary outcome* (Sibbald & Roland, 1998; Barbui *et al.*, 2007). The primary outcome is the pre-specified outcome of greatest clinical importance and is usually the one used in the sample size calculation (Accordini, 2007). In addition to the primary outcome, RCTs may have several other outcomes, called *secondary outcomes*. In contrast with the analysis of the primary outcome, the analysis of secondary outcomes and its interpretation may be complicated by at least two factors:

1) the trial may not have enough statistical power to detect differences (so it is possible to incur in a type II error, that is failing to see a difference that is present);
2) increasing the number of secondary outcomes generates the problem of multiplicity of analyses, that is the proliferation of possible comparisons in a trial (and increasing the number of comparisons increases the possibility to incur in a type I error, that is detecting significant differences by chance). For all these reasons, the results of the analysis of primary outcomes is considered less susceptible to bias than the analysis of secondary outcomes.

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Outcome reporting bias occurs when authors choose to report or highlight only some outcomes, deliberately avoiding to report the others (Chan *et al.*, 2004). Typically, outcomes that highlight a positive or significant result are more likely to be published in comparison with outcomes that fail to highlight a statistically significant result. Clearly, outcome reporting bias may represent a very relevant source of bias because it inevitably produces an exaggeration of the beneficial effects of treatments (Dwan *et al.*, 2008).

When should readers of scientific articles suspect the occurrence of outcome reporting bias? Ideally, readers of clinical trials should be able to recognise perfect coherence between what is reported as primary and secondary outcomes in a study protocol and what is reported in the published study report (Chan *et al.*, 2004). Table I, which provides an example of this ideal scenario for an hypothetical RCT, shows that in the study protocol one primary outcome is clearly highlighted (hospital admission), and, additionally, three other secondary outcomes are mentioned (quality of life, sexual adverse reactions, global functioning). In the study report (say for example a scientific article published in a scientific journal), the primary outcome that had been selected in the study protocol is clearly and unambiguously mentioned in the methods, reported in the results, and discussed in the discussion of the article. Similarly, all three secondary outcomes that had been mentioned in the study protocol are clearly and unambiguously mentioned in the methods, reported in the results, and discussed in the discussion of the article. Throughout the article that presents the results of this hypothetical RCT, the primary outcome is clearly distinguished from any other outcomes. This ideal scenario may not represent the current standard of reporting of clinical trials. Table

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II presents a more frequently seen scenario, characterised by lack of coherence between what is reported as primary and secondary outcomes in a study protocol and what is subsequently reported in the final study report. While in the study protocol a primary outcome is reported and unambiguously distinguished from the secondary outcomes, in the methods of the study report it is not clear what the primary outcome is, and one secondary outcome (global functioning) is not mentioned at all. In the results and discussion of the study report, additionally, one secondary outcome is given prominence, and the primary outcome is not mentioned at all. This situation is at high risk of bias, because typically the secondary outcome that is given visibility is the one that favours the new treatment under study, while the primary outcome that is not mentioned may have failed to favour the new treatment. This phenomenon is called outcome reporting bias.

Table I – *Ideal scenario of perfect coherence between what is reported as primary and secondary outcomes in a study protocol and what is reported in the final study report. The symbol ● highlights that the primary outcome is unambiguously distinguished from any other outcomes, identified with the symbol* **X**

STUDY PROTOCOL	**STUDY REPORT**		
	METHODS	**RESULTS**	**DISCUSSION**
Primary Outcomes:			
Hospital admission:	●	●	●
Secondary outcomes:			
Quality of life	**X**	**X**	**X**
Sexual adverse effects	**X**	**X**	**X**
Global functioning	**X**	**X**	**X**

Table II – *Example of outcome reporting bias (lack of coherence between what is reported as primary and secondary outcomes in a study protocol and what is reported in the final study report). While in the study protocol a primary outcome is reported and unambiguously distinguished from the secondary outcomes, in the methods of the study report is not clear what the primary outcome is, and one secondary outcome is not mentioned at all (global functioning highlighted with the symbol* **?**). *In the results and discussion of the study report, additionally, one secondary outcome is given prominence (quality of life, highlighted with the symbol ●), and the primary outcome is not mentioned at all.*

STUDY PROTOCOL	**STUDY REPORT**		
	METHODS	**RESULTS**	**DISCUSSION**
Primary Outcomes:			
Hospital admission:	**X**	**?**	**?**
Secondary outcomes:			
Quality of life	**X**	●	●
Sexual adverse effects	**X**	**X**	**X**
Global functioning	**?**	**?**	**?**

It may be argued that while checking the degree of coherence between what is reported in the study methods and what is reported in the results and discussion may be a relatively easy task for readers of reports of clinical trials, checking the degree of coherence between what is reported in the study protocol and what is reported in the study publication may not be feasible, simply because trial protocols are not accessible. If trial protocols are not accessible, the chances to identify outcome reporting bias are inevitably low. However, things have been changing in the international scenario. Almost all scientific articles that report the findings of clinical trials are obliged to declare that the study protocol had been registered into a repository of study protocols, and a number identifying the study protocol has to be provided, together with the web address of the protocol repository. Readers may therefore surf the web, access the study protocol, and check the consistency between what was reported in the study protocol and what is reported in the scientific publication.

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