Publication bias in oral and maxillofacial surgery journals: An observation on published controlled trials

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SUMMARY. Background: Publication bias (PB) diminishes the full distribution of research, distorts and discredits the scientific record, and thus compromises evidence-based practice. The objective of this study was to analyse published controlled trials with regard to PB in leading oral and maxillofacial surgery (OMS) journals. Methods: All controlled trials published in the International Journal of Oral and Maxillofacial Surgery, Journal of Cranio-Maxillofacial Surgery, Journal of Oral and Maxillofacial Surgery, and British Journal of Oral and Maxillofacial Surgery in 2008 were analysed for a primary outcome, country of authors, sample size, gender of the first author, funding source and location of the study. Results: Of 952 published articles, 53 controlled trials (5.7%) were identified. The OMS journals preferentially published controlled trials with a positive outcome (77.4%) and from high-income countries (73.6%). Single-centred trials (86.8%) with low sample size (n < 100; 69.8%) were published more frequently. The majority of the first authors were male (75.5%). Funding source disclosure in most studies (73.6%). Conclusions: Our results suggest the possible existence of PB in the OMS literature. Hence, it should be borne in mind that the published articles may not be representative of all scientific works, especially when systematic reviews and meta-analyses are conducted or read. In the meantime, journals should establish measures to eliminate PB to uphold scientific integrity. However, this study was an observation based on the published articles. An analysis of all submitted manuscripts would provide more accurate estimates of PB. Ethical considerations on PB are also discussed. © 2009 European Association for Cranio-Maxillofacial Surgery

Keywords: publication bias, controlled trial, oral and maxillofacial surgery, scientific integrity, evidence-based practice, medical ethics

INTRODUCTION

‘The human intellect ... is more moved and excited by affirmatives than by negatives.’

Sir Francis Bacon, 1st Viscount St Alban KC (1561–1626)

Case reports and case series provide descriptions of general characteristics and the distribution of disease, complications attributable to an intervention, rare diseases, and sometimes, generate hypotheses. However, their retrospective nature is an obvious weakness. Bias in study methodology may also overestimate or underestimate the results. Controlled trials are designed to overcome the weakness of observational studies. They yield more accurate estimates of fact and are thus higher in the hierarchy of scientific evidence (Petrisor et al., 2006). However, as Sir Francis Bacon reminds us, human interest and decision are generated towards positives. Not all controlled trials are published due to bias in submitting, reviewing, accepting and publishing results.

Publication bias (PB), a form of selection, is the influence of study results on the chances of publication and the tendency of investigators, reviewers, and editors to submit or accept manuscripts for publication based on the direction or strength of the findings of quantitative
studies (U.S. National Library of Medicine, 2009). A common form of PB is ‘positive outcome bias’ or ‘pipeline bias’ which is defined as the decreased tendency of studies being published when their results are near the null, not statistically significant, or otherwise ‘less interesting’ (Møller and Jennions, 2001; Phillips, 2004). In other words, journals (or editors or peer reviewers) are not beguiled by studies that demonstrate ‘nothing’.

A recent Cochrane review revealed that controlled trials with positive findings were given priority in publication (Hopewell et al., 2009). Moreover, they are more likely to be published in journals with a higher impact factor, or in multiple forms (and some are redundant publications), and probably be cited by other authors, than studies showing non-significant results (Thornton and Lee, 2000; Mahid et al., 2008). Other factors increasing the tendency to be published include large sample size, previous presentation at a scientific meeting, providing results that favour a new therapy, and being a part of doctoral dissertation. Moreover, study quality, English language, industrial sponsorship, authors’ gender, country of origin and location of studies also influence the chances of publication (Thornton and Lee, 2000; Olson et al., 2002; Harris et al., 2006). Magos et al. (2000) found bias against publication of surgical papers in prestigious medical journals: the Lancet, British Medical Journal (BMJ), New England Journal of Medicine and Journal of the American Medical Association (JAMA). PB not only lessens readers’ chance to achieve the full distribution of research, but also probably distorts and discredits the scientific record, such as a systematic review with or without a meta-analysis (Thornton and Lee, 2000; Harris et al., 2006; Mahid et al., 2008). It is therefore unethical if journals let PB emerge without adequate recognition and control.

Until now, PB in oral and maxillofacial surgery (OMS) literature has not been evaluated and reported. The aim of this study was to analyse published controlled trials with regard to PB in leading OMS journals.

MATERIALS AND METHODS

An electronic search was conducted to identify controlled trials, involving a therapy to living humans or parts of their bodies, published in the top 4 highly ranked OMS journals in 2008. The chosen journals were the International Journal of Oral and Maxillofacial Surgery (IJOMS), Journal of Cranio-Maxillofacial Surgery (JCMS), Journal of Oral and Maxillofacial Surgery (JOMS), and British Journal of Oral and Maxillofacial Surgery (BJOMS). They were chosen for their high impact factor and journal quality, as well as being the core OMS journals for most world regions (Lau and Samman, 2007; Brennan, 2009). We analysed only the published controlled trials because observational studies may yield bias, even though PB is absent, and because it remains difficult to evaluate the quality of observation studies (Thornton and Lee, 2000). According to Olson et al. (2002)’s criteria, this study included articles that 1) reported results of a prospective study, 2) assigned participants to an intervention, 3) had at least 1 comparison group, and 4) used a statistical test to compare differences in outcomes between groups. Such studies were either randomised or non-randomised.

Each eligible article was carefully screened by 2 independent assessors for information on characteristics examined previously by others (Olson et al., 2002; Harris et al., 2006; Youseft-Nooraie et al., 2006): a primary outcome (positive vs negative), country of authors, sample size, gender of the first author, funding source and location of the study (multicentre vs single centre). As described by Olson et al. (2002) and Harris et al. (2006), we considered a primary outcome ‘positive’ in case of 1) improved outcome with the tested intervention, 2) similar outcome with new treatment compared to standard treatments, 3) one that supported the study objective, 4) one with statistical significance ($P < 0.05$; $95\%$ confidence interval [CI] for difference excluding 0 or $95\%$ CI for ratio excluding 1), or 5) combinations of these, and ‘negative’ when it did not meet the aforementioned criteria.

Countries of authors were classified according to the World Bank income criteria (World Bank Group, 2007) into low, lower-middle, upper-middle and high-income groups. If the first-author gender was unclear, we did an internet search for the author by name and institution, and other strategies as described by Kurichi et al. (2005). Industrial support for only drugs or devices was not recognised as a funding source. When the authors declared no financial conflicts and did not mention a funding source, we speculated that the fund for that study came from their own department. If multiple countries were involved, we classified them according to the country of the supervising or principal institution.

If agreement between the 2 assessors could not be reached, advice was sought from a third party and the determination was made by consensus. To confirm the accuracy of categorisation and data entry between the reviewers, the results were analysed by the percentage of agreement and Kappa statistics ($\kappa$). We assumed that manuscripts with each parameter category, such as positive and negative outcomes, would be accepted for publication in equal proportion. The hypothesis was tested by chi-square test. Variables with $P$-value of less than 0.05 were considered statistically significant.

The recommendations of the ‘Helsinki declaration’ were thoroughly maintained during this study. Since this study did not involve human subjects or records, ethical approval by an ethics committee and consent from the authors of the articles studied were not required.

RESULTS

During the study period, 952 articles were published in the 4 OMS journals. Of these, 53 controlled trials (5.7%) met all inclusion criteria (IJOMS: 16/208 [7.7%]; JCMS: 3/65 [4.6%]; JOMS: 26/444 [5.9%]; BJOMS: 8/235 [3.4%]). There was an excellent agreement (100% inter-examiner percentage agreement, $\kappa = 1.0$) for inter-observer reliability in data extraction. A substantial number of the controlled trials presented positive outcomes (77.4%), were based on low sample size.
size ($n < 100; 69.8\%$) and from a single centre ($86.8\%$). They were conducted in 19 countries (high income = 11; upper middle = 4; lower middle = 3; low = 1), and most of the controlled trials ($n = 39; 73.6\%$) were from the high-income countries. The majority of the first authors were male (75.5\%). Funding source was not mentioned in most studies (73.6\%) (Table 1). Reporting of a new therapy was very common. It is interesting to note that the only 7 out of 26 ($26.9\%; P = 0.019$) and 1 out of 8 ($12.5\%; P = 0.034$) controlled trials in the JOMS and BJOMS were published from American and British authors, respectively.

**DISCUSSION**

PB becomes important in the evidence-based practice era. Many authors focus on the presence of PB in meta-analyses based on a belief that the literature reviewed should not rely on biased information. PB compromises the estimated effect of the intervention, misleading conclusions of reviews and meta-analyses and subsequently medical practice. A number of methods of detecting PB have been documented in the literature, such as proportion of significant studies, funnel plot, Egger’s test, Begg and Mazumdar adjusted rank correlation test, trim and fill method, and fail-safe number of unpublished studies. However, they always have limitations (Thornton and Lee, 2000; Møller and Jennions, 2001; Mahid et al., 2008).

PB arises whenever the strength and direction of the results of published and unpublished studies differ. It occurs in any steps before research is published. Investigators, promoters (fund givers) and/or journal editors may have a preference to submit or publish studies reporting positive results. The non-submission may be due to the negative results themselves and the lack of interest of researchers in publication of the negative results. Meanwhile, peer reviewers may be tempted to mistreat studies with inconclusive findings because of the speculation that they may debase themselves in the eyes of another reviewer, readers or the editor. Taken together, PB occurs easily and skew the outcome towards positive results (Thornton and Lee, 2000; Møller and Jennions, 2001; Mahid et al., 2008).

Our study suggests that the 4 leading OMS journals have a preference to publish controlled trials with a positive outcome. This preference may mislead readers about the effectiveness of the reported therapy. Bias in the dissemination of research, publication, interpretation and review of scientific findings is considered as ‘scientific misconduct’ (Chalmers, 1990; Pitak-Arnnop et al., 2008a). Several authors including the UK Cochrane centre team found that studies showing positive results were published more frequently and faster than the ones with inconclusive or invalidating results or with findings contrary to the study hypothesis. Most journals are unlikely to flourish if they publish studies which are scientifically weak (with inconclusive results) and irrelevant to health care. Therefore, they point to landmark studies that change medicine or science. Of course, articles with non-significant results are juxtaposed, and may become the ‘throwaways’ due to the negative findings (Stern and Simes, 1997; Thornton and Lee, 2000; Decullier et al., 2005; Hopewell et al., 2007, 2009). However, studies with negative results may be rejected because of their methodological weaknesses, obvious fraud or distortion. They may, therefore, be able to skew the overall effects of systematic reviews and meta-analyses as much as does PB (Thornton and Lee, 2000).

It is worth noting that the probability of publication is boosted by experimental quality, methodology rigour, level of replication, novelty of the results, and possibly, author or institute prestige. However, these factors do not affect PB (Møller and Jennions, 2001). Although a prospective study argues against PB in decision making of the JAMA’s editors (Olson et al., 2002), this finding cannot be generalised to other journals. The role of editors and reviewers in deciding which manuscript is to be published is rarely criticised and standardised within and between journals. Sporadic cases of PB have been documented. Wilmshurst (1991) revealed his experience with PB. He was invited to review an article of a poor quality and suggested that it be rejected. This decision was in agreement with the second referee. However, he saw the article published and found that the first author of that article was the editor’s colleague. He then performed the similar study with the 3-fold larger sample size. He failed to reach the same results with the earlier published article, and his manuscript was rejected for publication in that journal. Finally, he suggested this could be an intriguing example of the editorial bias which was related to author prestige. This case obviously distorts the medical literature. Falsified data was published, but the truth or at least a more reliable article with a larger sample size was not.

The ‘Helsinki declaration’ dictates that authors, editors and publishers should publish all high quality studies, irrespective of outcome (World Medical Association, 2008). Editor’s judgement on each manuscript ought to be mainly contingent on the clinical question addressed and quality of the research methods (Olson et al., 2002). The ‘Consolidated Standards of Reporting Trials’ (CONSORT) has been established to evaluate and improve the quality of reporting of randomised controlled trials (Moher et al., 2001). However, other research types remain difficult to assess. To highlight the value of scientific works, journals may require the summary box as seen in the BMJ (‘What is already known on this topic’ and ‘What the study adds’). This model can help editors, reviewers and readers comprehend the core value of each article.

Since PB limits the chance, young trainees, surgeons or researchers may add a ‘gift or guest author’, who is familiar with the editor, without the adequate participation in the scientific work. The misconception is that the well-known names would help articles to get published more easily. Inappropriate claims of authorship are certainly ‘research misconduct’ (Pitak-Arnnop et al., 2008a).

It remains unclear whether the peer-review process guarantees quality of the journals. Although it is generally accepted that peer-review functions as an independent filter of quality of submitted manuscripts,
it is prone to bias and abuse. PB can begin at the time when an editor decides whether or not an article will be sent to referees and by whom it will be peer reviewed. During external review process, opinions between referees are frequently inconsistent and biased by the reviewers’ backgrounds, including their research findings and country. For instance, a reviewer may block or delay studies that differ from his/her own experiment, but may accept articles from the same country (Chalmers et al., 1990; Møller and Jennions, 2001; Olson et al., 2002).

PB against the nationality may hamper medical progress of less developed countries. In our study, trials from high-income nations were more likely to be published, as was also found by Yousefi-Nooraie et al. (2006). Editorial board members of international journals usually come from developed countries. Apart from the higher quality and/or quantity of trials from developed world, PB against the nationality increases over time and may potentially cause differences in the amount of publications (Yousefi-Nooraie et al., 2006). Although the blinded review process is widely used, the author nationality may be presented elsewhere in a manuscript. Hence, anonymity of authors raises areas of critical concern.

Authorship patterns may indicate the participation of women in academic surgery (Kurichi et al., 2005). The gender gap in authorship still exists as evidenced by our observation and others studies (Kurichi et al., 2005; Taira et al., 2008). The number of women first authors in surgical literature remains low, despite increasing over time. It may be due to fewer female surgeons, or differences in career success and/or academic productivity between genders. Moreover, most surgical residents, surgeons, research leaders and departmental chairs in the USA, and editorial board members in top ranked surgical journals are male (Kurichi et al., 2005; Taira et al., 2008). However, our study could not identify a reason for the authorship inequality. To minimise the gender gap and PB against the female gender, many journals have now included only the initials (not first names) of all authors.

Trials with large sample sizes and/or from multiple centres are more likely to be published (Olson et al., 2002). However, sample sizes of the trials included in this study seems to be low. A possible explanation is that most of them are single-centre trials. When sample size is small, the probability of missing a true difference (Type II error) exists. Significance may only be achieved if chance exaggerates any true differences between the groups under study and thus the study suffers from ‘lack of power’. It is also widely accepted that many negative trials are negative because of this lack of power (Thornton and Lee, 2000; Alam et al., 2005). To detect a 50–80% relative efficacy benefit of one treatment over another, sample size in controlled therapeutic trials should range from 50 to 200 (Alam et al., 2005). However, several surgical diseases or conditions are infrequent, and various factors influence execution of research (such as numbers of patients, willing to participate). The accumulation of large sample sizes prolongs the study period and subsequently delays publication (Møller and Jennions, 2001; Pitak-Arnnop et al., 2008b). It remains unknown how many patients should be accepted for surgical publication, and this remains inconsistent between journals.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Published no. (%)</th>
<th>P-value</th>
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<tbody>
<tr>
<td>1. Study results</td>
<td></td>
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<tr>
<td>- Positive outcomes</td>
<td>41 (77.4%)*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>- Negative outcomes</td>
<td>12 (22.6%)</td>
<td></td>
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<tr>
<td>2. Group of countries</td>
<td></td>
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<tr>
<td>- High income</td>
<td>39 (73.6%)*</td>
<td>&lt;0.0001</td>
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<tr>
<td>- Upper-middle income</td>
<td>7 (13.2%)</td>
<td></td>
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<tr>
<td>- Lower-middle income</td>
<td>5 (9.4%)</td>
<td></td>
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<tr>
<td>- Low income</td>
<td>2 (3.8%)</td>
<td></td>
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<tr>
<td>3. Sample size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Large sample (≥100)</td>
<td>16 (30.2%)</td>
<td>0.0039</td>
</tr>
<tr>
<td>- Small sample (&lt;100)</td>
<td>37 (69.8%)*</td>
<td></td>
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<tr>
<td>4. Gender of the first author**</td>
<td></td>
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</tr>
<tr>
<td>- Male</td>
<td>37 (75.5%)*</td>
<td>0.0036</td>
</tr>
<tr>
<td>- Female</td>
<td>12 (24.5%)</td>
<td></td>
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<tr>
<td>5. Funding source</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Not mentioned</td>
<td>39 (73.6%)*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>- University</td>
<td>5 (9.4%)</td>
<td></td>
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<tr>
<td>- Government</td>
<td>6 (11.3%)</td>
<td></td>
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<tr>
<td>- Private organisation</td>
<td>3 (5.7%)</td>
<td></td>
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<tr>
<td>6. Location of study</td>
<td></td>
<td></td>
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<tr>
<td>- Single centre</td>
<td>46 (86.8%)*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>- Multicentre</td>
<td>7 (13.2%)</td>
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*Statistically significant.
**Gender of the first author was unidentified in 4 studies.
The relatively low number of published OMS controlled trials (5.7%) reflects the nature of surgery. A systematic review and meta-analysis may not be feasible or provide serious bias if observational studies are relatively high and thus excluded (Thornton and Lee, 2000; Pitak-Arnnop et al., 2008b). It may also be anticipated that a journal publishing many low-level evidence articles will have a low impact factor (Lau and Samman, 2007). However, it is still controversial whether surgery should be based only on high-level evidence, such as randomised controlled trials and meta-analyses, because they always represent an effective approach for a group of similar patients with a particular condition which may not be applicable to every patient. Randomised controlled trials and evidence-based practice are not synonym. Additionally, evidence-based practice never replaces the clinical expertise of each surgeon who knows well what is suitable and what should be avoided for his/her individual patient (Pitak-Arnnop et al., 2008b).

We found that only 26.9% and 12.5% of controlled trials in the JOMS and BJOMS were published from American and British authors, respectively. This suggests that both journals are sufficiently broad-minded to publishing research from other countries. Otherwise, it may support the notion that OMS specialist registrar programmes in the UK lack research training (Rehman et al., 2008), and the US maxillofacial surgeons’ time devoted to research is low (Aziz et al., 2007). A survey in France by Millat et al. (1999) revealed that many surgical professors and senior surgeons apparently lacked knowledge of and were unfamiliar with clinical trial conduct. Research methodology and research ethics have rarely been integrated into surgical residency training programmes. The shortage of experience, role models, encouragement and support contributes mainly to poor familiarity with research, and a lack of scientific works (Aziz et al., 2007; Rehman et al., 2008). Moreover, research misconduct may occur when a surgeon without adequate research experience conducts and publishes his/her research (Pitak-Arnnop et al., 2008a). To reach sustainable development of the OMS specialty, it is therefore prudent for the national and international professional organisations to establish and improve research training for OMS trainees and graduates.

A funding source, especially an industrial one, may unduly influence the study results and publication. The ‘Uniform Requirements for Manuscripts Submitted to Biomedical Journals’ (International Committee of Medical Journal Editors, 2008) and the ‘Helsinki declaration’ (World Medical Association, 2008) have therefore required authors’ statements on conflicts of interest (CoI). Trials supported by a manufacturer tend to be of high quality and have large sample sizes, and be published more frequently (Møller and Jennions, 2001). At the time of writing this manuscript, a storm of criticism on journal transparency and PB has slashed the privilege of the JAMA after the journal published a positive pharmaceutical trial without disclosure of CoI, whilst phone calls, personal attacks, and e-mails from the journal threatened the whistleblower, Jonathan Leo (Armstrong, 2009). This may indicate that transparency is lacking, even in a prestigious medical journal. However, the majority of the trials examined in our study did not mention funding sources. The OMS journals themselves did not require the author’s statement about funding sources and CoI at the end of each submitted manuscript and publish them regularly. Hence, the overall reporting rate of funding sources in the OMS journals remains low. This confirms the findings of our previous study (Pitak-Arnnop et al., 2009b). In early 2009, the IJOMS requires disclosures of funding support, competing interests and ethical approval in each submission, and publishes them regularly at the end of each publication. In the light of this finding, it is high time for Editors-in-Chief of the OMS journals to make a joint commitment to maintain the scientific and journal integrity as seen in other surgical specialties (Brand et al., 2004; Johnson et al., 2007; Pitak-Arnnop et al., 2009a,b).

A time lag in publication can be a form of PB. It diminishes precise and timely dissemination of knowledge. Stern and Simes (1997) found that studies with positive results had a median of 4.8 years to publication, but for those with negative results it was 8 years. In addition to the ‘pipeline bias’, delay in publication would underpin a larger treatment effect of a new therapy (based on a small sample size in a preliminary report). Patients may be enrolled into a clinical study that lacks scientific evidence (Hopewell et al., 2007; Mahid et al., 2008). This violates the principles of ‘Beneficence’ (do good) and ‘Non-maleficence’ (do no harm). However, in this study we did not analyse the time lag in publication. An association between PB and publication time is therefore beyond the scope of this investigation.

A number of methods have been introduced to eradicate the bias in the biomedical literature. These include adding another part in a journal as the ‘articles with negative results’ section, registration of all clinical trials, and publishing research as an online article or in online journals. Double-blinded reviewing process, declaration of CoI, reviewing focusing on quality indicators, omission of the author’s first names are also recommended (McNamee, 2001; Møller and Jennions, 2001; Mahid et al., 2008). Journals should declare the date of submission, acceptance and publication of each article, allowing possible monitoring and management of a time lag (Hopewell et al., 2007). Furthermore, authors may consider ‘journals of negative findings’ for publication (Pfjeffer and Olsen, 2002).

Given the design of our study, we are aware of several limitations. Firstly, since we analysed a limited number of the published articles over the course of 1 year, the findings should be interpreted cautiously. This study examined high-impact OMS journals with objective inclusion criteria by 2 independent assessors. However, we did not account for differences in submission to the journals. An evaluation of all submitted manuscripts, both accepted and rejected, grounded in rigorous analysis would yield an accurate assessment of PB. If manuscripts with positive and negative results were equally accepted for publication, the overall publication rate would be 16%, requiring 708 submitted manuscripts to be analysed (Olson et al., 2002). Thus, this study seems to be only a suggestion from an observation on the ‘published’ controlled trial. It is also possible that our results are only
'coincidental'. Secondly, our findings may not be applicable to other study designs or to other journals with fewer submissions or lower circulation.

CONCLUSION

The findings of this study suggest the possible existence of PB in the OMS literature. As Altman and Bland (1995) state: ‘absence of evidence is not evidence of absence’, it should be borne in mind that published articles are not all the scientific literature. This should be taken into account when one undertakes and/or reads meta-analyses and systematic reviews. To reach unpublished studies, searching all relevant databases including the ‘grey’ literature (meeting proceedings, symposiums, abstracts) and contacting experts in the field are recommended (Thornton and Lee, 2000; Möller and Jennions, 2001; Mahid et al., 2008).

It is the moral responsibility of researchers, fund givers and journals to disseminate research findings, regardless of outcome. Authors and fund providers should not have a preference to submit only studies reporting positive results. Meanwhile, journals should implement the ‘must have’ measures to diminish PB from their selection processes. In this way, scientific integrity will be upheld and maintained. Although many methods of determining PB have been addressed, they have limitations. Preventive measures do therefore become crucial. These efforts would contribute to unbiased translation of scientific evidence to patient care.

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DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

The authors had full freedom of investigation and there were no potential conflicts of interest.

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