

Clinical trial protocols: relevance and contributions beyond methodological quality

Protocolos de ensaios clínicos: relevância e contribuições além da qualidade metodológica

Fuad Ahmad Hazime¹ 
Vinicius Saura Cardoso² 

¹Corresponding author. Universidade Federal do Delta do Parnaíba (Parnaíba). Piauí, Brazil. fuad@ufpi.edu.br

²Universidade Federal do Delta do Parnaíba (Parnaíba). Piauí, Brazil. vsconfisio@ufpi.edu.br

The global health crisis resulting from the new coronavirus pandemic has demonstrated the extreme importance of clinical intervention research (clinical trials), and especially the need for methodological rigor in conducting protocols and interpreting their results. However, when there is restricted access and detailed knowledge of clinical protocols, the degrees of uncertainty about the safety and efficacy of a therapy increase considerably. In this context, the registration and prior publication of clinical trial protocols allow the comparison between what was planned and carried out by the researchers.¹ The registration process is easy to carry out and can be performed on open-access international virtual platforms, such as, for example, the American <https://clinicaltrials.gov> or the Brazilian <https://ensaiosclinicos.gov.br>. Registering clinical trial protocols has many advantages: (1) publicity and transparency about ongoing research; (2) fidelity to ethical precepts and good clinical research practices; (3) contributions to the state of the art and changes in clinical decision making; and (4) avoid unnecessary duplication and expenditure of resources. Considering the above potential benefits some scientific journals have embarked

on to require the registration of clinical protocols as a prerequisite for manuscript submission and subsequent publication.^{2,3} However, despite this important initiative, there are still failures in the adherence of published articles in relation to their respective records, especially in the selective report of clinical outcomes.^{4,5}

Currently, researchers have great interest in the publication of clinical trial protocols both in international and national journals. The prior publication of these protocols or clinical trial proposals contributes to the scientific community, health professionals, patients, funding agencies, and public health policies being able to update themselves on new clinical research in progress and follow up on future results.

There are also benefits to the authors themselves: (1) promotion of the group or research center; (2) draw the attention of other research groups to new partnerships; (3) possibility of authorship and intellectual contribution to the “state of the art” and (4) increase in the number of publications and academic scores.

Although the contributions and benefits mentioned above are necessary and legitimate, the publication of clinical research protocols should contribute beyond the aspects of transparency and methodological quality. The real contribution to the state of the art - or higher level of knowledge/development on a given topic/research field - comes from a protocol whose theoretical-scientific rationale explores new possibilities and presents plausible arguments.

In this sense, protocols that present an extension of their (previous) record in a scientific article format bring with them content with little contribution to the scientific community and the progress of science. On the other hand, the submission of protocols for publication is an opportunity for authors to demonstrate the relevance of their study, why their results can provide important information to guide the future use (or not) of a particular therapy. Moreover, why this research proposal will reduce the degrees of uncertainty about its therapeutic efficacy.

Perfect protocols, free from bias and bringing a final and decisive answer, are utopian and incompatible with human experimentation. However, these aspects can be better explored to reduce the weaknesses of a therapeutic proposal and the degrees of uncertainty about its relevance and potential applicability.

Another important issue, still little addressed in the protocols, is the excessive emphasis on statistical significance at the expense of clinical significance. A statistically significant difference or $p < 0.05$, for example, can be interpreted as follows: "my results have a probability less than 5% of having occurred by chance". This is an important step in describing the results; however, it does not mean that the therapy is clinically effective. It is necessary to demonstrate the magnitude of its effect.^{6,7} For instance, a therapy to treat chronic pain conditions may have a statistically significant outcome for pain relief compared to placebo treatment. However, a reduction in pain intensity (11-point Numerical Rating Scale) of less than 2 points is not considered a minimally important clinical difference.⁸ The information that the primary and secondary outcomes will be interpreted considering their clinical significance scores brings more transparency and reliability to the reader. Some journals are already requesting this from authors.⁹

We need to move forward quickly in incorporating information that brings relevant contributions to the progress of science, as other aspects should also be addressed in clinical protocols: the costs and consequences of a health intervention.

Competing interests

No financial, legal, or political conflicts involving third parties (government, corporations and private foundations, etc.) have been declared for any aspect of the submitted work (including, but not limited to grants and funding, advisory board participation, study design, preparation of the manuscript, statistical analysis, etc.).

References

1. Chan AW, Hrobjartsson A. Promoting public access to clinical trial protocols: challenges and recommendations. *Trials*. 2018;19(1):116. <https://doi.org/10.1186/s13063-018-2510-1>
2. De Angelis C, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R, et al. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. *Lancet*. 2004;364(9438):911-2. [https://doi.org/10.1016/s0140-6736\(04\)17034-7](https://doi.org/10.1016/s0140-6736(04)17034-7)
3. De Angelis CD, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R, et al. Is this clinical trial fully registered? A statement from the International Committee of Medical Journal Editors. *N Engl J Med*. 2005;352(23):2436-8. <https://doi.org/10.1056/nejme058127>
4. Mathieu S, Boutron I, Moher D, Altman DG, Ravaud P. Comparison of registered and published primary outcomes in randomized controlled trials. *JAMA*. 2009;302(9):977-84. <https://doi.org/10.1001/jama.2009.1242>
5. Sendyk DI, Souza NV, César Neto JB, Tatakis DN, Pannuti CM. Selective outcome reporting in root coverage randomized clinical trials. *J Clin Periodontol*. 2021;48(6):867-77. <https://doi.org/10.1111/jcpe.13451>
6. Currey JD, Baxter PD, Pitchford JW. Significance and importance: some common misapprehensions about statistics. *Cell Biochem Funct*. 2009;27(8):499-502. <https://doi.org/10.1002/cbf.1620>
7. Sullivan GM, Feinn R. Using Effect Size-or Why the P Value Is Not Enough. *J Grad Med Educ*. 2012;4(3):279-82. <https://dx.doi.org/10.4300%2FJGME-D-12-00156.1>

8. Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *J Pain*. 2008;9(2):105-21. <https://doi.org/10.1016/j.jpain.2007.09.005>

9. Cavalcante PGL, Baptista AF, Cardoso VS, Figueiras MC, Hasue RH, João SMA, et al. Transcranial Direct Current Stimulation Combined With Therapeutic Exercise in Chronic Low Back Pain: Protocol of a Randomized Controlled Trial. *Phys Ther*, 2020;100(9):1595-602. <https://doi.org/10.1093/ptj/pzaa105>