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EDITORIAL

Registration of clinical trials in anesthesiology: promoting transparency in clinical research

According to the World Health Organization (WHO), the registration of all interventional trials is a scientific, ethical, and moral responsibility. The WHO has published a minimum dataset recommendation, which has been adopted by many registers and used as criteria for complete registration by many scientific journals.[1] For the purpose of registration, a clinical trial is any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes.[1] When a trial is accepted onto the database, it receives a registration number, which can be quoted on subsequent publications.

Clinical research produces information that is critical to our understanding of any medical intervention. Researchers, universities, governments, and pharmaceutical companies conduct clinical studies to evaluate if a promising medical procedure or medication can lead to a safe and effective treatment for patients. Therefore, quality of medical care is strongly influenced by evidence-based medicine and shared decision making, both of which are based on information originating from clinical studies.

Researchers usually start with experimental testing and preclinical studies that provide basic answers about the potential mechanisms of an intervention. Then, studies involving human subjects provide a clearer picture of how the medication, device, or procedure will work. In fact, clinical trials are considered the central means by which preventive, diagnostic, and therapeutic strategies are evaluated in medicine.[2] Notably, if clinical trials are conducted covertly, or if their results are not properly shared, publication bias may be generated, and scientific evidence and medical practice is strongly compromised, negatively affecting patient care.[3] Hence, clinical trial transparency is pivotal to achieve an optimal evidence-based medical care and this is not different for clinical studies involving interventions in anesthesiology.

There are essentially three steps toward achieving "clinical trial transparency" in anesthesiology: prospective registration of clinical trials, adequate reporting of results, and sharing analyzable data.[4] Registration involves entering details of a clinical trial's design on a public database and should be performed before starting the study. The registration must include the detailed study protocol and statistical analysis plan, with research objectives, design and endpoints clearly specified.[4]

Importantly, there are several reasons why trials should be registered. Trial registration helps to alleviate publication bias, since strong evidence of selective reporting exists.[5] If all studies are registered before starting recruiting patients, nonpublication is visible and can be followed afterwards by other researchers. Furthermore, trial registration provides a record of the trial's outcomes as stated in the protocol *a priori*, avoiding changing endpoints or introducing new ones, with this flawed strategy largely depending on exploratory analysis of the final results. Trial registration may also improve collaboration among researchers by allowing researchers to be aware of ongoing trials. In this context, it may help researchers to identify where research is really warranted. Lastly, trial registration informs the public about current research and may allow potential participants to be aware of recruiting trials for which they might be eligible.[3]

Although there is plenty of benefits for a clinical trial registration in terms of accuracy, compliance, and transparency, previous evidence has indicated an alarming proportion of published clinical studies in the anesthesia literature still inadequately registered despite long-standing international guidelines recommending it.[6-8] For instance, Jones et al[6] have demonstrated that anesthesiology clinical trials display low rates of adequate registration and high rates of discrepancies between outcomes registered and the outcomes actually reported following the publication. In 2015, the most common reason for inadequate registration was registering the study after the first patient enrollment, and shockingly 42% and 90% of the trials had respectively at least one primary outcome and one secondary outcome discrepancy.[6] Of note, De Oliveira et al have found similar

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results indicating a high rate of major discrepancies between the published results and the original registered protocols, even in high-impact anesthesiology journals.[9]

More recently, Chong et al[10] performed an interesting study addressing discrepancies between trial protocols and subsequent publications by reviewing all studies submitted as abstracts to the American Society of Anesthesiologists annual meetings between 2010 and 2016. Authors have shown that the proportion of randomized controlled trials being prospectively registered in anesthesia remains low, as only 21% of 1070 clinical trials were registered before patient enrollment. Consequently, discrepancies between registry entries and corresponding journal publications have also been common.[10]

Most importantly, there is growing evidence that prospective registration of clinical trials reduce bias in clinical research. For instance, Lindsley et al[11] examined the association between clinical trial registration and risk of bias in clinical trials included in systematic reviews. As a secondary objective, authors evaluated the risk of bias among trials registered prospectively and retrospectively. The analysis focused on clinical trials published as of 2005 and included in a sample of 100 Cochrane systematic reviews published from 2014 to 2019. Of 1177 clinical trials identified, the authors showed that only 31% had been registered, and 36.7% of which were registered prospectively. Interestingly, this study has also demonstrated that clinical trial registration was associated with low risk of bias in five out of six domains, including a lower risk of selection bias due to inadequate allocation concealment, performance bias, and detection bias compared with retrospective clinical trial registration.[11]

Publication bias can affect many levels of evidence in clinical studies. For example, within systematic reviews they may result in incorrect interpretation of the data leading to inappropriate clinical decisions. In order to reduce the risk of bias, searching clinical trial registries for unpublished data is a relevant strategy. Unfortunately, so far, the majority of systematic reviews in anesthesiology did not include data from clinical trial registries.[12,13] In fact, the registration of all types of medical research is considered by many as good practice. Therefore, the registration of clinical research could be largely extended to other study designs, including observational studies and systematic reviews, as prevention or at least control for selective publication. Currently, many registers accept the registration of any design of trial, although the fields are generally based on prospective and interventional trial designs. Systematic reviews, similar to clinical trials, also may not be published if they reach unfavorable conclusions, and their registration in a specialized platform (International Prospective Register of Systematic Reviews — PROSPERO) is strongly recommended.

Since 2019, the *Brazilian Journal of Anesthesiology* (BJAN) requires the registration of any clinical trial in a valid and official registry platform according to the International Clinical Trials Registry Platform (ICTRP). There are several clinical trials registries endorsed by the ICTRP, the largest being ClinicalTrials.gov (https://clinicaltrials.gov/), run by the National Library of Medicine, and the EU clinical trials registry in Europe (EU-CTR — https://www.clinicaltrialsregister.eu/). However, some other national entities are considered primary registries for the WHO, as they meet specific criteria for content, quality and validity, accessibility, unique identification, technical capacity, and administration. Examples of primary registries include: Brazilian Registry of Clinical Trials (ReBEC), Australian New Zealand Clinical Trial Registry (ANZCTR), Chinese Clinical Trial Registry (ChiCTR), Clinical Trial Registry — India (CTRI), Japan Registry of Clinical Trials (jRCT), German Clinical Trials Register (DRKS), among others. In the BJAN, Brazilian researchers are advised to register their studies at the ReBEC, a Brazilian publicly-owned entity currently managed by the government, the Oswaldo Cruz Foundation, and non-profit organizations. All details of the studies reported in the ReBEC are publicly available. These characteristics for a registry platform are relevant, since it is fundamental that all registries are free to the public and open to all, should be non-profit organizations, and have mechanisms that ensure data are valid.

In summary, prospective clinical trial registration seems to be mandatory in order to achieve more clinical research transparency. However, a substantial proportion of trials across many disciplines are still published without such registration, which unfortunately is a fact for anesthesiology as well. This leads to reporting bias and doubts about trial efficacy and its integrity. Editors, reviewers, and publishers must also take some responsibility and move forward by increasing their efforts to demand prospective trial registration, a strategy that should be implemented in all anesthesia journals, including the BJAN. The international recommendations for prospective trial registration must be universally incorporated into the anesthesiology research in order to minimize misconduct and ensure clinical research integrity and accuracy.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. World Health Organization. International Clinical Trials Registry Platform (ICTRP). International Standards for Clinical Trial Registries (version 3.0) https://www.who.int/publications/i/item/international-standards-for-clinical-trial-registers [Accessed 18 September 2022].
2. Califf RM, Zarin DA, Kramer JM, Sherman RE, Aberle LH, Tasneem A. Characteristics of clinical trials registered in ClinicalTrials.gov, 2007-2010. JAMA. 2012;307:1838—47.
3. Pansieri C, Pandolfini C, Bonati M. The evolution in registration of clinical trials: a chronicle of the historical calls and current initiatives promoting transparency. Eur J Clin Pharmacol. 2015;71:1159—64.
4. Wager E, Elia N. Why should clinical trials be registered? Eur J Anaesthesiol. 2014;31:397—400.
5. Cook C, Jull G, Moore A. Registration of clinical trials for publication. Man Ther. 2014;19:279—80.
6. Jones PM, Chow JTY, Arango MF, et al. Comparison of registered and reported outcomes in randomized clinical trials published in anesthesiology journals. Anesth Analg. 2017;125:1292—300.
7. El-Boghdadly K, Wiles MD, Atton S, Bailey CR. Adherence to guidance on registration of randomised controlled trials published in Anaesthesia. Anaesthesia. 2018;73:556—63.

8. Østervig RM, Sonne A, Rasmussen LS. Registration of randomized clinical trials—a challenge. Acta Anaesthesiol Scand. 2015;59:986—9.
9. De Oliveira Jr GS, Jung MJ, McCarthy RJ. Discrepancies between randomized controlled trial registry entries and content of corresponding manuscripts reported in anesthesiology journals. Anesth Analg. 2015;121:1030—3.
10. Chong SW, Imberger G, Karahalios A, et al. Trial registration of abstracts from the American Society of Anesthesiologists Meetings 2010-2016: A review of prospective trial registration and selective outcome reporting. PLoS One. 2022;17:e0270841.
11. Lindsley K, Fusco N, Li T, Scholten R, Hooft L. Clinical trial registration was associated with lower risk of bias compared with non-registered trials among trials included in systematic reviews. J Clin Epidemiol. 2022;145:164—73.
12. Umberham BA, Detweiler BN, Sims MT, Vassar M. Clinical trial registry use in anaesthesiology systematic reviews: A cross-sectional study of systematic reviews published in anaesthesiology journals and the Cochrane Library. Eur J Anaesthesiol. 2017;34:797—807.
13. Barbosa FT, Lira AB, Oliveira Neto OB, et al. Tutorial for performing systematic review and meta-analysis with interventional anesthesia studies. Braz J Anesthesiol. 2019;69:299—306.

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