

## Short Communication

# Premature termination of interventional ophthalmology clinical trials from international registries

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## ABSTRACT

Globally, a multitude of interventional clinical trials are terminated prior to completion. We sought to identify and analyze trends related to the reporting of these trial results. We conducted a retrospective, cross-sectional study of interventional clinical trials in the 16 primary registries of the World Health Organization Network as well as ClinicalTrials.gov dating back to 2003. A total of 250 studies were identified, of which 135 (54%) were sponsored by academic institutions. A staggering 244 trials (98%) did not lead to publication of results. In sum, a total of 22,420 patients participated in clinical research from which the results were not widely disseminated. 75% of trials were discontinued for unspecified or unclear reasons; 10% were terminated due to inadequate patient accrual. New policies and initiatives have helped usher in an era of improved methods for trial reporting and, in turn, provided the opportunity to perform more interventional trials. However, further action is needed to ensure that findings of all trials are shared with the ophthalmic community in order to build a more comprehensive body of knowledge and decrease potential redundancy.

**Keywords:** Interventional clinical trials, Ophthalmology, Trial termination

## INTRODUCTION

Globally, a multitude of interventional clinical trials are terminated prior to completion. Such termination raises a variety of ethical, financial, and scientific concerns.<sup>1-2</sup> Most terminations appear to be the result of factors not involving interim analysis of trial results.<sup>3</sup> However, in the ophthalmology literature, there is a gap of knowledge related to the reporting of these trial results. We sought to describe the nature with which trials are terminated specifically in ophthalmology-related interventional clinical trials from international clinical trial registries.

## METHODS

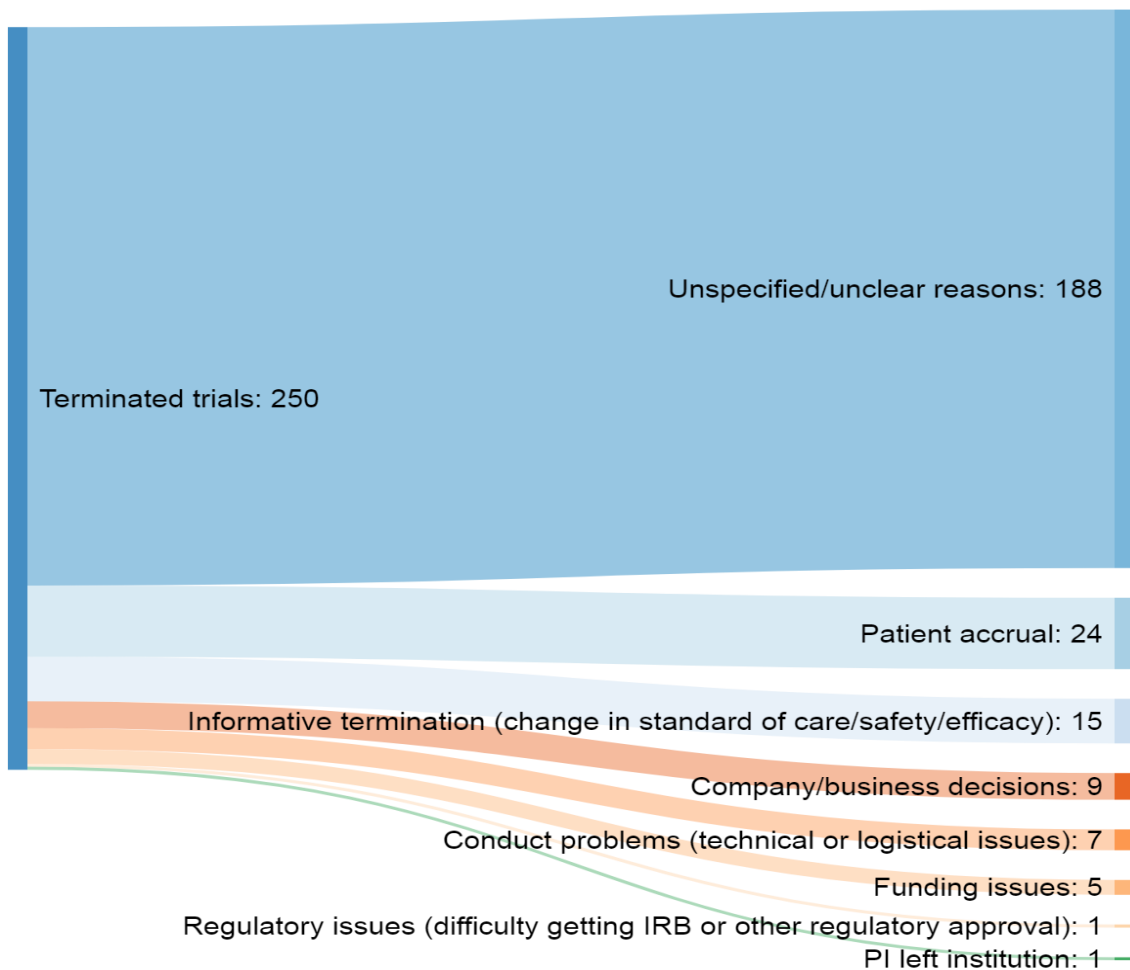
We conducted a retrospective, cross-sectional study of interventional clinical trials in ClinicalTrials.gov and in the following 16 primary registries of the World Health Organization Network as well as dating back to 2003: ANZCTR (Australian New Zealand Clinical Trials Registry), ChiCTR (Chinese Clinical Trial Registry), CRiS (Clinical Research Information Service - South Korea), CTRI (Clinical Trials Registry - India), DRKS (German Clinical Trials Register), EU-CTR (European Union - Clinical Trials Register), IRCT (Iranian Registry of Clinical Trials), ISRCTN (International Standard

Registered clinical/social study number), JPRN (Japan Primary Registries Network), NTR (The Netherlands National Trial Register), PACTR (Pan African Clinical Trial Registry), ReBec (Brazilian Clinical Trials Registry), REPEC (Peruvian Clinical Trial Registry), RPCEC (Cuban Public Registry of Clinical Trials), SLCTR (Sri Lanka Clinical Trials Registry), and the TCTR (Thai Clinical Trials Registry). Data were collected from the registries and the final search was performed on December 29, 2018. The data that were analyzed included trial phase, enrollment, funding sources, and reasons for study termination.

## RESULTS

A total of 250 studies were identified, of which 135 (54%) were sponsored by academic institutions. The included trials that employed interventions such as novel drugs (n=183; 73%), implanted devices/procedures

(n=59; 24%), and other (n=8; 3%). The conditions targeted by these trials included diseases of the retina/choroid (n=111; 44%), glaucoma (n=42; 17%), and diseases of the cornea (n=28; 11%), among others. Most of the trials were conducted in Europe (n=116; 46%), Japan (n=82; 33%), or North America (n=25; 10%). The European Union Clinical Trials Register conducted the greatest number of trials (n=94; 38%) followed by the Japan Primary Registries Network (n=82; 33%) and ClinicalTrials.gov (n=52; 21%). Approximately half of the included trials did not specify the phase of study; 28% were designated as phase 3 and 19% as phase 2 trials. A staggering 244 trials (98%) did not lead to publication of results. In sum, a total of 22,420 patients participated in clinical research from which the results were not widely disseminated. 75% of trials were discontinued for unspecified or unclear reasons; 10% were terminated due to inadequate patient accrual (Figure 1).



**Figure 1: Sankey diagram of reasons for trial termination.**

## DISCUSSION

With more trials comes the possibility of early termination. Trials are terminated for a variety of reasons, not all of which reflect failures in the clinical trial process or an inability to achieve the intended goals.<sup>4</sup> This being

said, trialists should still insist on the sponsor committing to bring trials to completion prior to participation.<sup>5</sup> Certainly, it is of great public interest that trials are completed where the best evidence base for various treatments is made widely available. In our analysis, it was difficult to ascertain a specific reason for why trials

were ultimately prematurely discontinued as a large portion of these trials did not share specific reasons for why the trials were stopped early. However, we determined that the second-most reason for premature trial discontinuation, i.e., problems with patient accrual, tracks similarly with the findings of most other trials whereby the recruitment of study patients has been cited as one of the most prevalent factors in clinical trial discontinuation.<sup>6</sup> Specific reasons for trial termination include issues surrounding patient accrual, management/business decisions, informative termination, conduct problems, funding issues, regulatory issues, and principal investigators leaving the institution for which they work.

## CONCLUSION

New policies and initiatives have helped usher in an era of improved methods for trial reporting and, in turn, provided the opportunity to perform more interventional trials. However, further action is needed to ensure that findings of all trials are shared with the medical community in order to build a more comprehensive body of knowledge and decrease potential redundancy.<sup>7</sup> Publication of inconclusive or negative results ensures that all research activities, regardless of outcome, contribute to global medical knowledge and the advancement of the field.

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## REFERENCES

1. Piuze N, Chughtai M, Khlopas A, Gwam CU, Muschler G, Spindler KP, et al. Early Termination

- of Randomized Clinical Trials in Orthopaedics. *Surg Technol Int.* 2017;30:290-4.
2. Baldi I, Lanera C, Berchiolla P, Gregori D. Early termination of cardiovascular trials as a consequence of poor accrual: analysis of ClinicalTrials.gov 2006–2015. *BMJ Open.* 2017;7(6):e013482.
3. Pak TR, Rodriguez MD, Roth FP. Why clinical trials are terminated. *BioRxiv.* 2015.
4. Williams RJ, Tse T, DiPiazza K, Zarin DA. Terminated Trials in the ClinicalTrials.gov Results Database: Evaluation of Availability of Primary Outcome Data and Reasons for Termination. *PLoS One.* 2015;10(5):e0127242.
5. Lievre M, Menard J, Bruckert E, Cogneau J, Delahaye F, Giral P, et al. Premature discontinuation of clinical trial for reasons not related to efficacy, safety, or feasibility. *BMJ.* 2001;322:603-5.
6. DeAngelis CD, 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. *JAMA.* 2004;292(11):1363-4.
7. Yilmaz T, Jutten RJ, Santos CY, Hernandez KA, Snyder PJ. Discontinuation and nonpublication of interventional clinical trials conducted in patients with mild cognitive impairment and Alzheimer's disease. *Alzheimers Dement (N Y).* 2018;4:161-4.

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