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## The transparent clinical trial : why we need complete and informative prospective trial registration

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## INVITED COMMENTARY

## The transparent clinical trial

### *Why we need complete and informative prospective trial registration*

Stephanie Weibel, Nadia Elia and Peter Kranke

European Journal of Anaesthesiology 2016, 33:72–74

This Invited Commentary accompanies the following original article:

Song Y, Shim J-K, Song J-W, *et al.* Dexmedetomidine added to an opioid-based analgesic regimen for the prevention of postoperative nausea and vomiting in highly susceptible patients: a randomised controlled trial. *Eur J Anaesthesiol* 2016; 33:75–83.

In a randomised controlled clinical trial published in this issue of the *European Journal of Anaesthesiology*, Song *et al.*<sup>1</sup> analyse the effect of dexmedetomidine as part of an opioid-based analgesic regimen on the occurrence of postoperative nausea and vomiting in highly susceptible patients undergoing spinal surgery. The authors demonstrated that dexmedetomidine significantly reduced the frequency of postoperative nausea and vomiting (PONV) from 1 to 3 h. The authors attributed this lowered severity of PONV to a significant opioid-sparing effect, elicited by dexmedetomidine administration, which was apparent up to 12 h postoperatively.

This trial was registered retrospectively in April 2013 at ClinicalTrials.gov (<https://clinicaltrials.gov>), more than 7 months after the first patient had been enrolled. At this stage of protocol registration, the authors intended their primary outcome to be postoperative opioid consumption at 48 h, with the incidence of PONV at 48 h as a secondary outcome.

In the published report, PONV, at an undefined time point, had become the primary endpoint, with the sample size justified accordingly. The authors claim that this interchanging of primary and secondary outcomes is based on a ‘mistake in the registration process’.

In this case, as both the interchanged outcomes present statistically significant differences between investigated groups (at some time points), such an explanation may be plausible. In another scenario, we could imagine that the primary and secondary outcomes were changed because the secondary outcome reached statistical significance, whereas the primary outcome did not, making the article more attractive and thus ‘more publishable’ when presented this way.

Empirical evidence suggests that between 40 and 62% of published trials had at least one primary outcome that was changed, newly introduced or omitted compared with the original protocol.<sup>2</sup> Several studies have analysed the nature of the discrepancy between the published primary outcome and that registered. They reported that about 30% of trials published in surgical journals had discrepancies in their primary outcome reporting that arose because ‘better’ or more ‘positive’ (statistically significant) results were favoured.<sup>3,4</sup> They also revealed that between 14 and 19% of the published primary outcomes in surgical journals were originally described as secondary outcomes in the registered protocol, and in this light, the ‘mistake’ of Song *et al.*<sup>1</sup> finds itself in good company. Sometimes the reasons underlying discrepancies between initial protocols and the published reports lie in the authors’ decision to publish different outcomes as the ‘main endpoint’ in separate, subsequent reports in different journals.<sup>5</sup> This reporting of different outcomes from identical samples in duplicate publications seems to be a common duplication pattern.<sup>6</sup> Both of these practices would be considered as ‘research malpractice’, or ‘misconduct’, if they were intentional and not explicitly declared, which is something we have no reason to suspect regarding the present trial.

What we can suspect in the present study, however, is the less well recognised problem of ‘data dredging’. Data

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dredging is defined by WIKIPEDIA as ‘the use of data mining to uncover patterns in data that can be presented as statistically significant, without first devising a specific hypothesis’ ([https://en.wikipedia.org/wiki/Data\\_dredging](https://en.wikipedia.org/wiki/Data_dredging); accessed 19 September 2015). Although the retrospectively registered protocol indicates that both the total dose and bolus administration of opioid, and the consequent PONV, were to be evaluated after 48 h, the published reports describe eight different time slots: 0 to 1, 1 to 3, 3 to 6, 6 to 12, 12 to 24, 24 to 36, 36 to 48, and from 0 to 48 h. It is of interest that the only time period wherein a difference in the incidence of PONV reached statistical significance between the two groups was from 1 to 3 postoperative hours. This was also the only result reported in the abstract, leading the authors to conclude that adding dexmedetomidine to fentanyl PCA exerted a beneficial influence on the frequency of postoperative nausea. Nowhere in the registered protocol can one find the author’s prehoc intention to analyse all these different time points. On the contrary, the protocol reports that PONV at 48 h was the (secondary) endpoint and therefore, logically, the conclusion of the article should have been that dexmedetomidine had no effect on PONV at 48 h. Only supplementary posthoc analyses could suggest that dexmedetomidine reduced PONV from 1 to 3 h, and subsequent research would be necessary to prove this point provided it was considered to have clinical relevance, which is doubtful.

### **Trial registration: a first step towards good quality research**

A cornerstone in ensuring transparency of clinical research and accountability in the planning, conduct and reporting of clinical trials is the introduction of trial registers. Prospective registration of study protocols can protect not only against nonpublication of negative trials (publication bias), selective reporting of only significant outcomes, but also against data dredging, provided registration was conducted in an appropriate manner. Moreover, it may prevent researchers from yielding to the sweet temptation of presenting ‘a positive’ result of the research work by retrospectively putting an emphasis on that specific outcome. In this particular case, we can see that an incomplete and retrospectively registered protocol brings more questions regarding the quality of the research than concrete answers. The sample size was not justified, the outcomes of interest were incompletely described, there was no description of the listed adverse effects and not a word was written regarding the strategy for data analysis (dealing with missing values, for example).

The full advantages of registration are only achieved when trials are registered before patient enrolment and complete registration should include all 20 items recommended in the WHO minimum Trial Registration Data

Set.<sup>7</sup> Another step towards improving transparency is provided by the International Committee of Medical Journal Editors (ICMJE), which has announced that their journals, amongst which are the most prestigious, will require, as a precondition of publication, registration in a public trials registry.<sup>8</sup> The *European Journal of Anaesthesiology* follows this initiative and requires authors to prospectively register the protocol of any trial that will start enrolment after 1 January 2015. This will be a mandatory requirement for subsequent publications in the journal.<sup>9</sup> Finally, the AllTrials initiative (All Trials Registered | All Results Reported) was launched in January 2013 to draw attention to the issue of unreported trial data. It calls for all past and present clinical trials to be registered and their results reported (<http://www.alltrials.net>).

### **Rethinking: the ‘negative’ is as valuable and informative as the ‘positive’ ... what really counts is methodological quality!**

For a long time, it has been recognised that when clinical investigators selectively report study findings, it is because of pressure from journals that prefer to publish significant positive results, rather than because the investigators are inherently devious.<sup>10</sup> Some journals, together with their editors and peer-reviewers, may have substantially contributed to the nonpublication of negative results and selective reporting of positive results, despite their affirmations to the contrary.<sup>11</sup> We will not speculate and elaborate too much about the reasons for this apparent phenomenon in science,<sup>11</sup> but a reduced likelihood to obtain subsequent citations (which is less advantageous for journals) may contribute to it. Authors have learnt that they are less likely to get published if their results do not support the intervention under investigation.<sup>12,13</sup>

It is time to recall Jules Verne writing in the *Voyage au Centre de la Terre* in 1864: ‘La science, mon garçon, est faite d’erreurs, mais d’erreurs qu’il est bon de commettre, car elles mènent peu à peu à la vérité’ [‘Science, my lad, has been built upon many errors; but they are errors which it was good to fall into, for they led to the truth’, ([https://en.wikiquote.org/wiki/Jules\\_Verne](https://en.wikiquote.org/wiki/Jules_Verne)), accessed 19 September 2015]. It is time to understand that it is not only positive results that point the way to improving clinical intervention. On the contrary! Negative (well designed and adequately powered) trial results have the ability to significantly influence healthcare for the better, by helping to prevent unnecessary suffering or exposure to yet another (unnecessary) clinical trial.<sup>14,15</sup> Nonsignificant or negative clinical findings share equal importance in navigating the clinical research jungle, and their publication is vital to avoid redundant research. The most important criterion of ground-breaking and trail-setting work is to have their foundation in methodological quality.

## Improving transparency in published clinical trials

Even in randomised clinical trials and other extensively designed studies, some posthoc decisions might need to be made. However, reports of such studies should distinguish clearly between prespecified analyses and posthoc explorations of the data.<sup>16</sup>

To enhance transparency of the published clinical trial, the authors should reveal all discrepancies between the trial protocol and final publication either within the article or as supplementary information. With no space limitations in an online area that can provide all information as supplementary data, it is ethically unacceptable to conceal information from readers.<sup>17</sup> This should be proactive, without the need (for readers) to search for such information and discrepancies in trial registries. On the contrary, journals need to appropriately consider 'negative' results arising from adequately powered trials. This should not be a difficult task if an appropriate sample size calculation has been performed with realistic assumptions that were eventually confirmed in the trial results.

In other cases, when the prehoc assumptions are not met, and the trial turns out to be underpowered, editors may agree to publish it (because all trial results are important, and may contribute to further knowledge through systematic reviews, for example), but great attention will be given to ensure that authors do not overinterpret their findings.<sup>18</sup> Results arising from an underpowered trial can at most only be hypothesis-generating.

Finally, although trial registration is fast becoming mandatory, adherence to a policy of complete transparency and the pursuit of methodological quality in clinical trials, with full involvement of authors, editors and peer-reviewers, is necessary to assure publication of unbiased, high-quality results.

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